Natriuretic Peptides for Diagnosis, Prognosis, and Management of Heart Failure

30

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Contents

Abstract

Heart failure is a complex syndrome that affects millions of people, and the incidence is rising steeply. The use of biomarkers, and especially the natriuretic peptides, has been increasingly investigated to assist in the care of these patients. Since the discovery of the natriuretic peptides over 30 years ago, significant progress in understanding these molecules has been achieved. The biological effects of the natriuretic peptides consist primarily of fluid balance, vasodilation, and maintenance of cardiovascular homeostasis, and the primary trigger of natriuretic peptide release is cardiac myocyte stretch from either volume or

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pressure overload. Over the last several years, multiple studies have been conducted involving particularly B-type natriuretic peptide (BNP) and amino-terminal pro-B-type natriuretic peptide (NT-proBNP) which focused on the utility of both for the diagnosis, prognosis, and management of heart failure. These studies have resulted in establishing a crucial role for the natriuretic peptides as an adjunct to clinical assessment of these complicated patients. In addition to their use in heart failure with reduced ejection fraction, data continue to emerge regarding their utility in heart failure with preserved ejection fraction as well as for heart failure screening. In the future, measurement of natriuretic peptides will be increasingly useful for personalized care of patients with heart failure and further integrated into routine care of patients with a wide array of related cardiac conditions.

List of Abbreviations

ADHF	Acutely Decompensated Heart Failure
ANP	Atrial Natriuretic Peptide
BACH	Biomarkers in Acute Heart Failure
BASEL	B-type Natriuretic Peptide for Acute Shortness of Breath Evaluation
BATTLESCARRED	NT-proBNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death
BNP	B-type Natriuretic Peptide
CNP	C-type Natriuretic Peptide
EF	Ejection Fraction
GISSI-HF	Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca–Heart Failure
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
IMPROVE-CHF	Improved Management of Patients with Congestive Heart Failure
LV	Left Ventricle
MR-proANP	Mid-regional Pro-atrial Natriuretic Peptide
NT-proBNP	Amino-Terminal Pro-B-type Natriuretic Peptide
PRIDE	ProBNP Investigation of Dyspnea in the Emergency Department
PROTECT	ProBNP Outpatient Tailored Chronic HF Therapy
RAAS	Renin Angiotensin Aldosterone System
STOP-HF	St. Vincent's Screening to Prevent HF; Natriuretic Peptide-Based Screening and Collaborative Care for Heart Failure
TIME-CHF	Trial of Intensified Versus Standard Medical Therapy in Elderly Patients with Congestive Heart Failure
Val-HeFT	Valsartan Heart Failure Trial

Key Facts of Heart Failure

- Heart failure is a condition that occurs when the heart cannot pump blood effectively to the rest of the body, typically as a result of poor heart contraction or impaired filling.
- Heart failure affects millions of people worldwide, and the incidence is increasing.
- There are two general types of heart failure: Heart failure with reduced ejection fraction (HFrEF) refers to the improper pumping of the heart, whereas heart failure with preserved ejection fraction (HFpEF) refers to the improper relaxation of the heart muscle with impaired filling of the ventricle.
- Heart failure can also be classified as acutely decompensated heart failure (ADHF) or chronic heart failure.
- Heart failure is a complex disease to diagnose and treat, and the use of the natriuretic peptide biomarkers is an important addition to the clinician's armamentarium.

Key Facts of the Natriuretic Peptides

- Natriuretic peptides are substances that are released by the cells of the heart in response to stretch from either volume or pressure overload. They result in dilation of blood vessels, diuresis, and loss of sodium in the urine as well.
- The most commonly utilized members of this class are atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and amino-terminal pro-B-type natriuretic peptide (NT-proBNP).
- Use of natriuretic peptide testing has been shown to improve diagnostic accuracy for heart failure.
- Concentrations of natriuretic peptides are powerfully prognostic across the entire spectrum of heart failure.
- Heart failure therapy "guided" by a goal to reduce BNP or NT-proBNP values appears to be a promising approach.

Definitions of Words and Terms

Cardiomyocyte Muscle cell found in the heart.

Ejection Fraction Numerical percentage of blood that is pumped out of the heart with each beat; a normal value is >50 %.

Half-life Time it takes for a quantity of a substance to become half of its original concentration.

Heart Failure Inability of the heart to supply blood effectively to the rest of the body; can be as a result of impaired pumping or impaired filling.

Homeostasis Ability of the body to maintain internal balance, regardless of external conditions.

Natriuretic Peptide Hormone that is secreted by the heart muscle in response to stretch that results in vasodilation, increased volume of urine, and increased excretion of salt via the urine, among other effects.

Introduction

Heart failure (HF) is an increasingly incident and prevalent diagnosis, representing the most common cardiovascular condition in those aged 65 years or greater. Indeed, HF is a growing pandemic affecting approximately 5.8 million people in the United States alone, with approximately 670,000 new cases diagnosed each year (Lloyd-Jones et al. 2010). With this growing tide of HF, there has come the recognition that means to supplement standard clinical judgment to establish HF diagnosis, estimate its prognosis, and objectively manage patients so affected are needed. In this regard, a number of objective tools have been developed to support standard care; among these is the measurement of circulating biomarkers. While numerous candidates for biomarker-based evaluation and management have been examined, the natriuretic peptides stand as the current gold standard for biomarker-based patient evaluation.

The natriuretic peptide family consists of multiple members, highly conserved across species. Several noncardiac natriuretic peptides exist such as urodilatin, a natriuretic peptide with primarily renal effects; relevant to the cardiovascular system in humans are atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). While CNP has a role in vascular homeostasis and thus its testing may have a future role in the evaluation of the patient with cardiovascular disease, the vast majority of clinical data regarding the use of natriuretic peptides to evaluate and manage patients is with the BNP class of biomarkers. Fewer data exist for ANP and related compounds, but the number of studies is growing for this class of peptide.

Discovery and Biology of Natriuretic Peptides

In 1981, de Bold and his colleagues discovered a substance that was extracted from rat atrial tissue that resulted in a tenfold increase in urine volume, a doubling of potassium excretion, a 30-fold increase in sodium and chloride excretion, and a reduction in arterial blood pressure when injected into anesthetized rats (de Bold et al. 1981). This substance was ultimately identified as the first member of the

natriuretic peptide family, ANP. A few years later in 1988, BNP, initially referred to as "brain" natriuretic peptide, was isolated from porcine neural tissue and was found to have similar activity to ANP (Sudoh et al. 1988); BNP was subsequently isolated from cardiac tissue, which was recognized to be its major source.

The natriuretic peptide system is a primitive and highly conserved group of peptides, whose phylogeny extends back to single-celled invertebrates. Given that the general function of the class of peptides is to regulate fluid homeostasis, it is theorized that the natriuretic peptide family of hormones evolved over millennia to play different, but somewhat related roles. For example, in plants, natriuretic peptide function may regulate function of water balance, while in teleost fish natriuretic peptides are theorized to assist in osmotic regulation (Gehring and Irving 2003; Takei 2008). The biological effects of ANP and BNP in humans are largely focused on regulation of fluid balance, vascular regulation, and cardiovascular homeostasis.

ANP is synthesized primarily in atrial cardiomyocytes, with a small amount produced by similar cells in the left and right ventricle, and it is secreted in response to wall stress. In contrast to the B-type peptides, ANP is stored intracellularly as a prohormone ($proANP_{1–126}$), which is cleaved by corin into a biologically inactive fragment ($N\text{-}ANP_{1–98}$) and a biologically active 28 amino acid peptide, $ANP_{99–126}$. The latter has an extremely short half-life of less than 5 min, which has rendered clinical measurement of ANP somewhat challenging (Munagala et al. 2004).

BNP is found both in atrial and ventricular myocytes, and levels of BNP are actually higher in atrial tissue, when compared to ventricular tissue. However, more BNP is produced by the ventricles given their significantly greater mass (Munagala et al. 2004). In contrast to ANP, BNP secretion relies on gene activation, and therefore only small amounts of BNP are stored. When the BNP gene is activated, most commonly secondary to wall stretch, a pre-propeptide consisting of 134 amino acids is produced and is subsequently cleaved into $proBNP_{1–108}$ and a small 26 amino acid signal peptide. $ProBNP_{1–108}$ is further cleaved by corin into BNP, a 32 amino acid biologically active molecule and amino-terminal-proBNP (NT-proBNP) and a 76 amino acid biologically inactive substance. In addition, though mechanisms remain unclear as to why this is the case, a variable amount of $proBNP_{1–108}$ is released by the cardiomyocyte. It is well established that this phenomenon is more common in patients with advanced HF. Figure 1 shows the processing of BNP and NT-proBNP.

The clearance of the natriuretic peptides is of some relevance for their clinical measurement. BNP has a half-life of 22 min, whereas NT-proBNP has a longer half-life of 120 min (Motiwala and Januzzi 2013; Munagala et al. 2004). As noted, ANP itself has a very short half-life; however, an assay directed at the mid-region of the pro-peptide of ANP (MR-proANP) is considerably more stable, with a half-life comparable to that of NT-proBNP (Morgenthaler et al. 2004).

There are multiple mechanisms of clearance for both ANP and BNP, which explain their shorter half-life. Three natriuretic peptide receptors have been identified (A,B,C); natriuretic peptide receptors A and B are coupled to a guanylyl

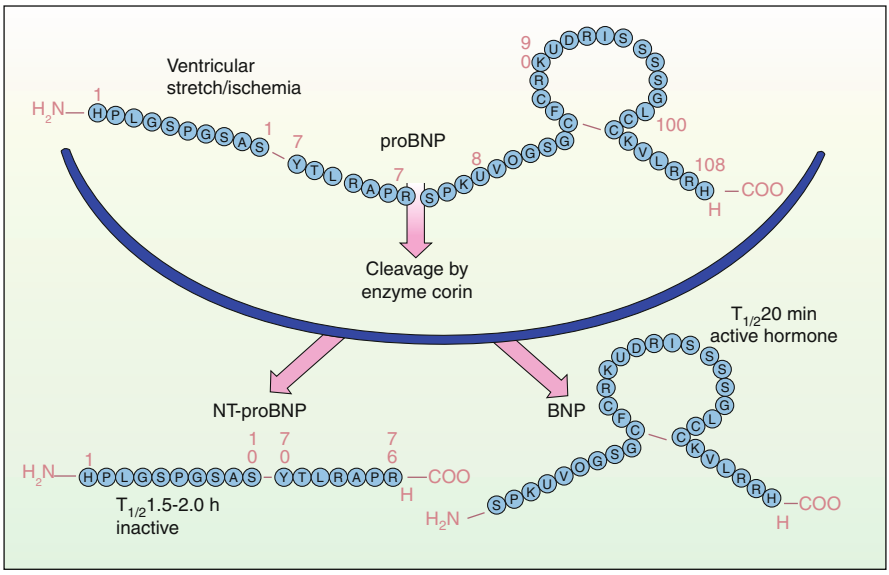

Fig. 1 Structure and processing of BNP. This drawing depicts the structure of pro-BNP and its cleavage by corin into BNP and NT-proBNP (Reprinted with permission from Motiwala and Januzzi 2013)

cyclase-dependent cascade through which their biologic and physiologic effects are exerted. Natriuretic peptide receptor A binds both ANP and BNP, but has greater affinity for ANP. It is found in large blood vessels, the kidney, and the adrenal glands. Natriuretic peptide receptor B primarily binds CNP and is the predominant receptor in the brain. It is also found in the kidney and adrenal glands. When the natriuretic peptide binds the receptor, guanylyl cyclase is activated resulting in an increase in intracellular cGMP. Natriuretic peptide receptor C is responsible for clearance of ANP and BNP and is not coupled to guanylyl cyclase. Once the natriuretic peptide binds to receptor C, it is internalized and degraded. The C receptor may have slightly reduced affinity for BNP, which may be responsible for its longer half-life relative to ANP. Another mechanism for ANP and BNP clearance is degradation by enzymes such as the neutral endopeptidases, meprin A, dipeptidylpeptidase-IV, and others; these enzymes degrade both ANP and BNP rapidly in vivo and in vitro. Finally, both ANP and BNP are cleared via passive removal from the body by organs with high blood flows, such as the kidneys (Levin et al. 1998; Suga et al. 1992).

In contrast to ANP and BNP, MR-proANP and NT-proBNP are biologically inactive and cleared passively also by organs with high degrees of blood flow. Though the misperception exists that NT-proBNP is "primarily" cleared by the kidneys, this is not correct, and indeed both BNP and NT-proBNP are equally dependent on renal filtration for their clearance, which is only 25 % overall (Munagala et al. 2004; van Kimmenade et al. 2009).

Triggers of Release and Physiologic Effects

The most significant trigger for natriuretic peptide release is cardiac myocyte stretch from either volume or pressure overload; though, many other factors may result in upregulation of the natriuretic peptide gene, such as the response to endothelin-1. Hypoxia is another trigger to natriuretic peptide gene expression and secretion (Motiwala and Januzzi 2013). Figure 2 illustrates the multiple cardiovascular triggers that can lead to increased natriuretic peptide secretion, providing insight into the complex regulation of this system. BNP gene induction is followed by an increase in synthesis and secretion of the natriuretic peptides from the ventricular and atrial myocytes (Mantymaa et al. 1993; Magga et al. 1997). As noted, in the case of ANP, storage of the peptide is found in cytosolic granules,

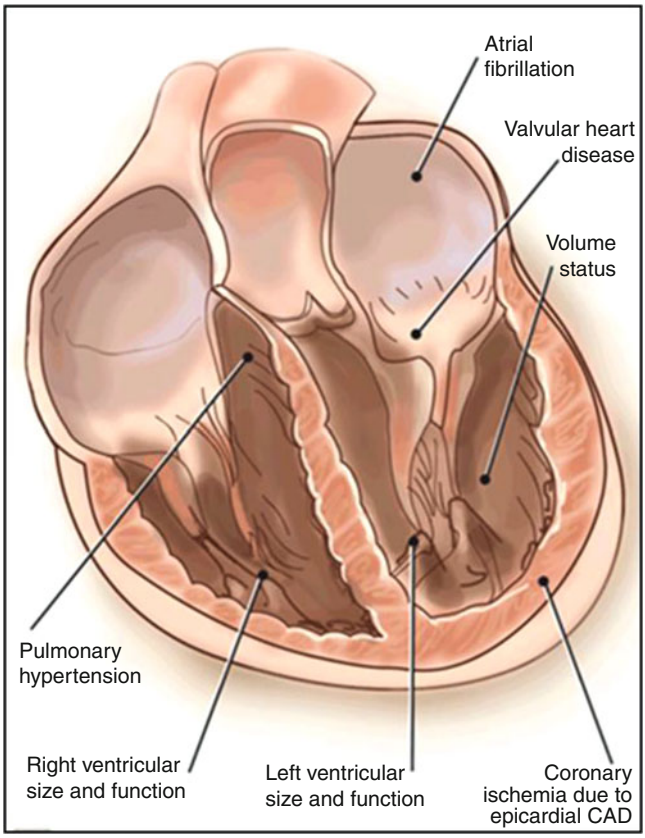

Fig. 2 Triggers of BNP release. The above drawing demonstrates the various cardiac factors that contribute to natriuretic peptide release (Reprinted with permission from Motiwala and Januzzi 2013)

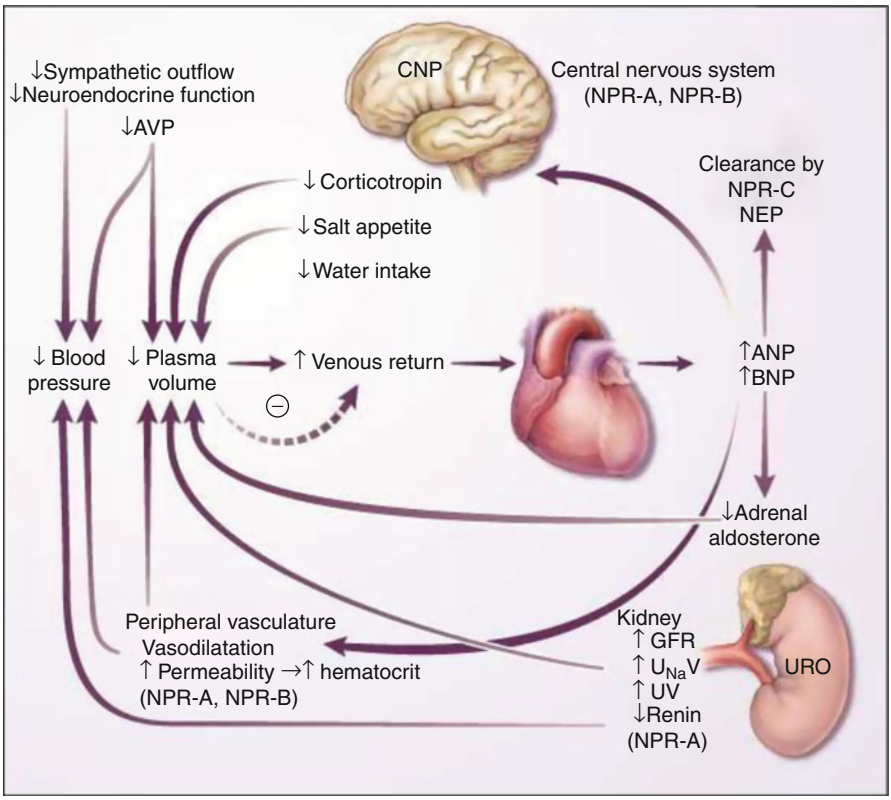

Fig. 3 Physiologic effects of natriuretic peptides. This schematic depicts the complex regulation of NP release and its effects on the body, focusing on the kidney, heart, central nervous system, and peripheral vasculature (Reprinted with permission from Levin et al. 1998)

while with the B-type natriuretic peptides, rapid release into the circulation follows synthesis (Munagala et al. 2004).

ANP and BNP exert a multitude of systemic effects. Vasodilation is secondary to both direct effects on the vasculature as well as from indirect, suppressive effects on the sympathetic nervous system, renin angiotensin aldosterone system (RAAS), and endothelin (Munagala et al. 2004). As their name implies, the natriuretic peptides result in diuresis and natriuresis due to increased filtration from mesangial cell relaxation, inhibition of solute transport across the proximal tubule, and reduced sodium reabsorption in the collecting tubule. Renal blood flow and glomerular filtration rate are also increased. The natriuretic peptides may also assist in reducing the hypertrophic response to pressure overload (Munagala et al. 2004), with a consequent antifibrotic, pro-lusitropic effect. Figure 3 summarizes the physiologic effects of the natriuretic peptides.

BNP, NT-proBNP, and HF

The natriuretic peptides are of increasing importance in modern HF evaluation and management and now have considerable support for both diagnostic and prognostic applications in contemporary clinical practice guidelines for HF (Yancy et al. 2013). This is because HF is a complex syndrome and to establish correct diagnosis and treatment are challenging, even in the hands of the most skilled clinician. While multiple evidence-based therapies exist, many affected patients do not receive them. Optimizing medications to achieve target doses is suboptimal and is especially difficult in older patients and patients with kidney disease (Heidenreich et al. 2012). Furthermore, use of guideline-directed medical therapies has been associated with a survival benefit that begins to plateau only after multiple agents have been administered (Fonarow et al. 2012). Thus, any tool that establishes HF presence, severity, and prognosis beyond clinical judgment, while simultaneously informing therapy decision making, would be welcome.

Of the natriuretic peptides, BNP and NT-proBNP have been extensively studied to assist in the diagnosis, prognosis, and management of HF. BNP and NT-proBNP share many similarities, but they also have some important differences, as noted above. Concentrations of both peptides tend to increase with age, are higher in women and in patients with hyperthyroidism, and are lower in obese patients (Das et al. 2005; Raymond et al. 2003; Schultz et al. 2004). In contrast, NT-proBNP has a longer half-life as noted and thus circulates in higher concentration than BNP (Motiwala and Januzzi 2013). Additionally, when measuring levels of BNP and NT-proBNP serially, they each have a different degree of biologic variability with BNP having a value of 40 % versus 25 % for NT-proBNP (Araujo et al. 2006; Schou et al. 2007). Table 1 highlights some of these differences.

Table 1 Comparison of BNP and NT-proBNP. This table shows the various similarities and differences between BNP and NT-proBNP

	BNP	NT-proBNP
Amino acids	32	76
Molecular weight (kDa)	3.5	8.5
Half-life (min)	20	60–120
Hormonal activity	Yes	No
Clearance	Neutral endopeptidases, passive clearance by multiple organs	Passive clearance by multiple organs
Correlation with GFR	++	+++
Clinical range (pg/mL)	0–5,000	0–35,000

Clinical Practice Guidelines

Numerous clinical practice guidelines have endorsed the use of natriuretic peptide testing for the evaluation and management of the patient with HF. For example, the 2013 American College of Cardiology/American Heart Association HF guidelines recently issued a Class I, level of evidence A recommendation for BNP and NT-proBNP for the diagnosis and prognostication of HF and also issued a Class IIa level of evidence B indication for use in management (Yancy et al. 2013). European guidelines similarly recommend that the natriuretic peptides can be utilized to exclude other etiologies of dyspnea and to provide information on prognosis (McMurray et al. 2012).

Diagnostic Evaluation of HF

The use of BNP in the diagnostic evaluation of acutely decompensated HF (ADHF) was initially established in the landmark Breathing Not Properly study from 2002. One thousand five hundred and eighty-six patients who presented to the emergency room with acute dyspnea were included in the study, and BNP was measured at the time of presentation. The clinical diagnosis of HF was assessed by two independent cardiologists, who were blinded to the BNP results. Forty-seven percent of the patients were diagnosed with dyspnea secondary to HF, and a BNP level of $\geq$100 pg/mL was more accurate for HF diagnosis than any physical exam or any single historical finding, with an odds ratio of 29.60 (Maisel et al. 2002). In a similar fashion, NT-proBNP was investigated in the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study, which included 599 patients who presented to the emergency room with dyspnea. Parallel to the Breathing Not Properly study, NT-proBNP had exceptionally good sensitivity (90 %) and specificity (85 %) for HF, as well as excellent positive and negative predictive value. An elevated NT-proBNP value was found to be the strongest independent predictor of the diagnosis of ADHF with an odds ratio of 44 (Januzzi et al. 2005b). Additionally, while an NT-proBNP cutoff of 900 pg/mL provided comparable performance to a BNP of 100 pg/mL, the PRIDE investigators and subsequent International Collaborative of NT-proBNP study established that age-dependent cut points for NT-proBNP were superior to a single cutoff point. Thus, an NT-proBNP of 450 pg/mL in patients aged <50 years, 900 pg/mL in patients aged 50–75 years, and 1,800 pg/mL for those aged >75 years was superior to a single cut point for the diagnosis of ADHF (Januzzi et al. 2006). The sensitivities, specificities, positive predictive values, and negative predictive values of various BNP and NT-proBNP cut points are shown in Table 2.

BNP and NT-proBNP also serve an important role in excluding the diagnosis of ADHF. For example, NT-proBNP has a negative predictive value of 99 % to rule out the diagnosis if the concentration is <300 pg/mL (Januzzi et al. 2006b). An additional benefit to measuring natriuretic peptides in the emergency department when evaluating patients presenting with acute dyspnea is a 26 % reduction in

overall cost as well as a shortening in length of hospital stay by 3 days (Mueller et al. 2004; Moe et al. 2007).

It is important to emphasize that like any diagnostic tool, a differential diagnosis must be considered when interpreting elevated concentrations of BNP or

Table 2 Cut points for clinical use of natriuretic peptides. This table summarizes the various cut points for BNP, NT-proBNP, and MR-proANP in both the inpatient and outpatient settings. Note the "gray zone" values as well as the age-stratified approach values shown

	Cutoff value	Sensitivity	Specificity	Positive predictive value	Negative predictive value
To *exclude* acutely decompensated HF:					
BNP	<30–50 pg/mL	97 %	*	*	96 %
NT-proBNP	<300 pg/mL	99 %	*	*	99 %
MR-proANP	<57 pmol/L	98 %	*	*	97 %
To *identify* acutely decompensated HF:					
Single cutoff point strategy					
BNP	>100 pg/mL	90 %	76 %	79 %	89 %
NT-proBNP	>900 pg/mL	90 %	85 %	76 %	94 %
MR-proANP	>127 pmol/L	87 %	79 %	67 %	93 %
Multiple cut-point strategy					
BNP, "gray zone" approach	<100 pg/mL to exclude	90 %	73 %	75 %	90 %
	100–400 pg/mL, "gray zone"	*	*	*	*
	>400 pg/mL, to rule in	63 %	91 %	86 %	74 %
NT-proBNP, "age-stratified" approach	>450 pg/mL for age <50 year	90 %	84 %	88 %	66 %
	>900 pg/mL for age 50–75 years				
	>1,800 pg/mL for age >75 years				
MR-proANP, "age-stratified" approach	>104 pmol/L for age <65 years	82 %	86 %	75 %	91 %
	>214 pmol/L for age ≥65 years				
Outpatient application					
BNP	<20 pg/mL (asymptomatic)	*	*	*	96 %
	or <40 pg/mL (symptomatic)	*	*	*	

(*continued*)

Table 2 (continued)

	Cutoff value	Sensitivity	Specificity	Positive predictive value	Negative predictive value
NT-proBNP, "age -stratified" approaches	<125 pg/mL for age <75 years	*	*	*	98 %
	<450 pg/mL for age ≥75 years	*	*	*	91 %
	or				
	<50 pg/mL for age <50 year	*	*	*	98 %
	<75 pg/mL for age 50–75 years	*	*	*	98 %
	<250 pg/mL for age >75 years	*	*	*	93 %
MR-proANP	Unknown	Unknown	Unknown	Unknown	Unknown

NT-proBNP. While HF is an important cause of elevated values of these peptides, there are many other cardiovascular and noncardiovascular conditions that may result in values of the NPs to be in a range "diagnostic" for HF. Furthermore, factors leading to lower than expected BNP or NT-proBNP exist as well. Clinician understanding of these nuances is critical, in order to correctly leverage the valuable information yielded by their testing, and Table 3 summarizes these instances.

Interpretation of BNP and NT-proBNP may be challenging in certain circumstances. For example, among patients with chronic HF, natriuretic peptides are expected to be elevated, due to underlying disease, but can be used as an adjunct to clinical assessment to help diagnose exacerbations of the diagnosis if knowledge of the baseline or "dry" natriuretic peptide concentration is present. An increase of 50 % above the established baseline natriuretic peptide in the appropriate clinical setting with associated signs and symptoms of heart failure is consistent with an episode of decompensation, as this is out of the range of normal biologic variability (Maisel et al. 2008).

Natriuretic peptide values that are in between the cut points for ruling in or ruling out acute heart failure are considered to be in the "gray zone." Values in this range are found in approximately 20 % of patients presenting to the emergency room with dyspnea. When a result in this zone is obtained, clinical correlation is crucial: in one study, the correct diagnosis for patients with a gray zone NT-proBNP was well predicted by the constellation of clinical signs and symptoms. In the context of a gray zone value, important diagnoses besides HF should be kept in mind, including arrhythmia, ischemic heart disease, and infectious or inflammatory pulmonary disease as the culprit (van Kimmenade et al. 2008).

Table 3 Factors leading to variation in BNP or NT-proBNP concentrations besides HF. This table demonstrates the various scenarios that can produce both elevated natriuretic peptide values, in addition to heart failure as well as reduced natriuretic peptide values

Causes of elevated NP Levels other than HF
LV dysfunction
Previous heart failure
Advanced age
Renal dysfunction
Ischemic heart disease
Pulmonary disease (e.g., acute respiratory distress syndrome, lung disease with right heart failure)
Pulmonary embolism
High output states (e.g., sepsis, cirrhosis, hyperthyroidism)
Atrial fibrillation, atrial flutter
Causes of lower NP levels than expected
Obesity
Flash pulmonary edema
Heart failure etiology upstream from LV (e.g., acute mitral regurgitation, mitral stenosis)
Cardiac tamponade
Pericardial constriction

Approximately half of patients with HF have normal left ventricular (LV) ejection fraction (EF); this is known as HF with preserved EF or HFpEF. When compared to patients with LV systolic dysfunction (so-called HF with reduced EF or HFrEF), natriuretic peptide levels with HFpEF tend to be lower but are nonetheless diagnostic in the great majority (van Veldhuisen et al. 2013). It is worth noting that indices of diastolic function (indirect measures of diastolic myocardial compliance) are strongly associated with concentrations of BNP and NT-proBNP, emphasizing that LV function alone is not the only predictor of their concentration (Chen et al. 2006).

Not surprisingly, both BNP and NT-proBNP have been shown to be useful in the diagnosis of HF in the outpatient setting. In contrast to the diagnostic application of BNP or NT-proBNP in the acute environment, both peptides have been mainly examined relative to their negative predictive value to exclude the diagnosis, rather than to confirm it. In this regard, the optimal reference limits for use in this setting are considerably lower than in patients with acute dyspnea (Table 2). For NT-proBNP, the ICON-Primary Care group showed that age stratification again improves diagnostic accuracy in this setting. If a patient is found to be above the BNP or NT-proBNP cutoffs, further diagnostic testing such as echocardiography is likely needed. Causes of falsely low BNP or NT-proBNP in the outpatient setting are comparable to those with acute dyspnea (Hildebrandt et al. 2010).

Another potential use of BNP or NT-proBNP in the nonacute setting is for the screening of at-risk patients for the presence of underlying structural heart disease. Although influenced by numerous cardiac correlates including systolic function, diastolic function, valvular heart disease, ischemic heart disease, and arrhythmia,

a single measurement of BNP or NT-proBNP may be able to identify reduced LV function in asymptomatic individuals (Maisel and Daniels 2012). Additionally, in recognition of their dependence on diastolic indices as well for their concentrations, both peptides appear to be useful in screening for diastolic ventricular dysfunction (Lubien et al. 2002).

Atrial Natriuretic Peptide

More attention has been given recently to ANP as a biomarker for HF. Though discovered before BNP or NT-proBNP, the reliable detection of circulating ANP is challenging as its half-life is only 2–5 min. The development of a mid-regional pro-peptide assay for ANP (MR-proANP) assay has led to the examination of its use for HF applications (Morgenthaler et al. 2004). Table 2 details suggested cutoff points for MR-proANP for clinical use.

The role of MR-proANP in the diagnosis of ADHF was first examined in 1,641 patients with acute dyspnea in the Biomarkers in Acute Heart Failure (BACH) trial. MR-proANP performed well in diagnosing ADHF and was non-inferior to BNP or NT-proBNP. A MR-proANP cutoff point of $\geq$120 pmol/L had a sensitivity of 97 %, specificity of 60 % with accuracy of 74 %, while BNP with a cutoff point of 100 pg/mL had a sensitivity of 96 %, specificity of 62 % and accuracy of 73 % (Maisel et al. 2010). In the PRIDE study analysis of MR-proANP, NT-proBNP performed slightly better than MR-proANP in the diagnosis of ADHF (AUC of 0.94 for NT-proBNP vs. 0.90 for MR-proANP, $p = 0.001$ for difference); however, MR-proANP was found to be an independent predictor of HF diagnosis even with NT-proBNP in a multivariable model (odds ratio = 4.34, 95 % CI = 2.11−8.92, $p < 0.001$). When added to NT-proBNP measurement, MR-proANP correctly reclassified patients who had false negatives and false positive results by NT-proBNP testing alone. Furthermore, in the PRIDE study, MR-proANP strongly and independently predicted 1 and 4-year mortality (adjusted hazard ratio [HR] = 2.99, $p < 0.001$ and 3.12, $p < 0.001$ respectively) and addition of NT-proBNP to these models did not attenuate the predictive power of MR-proANP. Adding MR-proANP to base models containing NT-proBNP significantly improved the C-statistic at 1 and 4-years and reclassified mortality risk as a part of a multimarker strategy in determining prognosis (Shah et al. 2012).

In chronic HF, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca–Heart Failure (GISSI-HF) study examined the predictive power of MR-proANP in stable, chronic HF patients. MR-proANP $\geq$278 pmol/L had the best prognostic accuracy for 4-year mortality among several novel and established biomarkers including NT-proBNP. In addition, MR-proANP added independent prognostic information beyond NT-proBNP and relevant clinical characteristics in a reclassification analysis. Using the same biomarkers, only the change in MR-proANP over 3 months was found to be significant in predicting mortality (Masson et al. 2010).

Although initial data from the BACH study suggested that MR-proANP was less likely to be affected by covariates that reduce diagnostic accuracy of BNP or NT-proBNP (such as age, renal function, or obesity), subsequent data from other sources suggest that factors influencing BNP or NT-proBNP are quite likely to exert a similar effect on MR-proANP. For instance, the presence of atrial fibrillation reduced the diagnostic accuracy of MR-proANP for ADHF diagnosis just as much as it did for BNP or NT-proBNP (Richards and Mueller 2013).

Potential Applications to Prognosis, Other Diseases or Conditions

The accurate prognostication of HF is a major unmet need. In addition to diagnosis, as alluded to above, the natriuretic peptides have been shown to assist in determining prognosis for patients with HF in a variety of clinical settings from those at risk for the diagnosis, to those with established chronic HF, as well as those with ADHF. In this regard, recent clinical practice guidelines have given a Class I, level of evidence A recommendation for BNP and NT-proBNP in this application (Yancy et al. 2013).

It is now well accepted that concentrations of BNP or NT-proBNP represent an important additive piece of prognostic information for patients across the spectrum of HF syndromes. In patients with ADHF from the PRIDE study, for example, an NT-proBNP level greater than 986 pg/mL on presentation to the emergency room was found to be the strongest independent predictor of death at 1 year in multivariable analysis with a hazard ratio of 2.88. The other factors also associated with an increase in mortality were age, urea nitrogen level, systolic blood pressure less than 100 mmHg, presence of a heart murmur, and New York Heart Association class (Januzzi et al. 2006a). The prognostic importance of NT-proBNP in the PRIDE study extended at least until 4 years from presentation (Januzzi et al. 2010). In a similar fashion, concentrations of BNP measured in the emergency setting predicted future HF events and mortality and were superior to clinical judgment for estimating HF severity (Maisel et al. 2004). Additionally, the "gray zone" natriuretic peptide values in ADHF mentioned above are also important in obtaining prognostic information, and these results should not be interpreted as "negative" given that these patients have a worse prognosis than those patients who have a truly negative NT-proBNP result (van Kimmenade et al. 2008).

While baseline natriuretic peptide values are exceptionally prognostic in patients with ADHF, a follow up, posttreatment value for the marker is even more prognostic. For example, a predischarge BNP value above 350 pg/mL was found to be substantially prognostic in an early analysis from Logeart and colleagues; furthermore, in a subsequent analysis, similar data were demonstrated for NT-proBNP, revealing that those with a >30 % reduction from baseline to discharge in their NT-proBNP concentrations had superior outcomes (Logeart et al. 2004; Bettencourt et al. 2004). Recently, a large, retrospective study including over 7,000 patients over the age of 65 showed that discharge BNP value was a prime

predictor for 1 year mortality as well as predictive of both 1 year mortality and rehospitalization, and it was especially helpful to reclassify the estimate of likelihood for hazard for patients judged to be intermediate risk (Kociol et al. 2011). Another study in patients hospitalized with heart failure demonstrated that a <50 % reduction in NT-proBNP was associated with a 57 % greater risk of readmission or death compared to those who had a >50 % reduction (Michtalik et al. 2011).

Similar themes are seen in those with chronic HF. As with ADHF, in chronic HF, natriuretic peptide measurements are quite prognostic; a systematic review reported a 35 % increase in the relative risk of death with each 100 pg/mL increase in BNP value (Doust et al. 2005). Beyond this, similar to those with ADHF, a follow-up measurement informs incremental prognostic data. For example, among more than 5,000 patients with stable, symptomatic HFrEF in the Val-HeFT study, changes over the follow-up period substantially reclassified risk. When divided into quartiles relative to a median BNP measurement of 97 pg/mL, measurements at baseline and 12 months were considered in four groups: low → low, high → high, high → low, and low → high. The patients in the low → low group had the best prognosis, and patients in the high → low group had a similar risk for morbidity and mortality at 12 months. On the other hand, the patients in the high → high group and low → high group had a significantly poorer prognosis when compared to the low → low group. The results are shown in Fig. 4 (Latini et al. 2006). A similar study was conducted using NT-proBNP with comparable results, implying that trends in natriuretic peptides may be a more optimal strategy to determine prognosis in patients with heart failure (Masson et al. 2008). Finally, BNP was compared to NT-proBNP in almost 4,000 patients from the Val-HeFT trial, and both BNP and NT-proBNP were found to be the most powerful independent markers for outcome in patients with heart failure. These peptides were found to be similar with respect to age, left ventricular function, left ventricular dimensions, and creatinine clearance, but NT-proBNP was superior to BNP in prediction of mortality and morbidity as well as hospitalization for heart failure (Masson et al. 2006).

Prognostic assessment for patients with HFpEF can also be ascertained from natriuretic peptide levels. One study examined over 4,000 patients with ejection fraction above 45 %, and NT-proBNP was found to be one of the strongest independent factors for all-cause mortality (Komajda et al. 2011). Furthermore, when compared to patients with HFrEF, a given BNP level was equally predictive of poor prognosis in patients with HFpEF (van Veldhuisen et al. 2013).

Management of HF

The management of patients with HF is complex, with several medications and therapies available in the physician's armamentarium. In the context of ADHF, the primary therapy applied is loop diuretic therapy, followed by careful addition or up-titration of other therapies. In chronic HF, addition and up-titration of agents besides loop diuretics is the primary goal, with a target of achieving maximally

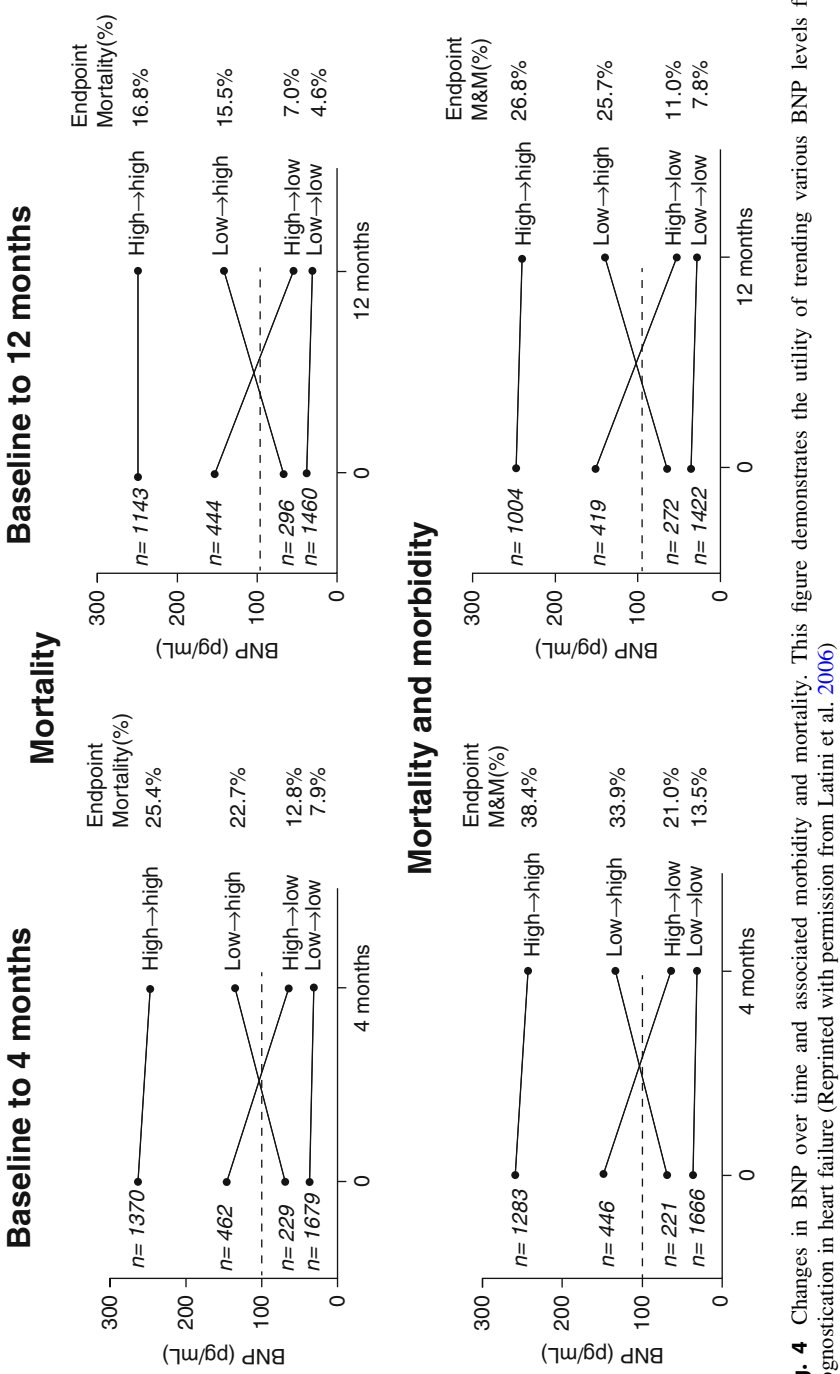

Fig. 4 Changes in BNP over time and associated morbidity and mortality. This figure demonstrates the utility of trending various BNP levels for prognostication in heart failure (Reprinted with permission from Latini et al. 2006)

tolerated doses of neurohormonal antagonists, vasodilators, and potassium sparing diuretics, while concomitantly minimizing loop diuretics whenever possible.

In both venues – acute hospital-based management as well as chronic outpatient evaluation and management – assessing the severity of congestion, the adequacy of diuresis, and understanding the correct sequence of addition and titration of therapies is complex. It is no surprise that recent studies suggest that in both ADHF and chronic HF, huge treatment gaps exist. Use of biomarkers such as BNP or NT-proBNP might be of benefit for addressing inadequacies in HF management. In this regard, there are two basic concepts to consider: the first is the use of BNP or NT-proBNP to accurately diagnose HF, gauge its severity, and correctly triage affected patients; the second concept is to use natriuretic peptides as a target of therapy.

The use of BNP or NT-proBNP to enhance clinical triage was studied in the B-type Natriuretic Peptide for Acute Shortness of Breath Evaluation (BASEL) and the Improved Management of Patients with Congestive Heart Failure (IMPROVE-CHF) studies, respectively. These studies clearly demonstrate that natriuretic peptide-enhanced diagnosis and triage were associated with fewer days spent in the intensive care unit, reduced health care expenditures, and better short- to intermediate-term outcomes (Boldanova et al. 2010; Moe et al. 2007). Thus, when used to augment the correctness of triage, natriuretic peptides seem to add considerably to clinical judgment.

Beyond their use to more accurately and confidently secure the diagnosis of HF and gauge its severity, the use of BNP or NT-proBNP concentrations as a target for therapies has been recently examined. This is predicated on several observations. First, secular trends in BNP or NT-proBNP add incremental prognostic information, as noted above, implying their serial measurement may be harnessed to assess risk over time. Second, following successful application of most HF therapies, a lowering of both BNP or NT-proBNP occurs, related to the various mechanisms of action of these agents, with effects on cardiac hemodynamics, filling pressures, and fibrosis (Motiwala and Januzzi 2013). Among the therapies that result in indirect reductions in BNP or NT-proBNP are loop diuretics, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, mineralocorticoid receptor antagonists, and beta blockers (Braunschweig et al. 2006; Tsutamoto et al. 2001; Motiwala and Januzzi 2013). Of note, beta blockers that lack vasodilatory properties can initially increase natriuretic peptide levels, though this effect is rarely clinically obvious, and independent of clinical decompensation (Davis et al. 2006; Frantz et al. 2005). Table 4 provides a summary of the effects of medications and other therapies on natriuretic peptide levels.

Thus, given the identification of prognostically important thresholds for BNP and NT-proBNP, and because of the links between therapy and reductions in both peptides, which is followed by better outcomes, several trials have been conducted to investigate the use of natriuretic peptide levels to "guide" HF management. These trials were heterogeneous in size, inclusion criteria, therapy approaches, and outcome measures but from these studies, a better clarity about the potential role of

Table 4 Effects of therapies on BNP and NT-proBNP levels. This table shows the effect of various heart failure therapies on natriuretic peptide values (Adapted by permission from Macmillan Publishers Ltd from Motiwala and Januzzi 2013)

Therapy	Effect on BNP/NT-proBNP
Diuresis (loop or thiazide)	↓
Angiotensin-converting enzyme inhibitors	↓
Angiotensin II receptor blockers	↓
β-blockers	Some transiently ↑, most ↓
Aldosterone antagonists	↓
Cardiac resynchronization therapy	↓
Exercise	↓
Rate control of atrial fibrillation	↓

BNP or NT-proBNP guided care has been gained. Comparisons between various biomarker-guided HF trials are shown in Table 5. Beyond these trials, two meta-analyses were conducted that include six and eight trials, respectively. They revealed an approximate survival benefit of 25–30 % with biomarker-guided care as shown in the forest plot in Fig. 5 (Felker et al. 2009; Porapakkham et al. 2010). Furthermore, there was greater optimization of medical therapy in the biomarker-guided therapy arms, without a difference in up-titration of diuretic therapy in either group (Felker et al. 2009). Across all studies, there was no significant increase in adverse events in the biomarker-guided therapy arms.

A few differences between biomarker-guided HF trials are important to note, as they illuminate why some studies met their primary endpoint and other did not. Firstly, among those studies that were unsuccessful, most had target BNP or NT-proBNP values that were prohibitively high; as noted above, prognostic thresholds for both peptides are relatively low (BNP ~ 100 pg/mL; NT-proBNP ~ 1,000 pg/mL). By aiming for higher target values, patients were left at unnecessary risk. Further, studies that were successful invariably had more aggressive care triggered in the biomarker-guided arm; in all but one of the neutral trials, the care in the natriuretic peptide-guided arm was no different than the usual care arm. Moreover, in all of the successful biomarker-guided studies, significant lowering of BNP or NT-proBNP was achieved, something not seen in the neutral studies. In the most recent randomized trial comparing biomarker-guided therapy with standard of care, the ProBNP Outpatient Tailored Chronic HF Therapy (PROTECT) trial, more aggressive care was seen in the biomarker-guided arm, resulting in greater addition or up-titration of both mineralocorticoid receptor antagonism as well as beta blockade. With these adjustments, substantial improvement in HF events was seen in the NT-proBNP-guided arm, where a low target was sought and achieved in a substantial percentage of study subjects (Januzzi et al. 2011).

Questions remain with respect to biomarker-guided HF care. For example, based on data from the Trial of Intensified versus Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) and NT-proBNP-Assisted

Table 5 Review of biomarker-guided therapy trials in heart failure. This table consolidates the major biomarker-guided therapy trials in chronic heart failure. Studies in red were neutral/negative, in blue were neutral/negative with positive trends, and in green were positive

Study	Age	Number of patients	HFpEF	NP target	NP level lower in study arm	Active treatment different from control arm	Excess adverse events in treatment arm	Follow up
STARBRITE (Shah, 2011)	60	130	No	BNP at hospital discharge (~450 pg/mL)	No	Yes	No	3 months
PRIMA (Eurlings, 2010)	72	345	Yes	NT-proBNP at hospital discharge	No	No	No	1.9 years (median)
SIGNAL-HF (Persson, 2010)	78	252	No	NT-proBNP 50% below trial entry value	No	No	No	9 months
UPSTEP (Karlström, 2011)	71	279	No	BNP < 150 pg/mL for age <75 BNP <300 pg/mL for age ≥ 75	Not reported	No	Not reported	12 months (minimum)
TIME-CHF (Pfisterer, 2009)	77	499	No	NT-proBNP <400 pg/mL for age <75 NT-proBNP <800 pg/mL for age ≥ 75	No	Yes	No	18 months
BATTLE-SCARRED (Lainchbury, 2009)	76	364	Yes	NT-proBNP < 1270 pg/mL	No	Yes	No	2.8 years (median)
Troughton, et al (Troughton, 2000)	70	69	No	NT-proBNP < 1692 pg/mL	Yes	Yes	No	9.5 months (median)
STARS-BNP (Jourdain, 2007)	65	220	No	BNP < 100 pg/mL	Yes	Yes	No	15 months (median)
Berger, et al (Berger, 2010)	71	278	No	NT-proBNP ≤ 2200 pg/mL	Yes	Yes	Not reported	12 month (minimum)
PROTECT (Januzzi, 2011)	63	151	No	NT-proBNP < 1000 pg/mL	Yes	Yes	No	10 months (mean)

Treatment To Lessen Serial Cardiac Readmissions and Death (BATTLESCARRED) studies, a hypothesis exists that states that biomarker-guided HF care is less effective in elderly patients. Further, it is not yet clear if the approach reduces mortality. Lastly, it remains unknown if the strategy can be used in patients with HFpEF as easily as it seems to be applied in HFrEF. In order to definitively address the question of survival using natriuretic peptide-guided therapy, an adequately powered, multicenter, randomized trial has recently launched, which will help answer these questions (http://clinicaltrials.gov/ct2/show/NCT01685840).

Recently, a different approach to BNP-guided care was explored in the St. Vincent's Screening to Prevent HF (STOP-HF) study. In this analysis, 1,235 study participants in primary care at high risk for HF onset (due typically to hypertension or diabetes mellitus) were randomized to usual care versus usual

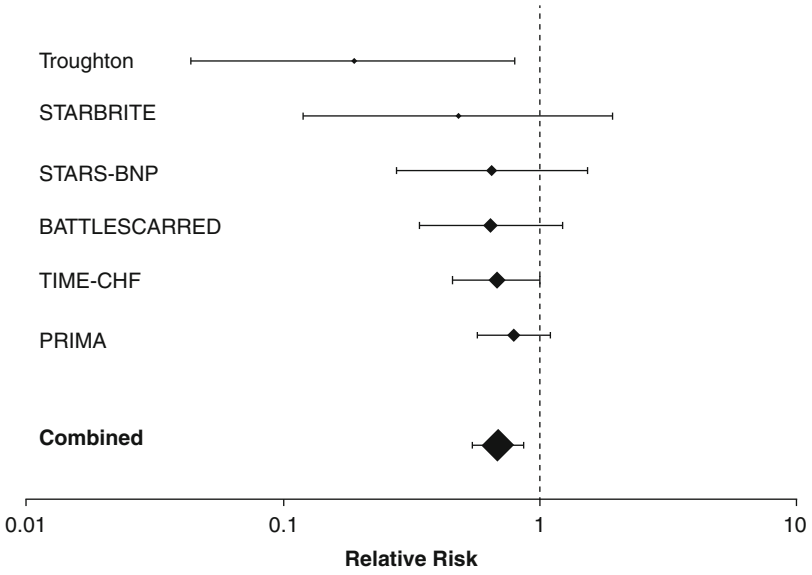

Fig. 5 Forest plot of all-cause mortality from 6 biomarker-guided trials. The plot shown here implies a mortality reduction from use of this approach (Reprinted with permission from Felker et al. 2009)

care plus BNP screening. In the latter group, if a patient was found to have a BNP value >50 pg/mL in yearly screening, the diagnostic and therapeutic approach to their care was intensified. Following an average follow-up period of 4.3 years, the primary endpoint of LV dysfunction or clinical HF was reduced by 42 % in the BNP-guided arm, with a comparable 46 % reduction in cardiovascular hospitalization. These data suggest that BNP or NT-proBNP-based evaluation and management may not only be applied to those with clinically manifest HF but also in those at risk for the diagnosis, where biochemical signatures of myocardial disarray may be detectable prior to the onset of clinical manifestations, at a time when the diagnosis may be averted (Ledwidge et al. 2013).

Conclusion

Since their discovery in 1981, the natriuretic peptides have been extensively studied. Their most important role has been assisting in the diagnosis and prognosis of HF, a syndrome that continues to affect millions of people, and their value for patient management appears likely. The natriuretic peptides serve as an important adjunct to clinical assessment and, in the future, may be used to personalize the care of patients with this complex disease.

Summary Points

- This chapter discusses the natriuretic peptide family, which is a group of hormones that is important in regulating fluid homeostasis across multiple species.
- These hormones have an important role in heart failure, and this chapter focuses on atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and amino-terminal pro-B-type natriuretic peptide (NT-proBNP). Other cardiac and noncardiac conditions can also produce an abnormal natriuretic peptide measurement.
- ANP is primarily produced by atrial cardiomyocytes and is stored intracellularly, whereas only a small amount of BNP is stored, and it is produced primarily by ventricular cardiomyocytes. Both hormones begin as a prohormone and are subsequently cleaved, and both hormones are released in response to wall stress.
- Each of these cardiac hormones has a different half-life which is determined by their various clearance mechanisms, including enzymatic degradation, binding to natriuretic peptide receptors, and passive removal from the body by organs that receive a high proportion of blood flow such as the kidneys.
- Release of the natriuretic peptides results in vasodilation, diuresis, and natriuresis. These hormones may also assist in decreasing the hypertrophic response to pressure overload.
- The natriuretic peptides have become increasingly important in diagnosing or excluding the presence of heart failure.
- Use of the natriuretic peptides for prognostication of heart failure is also recommended, and both individual measurements and trends in the values over time provide insight into prognosis.
- Natriuretic peptides can also be used to guide heart failure management. Large studies are currently underway to further investigate this approach.

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