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CONSENSUS STATEMENT

Natriuretic peptides: role in the diagnosis and management of heart failure: a scientific statement from the Heart Failure Association of the European Society of Cardiology, Heart Failure Society of America and Japanese Heart Failure Society

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Fukuoka, Toyama, Matsumoto, Kashihara, Sango, Osaka, Kawaguchi, Yonago, and Tokyo, Japan; Cleveland, Ohio; Dallas, Texas; Jackson, Mississippi; Falls Church, Virginia; Durham, North Carolina; Boston, Massachusetts, and San Francisco, California, USA; Warwick, UK; Clayton, Australia; Berlin, Germany; Wroclaw, Poland; Badalona and Barcelona, Spain; Bucharest, Romania; Athens, Greece; Brescia and Rome, Italy; Belgrade, Serbia

Natriuretic peptides, brain (B-type) natriuretic peptide (BNP) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) are globally and most often used for the diagnosis of heart failure (HF). In addition, they can have an important complementary role in the risk stratification of its prognosis. Since the development of angiotensin receptor–neprilysin inhibitors (ARNIs), the use of natriuretic peptides as therapeutic agents has grown in importance. The present document is the result of the Trilateral Cooperation Project among the Heart Failure Association of the European Society of Cardiology, the Heart Failure Society of America and the Japanese Heart Failure Society. It represents an expert consensus that aims to provide a comprehensive, up-to-date perspective on natriuretic peptides in the diagnosis and management of HF, with a focus on the following main issues: (1) history and basic research: discovery, production and cardiovascular protection; (2) diagnostic and prognostic biomarkers: acute HF, chronic HF, inclusion/endpoint in clinical trials, and natriuretic peptide-guided therapy; (3) therapeutic use: nesiritide (BNP), carperitide (ANP) and ARNIs; and (4) gaps in knowledge and future directions.

Keywords Heart failure • Natriuretic peptides • Diagnosis • Therapy

Natriuretic peptides, brain (B-type) natriuretic peptide (BNP) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) are useful to establish the presence and severity of heart failure (HF). The measurement of BNP, NT-proBNP or midregional proatrial natriuretic peptide (MR-proANP) can support the diagnosis of HF as a cause of symptoms in ambulatory and emergency department settings. However, it should be noted that increases are observed due to various cardiac as well as noncardiac causes. Higher levels of BNP and NT-proBNP are associated with a greater risk for adverse short- and long-term outcomes in HF, including all-cause and cardiovascular death. Predischarge BNP and NT-proBNP levels are strong predictors of the risk of death or hospital readmission for HF. They could help to predict postdischarge prognosis and optimize treatment. However, the efficacy for treatment guidance using serial BNP or NT-proBNP measurements remains unestablished.

In general, BNP and NT-proBNP have a number of similarities from a diagnostic standpoint, and either can be used in patient-care settings. BNP, but not NT-proBNP, is a substrate for neprilysin. Therefore, an angiotensin receptor–neprilysin inhibitor (ARNI) can increase BNP levels but not NT-proBNP levels. BNP and NT-proBNP measurements are also useful in patients at risk of HF. However, standardized screening for HF remains challenging as a result of the heterogeneity of risk factors across differing patient populations. Use of natriuretic peptides is recommended for initial diagnosis of HF by authors of the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America (HFSA) Guideline for the management of HF, the 2021 European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic HF, and the Japanese Circulation Society 2017/Japanese Heart Failure Society (JHFS) 2017 Guideline on the diagnosis and treatment of acute and chronic HF (*Table 1*).[1–3] However, there are several differences in the statements among three HF societies regarding the use of natriuretic peptides as biomarkers for risk stratification and prevention.

The objectives of this study were to provide an expert consensus that provides a comprehensive, up-to-date perspective on natriuretic peptides in the diagnosis and management of HF.

Methodology

Writing Committee Composition

The HFSA, the Heart Failure Association (HFA) of the ESC, and the JHFS selected the members of the writing committee, which consisted of 28 individuals with domain expertise in biomarkers and management of HF.

Consensus Development

On November 6, 2021, HFA, HFSA and JHFS convened a consensus conference to develop a paper on 'Natriuretic peptides: Role in the diagnosis and management of heart failure'. The work of the writing committee was accomplished via a series of Web conference meetings, along with extensive e-mail correspondence. The review work was distributed among subgroups of the writing committee based on interest and expertise. The proceedings of the work groups were then assembled, resulting in the proposed final paper. All members reviewed and approved the final version.

History and basic research: discovery, production and cardiovascular protection

Natriuretic peptide research began in 1956 with the discovery by Kisch of electron-dense granules named atrial-specific granules.[4] Twenty years later, in 1981, DeBold found diuretic and vasodilating activity in atrial extract.[5] At the end of 1983 and the beginning of 1984, DeBold and Matsuo and Kangawa succeeded in the isolation and identification of amino acid's primary structure independently.[6] They also discovered two peptides, BNP and C-type natriuretic peptide (CNP), from the porcine brain in 1988 and 1990, respectively.[7] The first biologically active receptor against natriuretic peptides, guanylyl cyclase-A (GC-A), was cloned by cross-hybridization based on the sequence of guanylyl cyclase of sea urchin by Garbers in 1988 and designated as GC-A.[8] The second biologically active receptor, GC-B, was cloned by Goeddel in Genentech.[9] GC-A and GC-B are also named natriuretic peptide receptor-A (NPR-A) and NPR-B, respectively.

Table 1 Recommendations for measurement of BNP or NT-proBNP in heart failure guidelines

	Recommendations	Class	Evidence
2022 AHA/ACC/HFSA	In patients presenting with dyspnea, measurement of BNP or NT-proBNP is useful to support a diagnosis or exclusion of HF.	I	A
	In patients with chronic HF, measurements of BNP or NT-proBNP levels are recommended for risk stratification.	I	A
	In patients hospitalized for HF, measurement of BNP or NT-proBNP levels at admission is recommended to establish prognosis.	I	A
	In patients at risk of developing HF, BNP or NT-proBNP-based screening followed by team-based care, including a cardiovascular specialist, can be useful to prevent the development of LV dysfunction or new-onset HF.	IIa	B-R
	In patients hospitalized for HF, a predischarge BNP or NT-proBNP level can be useful to inform the trajectory of the patient and establish a postdischarge prognosis.	IIa	B-NR
2021 ESC	Plasma concentrations of natriuretic peptides are recommended as initial diagnostic tests in patients with symptoms suggestive of HF to rule out the diagnosis. Elevated concentrations support a diagnosis of HF, are useful for prognostication, and may guide further cardiac investigation.	I	B
2017 JCS/JHFS	Confirm the diagnosis of HF.	I	A
	Assess the severity of HF.	I	A
	Assess the prognosis of HF.	I	A
	Monitor the efficacy of HF treatment.	IIa	B
	Screen patients susceptible to HF.	IIa	C

BNP, B-type natriuretic peptide; HF, heart failure; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide.

Atrial (A-type) natriuretic peptide (ANP) and BNP are cardiac hormones that bind to GC-A. ANP is synthesized mainly in the atria and BNP mainly in the ventricles. CNP is synthesized principally in endothelial cells and monocytes and binds to GC-B. CNP is also expressed and plays a significant role in the central nervous system and in chondrocytes in the bone. Biological actions of ANP and BNP through GC-A are diuresis and natriuresis, vasodilation, inhibition of aldosterone secretion, inhibition of myocyte hypertrophy and fibrosis, and inhibition of smooth muscle cell proliferation, suggesting that GC-A signaling functionally antagonizes angiotensin type 1 (AT1) signaling.[10] Cyclic guanosine monophosphate (cGMP) dependent protein kinase-dependent phosphorylation of regulator of G-protein signaling subtype 4 (RGS4) inhibits Gq signaling coupled to G-protein-coupled receptors, including AT1.[10]

ANP and BNP work as circulating hormones in the body and paracrine factors in the heart (*Figure 1*). The former includes vasodilation, diuresis and inhibition of aldosterone, and the latter has antihypertrophic and antifibrotic actions. In addition to interaction with AT1, GC-A signaling also functionally antagonizes mineralocorticoid receptor (MR) signaling by inhibition of translocation of MRs into the nucleus.[11]

Natriuretic peptides play key roles in HF, counteracting the effects of overstimulation of the sympathetic nervous system, the renin-angiotensin-aldosterone (RAA) system and the arginine-vasopressin (AVP) system.[12] ANP and BNP act via the NPR-A receptor to exert natriuretic, diuretic, hemoconcentrating, and vasodilating effects in association with suppression of the RAA system and sympathetic nervous system, as well as trophic effects that oppose cardiac hypertrophy and fibrosis (*Table 2* and *Figure 2*). CNP, operating via the NPR-B receptor, is not natriuretic, but it is central to vasomotion and opposes vascular cell hyperplasia (*Figure 2*). All 3 of these natriuretic peptides are cleared via the NPR-C receptor in concert with proteolysis (*Figure 3*).[13,14]

In an early stage of HF, natriuretic peptides play a beneficial role in maintaining homeostasis. However, with progressive deterioration of cardiac function, natriuretic peptides lose efficiency by one of the following mechanisms: a decrease in natriuretic peptide availability due to reduced production, increased removal, or enzymatic degradation through neprilysin; a reduced natriuretic peptide response due to reduced expression or sensitization of NPRs or inhibition of downstream signaling pathways; an increase in the proportion of inactive proBNP secreted from the heart; and/or an overlap of the effects of neurohormonal systems with functions contrary to natriuretic peptides, namely the RAA system and sympathetic nervous system. Nevertheless, an elevation in plasma levels of natriuretic peptides is commonly observed in HF, so the plasma measurement of BNP (and NT-proBNP) constitutes a marker of disease severity and a predictor of prognosis.

Diagnostic and prognostic implications in acute and chronic settings

Accurate diagnosis and prognosis are essential for optimizing medical care for serious cardiovascular conditions such as HF. Natriuretic peptides play a central role in both the diagnosis of HF as well as in the accurate assessment of short- and long-term prognosis. Given that HF is a clinical syndrome, characterized by a collection

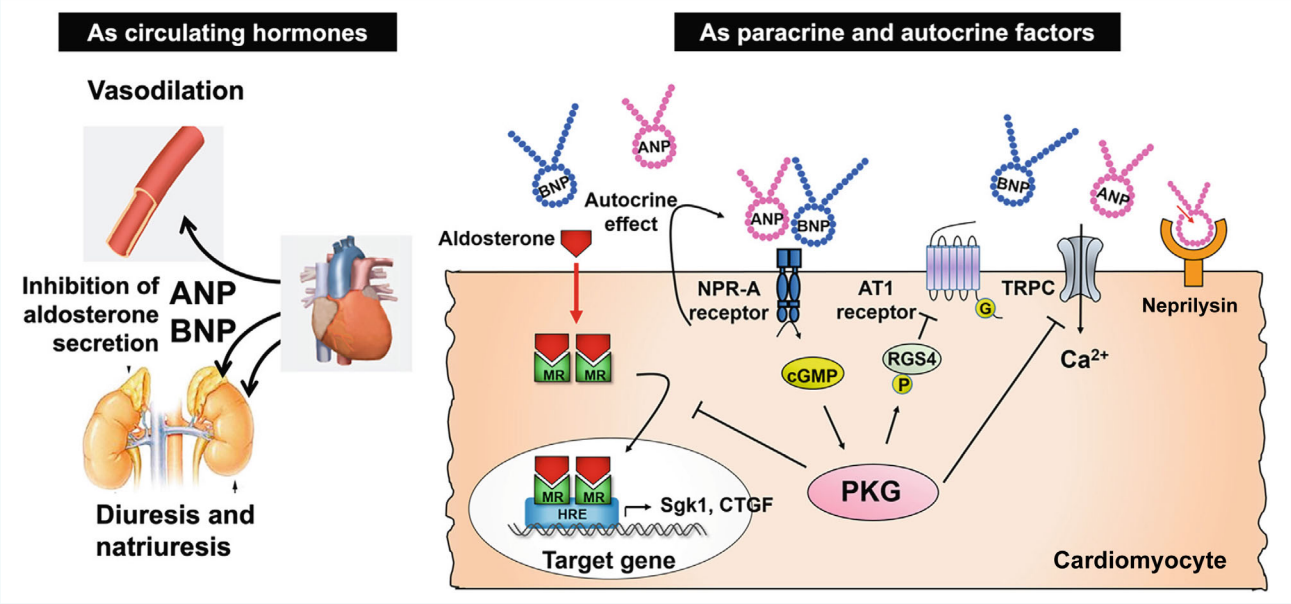

Figure 1 Actions of ANP and BNP as circulating hormones and local and paracrine factors. Plasma ANP and BNP levels are 10 pg–1000 pg/mL; LV tissue ANP and BNP levels are about 10 ng–1000 ng/g wet tissue. ANP, atrial natriuretic peptide; AT1, angiotensin II type 1; BNP, B-type natriuretic peptide; cGMP, cyclic guanosine monophosphate; CTGF, connective tissue growth factor; HRE, hormone response element; MR, mineralocorticoid receptor; NPR-A, natriuretic peptide receptor-A; PKG, protein kinase G; RGS4, regulator of G protein signaling 4; TRPC, transient receptor potential C. Modified from Biology 2022;11:1017. https://doi.org/10.3390/biology11071017

Table 2 Natriuretic peptides mediate potent cardiac antihypertrophic and antifibrotic effects beyond blood pressure reduction and volume

Preclinical evidence			
ANP	**CNP**	**BNP**	**Effects on cardiac remodeling**
✓	✓	✓	Inhibition of cardiac fibroblast proliferation
✓	✓		Inhibition of hypertrophy in cardiomyocytes and fibroblasts
✓			Inhibition of macrophage infiltration, collagen synthesis, and proinflammatory chemotactic factors
	✓		Relaxation of coronary arteries
✓	✓	✓	Reduction of infarct size

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

of recognizable signs and symptoms, additional diagnostics are of high potential value. Prior frameworks for the diagnosis of ambulatory patients with HF, such as the Framingham criteria, generally lacked optimal sensitivity and specificity.[37] There are abundant data supporting the role of natriuretic peptides in establishing the diagnosis of HF in many clinical settings, including for the initial diagnosis of HF in ambulatory patients with undifferentiated clinical symptoms (most commonly fatigue and/or dyspnea on exertion).[38]

Acute heart failure

Acute HF represents a broad spectrum of diseases states with heterogeneous clinical presentations and a large variety of precipitants and diversity of concomitant noncardiac comorbidities that may mimic many other life-threatening conditions, thereby conferring a high degree of uncertainty regarding the diagnosis, particularly in the emergency setting.[2] Natriuretic peptide testing has the potential to augment physicians' decision making across the spectrum of acute HF care settings, including initial presentation in an emergency department, during hospitalization and in the early postdischarge vulnerable phase (*Figure 4*).[15,16] Natriuretic peptides have the distinct advantage of objectivity, reproducibility and widespread availability, and they have been shown to define risk better than clinician judgment alone.[15–17]

Natriuretic peptides should be measured in all patients presenting with symptoms suggestive of new-onset or worsening HF, such as dyspnea and/or fatigue, because their use facilitates both early diagnosis or the early exclusion of HF.[2,16] Use of these biomarkers has the highest class of recommendation to support exclusion of HF due to their very high negative predictive value (94%–97%) (*Figure 5*).

In multiple studies, patients with acute HF were discharged when still congested, and the extent of residual congestion was associated with mortality and the risk of repeated hospitalizations due to HF.[18–20] Natriuretic peptides have a short half-life, so they are easily measured and provide quantitative markers of HF severity and prognosis, and they might be a useful guide to judging the success of therapy in acute HF.[15,16] The goal of using natriuretic

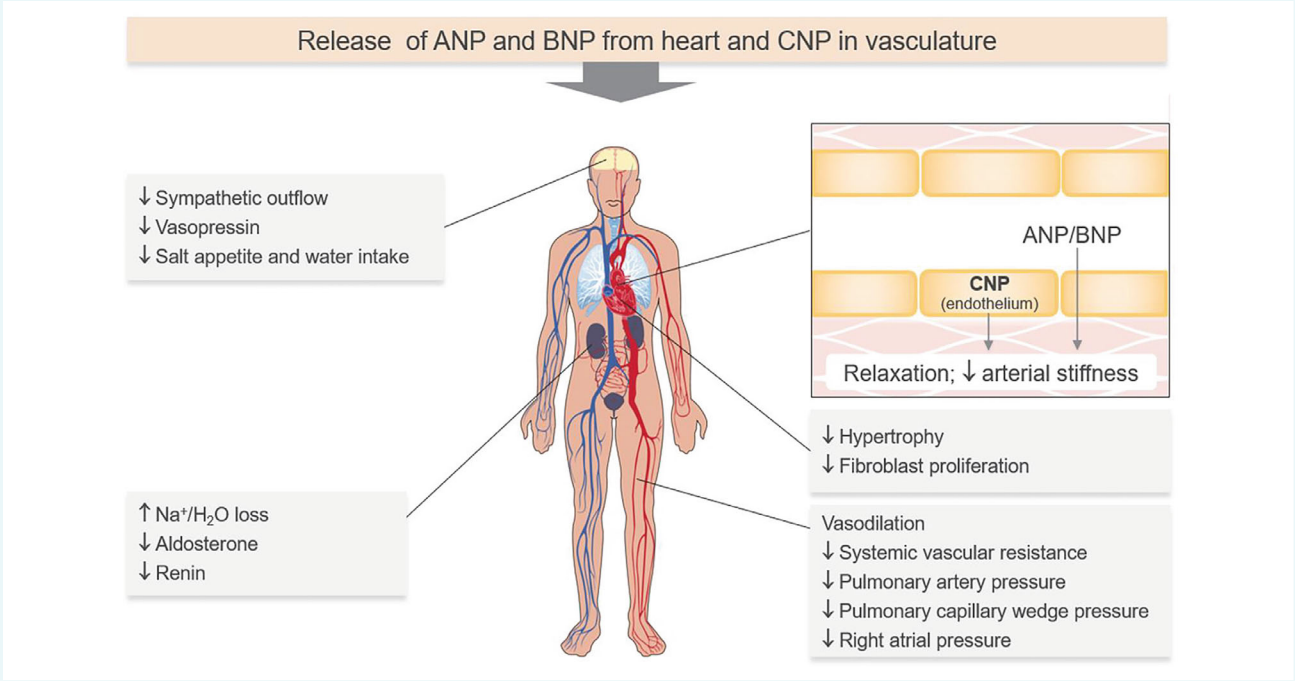

Figure 2 Natriuretic peptides have potential beneficial actions in heart failure. ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CNP, C-type natriuretic peptide; H_2O, water; Na, sodium.

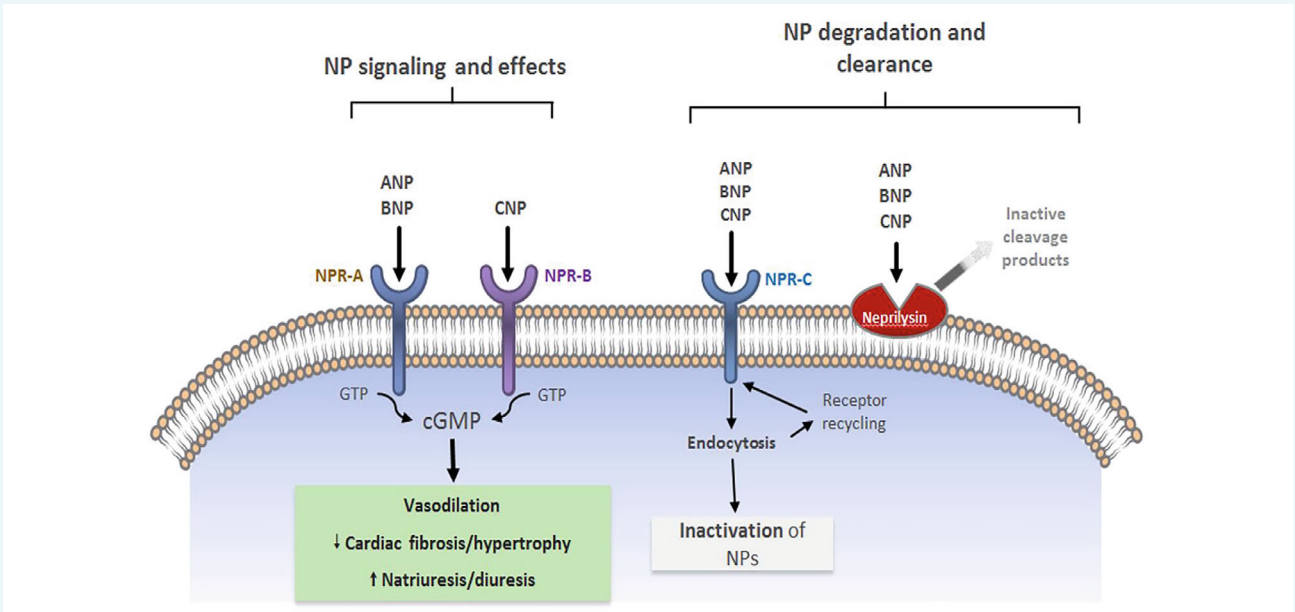

Figure 3 The natriuretic peptides are cleared by NPR-C and neprilysin. Neprilysin is responsible for the initial proteolytic cleavage of ANP and CNP and plays a role in processing BNP, but it does not cleave the amino-terminal prohormone fragments (NT-proANP and NT-proBNP). Much of the impact of inhibiting neprilysin in preclinical and clinical settings has been presumed to be due to enhanced bioactivity of natriuretic peptides. The ranking of avidity of neprilysin is CNP > ANP > BNP. In healthy conditions, proteolytic cleavage and removal by the "clearance" natriuretic peptide receptor NPR-C play equal roles in the metabolism of the NPs, but in high natriuretic peptide states such as heart failure, it seems likely that neprilysin plays an increasingly important role.[81] ANP, atrial natriuretic peptide; Ang, angiotensin; AT1, angiotensin II type 1; BNP, B-type natriuretic peptide; cGMP, cyclic guanosine monophosphate; CNP, C-type natriuretic peptide; GTP, guanosine triphosphate; NP, natriuretic peptide; NPR, natriuretic peptide receptor.

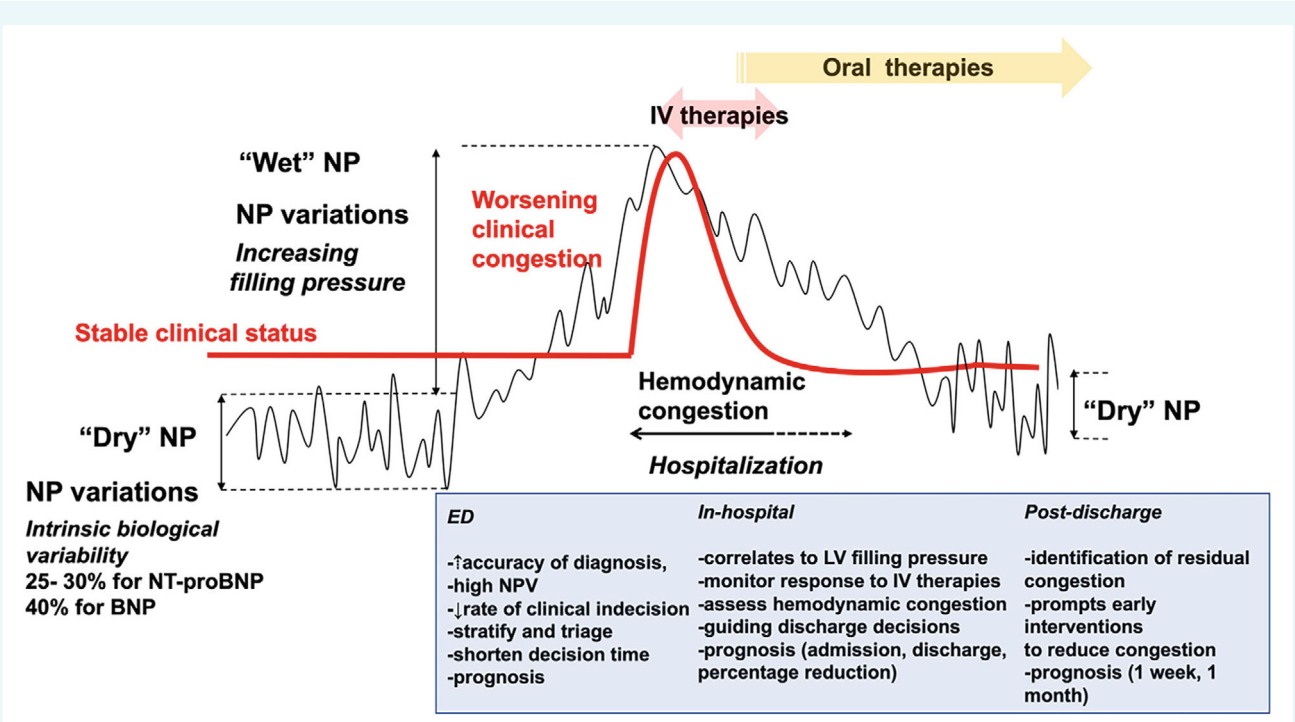

Figure 4 Natriuretic peptides' trajectory across the spectrum of acute heart failure care. Natriuretic peptide levels fluctuate in parallel with variations of left ventricular filling pressures during both decompensation and clinical improvement.[99–102] In this context, natriuretic peptides are helpful in judging whether patients' reported worsening symptoms are related to increased left-sided cardiac filling pressures but fail to capture the total contribution of right-sided heart failure[25,27] and lack a prognostic effect in those with predominant right-sided heart failure, such as in patients with severe tricuspid regurgitation.[104] ED, emergency department; IV, intravenous; LOS, length of stay; LV, left ventricular; NP, natriuretic peptides; NPV, negative predictive value.

peptides in acute-care settings was to determine whether patients received adequate decongestive therapy and whether their risk of rehospitalization was reduced as much as was feasible during acute treatment. Natriuretic peptides at discharge are reflective of the achievement of a more stable hemodynamic state following treatment for acute HF, and levels measured at hospital discharge when compared to admission values, were likely more appropriately related to both HF rehospitalization and mortality.[21,22] Measuring natriuretic peptide levels before discharge when optivolemic status has been achieved sets a baseline for continued longitudinal monitoring and further allows for individualized decision making about the timing, frequency and intensity of follow-up. Patients with lower natriuretic peptide values at the time of discharge and those who achieved greater relative reduction after acute HF treatment had substantially better prognoses than those who were released from acute care with higher concentrations.[21,23,24] Patients with acute HF and with higher or nonfalling concentrations may merit close follow-up, including monitoring at home.[25] Thus, evaluating relative modifications (%) based on each patient's plasma levels when stable (dry levels) may be more informative about the severity of intracardiac pressure/volume overload than using a single measurement. In this context, a practical approach would be to consider changes >30% as being clinically relevant.[2,21,24,26]

Although there are few data defining why natriuretic peptide levels do not decline in some patients despite treatment, several clinical scenarios should be considered. First, and most important, a persistently elevated natriuretic peptide concentration in a stably diuresed patient may actually be the patient's optivolemic (dry) natriuretic peptide level at this time point due to persistent increased ventricular wall stress, necessary to maintain adequate cardiac output. Higher natriuretic peptide levels identify treatment-resistant, high-risk patients with poor prognoses. Another possible scenario is that patients with concomitant right-sided HF and significant ascites and/or edema might diurese many liters further before natriuretic peptide levels actually drop. Higher natriuretic peptide levels are likely to be due to mobilization of third-space fluid, rather than the lowering of cardiac filling pressures.[17,27]

It remains unclear whether changing therapy based on measured predischarge natriuretic peptide levels can reduce rehospitalization or avert death. Results of the PRIMA II trial (Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?) demonstrated that NT-proBNP-guided therapy targeting an NT-proBNP reduction of >30% did not improve 6-month clinical outcomes.[28] This finding was consistent with previous observational studies in which authors found that 37%–47% of patients did not achieve the targeted BNP reduction of 30% despite inpatient therapy for acute decompensated HF.[29,30] In addition, investigators

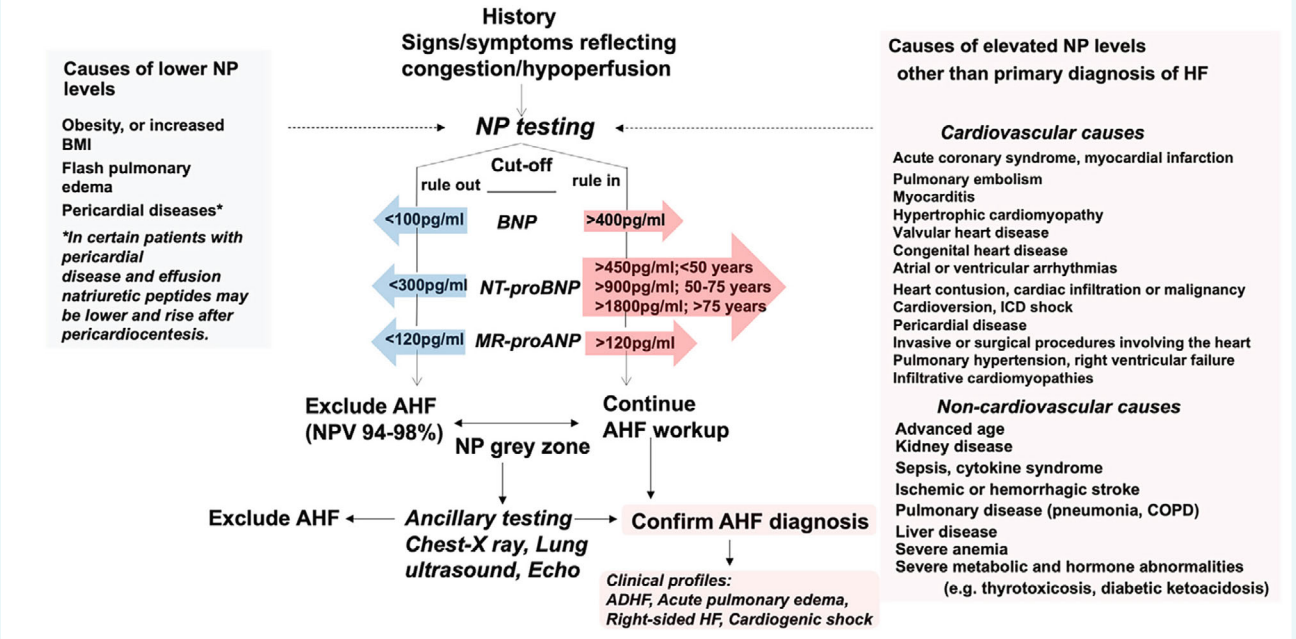

Figure 5 Use of natriuretic peptide testing for diagnosis of acute heart failure. In patients with suspected acute HF, a BNP cut-off concentration of 100 pg/mL provides an excellent NPV to exclude the presence of HF, while higher values (>400 pg/mL) deliver excellent positive predictive value (PPV).[2,16] For NT-proBNP, age-dependent rule-in cut-offs are preferred (450/900/1800 pg/mL). However, independent of age, an NT-proBNP concentration < 300 pg/mL provides a very high NPV for HF.[2,16,103–105] When considering rule-in thresholds, identification of any potential relevant confounder should be required.[17] Furthermore, patient-level changes need to be interpreted according to baseline levels.[2] Knowledge of each patient's individual natriuretic peptide concentration when stable (the so-called dry natriuretic peptide concentration) helps to interpret concentrations of these markers when these patients present with acute symptoms. A change of 25%–30% or more from the stable concentration suggests a change in clinical state, such as decompensation.[106] In addition, NPs have their intrinsic biological variability of (25% for NT-pro-BNP, as compared with 40% for BNP) and, consequently, a rise or fall in BNP or NT-pro-BNP greater than these amounts, relative to the previous value at each measurement, allows the clinician to identify a meaningful change.[15,107] Patients presenting with natriuretic peptide values between rule-out and rule-in thresholds are in the gray zone. In acute dyspnea, gray zone natriuretic peptide values are present in 20% of patients, and about 50% of these will have acute HF.[108] The gray zone levels are far more strongly associated with HF when concomitant clinical features are present, such as a history of HF, jugular venous pressure and prior diuretic use.[16,108] Patients with levels in the gray zone need extra physician attention and ancillary testing, such as chest x-ray and echocardiography. However, natriuretic peptides remain largely nonspecific for HF diagnosis, and some clinical conditions other than HF can result in an increase in NP levels, whereas other conditions, such as obesity, flash pulmonary edema and pericardial diseases, are associated with lower-than-expected NPs level.[15,16,58] Thus, individualized interpretation of biomarker levels, particularly in special populations and in the setting of competing diagnoses and comorbidities, is recommended.[2,58] ADHF, acutely decompensated heart failure; AHF, acute heart failure; BMI, body mass index; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; HF, heart failure; ICD, implantable cardioverter-defibrillator; MR-proANP, midregional proatrial natriuretic peptide; NT-pro-BNP, N-terminal fragment of brain natriuretic peptide; NP, natriuretic peptide; NPV, negative predictive value.

found that failure to reach the targeted threshold for BNP improvement was associated with significantly increased risk of mortality. In a recent study, 44% of patients admitted did not achieve the 30% target BNP threshold, and patients were at significantly increased risk for 180-day mortality compared to patients whose BNP levels responded to treatment.[31] It may be that despite identifying a higher risk population, it is difficult to reduce further residual high natriuretic peptide levels or that doing so does not confer extra clinical benefit. Thus, serial measurements of natriuretic peptide may not be useful to guide therapy, but they appear to be useful to define the high-risk group of BNP nonresponders. Importantly, this signifies that even if adverse events can be predicted, they might not be preventable.

When used as surrogate markers, although natriuretic peptide levels decreased in the acute setting, findings were not consistently translated to better long-term outcomes.[32] In addition, authors of recent trials of novel vasoactive agents cast doubt on the beneficial effects of early treatment strategies and on a pathophysiological link between favorable biomarker changes and better outcomes.[33,34] Circulating natriuretic peptide concentrations are determined not only by the ability to produce, secrete and clear the peptides, but also by underlying cardiac wall stress, the principal trigger for natriuretic peptide release.[27]

The cause of unexpectedly low natriuretic peptide levels is uncertain. Patients with disproportionately low natriuretic peptide levels should be observed carefully so as to avoid underestimation

of hemodynamic congestion and prognosis, especially those with high body mass indexes or HF with preserved ejection fraction (HFpEF).[35,36]

In the diagnostic workup of new-onset acute HF, plasma natriuretic peptide levels (BNP or NT-proBNP or MR-proANP) are "recommended," not just considered, if the diagnosis is uncertain and a point-of-care assay is available. Thresholds used to denote congestion consistent with acute HF in the appropriate clinical context include: BNP ≥100 pg/mL, NT-proBNP ≥300 pg/mL and MR-proANP ≥120 pg/mL.[2]

Chronic heart failure

Diagnostic performance characteristics of natriuretic peptides in the ambulatory setting differ from those of the acute setting, because natriuretic peptide concentrations are generally lower in ambulatory patients with HF and, thus, there is greater overlap with the normal range of values, especially in older patients. Additionally, comorbidities, such as atrial fibrillation, renal dysfunction, aging, and obesity, can all modify natriuretic peptide levels.[39] Despite these potential limitations, major clinical guideline authors recommended the use of natriuretic peptide assessment in the ambulatory setting with the highest recommendation and level of evidence, although guideline authors differ somewhat on the proposed diagnostic cut-points.[1,3]

Just as for diagnosis, establishing prognosis is a critical part of optimal HF management. Prognosis in HF varies substantially, and some more invasive or expensive therapies (such as mechanical cardiac-support devices or cardiac transplantation) are reserved for patients with the highest probability of poor outcomes. Although there are abundant prognostic markers that have been validated in HF, generally, natriuretic peptides have proved to be among the strongest single predictors of prognosis in patients with chronic HF. Natriuretic peptides have been validated as prognostic markers in both chronic HF with reduced ejection fraction (HFrEF)[40] and HFpEF.[41,42] Natriuretic peptides also predict the risk of incident HF in at-risk populations.[43] Although BNP and NT-proBNP provide generally similar information, they may diverge after initiating treatment with sacubitril/valsartan, although during longitudinal treatment, both provide prognostic value.[44] As in the case with diagnosis, natriuretic peptides are recommended for use in establishing prognosis in chronic HF by major society guidelines with the highest level of evidence.[1–3] 2021 ESC Guidelines proposed that a plasma concentration of BNP < 35 pg/mL, NT-proBNP <125 pg/mL, or MR-proANP <40 pmol/L make a diagnosis of HF unlikely.[2]

The role of incorporation in clinical trials

Natriuretic peptide concentrations have been increasingly incorporated in eligibility criteria for clinical trials involving patients with HF. In this implementation, they serve at least four roles. First, natriuretic peptides provide a readily obtained, objective laboratory sign corroborating the diagnosis of HF and are particularly useful in acute HF and HFpEF trials where confounding diseases are more prominent in the presentation (eg, dyspnea from chronic obstructive pulmonary disease exacerbation in an acute HF trial). Elevated natriuretic peptides have been incorporated as objective components of contemporary universal definitions of HF[45,46] and in national and international HF guidelines.[1,2,47] Second, selecting patients with HF and elevated natriuretic peptides enriches the study population for patients at greater risk of potential clinical endpoints. In COMMANDER-HF (A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure), a midtrial protocol amendment adding a natriuretic peptide-based inclusion criterion to the existing prior HF hospitalization criterion, enrolled patients with substantially greater event rates, including a 30% increase in the cumulative event rate of both hospitalization for HF and cardiovascular death.[48] Interestingly, there was also a 70% increase in the much lower baseline rate of noncardiovascular death. In the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction) trial, patients with HFrEF in the highest NT-proBNP quartile had a 5-fold greater rate of total number of HF hospitalizations compared to those in the lowest quartile.[49] Similarly, patients in the highest quartile of NT-proBNP enrolled in the HFpEF trial PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction) had nearly a 3-fold increase in the rate of total HF hospitalizations and cardiovascular deaths.[50] Additionally, natriuretic peptide inclusion criteria can reduce heterogeneity and regional variations in clinical trial populations.[51,52] Third, the effects of various therapeutic interventions on decreasing natriuretic peptide from elevated baseline concentrations has been an important measure of efficacy in many HF trials, especially in proof-of-concept phase 2 trials as surrogate endpoints. Although some have suggested that therapy-related changes in natriuretic peptide levels qualify as surrogates for HF outcomes,[53] in other analyses, authors have suggested that therapy-related changes in natriuretic peptide levels were modestly correlated with decreased HF hospitalization rates[54] but did not correlate with effects on cardiovascular or all-cause mortality.[54,55] Fourth, baseline natriuretic peptide levels can provide insight into subgroups of patients with potentially variable treatment and safety effects. In the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial, vericiguat provided greater clinical benefit in patients with lower natriuretic peptide levels and increased adverse outcomes in patients in the highest natriuretic peptide quartile,[56] whereas in the GALACTIC-HF (Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure) trial, omecamtiv mecarbil provided greater clinical benefit in patients with increasing natriuretic peptides and had no differential effect on safety.[57] Natriuretic peptides provided multiple important roles in contemporary clinical trials of patients with HF and, based upon this utility, the authors suggested that natriuretic peptides be a standard component of future HF trial-eligibility criteria.

Therapeutic use

Considerations in therapeutic approach

Guidelines from several leading HF societies all provide a Class I recommendation for measuring BNP or NT-proBNP for diagnosis or prognosis assessment in the management of chronic HF.[2,3,58] The value of BNP/NT-proBNP for that purpose is, thus, widely acknowledged. However, arguments remain about the usefulness of BNP/NT-proBNP as a guide for medical treatment. Several clinical trials testing relatively small samples assessed the efficacy of BNP-guided therapy and had mixed results, although subsequent meta-analyses suggested the potential benefit of this approach.[59] To gain a clearer understanding of the usefulness of BNP-guided therapy, the GUIDE-IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in HF) multicenter, randomized clinical trial was conducted.[60] That study was designed to compare the efficacy of NT-proBNP-guided HF treatment to that of optimal medical therapy alone in high-risk patients with HFrEF. Unfortunately, in terms of improved outcomes, the GUIDE-IT trial failed to show a benefit of NT-proBNP-guided therapy over usual care.

A deep dive into the GUIDE-IT trial can, nevertheless, help us to better understand the potential of BNP-guided therapy in the contemporary medical treatment of HFrEF. Importantly, the decreases in serum NT-proBNP were similar in the 2 groups in this study, and there was no significant difference in the proportions of patients achieving the target of NT-proBNP <1000 pg/mL at 12 months. Furthermore, in terms of the achievement of guideline-directed medical therapy (GDMT), there was no significant difference between the 2 arms. In earlier studies, there was a trend in which designs that led to intensification of GDMT and to significantly greater NT-proBNP/BNP reductions in the guided-therapy group than the usual-care group were successful, whereas those in which there was less difference in GDMT intensity and NT-proBNP/BNP levels between the 2 arms were unsuccessful.[59] It is, therefore, not unexpected that the GUIDE-IT trial showed a neutral effect of BNP-guided therapy. In a substudy of the GUIDE-IT trial, patients with NT-proBNP levels less than 1000 pg/mL 90 days after randomization had better outcomes, regardless of achieved GDMT.[61] That said, lower NT-proBNP concentrations were associated not only with lower risk but also with GDMT intensity, implying that GDMT intensification to achieve lower NT-proBNP/BNP concentrations is associated with better outcomes.

Recent clinical trials have shown the benefit of novel classes of medications for HFrEF when added to conventional GDMT. These include ARNIs, sodium–glucose cotransporter 2 (SGLT2) inhibitors and ivabradine. Notably, the clinical benefits of ARNIs, SGLT2 inhibitors and ivabradine were accompanied by reductions in NT-proBNP/BNP levels.[44,62,63] Given that the prognostic value of NT-proBNP changes during the course of HF treatment was retained in the GUIDE-IT trial, it is reasonable to hypothesize that a BNP-guided approach to achieve optimal GDMT may still prove to have value in the contemporary GDMT era, one in which we have more therapeutic options than before to improve HF outcomes. Further research to define the optimal therapy in contemporary settings, including the significance of a BNP-guided approach, is warranted.

Nesiritide, ularitide and ANP

Nesiritide, a recombinant BNP, was approved by the Federal Drug Administration in 2001 for the treatment of acute HF based on a reduction in pulmonary capillary wedge pressure and early relief of dyspnea.[64] In 2005, several meta-analyses of clinical trial data with nesiritide raised concerns regarding a potential increase in mortality rates and renal dysfunction.[65,66] Subsequently, the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure) trial was executed to assess definitively the safety and efficacy of nesiritide in acute HF. The design and primary results of ASCEND-HF have been published previously.[67,68] In brief, the international trial randomized 7141 participants with acute HF (regardless of ejection fraction and within 24 h of intravenous therapy) to nesiritide or placebo for 24–168 h, with coprimary endpoints of early dyspnea relief and 30-day rehospitalization for HF or death. The use of a bolus (or not) as well as the duration of treatment were determined by the principal investigator's discretion. Self-reported dyspnea was marginally improved by nesiritide but did not meet the prespecified criteria for statistical significance. There was no reduction in 30-day rehospitalization for HF or death with nesiritide. Nesiritide did not increase worsening renal function, but the proportion of patients with hypotension increased with nesiritide.

Key lessons learned from the ASCEND-HF trial related to foundational quality-by-design principles, as previously reviewed in the context of acute HF trials.[69] With regard to patient inclusion, ASCEND-HF was ejection fraction-agnostic, had fairly inclusive blood pressure criteria and used specific natriuretic peptide cut-offs. Authors of recent position papers summarized best practices regarding use of natriuretic peptides in trials.[70] Additional considerations related to the timing of the intervention (i.e. "door-to-window") with questions as to whether earlier interventions might improve outcomes. However, other trials such as TRUE-AHF (a phase III, multicenter, randomized, double-blind, placebo-controlled trial to Evaluate the Efficacy and Safety of Ularitide [Urodilatin] Intravenous Infusion in Patients Suffering From Acute Decompensated Heart Failure), which assessed the renal natriuretic peptide ularitide within 12 h of evaluation, did not lead to clinical benefits, albeit using a different therapy.[33] Geographical variations in terms of participants' characteristics, concomitant therapies and trial execution have also been reported in ASCEND-HF, which may have influenced trial results.[71] Interestingly, in a post hoc analysis of TRUE-AHF (an overall neutral trial), authors demonstrated a benefit of the 48-h clinical composite outcome with ularitide, with ineligible trial participants excluded.[33] With regard to trial design and execution, additional relevant lessons learned relate to trial monitoring and endpoint selection, as previously reviewed.[72] A question remains as to whether short-term infusions should be expected to translate to longer term clinical benefits. Moreover, the event rate was lower than expected in ASCEND-HF,[68] such that much larger trials may be necessary to demonstrate the clinical benefit of NP

therapies for patients with acute HF. Finally, the question remains unanswered: is nesiritide the optimal natriuretic peptide for treatment, considering its risk–benefit profile (including concerns related to hypotension). Additional medication considerations include whether or not a bolus is needed, what the optimal dosing amount is and what is the duration of therapy, as well as whether or not follow-up infusions are needed. Thus, ASCEND-HF and TRUE-AHF provide important insights regarding the therapeutic use of natriuretic peptides as well as insights relevant to future trial design and execution.

ANP has vasodilatory and natriuretic effects and inhibits the RAA system.[73–75] In Japan, recombinant human ANP, carperitide, has been used for the treatment of acute HF since 1995. It has been reported to improve the outcomes in patients with acute HF77 and to decrease congestion in patients with systolic blood pressure of 120 mmHg or higher.[77] However, in a recent report using the Japanese registry database, authors demonstrated that carperitide was related to worse outcomes when compared to nitrates.[78] In contrast, the consortium for pooled data analysis regarding hospitalized patients with HF in Japan, the COOPERATE-HF-J (Consortium for Pooled Data Analysis regarding Hospitalized Patients with Heart Failure in Japan) study, revealed that carperitide improved the prognosis of patients with acute HF.[79] These study findings suggest that blood pressure and renal function may influence the efficacy of carperitide.[80] To clarify the prognostic impact of carperitide in HF, large, well-designed clinical trials, especially focusing on its dosage, are definitely needed.

ARNIs

The main and unique effect of ARNIs, compared with angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), is neprilysin inhibition, a mechanism blocking the degradation of natriuretic peptides as well as other multiple peptides that have vasodilatory, natriuretic, antifibrotic, and antihypertrophic effects.[81] Neprilysin inhibitor effects lead to an improvement in cardiac function and reduced myocardial stress so that the synthesis of pronatriuretic peptides such as proBNP is decreased (*Figure 6*). Plasma levels of the NT-proBNP depend on proBNP production and are, therefore, markers of myocardial stress and function; hence, they are also markers of HF severity when patients are treated with ARNIs.

Plasma NT-proBNP levels were reduced by approximately 30% from baseline after treatment with ARNIs in randomized trials where ARNIs were compared with ACEis or ARBs in patients with either chronic HFrEF or those stabilized after an episode of acute HF or with HFpEF.[44,50,82–84] Interestingly, in the LIFE (LCZ696 in Advanced HF) trial, authors did not show a difference in changes from baseline in NT-proBNP plasma levels in patients randomized to ARNIs, compared to those on valsartan, and outcomes were similar in those taking the 2 drugs.[85]

The effects of ARNIs on plasma BNP levels may be more variable because neprilysin inhibition also blocks BNP degradation. Thus, plasma BNP levels are the result of 2 opposing mechanisms after ARNIs: improved myocardial function, which would decrease them, and neprilysin inhibition, which would increase them (*Figure 6*). Plasma BNP levels were slightly increased after ARNIs, compared with enalapril, in the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial.[44,84] A pooled analysis of EVALUATE-HF (Effect of Sacubitril/Valsartan vs Enalapril on Aortic Stiffness in HFrEF) and PROVE-HF (Prospective Study of Biomarkers, Symptom Improvement and Ventricular Remodeling During Entresto Therapy for HF) trials showed no significant

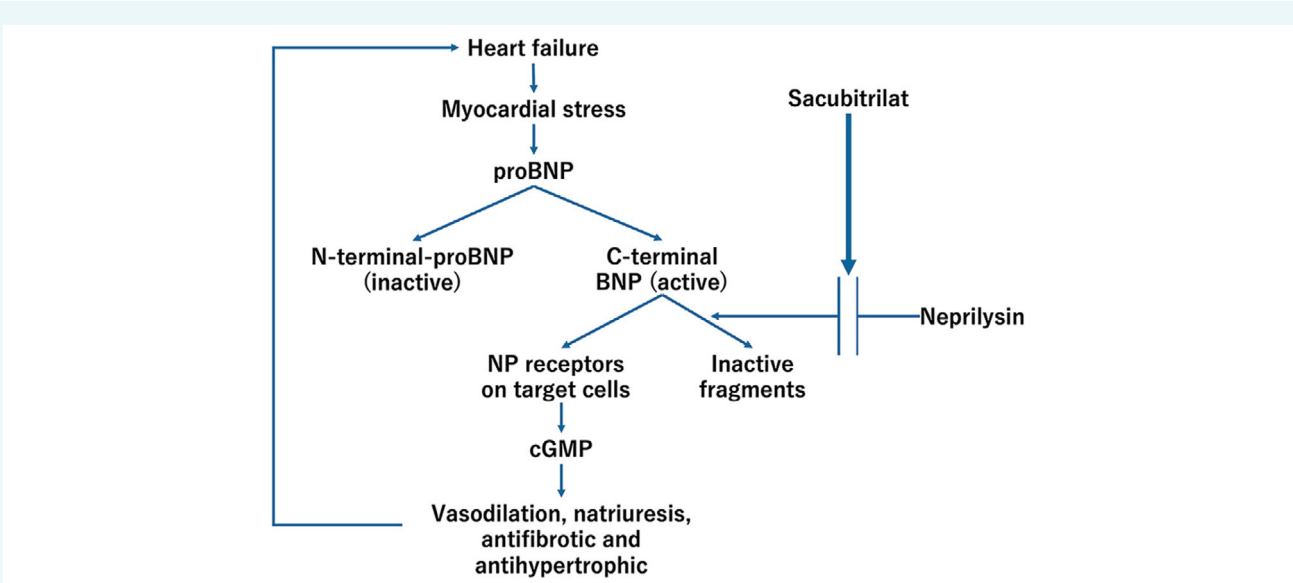

Figure 6 Mechanism of action of sacubitril, a neprilysin inhibitor. Sacubitrilat is the active metabolite of sacubitril. BNP, brain natriuretic peptide; cGMP, cyclic guanosine monophosphate.

change from baseline in BNP plasma levels, despite a 30%–34% decrease in NT-proBNP plasma levels, after ARNIs. BNP levels also remained correlated with NT-proBNP levels in this study.[86] However, NT-proBNP seemed to be a better marker of treatment response.[86] Also, plasma atrial natriuretic peptide levels increased after ARNI administration.[79]

In PROVE-HF, changes in plasma NT-proBNP levels were significantly correlated with changes in LV and left atrial volumes, LVEF and parameters of diastolic function, showing their value as predictors of the changes in cardiac function in addition to outcomes.[88] NT-proBNP plasma levels are excellent prognostic makers in patients with HF receiving ARNIs. Both baseline and postrandomization NT-proBNP values, as well as their changes from baseline to 1 month after randomization, had a continuous and highly significant relationship with the incidence of the primary outcome of cardiovascular death or HF hospitalizations in the PARADIGM-HF and in PARAGON-HF trials.[50,44,82–84] Although BNP levels showed a rightward shift after ARNIs in PARADIGM-HF, they had a similar prognostic accuracy similar to that of NT-proBNP.[44] Changes in ANP after ARNIs are also related to cardiac remodeling.[87]

Thus, multiple study investigators have confirmed the high prognostic value of plasma natriuretic peptide levels in patients with HF who are treated with ARNIs.[50,44,82–84] Plasma NT-proBNP levels are accurate markers of ARNIs' effects.[86] The relationship between decrease in plasma natriuretic peptide levels, reverse cardiac remodeling and better outcomes finds its best support in data concerning ARNIs.[88]

Gaps in knowledge and future directions

Despite the primacy of BNP and NT-proBNP as the biomarker standard for predicting prognosis in HF, important caveats regarding their use exist; addressing such questions might be expected to inform newer or more nuanced use of these important biomarkers.

These may be summarized into 3 main areas: (1) mechanistic insights, (2) implications for therapeutic approach, and (3) understanding the role of natriuretic peptides beyond the cardiovascular system.

Mechanistic insights

A common misconception is that concentrations of BNP or NT-proBNP mainly reflect congestion in all domains. Although this is true in severe, advanced HF or in decompensated disease in the acute setting where congestion is the primary determinant for natriuretic peptide elevation, in chronic stable disease, the main determinant of BNP or NT-proBNP concentrations is transmural wall stress, which is determined more by cardiac structural and functional correlates, including left atrial or left ventricle chamber diameter or thickness, valvular lesions or heart rhythm.[89] This helps to explain the value of BNP and NT-proBNP to prognosticate progression to symptomatic HF in those with stage A or B HF, where congestion is typically not the primary determinant of peptide release, as well as the strong association between natriuretic peptides and cardiac remodeling in stage C HF, which links closely with outcomes.

Among those with acute HF (marked by congestion), following diuretic therapy, robust reduction in NT-proBNP is strongly linked to subsequent favorable courses,[24] implying that relief of congestion is the mechanism of benefit. On the other hand, in individuals with stage C HFrEF without exaggerated congestion, early decrease in NT-proBNP to <1000 pg/mL following adjustment by GDMT was linked to a 74% reduction in subsequent cardiovascular death/HF hospitalization,[60] paralleled by greater amounts of improvement in LVEF by 1 year in those with larger NT-proBNP reductions,[90] emphasizing that the main trigger in this setting is cardiac remodeling. This dichotomy reveals important opportunities for better understanding of the triggers of natriuretic peptide release across the spectrum of HF and for informing therapy implications in HF.

In patients with HFpEF, determinants of BNP or NT-proBNP elevation are less well understood. Wall stress may be somewhat lower due to generally smaller LV chamber size in HFpEF, but more work is needed to understand the meaning of secular trends in BNP or NT-proBNP in those with normal LVEFs.

Last, although the impact of comorbidities affecting natriuretic peptide concentrations (such as kidney disease or obesity) has not been shown to undermine the prognostic meaning of these biomarkers completely, further data are clearly needed regarding the optimal interpretation of BNP or NT-proBNP in those affected with such relevant issues.

Implications for therapeutic approach

It is easy to understand the logic for measurement of BNP or NT-proBNP as a support of clinical judgment. Both are unmistakably prognostic in acute and chronic HF, but beyond informing risk about relevant outcomes in HF, ambiguity and ambivalence remain regarding how to alter treatment for patients based on abnormal natriuretic peptide concentrations. As noted, in acute HF, post-treatment natriuretic peptide values may inform alternative treatment strategies,[24] but such strategies have not been validated. In chronic HF, data exist regarding how lower concentrations of NT-proBNP are linked to superior outcomes and reversal of cardiac remodeling,[91] yet an algorithmic treatment approach to patients using biomarkers in the outpatient setting remains elusive. Addition of other biomarkers such as ANP, high-sensitivity cardiac troponin, or soluble ST2 (a protein biomarker of cardiac stress encoded by the IL1RL1 gene) to NT-proBNP or BNP may help to better understand underlying pathophysiology and risk in chronic HF.[87,92]

Although natriuretic peptides have revealed important aspects of pathophysiology in HF and provide useful clinical diagnostic and prognostic information for affected patients, they are but 1 class of biomarker. Abundant data indicate how other biomarkers reflecting other aspects of HF pathophysiology may add to prognostic information from BNP or NT-proBNP in both acute and chronic HF.[93,94] How such markers might be combined with

natriuretic peptides remains largely uncertain and deserves concerted focus.

Understanding the role of natriuretic peptides beyond the cardiovascular system

Natriuretic peptides are known to have protective effects not only on the heart but also on multiple organs via the cGMP–protein kinase G signaling pathway. In basic research, natriuretic peptides were involved in immune response, lipid metabolism and body temperature.[95–98] The pathophysiology of HF is not limited to hemodynamic insufficiency, and there are various mechanisms behind it. The potential use of natriuretic peptides as therapeutic agents may need to be reexamined from various perspectives.

Conclusion

This statement provides current evidence about the role of natriuretic peptides in the diagnosis and management of HF. It is expected to be scientifically and clinically relevant, with the ability to be of great value. Natriuretic peptides have universal applicability globally and high diagnostic, therapeutic and prognostic validity. We envision that this statement concerning the role of natriuretic peptides in the diagnosis and management of HF may be used by health care professionals in HF, in HF research and in a standardized fashion across scientific societies and guidelines.

Take-home Visual Data

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[Corrections added on 30 May 2023, after first online publication: Minor changes were made to add clarity about abbreviations used in the text.]

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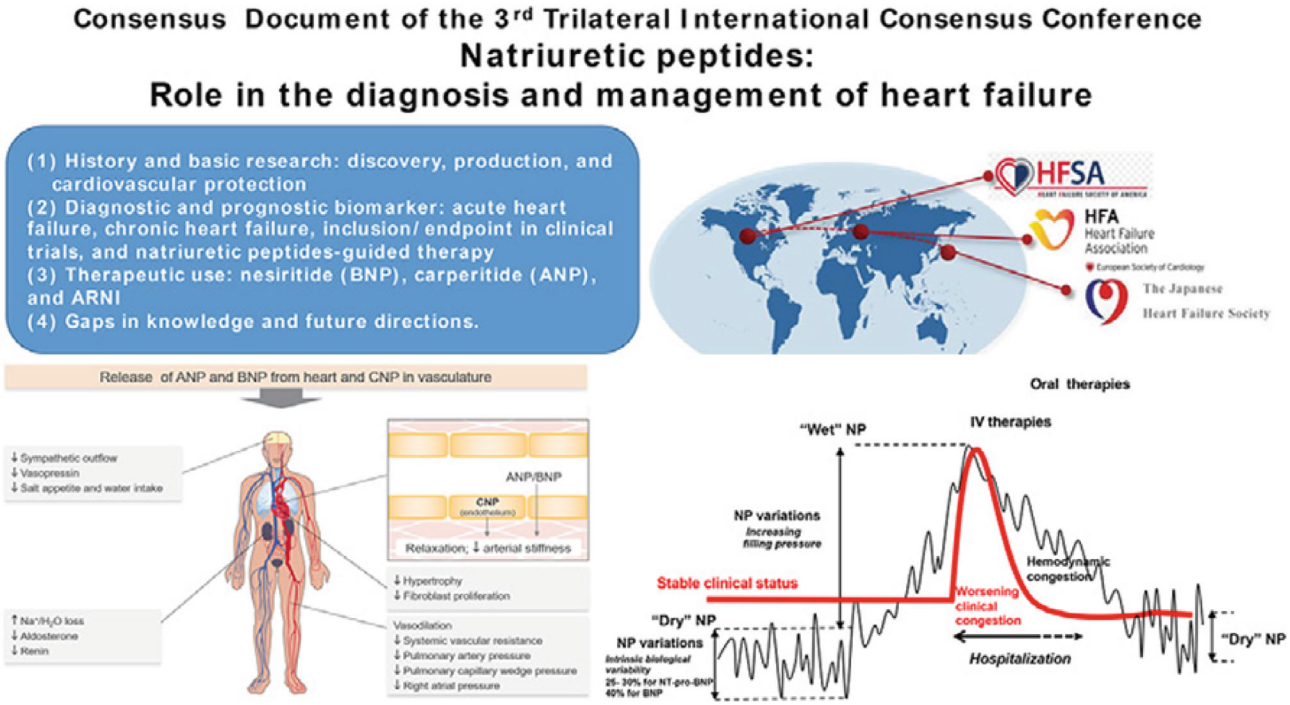

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