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NT-proBNP: A GUIDE TO IMPROVE THE MANAGEMENT OF PATIENTS WITH HEART FAILURE

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Abstract

N-terminal prohormone of brain natriuretic peptide (NT-proBNP) is a versatile biomarker, that has been extensively studied in large cohorts of individuals in the general population, in subjects at risk for developing left ventricular dysfunction and cardiovascular events, and in patients with chronic or acutely decompensated heart failure (HF).
In this paper, the pros and cons of using natriuretic peptide testing to manage patients with HF are presented and discussed over 3 broad areas: (1) dyspnea triage in the emergency room, (2) natriuretic peptide-guided treatment of chronic HF, and (3) management of patients with HF in primary care and nursing homes.

Introduction

It is always difficult to write something new in a review, but is even more so when a topic has been as extensively covered over the last few years as the role of natriuretic peptides (NPs) in the management of heart failure (HF). This review will present scientific evidence on NPs, with a focus on N-terminal prohormone of brain (or B-type) NP, generally known as NT-proBNP. To help the willing and curious reader, we also list five recent publications that give, in our opinion, an informed and balanced view on different uses of NP assays in HF and left ventricular (LV) dysfunction [1–5].
The incessant search for evidence makes the use of biomarkers in clinical practice difficult, and fosters a larger than ever number of publications focused on the clinical utility of different biomarkers. The strength of evidence has been evaluated by meta-analyses and selective bias has been found to be a common determinant of high associations with risk [6]. However, it should be considered that even some traditional biomarkers such as prostate serum antigen (PSA), blood glucose and glycosylated hemoglobin (HbA1c) remain under extensive scrutiny [7,8]. Upfront it is worth reminding the reader of the principles that hold in order for any biomarker to be used to guide patient management (e.g. diagnosis, prognosis, treatment, monitoring), which have been summarized as follows [9]:

- Accurate, repeated measurements must be available to the clinician at a reasonable cost and with short turnaround times
- The biomarker must provide information that is not already available from a careful clinical assessment
- Knowing the measured level should aid medical decision making.

The finding that biomarkers can contribute to improved management of the individual patient should reassure the pragmatic clinician: there is no such a thing as the laboratory 'obscuring' the brilliant clinical investigator. Rather than replacing clinical judgment, NPs can support and strengthen it. With this positive attitude, which may be called 'bias' by some, we will summarize here the pros and cons of using NP testing for managing patients with HF, focusing on the following three broad areas:

1) Dyspnea triage in the emergency room
2) NP-guided treatment of chronic HF
3) Management of patients with HF in primary care and nursing homes.

Natriuretic peptides

NPs are a family of hormones produced and secreted by the heart, with both the ventricular and atrial myocardium contributing to their release into the bloodstream where they are measured by different methods. The role of the atria in releasing atrial natriuretic peptide (ANP) and the ventricles in releasing BNP is not so clear-cut and, therefore, NPs are not chamber specific. In other words, both ANP and BNP are elevated in the case of atrial or ventricular dilation. NPs have important actions such as vasodilation, natriuresis, and anti-fibrosis which make them major players in the adaptive response of the body to a decrease (over the short or long term) in cardiac function. Their actions are, in essence, beneficial, at variance with other biomarkers which play no role or a negative role in the index disease (see for example the inflammatory markers, tumor necrosis factor [TNF], C-reactive protein [CRP], etc), for this reason, NP analogs, such as nesiritide, have been synthesized for use in the acute treatment of HF. NT-proBNP is released from the myocardium in response to cardiac volume overload and consequent wall stress; however, myocardial ischemia per se also induces release of NPs, thus explaining (at least in part) the raised levels of NP in acute coronary syndromes. This leads to increased circulating NP according to the severity of cardiac disease. Based on these facts, the assay of circulating NPs has gained a role in several clinical settings involved in the management of patients with acute and chronic HF, so that the topic has been extensively reviewed [1,2,4,10].

Point-of-care testing of NPs

Although it goes beyond the scope of the present review, it is worth summarizing the features of point-of-care (POC) assays compared with traditional laboratory assays of NPs in a few lines. Clinicians need laboratory tests which can help in decision making with regard to diagnosis, prognosis, monitoring and treatment of the patient with HF. In an acute setting such as the emergency room (ER), there is a need for a rapid response following a test. POC measurement of cardiac biomarkers has the potential for faster turnaround times and consequent increases in the speed of diagnosis and subsequent triage of patients within the ER. More specifically, POC testing can be helpful when transport to a central laboratory is inconvenient or untenable, when timely processing is difficult or unfeasible, or where immediate access to results may improve outcomes. Testing by the central laboratory involves a larger number of steps than POC. After blood sampling, blood must be transported to the laboratory, processed to undergo analysis, and after the assay has been performed, the result must be validated before being transmitted to the clinician. By contrast, POC testing involves just blood collection, and assay time (usually of the order of 10–20 minutes) and the result is immediately available to the clinician. The overall decrease in turnaround time also reduces the chances of error in sample handling (i.e. tube identification, tube loss). Among the drawbacks that must be carefully considered before introducing a POC test in routine use are: assessment of the relative performance of the new test versus the standard laboratory-based test, the direct cost which is usually higher for POC, and the correct implementation of the new test system within the health care system, accounting also for the opposition by clinical chemists.

Dyspnea in the emergency room

The assessment of patients with suspected HF places a substantial burden on an ER, and HF is diagnosed in the ER with increasing frequency [10]. Moreover, so-called acute [decompensated] HF occurs in many instances as an acute exacerbation of chronic HF, and is a major cause of ER and hospital admission in the United States and Europe [11,12]. Dyspnea has been observed in about half of patients who received a primary diagnosis of HF in the ER, although it is well known to the ER physician that a number of other conditions present with dyspnea, including asthma, pulmonary edema, chronic obstructive pulmonary disease, pneumonia, and myocardial ischemia. Rapid and accurate assessment of acute HF is, therefore, a priority when a patient presents with dyspnea in an ER setting. In recent years, the measurement of BNP or NT-proBNP has become increasingly established for the management of patients presenting to an ER with dyspnea or other symptoms suggestive of HF to distinguish acute HF from these other conditions [12]. The largest study using the Triage® POC in the ER was the Breathing Not Properly trial which enrolled 1586 patients presenting to the ER with acute dyspnea. Two independent cardiologists diagnosed HF in 744 of the patients (47%) based on clinical data. Mean BNP plasma concentrations at admission were 675 and 110 ng/L in patients with and without HF, respectively [13]. The level of BNP was by itself the strongest predictor of a correct diagnosis of HF, with a cut-off of 100

ng/L (sensitivity 90%, specificity 76% for distinguishing HF from other causes of dyspnea). Based on the results of the Breathing Not Properly trial, the US Food and Drug Administration (FDA) granted the indication for the Triage POC as an aid in the differential diagnosis of congestive HF in patients presenting with shortness of breath. More studies along the same lines have been conducted since Breathing Not Properly without substantial disagreements with the original results. Therefore, the use of a quick and reliable assay of NPs in the ER for triage of the patient presenting with acute dyspnea is now part of European and US Cardiology Guidelines [12,14] and part of the clinical routine. The Breathing Not Properly trial was 'replayed' by the same group with the Biomarkers in Acute Heart Failure (BACH) trial, a prospective, multicenter, international study of 1641 patients presenting to the ER with dyspnea [15]. Mid-region pro-atrial NP (MR-proANP) (≥120 pmol/L) proved non-inferior to BNP (≥100 pg/mL) for the diagnosis of HF (accuracy difference 0.9%). In tests of secondary diagnostic objectives, MR-proANP levels added to the utility of BNP levels in patients with intermediate BNP values and with obesity but not in patients with renal insufficiency, the elderly, or patients with edema. None of the biomarkers was able to predict re-hospitalization or visits to the ER. In conclusion, MR-proANP appears to be as useful as BNP for acute HF diagnosis in dyspneic patients.

Smaller studies have been conducted on NT-proBNP, suggesting that it may be of use in the acute setting to help diagnosis [16]. Although it seems reasonable to consider the different NPs equivalent in diagnosing HF in the ER, the evidence for NT-proBNP is currently limited; however, these data should be extended by the ongoing Providing Rapid Out of Hospital Acute Cardiovascular Treatment (PROACT) study which is currently assessing the effects of NT-proBNP level assayed in the ambulance by POC (ClinicalTrials.gov NCT01634425). The issue now is to make good use of the test in the acute setting, rather than repeatedly showing its usefulness.

The management of HF in the ER is not limited to its diagnosis at presentation but encompasses its treatment leading to discharge. One of the earliest studies showing that a decrease in NT-proBNP could predict a safe discharge of patients admitted with acute HF was by Bettencourt and collaborators [17].

NP-guided treatment of chronic HF

It is well accepted that many patients with chronic HF are not adequately treated and that a simple and effective way to improve the management of these patients is highly desirable. Together with other approaches (i.e. nursing-based strategies, telemedicine, implantable hemodynamic monitoring), the relatively simple approach based on NP guidance for the treatment of HF has been proposed and studied for over 10 years.

The rationale for using NP level monitoring to guide treatment of HF stems from the observation that several drugs proven to be beneficial in HF (i.e. angiotensin converting enzyme [ACE] inhibitors, angiotensin receptor blockers, aldosterone antagonists, beta-blockers) decrease circulating concentrations of NPs. Post-hoc analyses have shown that the decrease in NPs over time was associated with improvements in symptoms and survival in patients with chronic HF. The earliest evidence comes from analysis of the Valsartan Heart Failure Trial (Val-HeFT; Figure 1) [18]. These studies showed that not only high levels of NP, but also rising concentrations of NPs from low to high, were associated with poorer outcomes. In this particular case, NT-proBNP performed somewhat better than BNP as a prognostic marker.

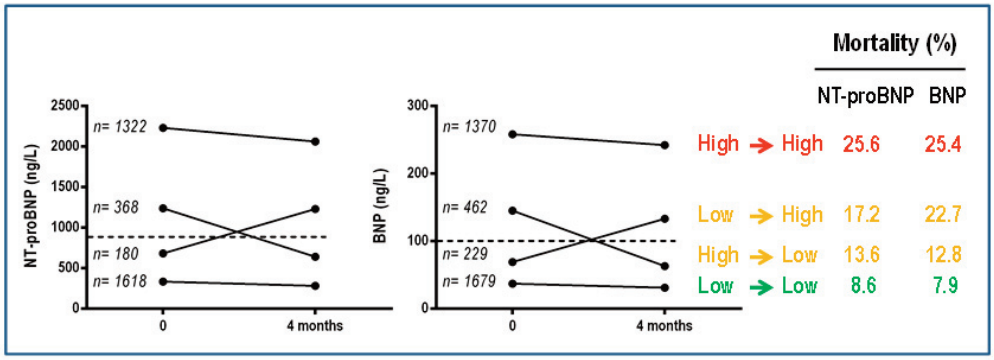

Figure 1
Changes in BNP and NT-proBNP concentrations over 4 months in the Valsartan Heart Failure Trial and all-cause mortality [18,49].

Patients enrolled in the Val-HeFT trial were grouped according to the trajectory of baseline and 4-month concentrations of NT-proBNP or BNP below or above their respective corresponding medians. The number of patients in each of the four groups is indicated on the left, and 23-month all-cause mortality rate on the right. Redrawn from data from 18 and 49.

These studies and others led to prospective studies aimed at demonstrating the use of NPs as a guide to optimize the management of HF. The areas of debate have been clearly outlined and the entire topic has been extensively reviewed [1] with meta-analyses conducted [19,20]. Two issues related to biomarker-guided HF therapy are still controversial: the safety of the strategy and the potential for an interaction with age. The more convincing analysis of safety is that of the Trial of Intensified (BNP-guided) Versus Standard (symptom-guided) Medical Therapy in Elderly Patients with Congestive Heart Failure (TIME-CHF; the largest trial to date with 499 patients randomized), showing no differences in dropout rate or in adverse events between the NT-proBNP-guided therapy or symptom-guided groups. In particular, worsening of renal function and hyperkalemia, two major concerns associated with intensification of HF therapy, occurred at the same incidence in both randomized groups [21,22].

The two most representative studies in NP-guided therapy of HF, the NT-proBNP-assisted treatment to lessen serial cardiac readmissions and death (BATTLESCARRED) and TIME-CHF randomized patients stratified by age: in both studies, NP-guided therapy did better in younger patients. The lack of efficacy in older patients is an intriguing issue which does not appear to be related to a higher incidence of adverse effects in this age group [23].
Aiming at a resolution of the outstanding uncertainties regarding the role of NPs in guiding the management of chronic HF, the US National Heart Lung Blood Institute has funded the new Guiding Evidence Based Therapy Using Biomarker Intensified Treatment (GUIDE-IT) trial. GUIDE-IT is a multicenter, randomized, parallel control group, unblinded trial comparing NT-proBNP guided therapy with usual care in 1100 patients with HF and LV ejection fraction (LVEF) <40% at discharge from hospitalization for HF. The primary endpoint is time to cardiovascular death or first hospitalization for HF.

Overall, in the area of NP-guided therapy of chronic HF with depressed LVEF, evidence is largely based on NT-proBNP: 1958 patients managed with NT-proBNP compared with 629 patients with BNP [1]. Although there is no strong scientific basis for choosing one or the other, the two most frequently advocated reasons for preferring NT-proBNP to BNP are: (1) a relatively longer plasma half-life of NT-proBNP which would lead to a higher stability of its levels in the individual patient, and (2) suggestions from the Val-HeFT trial that it may perform better than BNP overall in predicting outcomes [18].

An outstanding issue is whether NP-guided therapy may be beneficial in patients with HF and preserved ejection fraction (HFPEF). In this population that more frequently consists of elderly females with comorbidities, monitoring of NT-proBNP has led to contradictory findings: while in the Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial the angiotensin receptor blocker irbesartan reduced outcomes only in patients with low NT-proBNP at entry [24], in the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial, the ACE inhibitor perindopril reduced the risk only in patients with higher NT-proBNP at entry [25]. Based on these contradictory results, Packer warns against relying on NP measurement to improve management of a patient with HFPEF [26]. Indeed, a post-hoc analysis of the 123 patients with HFPEF in TIME-CHF showed that (1) outcomes in HFPEF were not better than in the 499 patients with HF and reduced EF (HFREF), and (2) the effects of NT-proBNP-guided management in HFPEF were opposite compared with HFREF. The authors thus suggested that, in contrast to HFREF, NT-proBNP-guided therapy may not be beneficial in HFPEF [27].

HF management with NT-proBNP for patients in primary care and nursing homes

Epidemiological trends indicating an increasing incidence and prevalence of HF call for an effective preventive approach to HF. Present strategies based on risk factor intervention in high-risk populations have shown some reductions in the incidence of new-onset HF [28,29], but also difficulties in achieving adequate risk factor control and suggesting they may not be as effective as desired [30]. NPs, in addition to elements of clinical history and physical examination, are useful for the diagnosis of HF in unselected patients suspected of having new-onset HF in primary care [31,32]. Recent meta-analyses have confirmed that NPs have robust additional diagnostic value in primary care and improve discrimination between individuals with or without confirmed HF, on top of signs and symptoms [33]. NT-proBNP, but not the classical inflammatory marker high sensitivity CRP (hsCRP), also improved the prediction of incident major cardiovascular events and death in 4775 primary care subjects enrolled in the Diabetes Cardiovascular Risk Evaluation Targets and Essential Data for Commitment of Treatment (DETECT) study [34]. NT-proBNP was also a very effective predictor of cardiovascular mortality in elderly patients (mean age 73 years) with symptoms of HF in primary health care [35]. Therefore, the combination of NP-based screening with traditional risk factors to refine risk prediction, identify patients at-risk of cardiovascular events and intensify their management, may provide an approach to prevention of HF in primary care. This hypothesis has recently been tested in the St Vincent's Screening to Prevent Heart Failure (STOP-HF) trial that recruited 1374 participants with cardiovascular risk factors in 39 primary care practices in Ireland. Patients were randomized to receive usual primary care or NP screening, and for those with a BNP level ≥50 pg/mL, echocardiography and collaborative care between their primary physician and specialist cardiovascular care [36]. The trial demonstrated a significant reduction of newly diagnosed HF, asymptomatic LV dysfunction, and also emergency cardiovascular hospitalizations in the intervention group using NP-guided care in this large community cohort. The strategy was also associated with improved risk

factor control, increased use of renin–angiotensin–aldosterone inhibitors, and increased use of cardiovascular diagnostic procedures [36].
NT-proBNP has been evaluated to guide treatment in patients with symptomatic HF in primary care. In the Swedish Intervention Study – Guidelines and NT-proBNP Analysis in Heart Failure (SIGNAL-HF), 252 patients in primary care with a diagnosis of chronic HF and elevated NT-proBNP concentration (>800 ng/L for males, >1000 ng/L for females) were randomized to two treatment strategies according to guideline recommendations, clinical signs and symptoms, with or without NT-proBNP monitoring [37]. Symptoms and signs guided the investigators in making the decision to intensify treatments in both arms; in addition, a reduction of at least 50% from baseline in NT-proBNP was targeted in the NT-proBNP arm, if tolerated by the patient. NT-proBNP-guided treatment did not result in important improvements in the primary outcome, a composite endpoint of days alive, days out of hospital and symptom score from the Kansas City Cardiomyopathy Questionnaire, beyond what could be achieved by education and structured HF treatment according to guidelines.
Nursing or care homes represent another healthcare context in which NT-proBNP is currently evaluated for the early identification of (very) elderly subjects with LV dysfunction and clinical HF [38–40], for risk stratification [41], and for their clinical management. Although NPs did not seem to provide incremental accuracy for the differential diagnosis of HF beyond that achieved with a portable echocardiograph in 405 older institutionalized individuals (mean age 84 years) characterized by a high rate of undetected or misdiagnosed HF [42], integrated programs of management of HF in nursing homes are currently evaluating the clinical utility of NPs in this particular setting [43].

Monitoring of NT-proBNP to reduce readmissions after hospitalization for HF

Repeated readmissions after hospitalization for HF are common, with approximately one in four patients re-hospitalized within 1 month after discharge. This high rate places a considerable economic burden on health care systems, leading some of them to adopt this metric as an indicator of quality of care and as a criterion for reimbursement. Reducing readmissions has therefore become a major objective through strategies that aim at improving in-hospital multidisciplinary care, post-discharge follow-up, home-based monitoring and at enhancing patients' education and self-management. Circulating NPs may be helpful in this context for early detection of new acute decompensation in the absence of physical signs or imaging findings. They can predict which patients at discharge are at higher risk for readmission and require more intensive outpatient care [44,45], and detect early objective changes in wall stress that anticipate cardiac decompensation and require an adjustment of medical therapy. Individualized post-discharge intensive management of high-risk patients guided by short-term changes in NT-proBNP concentration in addition to multidisciplinary care reduced re-hospitalizations and improved outcome (combined endpoint of death or HF re-hospitalization) in a prospective, randomized pilot study [46]. Another pilot study has recently shown that daily home self-testing and telemonitoring of NPs is feasible and safe after hospital discharge for acutely decompensated HF or with signs or symptoms of worsening HF [47]. Interventional trials with home testing of NPs are now warranted to ascertain whether a tailored adjustment of therapy can prevent hospital readmissions and improve clinical outcomes. However, hospital readmissions for HF account for only approximately 35% of all 30-day readmissions after hospital discharge for HF [48]. In addition, patients hospitalized for acutely decompensated HF are often elderly with several co-morbidities, and prone to readmissions for non-cardiovascular reasons. Hence, cardiac markers are likely to pick up only a fraction of all hospital readmissions and integrated multidisciplinary strategies are needed.

Conclusions

NT-proBNP is a versatile biomarker that has been extensively studied in large cohorts of individuals in the general population, subjects at risk for developing LV dysfunction and cardiovascular events, and in patients with chronic or acutely decompensated HF. There is a general consensus that it is a powerful marker of risk across the spectrum of HF stages. How to translate this unique feature into the effective clinical management of patients with HF is the current challenge that faces physicians caring for patients at home or in primary care. Bedside or POC devices for easy and fast NP testing may play an important role in this situation. In the context of suboptimal medical therapy in HF, and although guided therapy with NPs remains controversial (in particular with regard to safety issues and the relationship with age), this strategy should be pursued to reduce unacceptably high mortality and the frequent re-hospitalizations that put a serious economic burden on healthcare systems.
[Word count, main body: 3437 excluding references]

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