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How to Use Natriuretic Peptides in Patients with Heart Failure with Non-Reduced Ejection Fraction?

A Position Paper from the Heart Failure Working Group of Turkish Society of Cardiology

ABSTRACT

Natriuretic peptides are widely used in all types of heart failure. Previously, we defined heart failure with non-reduced ejection fraction as patients with heart failure symptoms and/or signs and who have left ventricular ejection fraction > 40%.[1] For the diagnosis of heart failure with preserved ejection fraction, the presence of raised natriuretic peptides is one of the major components of the diagnosis, and raised natriuretic peptides make the diagnosis more likely in patients with heart failure with mildly reduced ejection fraction.[2] The majority of the existing studies have described the utility of natriuretic peptides in patients with heart failure with reduced ejection fraction, but there is not enough data on natriuretic peptides in heart failure patients with heart failure with non-reduced ejection fraction. Despite the insufficient information regarding the usage of natriuretic peptides in heart failure with non-reduced ejection fraction, it is obvious that there is an unmet need to guide how to use natriuretic peptides in these patients. The main goal of this article is to discuss the role of natriuretic peptides in diagnosis, prognosis, and guidance of heart failure treatment in patients with heart failure with non-reduced ejection fraction. The present review discusses the role of natriuretic peptides in heart failure with non-reduced ejection fraction focusing on: the characteristics of natriuretic peptides, primary prevention of heart failure, diagnosis of heart failure with non-reduced ejection fraction in different patient characteristics and co-morbidities, prognosis of heart failure, monitoring of heart failure treatment and, how to use in worsening heart failure.

Keywords: B-type natriuretic peptide, heart failure, heart failure, chronic

RATIONALE

Natriuretic peptides (NPs) are widely used in all types of heart failure (HF). Previously, we defined HF with non-reduced ejection fraction (HFnEF) as patients with HF symptoms and/or signs and who have left ventricular ejection fraction (LVEF) > 40%.[1] For the diagnosis of HF with preserved ejection fraction (HFpEF), the presence of raised NPs is one of the major components of the diagnosis, and raised NPs make the diagnosis more likely in patients with HF with mildly reduced ejection fraction (HFmrEF).[2] The majority of the existing studies have described the utility of NPs in patients with HF with reduced ejection fraction (HFrEF), but there is not enough data on NPs in HF patients with HFnEF (HFpEF and HFmrEF). Despite the insufficient information regarding the usage of NPs in HFnEF, it is obvious that there is an unmet need to guide how to use NPs in these patients. The main goal of this article is to discuss the role of NPs in diagnosis, prognosis, and guidance of HF treatment in patients with HFnEF .

The present review discusses the role of NPs in HFnEF focusing on,

- the characteristics of NPs;
- primary prevention of HF;
- diagnosis of HFnEF in different patient characteristics and co-morbidities;
- prognosis of HF;

CONSENSUS REPORT

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- monitoring of HF treatment; and
- how to use in worsening HF.

CHARACTERISTICS OF NATRIURETIC PEPTIDES IN HEART FAILURE WITH NON-REDUCED EJECTION FRACTION

There are 3 NPs: atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP).[3]

Atrial natriuretic peptide is mainly secreted in the atria.[4] Initially pre-proANP (151 amino acids) is secreted in response to myocardial stretch and cleaved into proANP (126 amino acids), which is deposited in granules inside the atrial myocardium. A transmembrane protease cleaves the secreting proANP into its biologically active form ANP (28 amino acids) and its inactive form, NT-proANP (98 amino acids).[5] Atrial natriuretic peptide has numerous biological effects, including lowering of blood pressure and renin-angiotensin-aldosterone system (RAAS) inhibition. The levels of NT-proANP are correlated with AF type, left atrial (LA) dimensions, and LA pressure, but it's an impractical biomarker in everyday clinical practice.

B-type natriuretic peptide is mainly produced and released by cardiac myocytes in response to volume overload-induced ventricular wall stress.[6] Beside myocardial wall stress, cardiomyocyte damage or hypoxia may also activate NP gene expression in ventricular myocardium. The synthesis of the precursor molecule preproBNP, which is encoded by the gene NPPB, is the first step in the production of BNP. PreproBNP (134 amino acids) is rapidly cleaved into a signal peptide of 26 amino acids and intermediate mediator proBNP (108 amino acids), then ProBNP breaks down and cleaved into a biologically inactive molecule NT-proBNP (76 amino acids), and a biologically active molecule BNP (32 amino acids). Within a few minutes, NT-proBNP, BNP, and nonfragmented proBNP are released into circulation.[7] Biologically active BNP exerts vasodilator effects, promotes natriuresis and diuresis. Additionally, it inhibits myocardial fibrosis and necrosis.[8] NT-proBNP and BNP are released into the circulation in a 1 : 1 ratio, but due to the slower clearance of NT-proBNP, its blood level is higher than BNP.[9] Both BNP and NT-proBNP are used for diagnostic and prognostic purposes in HF patients.

C-type natriuretic peptide is secreted by endothelial cells in response to vascular lesions in the myocardium, endothelium, chondrocytes, brain, and blood cells. It inhibits fibrosis, platelet aggregation, and tissue plasminogen activation. C-type natriuretic peptide levels tend to increase in advanced HF.[10] Biological effects of NPs determine their use as a biomarker[11] (Table 1). NT-proBNP and BNP are biologically more stable molecules than ANP; therefore, they both are more useful biomarkers for HF patients. The greater biological stability of MR-proANP makes it a promising biomarker for the diagnostic and prognostic purposes in HFpEF. A novel NP, middle-range proANP (MR-proANP) which derives from an intermediate region of NT-proANP has a greater stability. It correlates with increased LA dimensions and with NYHA class in several studies.[12] Its diagnostic and prognostic utility may be superior to NT-proBNP in HFpEF.

Table 1. The Biological Characteristics of Natriuretic Peptides

Natriuretic Peptide	Secretion Mechanism	Biological Activity	Half Time (Minutes)
BNP	Secreted from ventricle in response to increased ventricular wall stretch	Active	20
NT-pro BNP	Secreted from ventricle in response to increased ventricular wall stretch	Inactive	120
ANP	Secreted from atrium in response to increased atrial wall stretch.	Active	2.5
NT-pro ANP	Secreted from atrium in response to increased atrial wall stretch.	Inactive	60-120
CNP	Secreted from endothelial cells in response to vascular lesions.	Active	2.6

ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CNP, C-type natriuretic peptide; NT, natriuretic peptide.

As a conclusion, BNP has stable biological characteristics than ANP; therefore, BNP and NT-proBNP are more usable biomarkers for HF patients. However, MR-proANP has greater biological stability than others and have also diagnostic and prognostic values in patients with HFnEF.

DIAGNOSTIC ROLE OF NATRIURETIC PEPTIDES IN CHRONIC HEART FAILURE WITH NON-REDUCED EJECTION FRACTION

The diagnosis of HFnEF requires corroboration of increased LV filling pressure either by objective evidence of pulmonary or systemic congestion or elevated NPs. Natriuretic peptide plasma concentrations show a continuous relationship with LV filling pressure, nevertheless, guidelines suggest cut-off values for NPs to "rule-out" or "rule-in" the diagnosis. In latest ESC and AHA/ACC/HFSA guidelines, the recommended rule-in values for diagnosing chronic HF do not differ between HFrEF, HFnEF patients in sinus rhythm (SR), and BNP levels ≥35 pg/mL or NT-proBNP levels ≥125 pg/mL are used for all patients. For HFpEF patients with atrial fibrillation (AF), the cut-off values increase 3-fold (Table 2). Despite its better association with LV filling pressures, less data are available for MR-proANP in chronic HFnEF patients, but the generally suggested cut-off value to rule-out HF is <40 pmol/L and the level with the highest accuracy to rule-in is >120 pmol/L.[13,14]

HFA-PEFF diagnostic algorithm suggests similar levels for the diagnosis of stable symptomatic HFpEF patients but those with a NT-proBNP >220 pg/mL and BNP >80 pg/mL receive 2 points (major criteria) and those with levels between 125-220 and 35-80 pg/mL, respectively receive 1 point (minor criteria). In the presence of AF, the cut-off values are multiplied by 3. The H2PEFF score does not include NPs among the scoring parameters but a NT-proBNP level >450 pg/mL was found highly specific for the presence of HFpEF diagnosed by invasive exercise testing.[15]

Table 2. Cut-Off Values for the Diagnosis of HFnEF in Guidelines and Clinical Trials

	ESC 2021 ACCF/ AHA/HFSA 2022	TOPCAT[16]	PARAGON-HF[20]	PARALLAX[21]	DELIVER[22]	EMPEROR-Preserved[23]
Study groups		Age ≥ 50 years, NYHA II-IV, EF ≥45%	Age ≥ 50 years, NYHA II-IV, EF ≥45%	Age ≥ 45 years, NYHA II-IV, EF >40%	Age ≥ 40 years, NYHA II-IV, EF >40%	Age ≥ 18 years, NYHA II-IV, EF >40%
Biomarker	BNP and NT-proBNP	BNP and NT-proBNP	NT-proBNP	NT-proBNP	NT-proBNP	NT-proBNP
Sinus rhythm	BNP ≥ 35 pg/mL NT-proBNP ≥ 125 pg/mL	BNP ≥ 100 pg/mL NT-proBNP ≥ 360 pg/mL	>300 pg/mL	>220 pg/mL	≥300 pg/mL	≥300 pg/mL
Atrial fibrillation/ flutter	BNP ≥ 105 pg/mL NT-proBNP ≥ 365 pg/mL		>900 pg/mL	>600 pg/mL	≥600 pg/mL	≥900 pg/mL

BNP, B-type natriuretic peptide; HFnEF, heart failure with non-reduced ejection fraction; NP, natriuretic peptide.

Following the TOPCAT trial's failures, NPs have become a main inclusion criterion in interventional clinical HFnEF trials (Table 2).[16] Especially after the emergence of ARNI therapy, NT-proBNP has been used more commonly with required cut-off values higher than in the guidelines. A position paper suggested that for risk enrichment in HFpEF, cut-off values should be BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL.[17]

In chronic HFnEF, levels of NPs are lower than in HFrEF, and up to one-third of patients have NP levels below the universal thresholds.[18,19] Especially when there is obesity or left ventricular hypertrophy with reduced wall stress, NPs may not be elevated.

Recommendations

- Natriuretic peptides, together with echocardiography, are the most useful methods for diagnosing chronic HFnEF, but they should always be evaluated in light of clinical data while keeping in mind the circumstances that could result in falsely high or low readings.
- In patients presenting with HF symptoms, measurement of BNP or N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) is useful to support a diagnosis or exclusion of HFnEF.
- NT-proBNP >220 pg/mL; or BNP >80 pg/mL in SR and NT-proBNP >660 pg/mL or BNP >240 pg/mL in AF may be used in the diagnosis of HFnEF.

AGE AND GENDER DIFFERENCES OF NATRIURETIC PEPTIDES IN HEART FAILURE WITH NON-REDUCED EJECTION FRACTION

Age and gender are the most frequent cofounders of NP concentrations. Studies showed that plasma NP levels are significantly higher in women than in men and older age is also found to be significantly associated with higher NP levels with a striking increase after age 50.[20-23] These associations are independent of other factors. Patients with HFpEF and HFmrEF are generally female and older, and therefore, age and gender should always be taken into account for the interpretation of NP levels in these patients' population.

The concomitant increases in subclinical cardiac illnesses in older persons are assumed to be the main cause of the age-associated increase in NP levels.[24-27] An increase in NP gene expression has also been reported with advanced age. Clinical studies have suggested a decrease in the clearance of NPs from plasma in elderly patients, even in the absence of renal dysfunction. Furthermore, a reduction in nonrenal clearance mechanisms, such as platelet-associated clearance receptors, is supposed to contribute to the higher levels of NP seen in the elderly.[24-26]

Women have significantly higher NP levels than men. Although the physiologic basis for these sex-related differences is unclear, higher levels of NPs in women are thought to be due to stimulatory effects of female sex hormones on NP gene expression and extracardiac sources of NPs within the female reproductive tract.[24] Given the inverse relation between renin and NPs, lower renin levels in women than in men is also thought to be another mechanism of higher levels of NPs in women.[24]

Both age- and gender-related increases in NP levels may lead to an increased risk of a false positive diagnosis of HF in an elderly or female patient.[26] On the other hand, a higher decision limit could result in false negative diagnosis in the younger age group. The number of patients in the studies is too small to investigate different decision limits in different age groups and in females.[26] However, the magnitude of gender-related differences is regarded as fairly small and of only minor importance in clinical studies, and thus same decision limit is suggested to be used in females and males.[26] In the HF guidelines, there is currently no recommended gender-related cut-off levels of NPs for females or males.[28] However, in clinical practice, patient's gender should be taken into account while interpreting the NP level.

An increase in NP levels could suggest diagnosis of HFnEF with almost similar precision as in HFrEF. However, NP levels are generally lower in patients with HFnEF. Rule-out cut-off values to exclude HF diagnosis (BNP <35 pg/mL and NTproBNP <125 pg/mL) are the same for HFnEF and HFrEF in the HF guidelines. Higher NP values suggest further examination but do not provide diagnosis alone.[2,29,30] Some authors proposed age-specific rule-out cut-points of NTproBNP on the basis of chronic HF: <50, <75, and <250 pg/mL for ages <50, between 50 and 75, and ≥75 years, respectively.[26] In the HF guidelines rule-out cut-off points for acute HF has

been defined as <100 pg/mL for BNP and <300 pg/mL for NTproBNP.[2] In some HF guidelines, age-specific diagnostic rule-in cut-off points has been defined in the setting of acute HF: >450, >900, and >1800 pg/mL for ages <50, between 50 and 75, and ≥75 years, respectively, for NTproBNP; and >400 pg/mL for BNP without any age criterion.[28] However, HF guidelines have not recommended gender- and age-specific cut-points of NP levels for the diagnosis of chronic or acute HFnEF.

Recommendation

- Although gender- and age-specific cut-off points of NP levels are not recommended to use in the diagnosis of HFnEF, higher NP cut-off levels are expected in older age.
- In the setting of acute HF: rule in cut-off points >450, >900, and >1800 pg/mL for ages <50, between 50 and 75, and ≥75 years, respectively, for NTproBNP; and >400 pg/mL for BNP without any age criterion.

NATRIURETIC PEPTIDES IN DIAGNOSING HEART FAILURE WITH NON-REDUCED EJECTION FRACTION IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Heart failure and renal dysfunction coexist very frequently and portend a detrimental combination. Numerous studies have shown that chronic kidney disease in HF patients is associated with increased mortality.[31] Although this is true for both HFrEF and HFpEF patients, this association has lately been suggested to be more pronounced in HFpEF patients.[32] The incidence of both HFpEF and kidney disease has been steadily rising and will further increase due to aging of the general population and epidemics of hypertension and diabetes which are common etiologic factors in the development and advancement of both diseases.[33] One-third of chronic HF patients have renal dysfunction.[34] The interaction between HF and renal dysfunction is not only critical for challenging the treatment but also the diagnosis of HF relevant to the use of NPs. Since NPs are elevated in acute/chronic renal dysfunction, the interpretation of NPs for identifying HF patients is difficult. The cause of higher NPs in renal failure is multifactorial. One reason is the counter-regulatory response of the heart to renal dysfunction. The cardiorenal syndrome type III (acute renal dysfunction) or IV (chronic renal dysfunction) is a condition in which renal dysfunction leads to HF. The other reason is the decrease in the passive clearance of NPs, particularly NT-proBNP by kidney. The levels of NP should always be interpreted in consideration of renal function. For the optimal diagnostic performance, the cut-off point of NPs should be set higher in case of renal dysfunction.[35] A study investigating the diagnostic utility of NT-proBNP in chronic kidney disease proposed that age-stratified cut-off points for acute HF diagnosis, which are 450, 900, and 1800 pg/mL for those aged <50, 50-75, >75 years, respectively, apply to patients with renal dysfunction without further adjustment for renal function.[36] In the PRIDE study, which examined the interaction of renal function and NT-proBNP, a cut-off point of 1200 pg/mL was found to identify acute HF among patients with GFR less than 60 mL/min.[37] Since there are no clear guidelines, we can debate what that number should be the diagnostic cut-off in HFnEF patients with renal dysfunction. Undoubtfully, that number should be higher than in patients with normal kidney function because kidney failure itself, either acute or chronic, raises NPs. Higher cut-off values for NPs will improve the specificity of NPs and help to exclude the diagnosis of HF in acute/chronic kidney disease patients. Due to its relatively less reliance on renal clearance, BNP may be a more reliable biomarker in renal dysfunction.[38]

Recommendations

- The effect of renal dysfunction for BNP is smaller than NTproBNP.
- In case of chronic and acute kidney disease, higher cut-off values for NTproBNP should be set for ruling HFnEF out. The rule-out cut-off to 200 pg/mL rather than 100pg/mL seems adequate for BNP.
- The testing of NP for HF should be discouraged in patients on dialysis.

NATRIURETIC PEPTIDES IN DIAGNOSING HEART FAILURE WITH NON-REDUCED EJECTION FRACTION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is a leading cause of disability and mortality. Cardiovascular disease, especially HF is an important comorbidity in this patient population. It has been reported that congestive HF affects 20%-70% of COPD patients and cardiovascular disease is responsible for one-third of deaths.[39,40] Studies on NPs in COPD population demonstrated that they are useful in identifying cardiovascular disease, stratifying risk, and probably predicting prognosis.[41] No detailed data are available regarding the underlying classification of HF, and there are no studies that only include patients with HFnEF.

In a meta-analysis by Hawkins et al[42] NPs were studied in COPD patients. In stable ambulatory patients without HF, NPs were normal or mildly elevated. In patients with concomitant left ventricular dysfunction, the levels were significantly higher. The levels were also shown to be greater in patients with comorbidities such ischemic heart disease, pulmonary emboli, arrhythmia like AF, valvular heart disease, renal impairment, and pulmonary hypertension.[42]

The NP levels were shown to be modestly higher during acute exacerbations. In a study done by Li et al[43] the sensitivity and specificity of NT-proBNP concentrations for in-hospital mortality was explored. The cut-off value was 551.35 ng/L with a sensitivity of 0.97 and specificity of 0.66.[43] History of congestive HF (no information on LVEF) and renal dysfunction were other variables for mortality in the same study. One-year mortality was also statistically higher with NT-proBNP levels >551.35 ng/l and this association persisted in patients with and without a history of HF. Another study conducted in the UK looked at patients who had been hospitalized with an acute exacerbation of COPD. About 20% of the patients had known HF at the time of admission. Over 40% of the patients had a new diagnosis of HF. A NT-proBNP level ≥400 pg/mL had a negative predictive value of 77.8% and positive predictive value of 82.8%.[44] Once more, no LVEF was reported. Elevated NPs are likely related to right heart remodeling,

pulmonary vascular remodeling, and left ventricular systolic and diastolic dysfunction.

Natriuretic peptides are often elevated in patients with COPD. Coexisting HF is probably one of the most important comorbidities contributing to this elevation. No data that cover only HFnEF is present. Ischemic heart disease, valvular heart disease, arrhythmia, and renal dysfunction are identified as other risk factors and these probably are associated with HFnEF.

Recommendation

- Detailed cardiovascular examination is required to support the diagnosis of HFnEF in COPD patients who have high levels of NPs. No absolute cut-off value is defined for diagnosing HFnEF.

THE DIAGNOSTIC ROLE OF NATRIURETIC PEPTIDES IN OBESE PATIENTS WITH HEART FAILURE WITH NON-REDUCED EJECTION FRACTION

Body mass index has an almost linear relationship with circulatory NP concentration, regardless of the presence or absence of HF. The cause of this association is multifactorial and possible factors are summarized in Figure 1.[45] Owing to this inverse relation, nearly 20% of overweight and obese patients with acute decompensated HF had a BNP concentration of less than 100 pg/mL on admission, with the latter being the recommended cut-off value in 2021 European Guidelines on Heart Failure.[1,46] The severity of obesity also affects the diagnostic accuracy of NPs. A BNP cut-off value of 110 pg/mL still had more than 90% sensitivity to accurately identify acute HF in patients with a BMI of 25-35 kg/m^2, while the same figure was 54 pg/mL for those with a body mass index of >35 kg/m^2.[47] NT-proBNP appears to be less sensitive to BMI as compared to BNP, with a cut-off of 900 pg/mL being false negative in 10% of overweight cases and 15% of cases with obesity in a ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) substudy.[46] When age-stratified NT-proBNP cut-off values were used to rule out acute HF in the same population, NT-proBNP had a 100% sensitivity at a cost of limited specificity. To note, the exact percentage of patients with HFnEF was unknown in both studies.

Obesity is associated with a marked decrease in NPs not only in patients with acute HF but also in those with chronic HF.[48] Indeed, inaccuracy may be even greater for chronic HFnEF given that NP concentrations are usually lower in this setting.[49,50] Unfortunately, studies that formed the basis of current guideline-recommended cut-off values of NPs in the setting of chronic HF had rather small sample sizes and no exact data were available with regard to the proportion of patients with HFnEF. Obesity is the primary factor that leads to normal NP concentrations in patients with HFpEF, as demonstrated in a recent study in which 80% of patients with HFpEF and an NT-proBNP level <125 pg/mL were obese.[51] Similarly, 25%-30% of patients with HFpEF may be "BNP deficient," most of whom are either overweight or obese.[52] Thus, the cut-off values recommended by the 2021 ESC Guidelines for Heart Failure for the diagnosis of chronic HFpEF (BNP >35 pg/mL or NT-proBNP >125 pg/mL) seem to be insufficient to rule out a diagnosis of HF in obese patients, but these numbers should still be useful for rule-in.[2] Unfortunately, there is insufficient data to advise a cut-off limit for NPs in patients with HFmrEF, but a reasonable approach would be to follow threshold values appropriate for HFpEF.

Recommendation

- Lower NP levels are expected in obese patients, so neither BNP nor NT-proBNP are reliable for ruling out *chronic HFnEF* in those patients, but guideline-recommended thresholds (BNP >35 pg/mL or NT-proBNP >125 pg/mL) can be used to rule in HF.
- Weight-adjusted BNP values have adequate accuracy to rule-in or rule-out *acute HF* in overweight/obese patients, while age-adjusted NT-proBNP cut-off values have at least adequate sensitivity for ruling out *acute HF*.

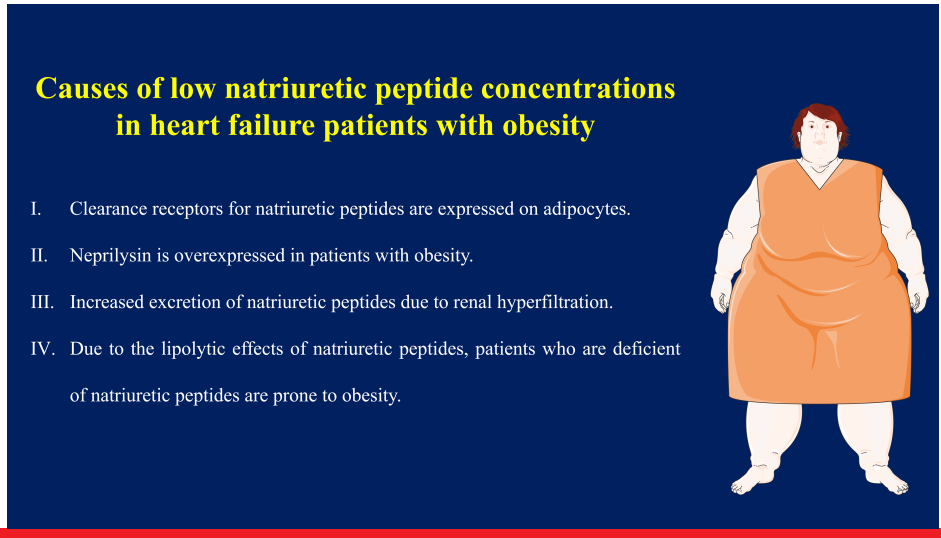

Figure 1. The possible reasons for lower natriuretic peptide levels in obese patients with HFnEF. HFnEF, heart failure with non-reduced ejection fraction; NPs, natriuretic peptides.

THE DIAGNOSTIC ROLE OF NATRIURETIC PEPTIDES IN HEART FAILURE WITH NON-REDUCED EJECTION FRACTION IN PATIENTS WITH ATRIAL FIBRILLATION/ FLUTTER

Heart failure and AF frequently coexist and both conditions are known to increase NPs. While NPs have greatly impacted the diagnosis of HF, their use has been limited in the setting of AF, and careful interpretation is warranted. Furthermore, this coexistence is frequently unrecognized due to overlapping symptoms.

In the setting of AF, the performance of NT-proBNP in the identification of HF is far lower, with a negative predictive value of only 86% for patients with NT-proBNP below 125 pg/mL. Using these cut-offs, a substantial proportion of patients with AF and HF will not be identified.[53] Since AF per se is associated with higher NP levels, a higher cut-off should be considered in these patients to exclude HF. On the other hand, patients with AF may have elevated NP levels even in the absence of HFnEF especially HFpEF. Therefore, partition values may need to be adjusted in patients with HFnEF and AF.

In AF, elevated NPs reflect increased LA pressure and adverse remodeling.[54] Loss of atrial contraction and elevation of atrial pressure stretches the atrial wall leading to alternation of the left ventricular filling, and ventricular production of NPs.[55] It is also thought that an increased ventricular rate during AF leads to myocardial ischemia, further volume and pressure overload, thus resulting in the ventricular production of NPs.[55] Restoration of SR goes along with decreasing concentrations and higher levels on NPs in patients with sustained AF than paroxysmal AF.[56]

Atrial natriuretic peptide is secreted predominantly by the atria, and its plasma concentrations are increased in patients presenting with AF.[57] However, its short half-life limits its widespread use in clinical practice.

Mid-regional-proANP (a stable fragment of the ANP precursor hormone) has been correlated with incidental AF.[57] However, an inverse relationship between ANPs and long-standing AF also appears to exist. N-terminal ANP is highly correlated with AF, but the fact that it is substantially impacted by AF limits this peptide's value as a marker of LV dysfunction.

Conversely, BNPs are not independently influenced by AF and show a strong correlation with EF, even in this population with atrial overload, which is a potential explanation for its high sensitivity and specificity as a diagnostic marker for LV dysfunction.[58]

Definitive cut-offs to diagnose HFpEF in patients with SR or in AF are not well established, and trials have used different values.[59] In the setting of screening HFpEF average NPs have been reported to be 3-3.5-fold higher in patients with AF than in patients in SR.[59] In symptomatic HFpEF with AF, levels tend to be even higher.[59] For diagnosing HFpEF in patients with AF, 3 times higher than used for patients in SR are hence recommended.

Table 3. Diagnostic Cut-Off Points of Natriuretic Peptides in Patients with HFnEF and Atrial Fibrillation

Natriuretic Peptides	Major Criterion	Minor Criterion
NT-proBNP	>660 pg/mL	365-660 pg/mL
BNP	>240 pg/mL	105-240 pg/mL

BNP, B-type natriuretic peptide; HFnEF, heart failure with non-reduced ejection fraction.

Heart Failure Association of the European Society of Cardiology recommends the use of major and minor diagnostic criteria according to the severity of an abnormality and the presence of modifiers such as AF to diagnose HFpEF.[59] According to this consensus paper, major criteria (and cut-points) have been selected for their high specificity, while minor criteria should be more sensitive (Table 3).

In terms of biomarker levels, patients with HFmrEF are in between HFpEF and HFrEF. Secretion of NPs in HFmrEF is linked to a combination of cardiac stretch and inflammation. Patients with HFmrEF patients are known to have lower NP levels compared with HFrEF and have higher NP levels compared with HFpEF.[60] Although there is not enough data about the NPs levels in patients with AF and HFmrEF, we can extrapolate this finding to those patients.

Further studies are required to confirm optimal cut-off values of NPs (and subtypes) in patients with AF and HFnEF, and frequent controls are required for AF.

THE EVALUATION OF NATRIURETIC PEPTIDES IN WORSENING HEART FAILURE WITH NON-REDUCED EJECTION FRACTION

Heart failure is a chronic disease with a fluctuating course in which remissions and worsening events could occur on different occasions. Heart failure with non-reduced ejection fraction represents as a major phenotype in which patients have clinical features of HF in the presence of mildly abnormal or preserved LVEF along with abnormalities of left ventricular filling yielding different degrees of diastolic dysfunction. Since NPs are semi-quantitative biomarkers of ventricular loading, they can reflect fluctuating course in the setting of worsening HF.

Hence, NPs are elevated in patients with HFnEF reflecting the severity of cardiac morphological and functional abnormalities and the levels are related to hemodynamics, though, NPs are less impressively increased compared to patients with reduced ejection fraction.

Considering worsening HF, guidelines do not make any distinction and use the similar thresholds for diagnosis of worsening HF in HFnEF versus HFrEF.[2] Of note, these thresholds are mainly utilized for exclusion purposes. However, since there are several co-morbidities accompanying HFnEF including confounding and opposing effects of obesity and AF both of which are frequent co-morbidities, these have to be considered for worsening events. In one study, it was shown that in one-third of HFpEF patients, BNP levels were below 100 pg/mL, which is a typical exclusion cut-off for worsening HF in the guidelines, despite increased filling

pressures via cardiac catheterization.[61] In another study, 22% of patients with worsening HFnEF had BNP less than 200 pg/mL. Of note, BNP < 200 pg/mL designated good prognosis in acute HFrEF whereas it was related to poor prognosis in acute HFnEF.[62] Even in the pioneering Breathing Not Properly study, cut-off BNP of 100 pg/mL had a sensitivity of 95% for worsening HFrEF and 86% for worsening HFnEF.[63]

Therefore, low NPs should be interpreted cautiously in the suspicion of HFnEF and a structured evaluation pathway should be integral part of assessment.

Nevertheless, in-hospital assessment could influence prognosis in HFnEF. In a study of patients with worsening HFnEF, NT-proBNP ≥1500 ng/L at discharge (HR: 5.23, $P < .001$) was negative and ≥50% NT-proBNP reduction during hospital stay (HR: 0.62, $P = .019$) was positively related to outcome.[64]

Of note, MR-proANP has been introduced into HFnEF diagnostic pathway. As MR-proANP levels had a significantly higher AUC compared to NT-proBNP (0.844 vs. 0.518, $P < .001$) in HFnEF patients.[65] Besides, MR-proANP concentrations, which were linked to LA volume, were related to NYHA class contrary to NT-proBNP. MR-proANP levels were also found to be elevated even in patients with non-diagnostic NT-proBNP levels.[9]

Recommendations

- In patients presenting with worsening HF symptoms, measurement of BNP or NT-proBNP is useful to support a diagnosis or exclusion of HF.
- In patients with worsening HF symptoms, lower NP levels are expected in HFnEF than HFrEF. However, guideline-recommended thresholds (BNP >100 pg/mL or NT-proBNP >300 pg/mL) might be used to rule in acute HF.

PROGNOSTIC ROLE OF NATRIURETIC PEPTIDES IN PATIENTS WITH HEART FAILURE WITH NON-REDUCED EJECTION FRACTION

Myocardial stretch and wall tension is the main determinate in plasma levels of NPs which explains higher plasma levels in HFrEF compared to HFnEF despite similar survival.[66] Different co-morbidities associated with HFnEF may be related to higher or lower levels of NPs.[67] Diagnostic capabilities of NPs were well-studied and have their place in HF guidelines.[28,68]

The NPs reveal important predictions in both patients with HFrEF and HFnEF. Systematic meta-analyses of different studies evaluated patients who were asymptomatic, stable, hospitalized with acute HF, and hospitalized advanced HF patients. The results of these analyses determined different NP levels for prediction of all-cause mortality, re-hospitalization, and death due to HF.[69-71]

The prognostic role of NPs may be considered both in patients during their outpatient clinical visits and in patients before discharge following their acute HF hospitalizations. Higher levels of NPs are related to all-cause mortality, cardiovascular death, and major cardiovascular events for both short- and long-term periods.[71,72] In patients with chronic HFrEF, those with decrease in NT-proBNP ≤1000 pg/mL during GDMT had better outcomes.[73] Natriuretic peptides are well correlated with HF severity and prognosis suggesting that they may guide treatment adequacy in the predischarge period. Studies depicted a critical prediction for 1-year mortality and re-hospitalization in patients with acute HF.[74,75] This prognostic information is essential regarding the clinical assessment of these patients who failed to decrease re-hospitalization and mortality. Current information shows not only clinical assessment but also echocardiography also hammered by NPs.

The outpatient clinical setting is another challenge for cardiologists who have very little information on chronic HF patients. Serial measurements of NPs also determined as powerful tools for prognosis in these patients. Studies showed a serial assessment of not only HFrEF but also HFnEF patients put out a similar success. For this purpose, a specific cut-off point may not be efficient as stated in the papers but a cut-off point specific to that 1 patient should be the goal. Small changes in NPs during the follow-up could be related to co-morbidities however, a change of more than 50% should be accepted as a change in filling pressures.[28]

Recommendations

- In patients with chronic HFnEF, measurements of BNP or NT-proBNP levels are recommended for risk stratification.
- In patients hospitalized for HFnEF, measurement of BNP or NT-proBNP levels at admission is recommended to establish prognosis.
- In patients hospitalized for HFnEF, a predischarge BNP or NT-proBNP level can be useful to establish post-discharge prognosis

NATRIURETIC PEPTIDES IN MONITORIZATION AND OPTIMIZATION OF THERAPY IN HEART FAILURE WITH NON-REDUCED EJECTION FRACTION

A pre-specified analysis of TIME-CHF which was designed to compare NT-proBNP-guided versus symptom-guided management in patients with chronic HF showed that opposite effects of NT-proBNP-guided management on 18-month outcomes were observed in HFpEF compared with HFrEF. It was thought that NT-proBNP-guided therapy may not be beneficial in HFpEF.[76]

The STRONG-HF study designed to test whether rapid up-titration of renin-angiotensin aldosterone system (RAAS) inhibitors (ACE inhibitor, ARB, or ARNI), β blockers, and mineralocorticoid receptors after an admission for acute HF was safe and could improve the prognosis in 180 days after discharge.[76] Results showed that high-intensity strategy was safe and associated with a reduced risk of death or being readmitted for HF. A total of 33% of the study patients were with HFnEF and the results were consistent in these patients. The post hoc subgroup analysis of primary endpoint showed that the benefit of high-intensity care after worsening HF is more distinct in patients who have >median (2859 pg/mL) baseline NT-proBNP levels. The high-intensity care group had lower NT-proBNP concentrations at day 90 than those in the usual care group.[76,77]

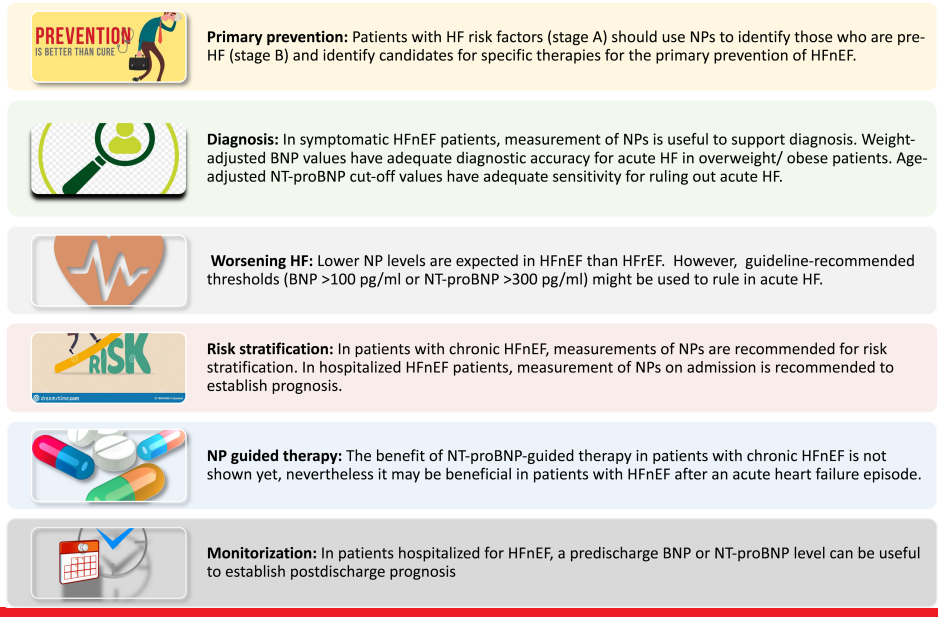

Figure 2. Recommendations for the practical use of NPs in patients with HFnEF. HFnEF, heart failure with non-reduced ejection fraction; NPs, natriuretic peptides.

Recommendation

- The benefit of NT-proBNP-guided therapy in patients with chronic HFnEF is not shown yet, nevertheless it might be beneficial in patients with HFnEF after an acute heart failure episode.

NATRIURETIC PEPTIDES IN PRIMARY PREVENTION OF HEART FAILURE WITH NON-REDUCED EJECTION FRACTION

The patients with hypertension, atherosclerotic cardiovascular disease, diabetes, metabolic syndrome and obesity, exposure to cardiotoxic agents, genetic variant for cardiomyopathy, or positive family history of cardiomyopathy are at risk for HF and named as Stage A HF (at risk for HF) in ACC/AHA HF guidelines if they do not have any HF symptoms.[30] We need to modify and control the risk factors of these patients and follow-up closely to prevent the development of HF.

Participants with stage 1 hypertension but elevated NT-proBNP had greater cardiovascular risk compared with those with stage 2 SBP but lower NT-proBNP.[78] Given the high prevalence of underdiagnosed HF in individuals with T2DM, the finding of elevated NT-proBNP may contribute

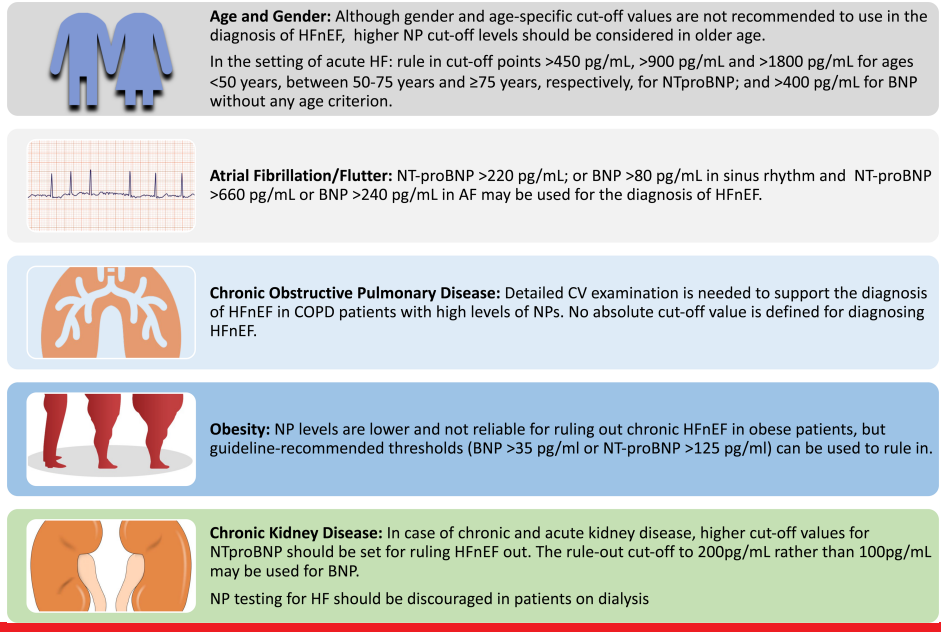

Figure 3. Recommendations for the use of NPs in HFnEF patients with specific conditions. HFnEF, heart failure with non-reduced ejection fraction; NPs, natriuretic peptides.

to early diagnosis, as well as the identification of people at higher risk of developing HF. Among unselected or high-risk patients with T2DM, elevated NT-proBNP, generally >125 pg/mL, was associated with an increased risk of CV outcomes and death. This cut-off point was well demonstrated in an unselected cohort of T2DM patients, where NT-proBNP greater than or equal to 125 pg/mL was able to predict unplanned hospitalization for CV events or death in the short term of 12 months.[79] In addition, NT-proBNP <125 pg/mL had a negative predictive value of 97.6% and a sensitivity of 0.795% to identify individuals who are not at intermediate risk for CV events.[79] Considering the negative predictive value of NT-proBNP <125 pg/mL, this biomarker stands out as a useful tool for initial screening, allowing to distinguish individuals with T2DM at high risk of death and CV events from those at low risk.

The asymptomatic patients with HF risk factors who have any of structural heart disease, evidence for increased filling pressures, and elevated NPs or troponin levels (in the absence of competing diagnoses that result elevation in these biomarkers) are in Stage B HF means pre-HF.[30] We should treat the structural heart disease to prevent HF in pre-HF patients.

We think that all of the patients who are at risk for HF and most of patients who are in pre-HF stage might have non-reduced LVEF.

Recommendation

- Using NPs are recommended in patients with HF risk factors (stage A) to reveal who are at pre-HF stage (stage B) and find the potential nominees for specific therapies for the primary prevention of HFnEF
- The full recommendations about the usefulness of NPs in patients with HFnEF are summarized in Figure 2. Figure 3 shows the recommendations for the use of NPs in HFnEF patients with specific conditions and co-morbidities.

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