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Review

# State of the art: Using natriuretic peptide levels in clinical practice

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**Abstract**

Natriuretic peptide (NP) levels (B-type natriuretic peptide (BNP) and N-terminal proBNP) are now widely used in clinical practice and cardiovascular research throughout the world and have been incorporated into most national and international cardiovascular guidelines for

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heart failure. The role of NP levels in state-of-the-art clinical practice is evolving rapidly. This paper reviews and highlights ten key messages to clinicians:

- NP levels are quantitative plasma biomarkers of heart failure (HF).
- NP levels are accurate in the diagnosis of HF.
- NP levels may help risk stratify emergency department (ED) patients with regard to the need for hospital admission or direct ED discharge.
- NP levels help improve patient management and reduce total treatment costs in patients with acute dyspnoea.
- NP levels at the time of admission are powerful predictors of outcome in predicting death and re-hospitalisation in HF patients.
- NP levels at discharge aid in risk stratification of the HF patient.
- NP-guided therapy may improve morbidity and/or mortality in chronic HF.
- The combination of NP levels together with symptoms, signs and weight gain assists in the assessment of clinical decompensation in HF.
- NP levels can accelerate accurate diagnosis of heart failure presenting in primary care.
- NP levels may be helpful to screen for asymptomatic left ventricular dysfunction in high-risk patients.



*Keywords:* Natriuretic peptides; Clinical practice; Diagnosis

## 1. Introduction

The FDA clearance of B-type natriuretic peptide in the fall of 2000 as an adjunct to the diagnosis of heart failure (HF) has generated both excitement and controversy. The rapid adoption of both BNP and N-terminal proBNP (natriuretic peptides (NP)) suggests that their clinical application exceeds their use as rule-out blood tests for heart failure. Indeed, there are data suggesting that at some level, with consideration for the confounders of chronic elevations and non-HF disease states that may elevate NPs, an elevated NP level may represent a reasonable "rule-in" biomarker that is also highly prognostic for clinically relevant outcomes in both HF and acute coronary syndrome. There is also early support for the concept that NP levels are modulated by medications and may help guide treatment in both the inpatient and outpatient setting.

The widespread promulgation of relatively straightforward and easily accessible tests, including NPs, has a potential downside — too many tests are ordered for reasons beyond the intended use. Physicians have voiced appropriate concern over how best to integrate NP testing into the clinical arena so that they can make informed decisions in diagnosing and managing patients. Extrapolation from peer-reviewed literature is required when considering individual patients, and it is here that clinical acumen and user experience play an important role.

The purpose of this review is to provide clinicians with advice on the use of NP levels in their daily practice. The recommendations presented are consensus based, i.e. based on evidence combined with the clinical judgment of the majority of a group of experts. Some recommendations could be criticized for leaning to one side or the other of a controversial issue. However, the authors are all intimately involved in the area of HF, and many use NP levels on a daily basis. As general recommendations apply to both BNP and NT-proBNP, examples will be given with both peptides. Although the levels correlate with each other, the individual values of the two NPs are NOT interchangeable. They have different half-lives, different modes of degradation, and most important, different ranges and cut-off values. However, their similarities far outweigh their differences, and for the purpose of the reader, the two should be considered basically

Table 1
History of B-type natriuretic peptide testing

| | |
|---|---|
| 1988 | Sudoh et al. isolate BNP from porcine brain tissue [4] |
| 1991 | Mukoyama et al. demonstrate that BNP is a normal cardiac hormone secreted primarily by the ventricles [5] |
| 1993 | Shionogi & Co, Ltd. develop the first commercial BNP assay (RIA) in Japan |
| 1994 | Davis et al. provide the first report suggesting that BNP is useful in diagnosing HF in dyspnoeic patients [6] |
| 1994 | Multiple reports of elevated BNP levels in HF [7,8] |
| 1995 | Hunt et al. — first report of NT-proBNP circulating in human plasma [9] |
| 1997 | Cowie et al. show that BNP has high accuracy to diagnose CHF in the primary care setting [10] |
| 1998 | McDonagh et al. demonstrate that BNP is reliable in the detection of left ventricular dysfunction [11] |
| 2000 | Biosite, Inc. introduces the BNP point-of-care assay |
| 2001 | Maisel et al. publish the first point-of-care BNP in the ED and hospital settings [12,13] |
| 2002 | Breathing Not Properly Study published [14] |
| 2003 | Lainchbury et al. — first report of NT-proBNP in the diagnosis of HF [15] |
| 2003 | Central lab assays become available: Bayer Healthcare, LLC, Diagnostics Div., ADVIA Centaur, ShionoRIA BNP assay in US (central lab) and Roche Elecys |
| 2004 | BASEL trial showing reduction in morbidity and treatment cost with BNP published [16] |
| 2005 | Beckman central lab (Biosite antibody) and Abbott Diagnostics, AxSYM BNP assay (central lab) becomes available |
| 2005 | PRIDE study on NT-proBNP in AHF published [17] |
| 2005 | ESC Guidelines for acute and chronic Heart Failure Endorse BNP [18,19] |
| 2006 | Biosite Triage BNP Test receives CLIA waiver for whole blood use. AHA/ACC Guidelines for Heart Failure Endorse Class II a recommendation for NPs. (Level of evidence A) [20] |

equal. Two important principles should underlie the clinical use of NPs. First, a NP level is NOT a stand-alone test. It is always of greatest value when it complements the physician's clinical skills along with other available diagnostic tools and should always be interpreted in consideration of renal function and body mass index (BMI). Second, NP levels should be interpreted and used as continuous variables in order to make full use of the biological information provided by the measurement (like for example calculated glomerular filtration rate or LDL-cholesterol). Cut-off levels may still be useful to make the application of NP easy for physicians without extensive experience with NP testing.

## 2. Natriuretic peptides — history and physiology

The abbreviated history of NPs is presented in Table 1. BNP initially was isolated and named after the porcine "brain". However, with the primary site of synthesis localized to the cardiac ventricular myocytes, the term "B-type" natriuretic peptide is now favoured. The best current understanding suggests that in the setting of volume expansion or pressure overload, the resulting wall stress initiates synthesis of pre-pro-BNP in the ventricular myocardium [1], although some have questioned the correlation between individual changes in blood volumes and NP levels [2].

After synthesis, the peptide is cleaved first to proBNP, then to the biologically active BNP and the inactive amino-terminal fragment, NT-proBNP. The release of BNP results in improved myocardial relaxation and serves an important regulatory role in response to acute increases in ventricular volume by opposing the vasoconstriction, sodium retention, and antidiuretic effects of the activated renin–angiotensin–aldosterone system [3].

Fig. 1 illustrates the haemodynamic determinants of BNP. A given level of BNP is a summation of many inputs and is a measure of many aspects of cardiac function.

## 3. Use of natriuretic peptide levels in patients presenting with acute dyspnoea

In many industrialized nations, HF, a progressive disease with a mortality exceeding most cancers, represents one of the most expensive disorders to the medical system [21]. Most patients with HF eventually present to the emergency department (ED) or hospital. Because HF occurs predominantly in older subjects, its presentation is often complicated by multiple co-morbidities that are common in this population. This is unfortunate, since the most common presentation of HF is dyspnoea, a complaint that is neither specific nor sensitive for predicting the presence of HF. Thus, the challenge for the emergency physician is to triage rapidly and accurately patients presenting with dyspnoea due to HF from those with many other common aetiologies with similar presentation.

NP testing improves diagnostic accuracy and thus has become a standard part of the evaluation in patients

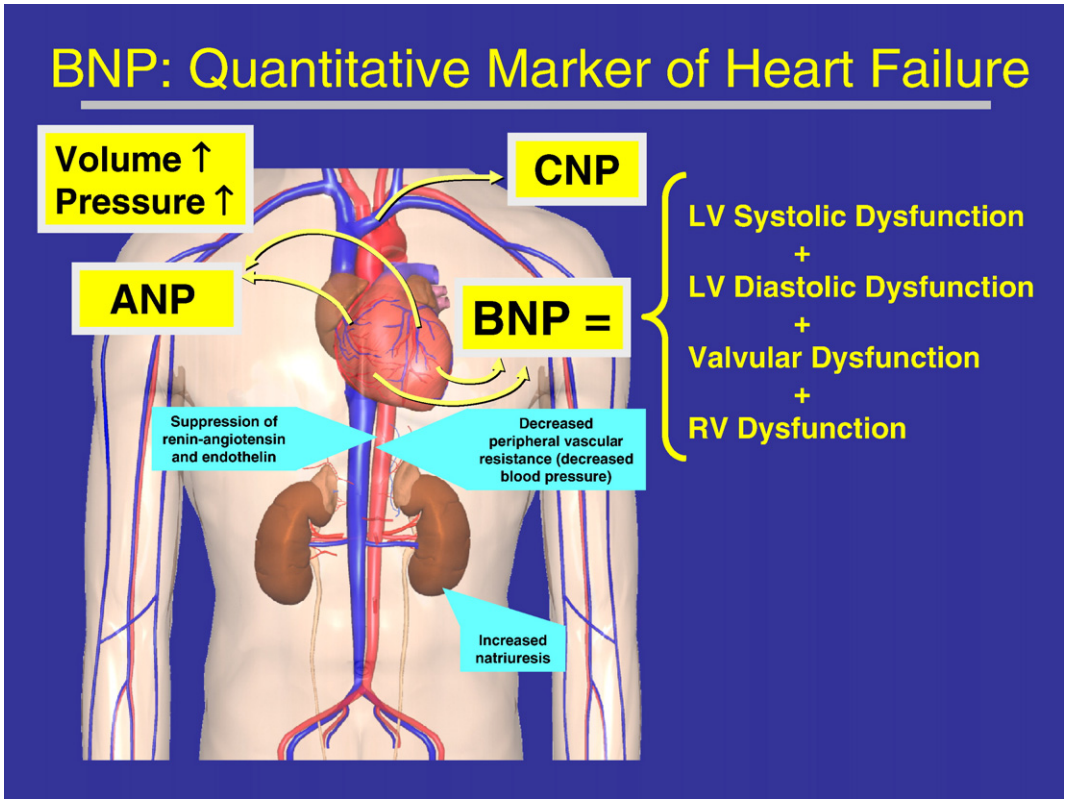


Fig. 1. Haemodynamic determinants of BNP.

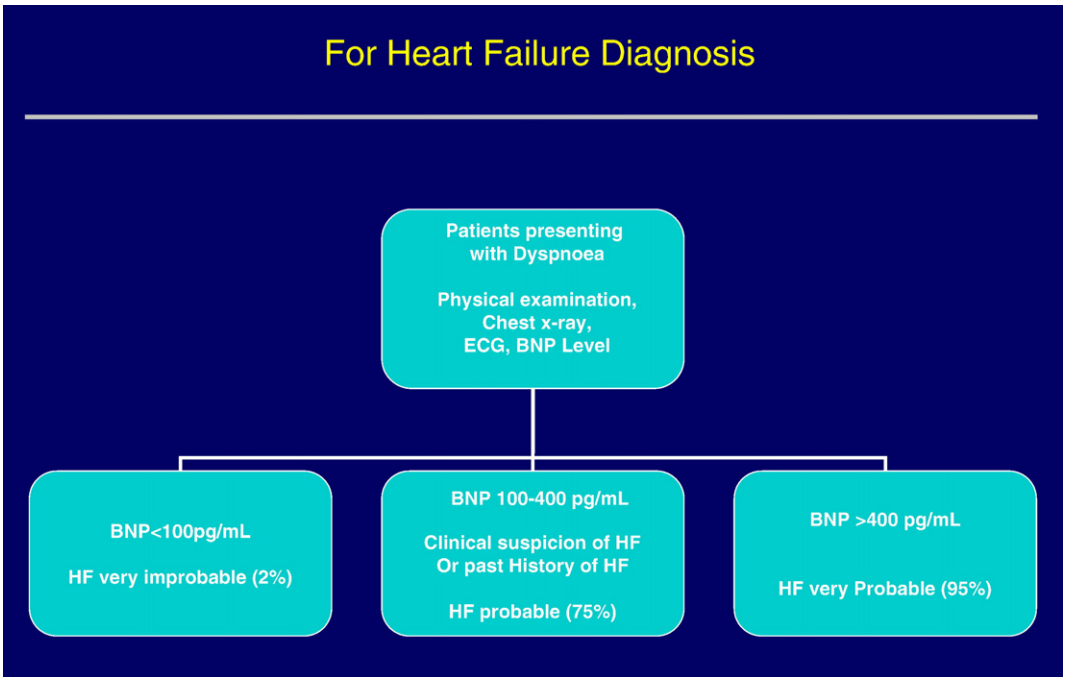


Fig. 2. BNP Consensus Algorithm.

presenting to the ED with dyspnoea. NP levels improve the accuracy of physician decision-making; errors decline, and a marked reduction in the rate of clinical indecision would have occurred if NP levels were considered as part of the initial evaluation [14,16,22,23].

As a quantitative marker of HF, NP levels are best interpreted as a continuous variable. The higher the NP value the greater the likelihood that the dyspnoea is due to HF. While the use of cut points can be criticized, for clinical usefulness specific cut-off values can provide benchmarks correlating with relevant statistical thresholds. When BNP is low (<100 pg/ml), it is unlikely that HF is contributing to the clinical presentation. On the other hand, a high BNP (>400 pg/ml) suggests that HF is a contributor to the patient's symptoms with specificity exceeding 90% (Fig. 2). The "rule-out" level (BNP <100 pg/ml) can exclude HF from the differential diagnosis. However to "rule in" HF (BNP>400 pg/ml) is more complex. This requires addressing the fact that BNP may be persistently elevated in chronic HF and may

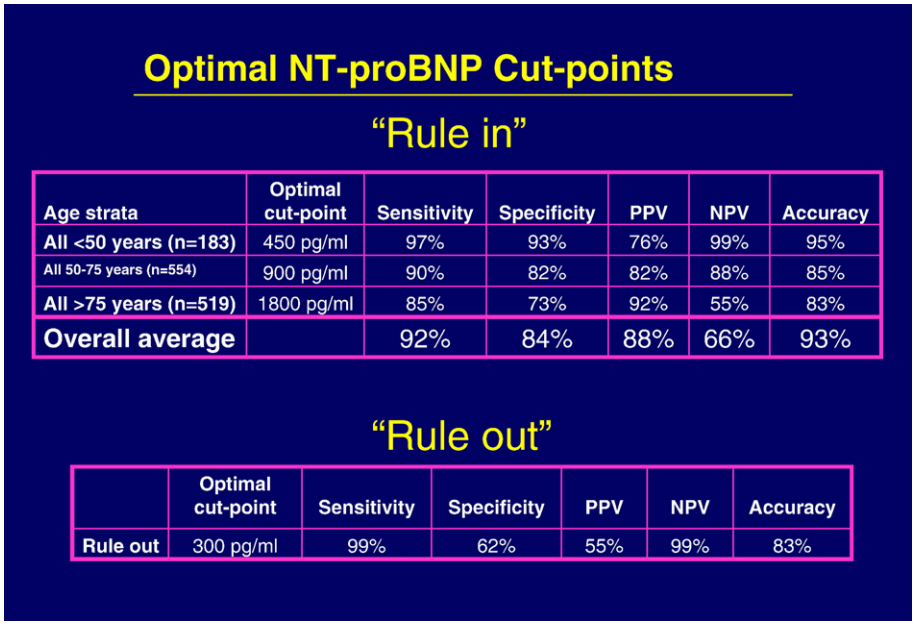


Fig. 3. Optimal cut points for NT-proBNP in the ED.

not be representative of an acute haemodynamic change. Other conditions that result in an increased BNP should also be considered, including both those that result in myocardial stretch (acute pulmonary embolus, acute coronary syndrome, primary pulmonary hypertension, etc.) and renal failure.

While a 2 cut-point approach provides high diagnostic accuracy, this does leave a "grey zone" of BNP values between100 and 400 pg/ml where clinical acumen and ancillary testing are often required to make a correct diagnosis. If a large proportion of patients with acute breathlessness had values in the grey zone this could reduce the clinical utility of NP but, in practice, 75% of patients have values above or below these cut-off values [13,14,16,22].

A recent pooled analysis examined the utility of NT-proBNP in the diagnosis of heart failure [23]. When using NT-proBNP, a cut point of 300 pg/ml is proposed to "rule out" a diagnosis of HF, while higher age-dependent cut points are suggested to "rule in" HF [17] (Fig. 3). Patients with NT-proBNP levels >450 pg/ml (<50 years), >900 pg/ml (50–75 years), and >1800 pg/ml (>75 years) all have a high likelihood of heart failure as the diagnosis.

As a quantitative marker of HF, the use of NP levels is not only helpful for diagnosis, but also for risk stratification and may therefore assist in triage decisions. Initial ED NP levels identify the risk of death or readmission within 30 days. Inpatient mortality has been shown to be related to admission BNP in a linear manner [24,25]. Patients with a BNP at presentation >1730 pg/ml (fourth quartile) had an in-hospital mortality rate that was more than three-times that of patients with BNP levels<430 pg/ml (first quartile). [25]. NT-proBNP levels in the ED>1000 pg/ml are associated with severe heart failure and an adverse prognosis. [17].

Results from two large randomised controlled studies provide further support for the use of NP testing in the ED [14,26,27]. In the BASEL study, a single measurement of BNP in the ED added to the clinical evaluation, reduced the time to the initiation of the correct treatment, reduced in-hospital days and reduced overall cost by 26%. Importantly the improvement in outcome and the reduction in total costs persisted at six months [26]. Therefore, in patients presenting with dyspnoea the use of NP levels is not only cost-effective but also cost saving. Recent data from the Canadian IMPROVE-CHF study confirmed that the findings of the BASEL study also apply in a universal health coverage system [27]. The knowledge of NT-proBNP levels (measured at presentation and at 72 h) in IMPROVE-CHF reduced the duration of the ED visit by 21%, the number of patients re-hospitalised over 60 days by 35%, and direct medical cost of all ED visits, hospitalisations, and subsequent outpatient services at 60 days by 15%.

Therefore, NP testing should be considered for most patients within the "at risk for heart failure" demographic and presenting to the ED with acute dyspnoea. For logistic and practical reasons, this approach seems preferable to selective testing. Even in those patients in whom the diagnosis seems certain, a NP level in the ED gives important information concerning short and intermediate-term prognosis. Despite this apparent recommendation for near global assessment of NPs in patients presenting with dyspnoea, the likelihood of a test is related to the pre-test probability of disease. If the clinical scenario is overwhelmingly consistent with HF or more importantly is clearly unrelated to HF, there is no need to perform the assay for diagnostic purposes. For example, in a patient in whom dyspnoea is associated with a known cause, such as an adult presenting with trauma or a paediatric patient with known asthma, a NP level is not needed.

NP levels may guide the intensity of ED treatment, aid in the decision to admit or not admit a patient to the hospital, and clarify the urgency of post-discharge follow-up. For example the non-obese patient with HF whose BNP level is <250 pg/ml is generally at low risk for subsequent adverse cardiac events and may be discharged from the ED after relief of symptoms, as long as problems other than HF requiring admission are not present [24]. Conversely, the greater the NP level, the worse the severity of HF and the higher the incidence of short and long-term mortality.

### 3.1. Caveats in using NP levels

#### 3.1.1. "Grey zone"

The grey zone is defined as follows:

| BNP [28] | NT-proBNP [27] |
|---|---|
| 100–400 pg/ml | <50 years old 300 450 pg/ml<br>50–75 years 300–900 pg/ml<br>>75 years 300–1800 pg/ml |

The grey zone needs extra physician attention and ancillary testing. While the final diagnosis is often mild to moderate HF [14,28], other causes of a modest rise in NP level should be considered. This includes non-cardiac pathology that causes myocardial stress, and includes pulmonary hypertension and RV dysfunction secondary to pulmonary embolism, acute coronary syndrome, atrial fibrillation, or chronic obstructive pulmonary disease with cor pulmonale [29]. Patients with pneumonia can also have modest increases in NP levels. Renal dysfunction will be discussed below. The medium-term prognosis for dyspnoeic patients with LV dysfunction and BNP levels in the grey zone is fairly good but outcome may also be determined by the severity of any co-morbid condition. The grey zone levels are far more strongly associated with heart failure when concomitant clinical features are present, such as a history of heart failure, jugular venous pressure, and prior diuretic use [30].

#### 3.1.2. Pulmonary disease

In patients with chronic pulmonary disease, differentiating between pulmonary causes of dyspnoea versus confounding cardiac disease can be clinically challenging.

Although the presence of pulmonary hypertension and RV dysfunction may increase NP levels into the grey zone, few patients with moderate COPD have a BNP>100 pg/ml or NT-proBNP levels>350 pg/ml. In patients with pulmonary hypertension and RV dysfunction (e.g. in severe chronic obstructive pulmonary disease, pneumonia, and primary pulmonary hypertension), NP levels are often in the grey zone and occasionally in the diagnostic zone for HF, reflecting the existence of major RV stress and, in effect, right heart failure [31–36]. The accuracy of NP to diagnose HF is unchanged in the presence of pre-existing pulmonary disease [36,37]. Data from the BASEL study suggest that monitoring of NP levels also improves patient management and reduces treatment costs in this important patient subgroup [37].

NP levels may also be increased into the grey zone, and possibly higher, in the setting of acute right ventricular strain as a result of a pulmonary embolism. NP levels should not replace the standard diagnostic process when this condition is suspected; it is elevated in ~30% of patients and is associated with a worse outcome, especially when it occurs in the presence of elevated troponin levels [38].

#### 3.1.3. Renal disease

There is an important interrelationship between cardiac and renal dysfunction. About one third of outpatients with chronic HF have renal insufficiency, defined by an eGFR (estimated glomerular filtration rate, MDRD formula) less than 60 ml/min [39]. Current data suggest that the cause of elevated NP levels in renal failure is multifactorial, representing in part a true counter-regulatory response from the heart to the kidney, and not simply diminished passive renal clearance [40–43].

In order to maintain optimal diagnostic performance, the cut point for detecting HF may need to be raised when eGFR is less than 60 ml/min [42]. It is important to note that due to the lack of data, NP testing for heart failure should be discouraged in patients on dialysis.

Importantly, high NP levels should not be ignored in the setting of renal dysfunction. Given the strong relationship between cardiac and renal disease, clearly elevated NP values suggest that cardiac disease is present and should influence clinical decision-making.

#### 3.1.4. Obesity

NP levels (both BNP and NT-proBNP) are lower in obese people, both with and without HF [44–47]. Although the reason for this interaction remains undetermined, the increased concentration of the NP Receptor-C clearance receptor on adipocytes has led some to postulate that increased clearance might be the reason for lower NP levels [48,49]. To optimize diagnostic accuracy, lower cut-off values should be used. As there seems to be a linear decrease in NP levels with increasing BMI, the higher the BMI the lower the cut-off level which provides the highest accuracy [50,51]. A very low BNP cut-off level (<50 pg/ml) should be used to rule out HF in obese patients (BMI>35 kg/m$^2$). For reasons of simplicity, it seems justified to conversely double the NP value of an obese patient to correct for the increased BMI. Despite the lower circulating levels, NP levels retain a prognostic capacity in obese patients [50].

With regard to NT-proBNP, an analysis of the ICON study demonstrated that rule-out values remained robust irrespective of BMI [51].

#### 3.1.5. Diastolic dysfunction

The severity of diastolic dysfunction is correlated to increased levels of both BNP and NT-proBNP [52,53]. NP levels by themselves cannot be used to differentiate systolic from “diastolic dysfunction” in the ED. In fact, the inverse relationship between ejection fraction and NP levels is poor, with an area under the curve (AUC) of the receiver operated characteristic (ROC) curve in the 0.6–0.7 ranges. This is consistent with the known physiology of BNP, which reflects ventricular stress rather than contractility or mass.

Diagnosing “diastolic dysfunction” in asymptomatic or minimally symptomatic individuals is still a work in progress, as age, gender, and gold standards for diastolic dysfunction come into play. There is further discussion below in the section on screening for cardiovascular dysfunction.

### 3.2. Caveats: low levels of natriuretic peptides

#### 3.2.1. HF due to causes upstream from the LV

When HF is due to a cause upstream from the LV, for example in mitral stenosis or acute mitral regurgitation, NP levels may not be very high despite severe symptoms. The absence of a significant rise in LV wall stress in these acute settings explains the lack of marked NP production, and while NP levels may still be higher than normal, they will not rise to the same degree as when the HF occurs with a concomitant overload on the LV. Similarly, pericardial abnormalities, such as constriction and tamponade, can sometimes cause symptoms of HF; however, since the myocardial wall is not abnormally stressed, NP levels are typically normal or only slightly elevated [54,55].

#### 3.2.2. Flash pulmonary oedema

NP levels may be relatively low in patients presenting with HF symptoms that develop abruptly, within approximately 1 h. In this setting, the time interval between the initial trigger and the measurement of NP levels is so short that it precedes the up-regulated peptide synthesis. Since only very small quantities of BNP (compared to ANP) are stored in secretory granules, the development of elevated NP levels in “flash” pulmonary oedema is dependent upon the *de novo* synthesis and secretion of the peptide [56]. The incidence of this phenomenon seems to be very low [14,16,17]. Perhaps ANP levels might someday be a better marker in this condition.

### 3.3. Practical points and recommendations

- A NP level can be used to quantify the severity of HF, reflecting systolic and diastolic left ventricular dysfunction, as well as valvular heart disease and right ventricular dysfunction.
- Patients presenting with dyspnoea, especially of uncertain origin, to emergency services should undergo a history, physical examination, chest X-ray, ECG and blood should be sampled for a NP and renal function measurement.
- NP level should be interpreted as a continuous variable. When using cut-off values for BNP in patients with acute dyspnoea, apply two values: one to "rule out" (<100 pg/ml) and one to "rule in" HF (>400 pg/ml). When considering BNP to rule in HF, chronic HF elevations and non-HF pathology that may increase BNP must be considered. The grey zone between 100 and 400 pg/ml needs additional physician interpretation. When using NT-proBNP, apply one rule-out value (<300 pg/ml) and one of three rule-in values based on age. Other clinical features may be of great assistance in obtaining the diagnosis of HF.
- The rule-out values for both BNP and NT-proBNP in the acutely dyspnoeic patient do not need to be adjusted for age or sex. To optimize diagnostic accuracy with either NP, adjustments should be made for renal dysfunction and obesity.
- The knowledge of a patient's baseline NP level may further improve ED physician diagnostic accuracy.
- The grey zone is observed in 25% of dyspnoeic patients, three-quarters of whom have HF as the ultimate diagnosis. These patients usually have mild HF and a good prognosis.
- There appears to be a linear inverse relationship between BMI and BNP levels. Patients who are obese (BMI>30 kg/m$^2$) should have their BNP doubled to use the standard cut points. Alternatively, the rule-out value for BNP in obese patients presenting with acute dyspnoea is lower than the standard rule-out values. Thus far, there have been no suggested corrections for NT-proBNP and BMI.

## 4. NP levels in the inpatient setting

One third or more of patients with a discharge diagnosis of HF will be readmitted within 3–6 months and this greatly adds to the cost of care [57,58]. Patients who are admitted to the hospital with decompensated HF usually respond symptomatically to treatment, but there has been no good method to evaluate the relationship between acute response and long-term outcome before NPs. The fact that NPs have a short half-life, are easily measured, and provide a quantitative marker of HF severity and prognosis, suggests that they might be a useful guide to therapy in acute HF.

Overall, the use of NP testing once a patient has been admitted has been studied less extensively as compared to the use in the ED. In particular, we lack data from randomised controlled trials.

Although some studies question the relationship between pulmonary artery wedge pressure (PAWP) and NP levels [59–61], elevated levels commonly indicate an increased PAWP in patients admitted with volume overloaded, decompensated HF. Although this relationship has not been duplicated in all evaluations, a treatment that reduces PAWP will frequently lead to a fall in NP levels, as long as the patient is maintaining an adequate urine output [62].

Conceptually, the NP level of a patient who is admitted with decompensated HF is comprised of two components, that of a baseline, optivolaemic (dry) NP level and that occurring from acute pressure or volume overload (the wet) NP level. At the point of decompensation, a patient's NP

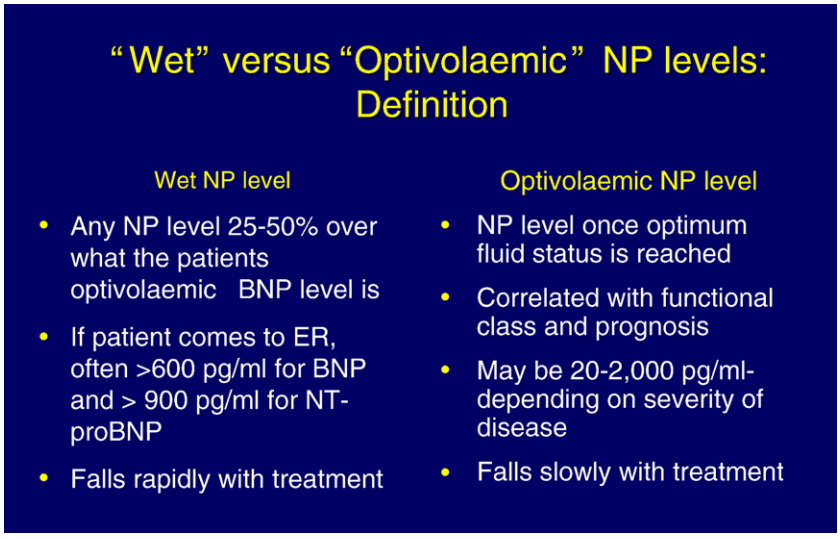


Fig. 4. Wet versus optivolaemic BNP levels (optivolaemic = baseline).

level is the sum of the baseline NP level plus what volume overload adds (Fig. 4).

Blood levels of NPs rise to very high levels in the setting of acute HF. Nevertheless, recent studies support the idea that HF patients actually manifest a state of BNP insufficiency, due to both a deficiency of biologically active BNP and resistance to its effects [63]. Evidence for a state of deficiency comes from molecular analysis of BNP in subjects with acute HF, which reveals two distinct circulating forms of BNP: a high-molecular weight form, thought to be the biologically inactive proBNP, and a low-molecular weight form, the 32-amino acid active BNP [64]. Abnormal processing of proBNP into less active forms may also factor into the state of relative BNP insufficiency [65].

Although there is little objective data defining why NP levels do not decline in some patients despite treatment, several clinical scenarios should be considered. First and most importantly, a high NP level may actually be the patient's optivolaemic (dry) NP level due to persistent increased ventricular wall stress, even after resolution of acute episodes of volume overload. It is also possible that with excessive parenteral diuretic treatment, intravascular dehydration results in a pre-renal state. While in normal patients the kidney partially clears BNP and NT-proBNP, with decreasing GFR, increased levels of both NPs are well described. In fact, NP levels can be markedly elevated in anephric dialysis patients, compared to those with normal renal function. Therefore, worsening azotaemia from excessive diuresis may result in increasing NP levels. Another possible scenario is that a patient with concomitant right-sided HF and significant ascites and/or oedema might diurese many litres before NP levels actually drop. This is likely due to mobilization of third-space fluid rather than lowering of cardiac filling pressures. Continuing diuresis and/or vasodilatation should eventually lower "wet" NP levels. Finally, in some cases treatment simply does not effectively reduce central cardiac haemodynamics and therefore does not improve cardiomyocyte stress and one should not expect to see a decline in this setting.

We suggest to measure NP levels routinely at the time of admission and prior to discharge when optivolaemic status is achieved. The latter measurement is supported by studies documenting increased prognostic information as compared to the level measured at admission [66,67]. Repeat NP measurements should be considered in the event of clinical deterioration or to evaluate adequacy of therapy, but is currently not indicated in the vast majority of inpatients with HF.

Some studies have found that the lower the discharge optivolaemic NP level is, the lower the risk of death and re-hospitalisation [66,67]. We suggest that this is because a relatively low NP level usually represents a more stable patient (NYHA I–II) and one that is more likely to be in a true euvolaemic state. However, the literature is not consistent and a precise relationship between discharge BNP levels and long-term outcomes is unclear. Some large clinical trials report that despite a reduction in mean BNP there were no differences in long-term benefits [68,69]. In the randomised IMPROVE-CHF study, with follow-up NP data available, clinical benefit was demonstrated. Unfortunately there was limited investigation as to how the data was used to guide therapy, and the authors hypothesized that the majority of benefit derived from accurate HF detection at the time of presentation. It is still debated whether the baseline or final NP is the most important parameter for hospitalised patients, or whether they may reflect similar information since the range of "risk" can be quite large and should be interpreted as a continuous variable. Overall, we believe that knowing a patients' baseline optivolaemic NP level is likely to be important in monitoring the patient in the first thirty days after discharge.

While some studies have shown that a relative drop (approximately 30%) in the NP level is associated with a good short-term prognosis [70], the absolute NP level at discharge appears to be a better reflection of the state of the ventricle and whether optivolaemic status has been reached (<350 pg/ml for BNP and <4000 pg/ml for NT-proBNP). A patient in whom NP has risen during hospitalisation or has dropped but is still in the 600–700-pg/ml range for BNP and >7000 pg/ml for NT-proBNP at discharge has an increased risk of cardiovascular events [67]. Changing therapy based on measured NP levels has not yet been shown to be beneficial, but more aggressive monitoring and therapy may be wise. Pre-discharge NP levels appear to be more cost-effective than comprehensive Doppler-echocardiographic examination for the prediction of future cardiac death or HF re-hospitalisation [59].

### *4.1. Practical points and recommendations*

- NP levels substantially above previous levels (>50%) usually reflect volume overload.
- A patient admitted with acute breathlessness due to HF and a high BNP level (generally >600 pg/ml for BNP and 6000 pg/ml for proBNP) usually has high filling pressures secondary to volume overload, and a treatment-induced decrease in PCWP will commonly lead to a rapid drop in NP levels.
- Altered forms of BNP might account for some of the apparent increase in BNP levels measured with conventional assays in patients with decompensated HF.
- NP levels should always be interpreted together with a measure of renal function.
- NP levels should be measured routinely on admission and prior to discharge when the patient is considered optivolaemic.
- While a drop in NP level in response to treatment is important, the final NP level seems to be the most accurate predictor of death or readmission.
- BNP <350–400 pg/ml or NT-proBNP <4000 pg/ml at the time of discharge, especially in the setting of optivolaemia, predicts a stable post-hospital course.

- If NP levels fail to decrease with appropriate and intensive therapy or remain elevated at the time of discharge, anticipate a poor prognosis. Consider more aggressive in-hospital treatment and careful post-discharge monitoring.

## 5. The use of NP levels in the intensive care unit

The diagnostic problems in the intensive care unit (ICU) are at least as challenging as in the ED. Major differences in patient characteristics, disease severity, co-morbidity, and therapies between the ICU and the ED require that the potential clinical use of NP levels in the ICU be defined by specific ICU studies.

Despite decades of clinical use of invasive haemodynamic measurements and echocardiographic examinations, we are just beginning to appreciate the syndrome of HF in the ICU. While NP levels seem to have high accuracy in the identification for cardiac dysfunction in the ICU, the rule-out levels may be higher, around >150 pg/ml in the case of BNP, to maintain specificity [71]. In a consecutive series of ICU patients, a BNP of <150 pg/ml had a negative predictive value of 97% for the presence of cardiac dysfunction. Because patients with cardiac pulmonary oedema have substantially higher NP levels than patients with the acute respiratory distress syndrome, NP levels are fairly accurate (AUC 0.8) in the differential diagnosis of cardiogenic versus non-cardiogenic pulmonary oedema [72].

NP levels are elevated not only in cardiogenic shock, but also in severe sepsis and septic shock. This is most likely due to sepsis-induced inflammatory myocardial dysfunction [73]. Furthermore, NP levels do not reliably predict pulmonary capillary wedge pressure in consecutive ICU patients, even less so in patients with shock [74,75]. Thus, NPs DO NOT seem to be useful diagnostically when the differential diagnosis includes shock of any type [75].

NP levels may assist in ventilator weaning. Plasma NP is higher in patients who fail a weaning trial as compared to those with successful weaning [76]. It may also identify patients in whom treatment should be intensified or changed for successful extubation. Finally NP levels provide powerful prognostic information regarding perioperative complication rates in patients undergoing cardiac or vascular surgery, and predict length of stay, morbidity, and mortality [77].

In conclusion, despite a clear clinical need, currently available data are insufficient to define precisely the role of NP levels in the clinical ICU routine. Diagnosis of respiratory failure and timing of extubation seem to be the most promising indications [78].

### 5.1. Practical points and recommendations

- NP levels identify cardiac dysfunction in the ICU but at higher rule-out values.
- NP levels may be useful in distinguishing between cardiogenic and non-cardiogenic pulmonary oedema.
- NP levels are elevated in severe sepsis, septic shock, and cardiogenic shock. Therefore, they are not useful in the differential diagnosis of shock. NP levels cannot reliably predict PCWP in those conditions.
- NP levels may be helpful in the timing of extubation.
- NP levels predict perioperative cardiac complications.

## 6. Monitoring NP levels post-hospitalisation: implications for NP-guided outpatient treatment

### 6.1. Variability and decompensation

Interpretation of NP levels requires an understanding of the variability of these peptides. When a change in a NP level is not accompanied by a change in clinical status, this might reflect biological variability or a change in cardiac or renal function that has not yet resulted in symptoms or signs. As a result of both analytical and biological variabilities (haemodynamic, renal, etc.), reference change values (RCV) have been reported to be large for both BNP and NT-proBNP, varying from 40–130% [79–81]. As these studies assumed that unchanged symptoms equalled unchanged cardiac status, considerable uncertainty remains regarding these estimates. As emphasized for all indications, incorporating the NP measurement into the overall clinical assessment is also very important in the outpatient setting. For patients in a heart failure programme who have NP levels measured when stable, an increase in NP of e.g. 50% over baseline values accompanied by appropriate symptoms and signs confirms a clinical diagnosis of decompensation.

It must also be considered that less than a 50% change in NP level may be within the range of biological variability in some patients, and not representative of a clinical event. In establishing whether a patient has worsening heart failure one needs to be aware of their optivolaemic NP level before interpreting a value in the setting of possible clinical deterioration. Although there is limited evidence-based data to support the impact of hospitalisation avoidance with NP levels, the consensus of authors suggest that one of the best ways to keep a person out of the hospital is not to let the discharge NP level rise. Early after discharge, elevations in NP levels are often associated with volume overload and diuretics may need adjustment.

The combination of symptoms, weight gain, and NP levels may be the best way to diagnose early decompensation. A proposed algorithm for detecting decompensation is illustrated in Fig. 5 (right-hand figure) for patients performing daily weight monitoring in a telemedicine programme. Please note that the cut-off values suggested are to a large extent not based on prospective studies, but on expert opinion on how to balance possible variability against prospective data indicating that changes in NP of as little as 25% do have prognostic importance. If weight is increased and either shortness of breath or oedema is present, an adjustment in medications (usually diuretics) is made over

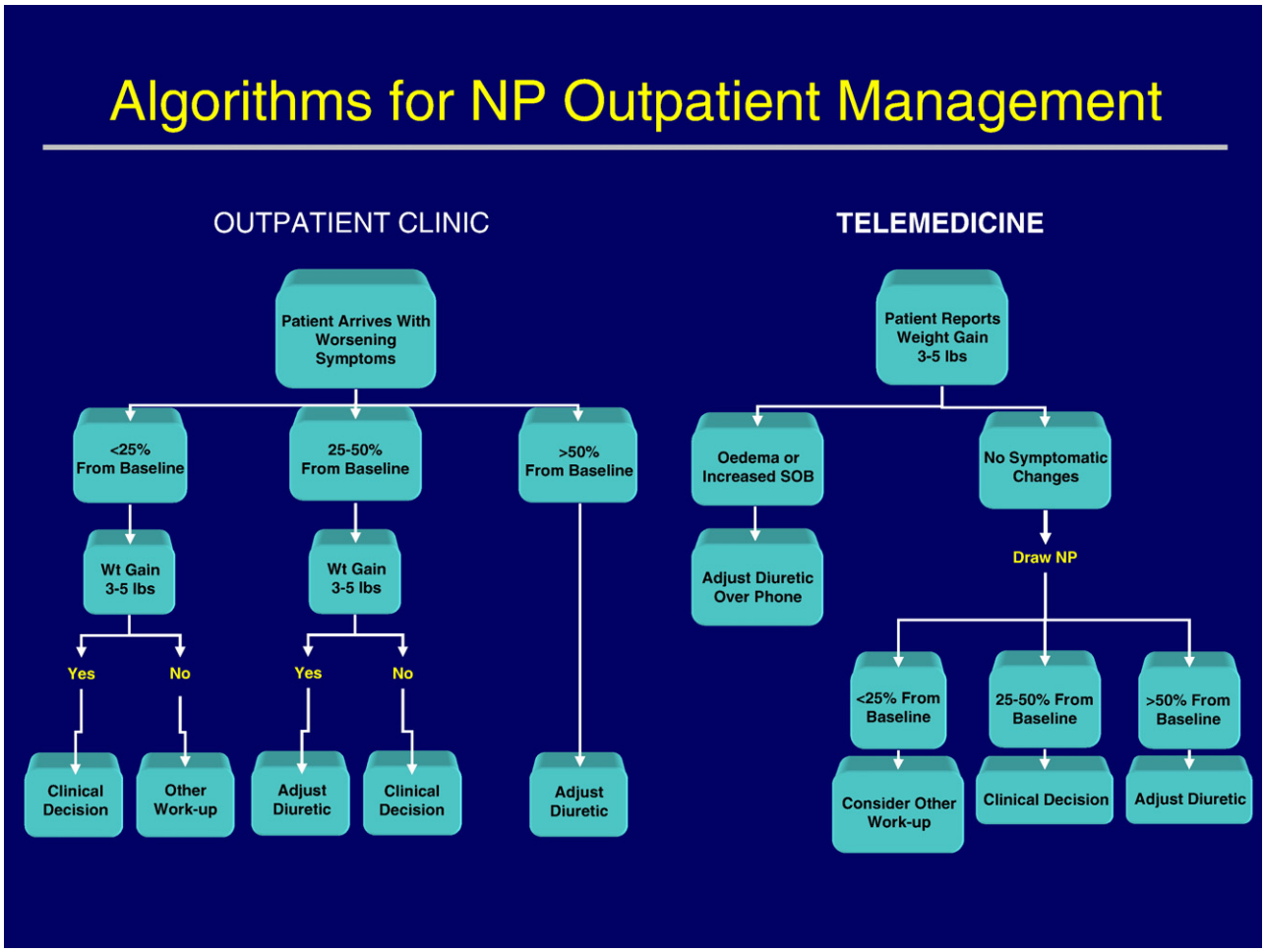


Fig. 5. Algorithms for outpatient management.

the telephone. If not present, a NP level is drawn in the lab or possibly in the near future, by finger-stick at home. In HF patients, a 50% increase over their optivolaemic baseline is considered significant and requires intervention. A 25–50% increase calls for continued clinical judgment and consideration of the biological variation of NPs. When the increase in NP level is negligible (<25%), other causes of weight gain are sought. A similar algorithm can be used in patients presenting to clinics with worsening symptoms of HF (Fig. 5, left-hand figure). As for inpatients, proper adjustment of HF management requires NP to be measured together with renal function.

### 6.2. Outpatient titration

The relationship between the drop in the NP level and the improvement in patient's symptoms and subsequent outcome suggests that NP-guided treatment might assist in adjusting chronic therapy. There are precedents for using surrogates to titrate treatment in conditions such as hypertension (measuring blood pressure), diabetes (glucose and haemoglobin A1c measurements), kidney disease (creatinine), and lipid disorders (lipid profile). But thus far there has been no effective surrogate for HF treatment that is reliable, objective, easy to use, and cost-effective. Since NP levels may reflect end-diastolic wall stress, which is elevated by both increased filling pressures and by LV dilation [82], measuring serial levels over time may provide a way, in conjunction with clinical acumen, to monitor the effects of drug therapy on LV remodelling [83].

In a pilot study of 69 patients with HF and systolic LV dysfunction randomised to receive therapy guided by NP levels or standard care, NP-guided treatment reduced total cardiovascular events and delayed time to first event [84]. Similarly, the STARS-BNP trial, a multicentre study under the auspices of the Heart Failure working group of the French Society of Cardiology conducted a randomised trial to assess the benefits of titration of therapy in an attempt to achieve BNP values of <100 pg/ml. They showed that this approach reduced the composite primary endpoint of HF deaths and HF hospitalisation [85] compared to guideline-directed therapy. The authors suggested that 300 pg/ml was a more attainable and still useful target BNP level to aim for, rather than 100 pg/ml. While we recommend that the best

outcomes may be obtained by driving the BNP to <100–300 pg/ml, this is based on extrapolation and the most appropriate way to achieve this goal remains under discussion as higher diuretic doses may lead to the possibility of worse outcomes as well. Furthermore, the precise ranges and time intervals of testing are still under intense investigation. Results of currently enrolling studies will help to define these parameters. Not all studies have demonstrated that changes in BNP levels are associated with improved outcomes. In a study by Miller et al. [86] 190 patients were followed for 2 years with serial BNP measures. The authors noted that an elevation of BNP from normal, at any time during the study, was associated with a poor outcome. However, once BNP was elevated, further changes (either increases or decreases) remained associated with the same risk of adverse events (hazard ratio, 5.09; $P<0.001$).

It is possible that NP-guided therapy is successful simply because it serves as a reminder to physicians to give evidence-based treatment; in the previously mentioned STARS-BNP trial many patients were not yet receiving appropriate doses of guideline-directed therapy. The relevance of these trials is generally limited by the selective enrolment of relatively young patients with systolic HF and little co-morbidity. Ongoing studies will provide further insights into the potential benefit of NP-guided therapy in older populations and in the elderly with diastolic HF [87].

It appears that ACE inhibitors, angiotensin receptor blockers, spironolactone, and perhaps long-term beta-blockers (in the short-term beta-blockers increase NP levels) drive NP levels down [8–93]. In the Valsartan Heart Failure Trial (Val-HeFT) and CARE-HF studies, changes in BNP over time induced by pharmacological or device therapy were shown to predict morbidity and mortality better than initial values [92,93]. From an economic perspective, there are currently insufficient data to determine whether regular assessment of NP levels is cost-effective for outpatient titration [90]. Finally an important analysis from the COMET trial demonstrated the prognostic importance of plasma NT-proBNP in chronic heart failure patients taking beta-blockers [94].

#### 6.2.1. Key findings

- NP levels are commonly reduced by treatment with diuretics, ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists and cardiac resynchronization therapy (CRT). Beta-blockers may increase NP levels in the first weeks and months after administration but after 6–12 months may cause NP levels to fall.
- Several small controlled trials using NP-guided therapy demonstrate a significant reduction in the primary combined endpoint of HF death and re-hospitalisation.
- Regular assessment of renal function is required to avoid deterioration in renal function when using this approach.

#### 6.2.2. Practical points and recommendations

- NP levels drawn early after discharge may confirm the adequacy of outpatient therapy. Increases in NP levels following hospital discharge may reflect inadequate therapy.
- There is considerable day-to-day variation in NP levels. A 50% increase in NP levels, compared to those taken when the patient was stable, suggests decompensation when appropriate symptoms and/or signs are present. An increase of 25–50% may represent decompensation but clinical judgment should be the deciding factor. An increase in NP level of <25% (or a decrease) may be the result of biological variation unrelated to a change in clinical status and suggests that decompensation has not occurred or may be reflective of early physiological changes. Ultimately clinical judgment must adjudicate these possibilities. The baseline sample should be drawn when the patient is clinically stable to permit interpretation in this manner.
- The combination of symptoms, weight gain, and NP levels may be the best way to predict early decompensation.
- Tailoring therapy to achieve a target BNP/NT-proBNP is a promising approach but further research is required.

### 6.3. Screening for sub-clinical disease

Many people with substantial LV dysfunction do not have symptoms [95–97] but might be identified by a simple screening test such as BNP/NT-proBNP. Although echocardiography is the current gold standard for detection of LV dysfunction and many other structural cardiac abnormalities, its cost and limited availability make it an impractical choice for mass screening. Also, the echocardiographic detection and quantification of LV diastolic dysfunction can be challenging in clinical practice.

The success of a population-based screening programme for a disease condition is dependent on disease prevalence, the availability of a screening test that is acceptable, safe and inexpensive, the presence of effective treatment for detected disease, as well as the existence of, and compliance with, a follow-up care system for people at risk or with positive tests [98,99]. NPs are attractive candidates for screening the general population for sub-clinical disease for several reasons. First, LV dysfunction and the other cardiovascular diseases that are detectable by elevated NP levels are common and cause significant morbidity and mortality [100]. Second, NP levels may be elevated early in the disease process, allowing for timely detection of disease prior to symptom onset [101]. Third, early treatment of latent disease with medications such as angiotensin converting enzyme inhibitors improves outcomes by preventing the development of symptomatic HF [102]. Finally, several studies have shown that, in the right setting, screening with NPs may prove cost-effective [103–105].

Several investigations have evaluated the use of NP levels to identify asymptomatic subjects with poor ventricular function. Most concluded that due to the relatively low prevalence of disease, the best potential

application for NPs is to utilize their high negative predictive value for "ruling out" disease [106–108]. Other studies looking to screen for a broader range of sub-clinical cardiovascular disorders also found excellent negative predictive value [109].

NPs may be useful for detecting a range of clinical disorders. In the Framingham Offspring Study of 3346 asymptomatic middle-aged subjects, Wang et al. found that BNP levels independently predicted mortality, heart failure, stroke or transient ischaemic attack, and atrial fibrillation, even after adjusting for traditional risk factors [110]. BNP levels above the 80th percentile (~20 pg/ml) carried a 62% increased risk of death and a 76% increased risk of a first major cardiovascular event. With each increment of one standard deviation in log BNP levels, there was a 27% increase in risk of death, a 77% increase in risk of HF, a 66% increase in the risk of atrial fibrillation, and a 53% increase in the risk of stroke or transient ischaemic attack. Thus, even small elevations of BNP levels (in the 20–100 pg/ml range), significantly less than traditional cut points for acutely dyspnoeic patients, may serve as an early warning sign, aiding in the timely detection of cardiovascular disease.

The main stumbling blocks to implement screening is the perceived cost and the lack of randomised studies showing that screening the population for asymptomatic left ventricular dysfunction (ASLVD) alters the natural history of the condition. It should be pointed that few screening strategies for other conditions have shown in a randomised trial that screening improves outcome.

#### 6.3.1. Practical points and recommendations

- NP testing might be appropriate for screening large asymptomatic populations for left ventricular systolic dysfunction either at low or high risk (post-MI patients, diabetic patients, poorly controlled hypertension, people aged >70 years) with echocardiographic assessment of patients with high levels.
- Optimal cut points for excluding HF in the office are BNP <20 pg/ml and NT-proBNP: 125 or 450 pg/ml for <75 and >75 years of age.

## 7. BNP in current guidelines

As with every new diagnostic or treatment modality, there is often a lag between the evidence and the integration into national and international guidelines. However, it is very encouraging to see that only a few years after introduction into clinical practice, all major cardiovascular guidelines recommend the use of NP levels in some context.

## 8. Directions for future research

While there have been significant strides in NP research over the past five years, there are still many important areas to explore. The following is a partial list of research needs with regards to NP levels.

### 8.1. Emergency department

- Define target values for NP levels for response to therapy in the ED.
- Randomised clinical trials (RCT) to evaluate safety and efficacy of NP-guided management regarding hospital admission versus ED management.
- Determine whether NP levels, used in a multimarker panel, may aid in the early diagnosis or rule out of ACS.
- Better define caveats for using NPs for the diagnosis/management of HF in the very elderly.
- Determine if the use of NPs in the pre-hospital arena by emergency medical technicians results in improved outcomes.

### 8.2. Diastolic function

- Use NP levels for patient inclusion in studies evaluating treatment of patients with diastolic dysfunction.
- Explore the combination of a NP level plus echocardiography as a potential gold standard for the diagnosis of diastolic dysfunction.
- Better define cut points for establishing severity of diastolic dysfunction.

### 8.3. Inpatient monitoring of NP levels

- Define target values for NP levels for response to therapy.
- Conduct RCT to evaluate safety and efficacy of NP-guided hospital management regarding treatment and discharge.
- Determine the value that NP levels can serve as a surrogate for dyspnoea in clinical trials.

### 8.4. Outpatient monitoring

- Determine the value of NPs for deciding on the strategy of care (i.e. persistent high NP leads to intensive specialist follow-up; low NP leads to more community physician and HF nurse follow-up).
- Conduct further RCTs to evaluate safety and efficacy of NP-guided therapy.
- Determine whether reduction in NP levels (absolute or percent reduction) or achieving a target level is the most appropriate treatment goal.
- Determine if patient-directed NP-guided treatment is feasible, cost-effective and results in improved outcomes (similar to glucose monitoring in diabetics).

### 8.5. Screening

- Conduct studies to demonstrate that screening-using NP improves patient outcome.

*8.6. Acute coronary syndromes*

- Use of NP to stratify risk and target high-risk patients needing aggressive intervention.

## 9. Conclusion

NP levels can help clinicians manage patients in a great variety of settings. They are helpful in screening to identify or exclude cardiovascular disease, for the differential diagnosis of symptoms that might be due to HF and are astonishingly powerful prognostic tools. Each assay gives different values for BNP and NT-proBNP and the clinician should become familiar with just one, at least initially. Plasma concentrations should be interpreted in the context of the clinical setting and in conjunction with a test of renal function. Serial measurement determines whether a patient's prognosis has changed in response to therapy but it is not yet clear whether and how this should be used to guide treatment.

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## References

[1] Maeda K, Tsutamoto T, Wada A, Hisanaga T, Kinoshita M. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. Am Heart J 1998;135:825–32.

[2] K. James, R. Troughton, J. Feldschuh, D. Soltis, D. Thomas, F. Fouad-Tarazi, Blood volume and brain natriuretic peptide in congestive heart failure: a pilot study. Am Heart J, 150:5, 984–986.)

[3] Nakagawa O, Ogawa Y, Itoh H, et al. Rapid transcriptional activation and early mRNA turnover of brain natriuretic peptide in cardiocyte hypertrophy. Evidence for brain natriuretic peptide as an "emergency" cardiac hormone against ventricular overload. J Clin Invest 1995;96:1280–7.

[4] Sudoh T, Minamino N, Kangawa K, Matsuo H. Brain natriuretic peptide-32: N-terminal six amino acid extended form of brain natriuretic peptide identified in porcine brain. Biochem Biophys Res Commun Sep 15 1988;155(2):726–32.

[5] Mukoyama M, Nakao K, Hosoda K, et al. Brain natriuretic peptide as a novel cardiac hormone in humans: evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. J Clin Invest 1991;87:1402–12.

[6] Davis M, Espiner E, Richards G, et al. Plasma brain natriuretic peptide in assessment of acute dyspnea. Lancet 1994;343:440–4.

[7] Yasue H, Yoshimura M, Sumida H, et al. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. Circulation 1994;90:195–203.

[8] Yoshimura M, Yasue H, Okumura K, et al. Different secretion patterns of atrial natriuretic peptide and brain natriuretic peptide in patients with congestive heart failure. Circulation 1993;87:464–9.
[9] Hunt, et al. Biochem Biophys Res Commun 1995;214:1175–83.
[10] Cowie MR, Struthers AD, Wood DA, et al. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. Lancet 1997;350:1349–53.
[11] McDonagh TA, Robb SD, Murdoch DR, et al. Biochemical detection of left-ventricular systolic dysfunction. Lancet Jan 3 1998;351 (9095):9–13.
[12] Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-natriuretic peptide (BNP) in the diagnosis of congestive heart failure in an urgent-care setting. J Am Coll Cardiol 2001;37:379–85.
[13] Cheng V, Kazanagra R, et al. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. J Am Coll Cardiol 2001;37(2):386–91.
[14] Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347:161–7.
[15] Lainchbury R, et al. jacc 2003;42:48–736.
[16] Mueller C, Scholer A, Laule-Kilian K, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. N Engl J Med 2004;350:647–54.
[17] Januzzi Jr JL, Camargo CA, Anwaruddin S, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol 2005;95:948–54.
[18] Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure (update 2005). Eur Heart J 2005;26:1115–41.
[19] Nieminen MS, Bshm M, Cowie MR, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure on the European Society of Cardiology. Eur Heart J Feb 2005;26(4):384–416.
[20] ACC/AHA collaborate on guidelines for the evaluation and management of heart failure. Am Fam Phys May 1 1996;53(6):2196–8.
[21] Krumholz HM, Wang Y, Parent EM, et al. Quality of care for elderly patients hospitalized with heart failure. Arch Intern Med 1997;27 (157):2242–7 (19).
[22] McCullough PA, Duc P, Omland T, et al. B-type natriuretic peptide and renal function in the diagnosis of heart failure — an analysis from breathing not properly (BNP) multinational study. Am J Kidney Dis March) 2003;41(3):571–9.
[23] McDonagh TA, Holmer S, Raymond I, Luchner A, Hildebrant P, Dargie HJ. NT-proBNP and the diagnosis of heart failure: a pooled analysis of three European epidemiological studies. Eur J Heart Fail 2004;6(3):269–73.
[24] Maisel A, Hollander JE, et al. Primary results of the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT). A multicenter study of B-type natriuretic peptide levels, emergency department decision making, and outcomes in patients presenting with shortness of breath. J Am Coll Cardiol 2004;44(6):1328–33.
[25] Fonarow GC, Heywood JT, Heidenreich PA, Lopatin M, Yancy CW, ADHERE Scientific Advisory Committee and Investigators. Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. J Am Coll Cardiol May 15 2007;49(19): 1943–50 Electronic publication ahead of print 2007 Apr 30.
[26] Mueller C, Laule-Kilian K, Schindler C, et al. Cost-effectiveness of B-type natriuretic peptide testing in patients with acute dyspnea. Archives of Internal Medicine 2006;166:1081–7.
[27] Moe GW, Howlett J, Januzzi JL, Zowall H. N-terminal pro-B-type natriuretic peptide testing improves the management of patients with suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. Circulation 2007;115:3103–10.
[28] Brenden CK, Hollander JE, Guss D, et al. Gray zone BNP levels in heart failure patients in the emergency department: results from the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT) multicenter study. Am Heart J May 2006;151(5): 1006–11.
[29] Shelton RJ, Clark AL, Goode K, Rigby AS, Cleland JG. The diagnostic utility of N-terminal pro-B-type natriuretic peptide for the detection of major structural heart disease in patients with atrial fibrillation. Eur Heart J Oct 2006;27(19):2353–61 Electronic publication ahead of print 2006 Sep 4.
[30] van Kimmenade RR, Pinto YM, Bayes-Genis A, Lainchbury JG, Richards AM, Januzzi Jr JL. Usefulness of intermediate amino-terminal pro-brain natriuretic peptide concentrations for diagnosis and prognosis of acute heart failure. Am J Cardiol Aug 1 2006;98(3):386–90.
[31] Bando M, Ishii Y, Sugiyama Y, Kitamura S. Elevated plasma brain natriuretic peptide levels in chronic respiratory failure with cor pulmonale. Respir Med 1999;93:507–14.
[32] Nagaya N, Nishikimi T, Okano Y, et al. Plasma brain natriuretic peptide levels increase in proportion to the extent of right ventricular dysfunction in pulmonary hypertension. J Am Coll Cardiol 1998;31:202–8.
[33] Nagaya N, Nishikimi T, Uematsu M, et al. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. Circulation 2000;102:865–70.
[34] Leuchte HH, Holzapfel M, Baumgartner RA, et al. Clinical significance of brain natriuretic peptide in primary pulmonary hypertension. J Am Coll Cardiol 2004;43:764–70.
[35] Morrison LK, Harrison A, Krishnaswamy P, Kazanegra R, Clopton P, Maisel A. Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. J Am Coll Cardiol 2002;39:202–9.
[36] McCullough PA, Hollander JE, Nowak RM, et al. Uncovering heart failure in patients with a history of pulmonary disease: rationale for the early use of B-type natriuretic peptide in the emergency department. Acad Emerg Med 2003;10:198–204.
[37] Mueller C, Laule-Kilian K, Frana B, et al. The use of B-type natriuretic peptide in the management of acute dyspnea in patients with pulmonary disease. Am Heart J 2006;151:471–7.
[38] Kucher N, Printzen G, Goldhaber SZ. Prognostic role of brain natriuretic peptide in acute pulmonary embolism. Circulation 2003;107:2545–7.
[39] Dries DL, et al. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol 2000;35(3):681–9.
[40] Fonarow GC. The Acute Decompensated Heart Failure National Registry (ADHERE):opportunities to improve care of patients hospitalized with acute decompensated heart failure. Rev Cardiovasc Med 2003;4(Suppl 7):S21–30.
[41] McCullough PA, Sandberg KR. B-type natriuretic peptide and renal disease. Heart Fail Rev 2003;8:355–8.
[42] McCullough PA, Duc P, Omland T, et al. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. Am J Kidney Dis 2003;41:571–9.
[43] Hogenhuis J, Voors AA, Jaarsma T, et al. Anaemia and renal dysfunction are independently associated with BNP and NT-proBNP levels in patients with heart failure. Eur J Heart Fail 2007;9(8): 787–94.
[44] Wang TJ, Larson MG, Levy D, et al. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. Am J Cardiol 2002;90:254–8.
[45] Mehra MR, Uber PA, Park MH, et al. Obesity and suppressed B-type natriuretic peptide levels in heart failure. J Am Coll Cardiol 2004;43:1590–5.
[46] Wang TJ, Larson MG, Levy D, et al. Impact of obesity on plasma natriuretic peptide levels. Circulation 2004;109:594–600.
[47] Daniels LB, Clopton P, Bhalla V, et al. How obesity affects the cut-points for B-type natriuretic peptide in the diagnosis of acute heart failure. Results from the Breathing Not Properly Multinational Study. Am Heart J 2006;151:1006–12.

[48] Sarzani R, Dessi-Fulgheri P, Paci VM, Espinosa E, Rappelli A. Expression of natriuretic peptide receptors in human adipose and other tissues. J Endocrinol Invest 1996;19:581–5.
[49] Dessi-Fulgheri P, Sarzani R, Rappelli A. The natriuretic peptide system in obesity-related hypertension: new pathophysiological aspects. J Nephrol 1998;11:296–9.
[50] Horwich TB, Hamilton MA, Fonarow GC. B-type natriuretic peptide levels in obese patients with advanced heart failure. J Am Coll Cardiol 2006;47:85–90.
[51] Bayes-Genis A, Lloyd-Jones DM, van Kimmenade RR, et al. Effect of body mass index on diagnostic and prognostic usefulness of amino-terminal pro-brain natriuretic peptide in patients with acute dyspnea. Arch Intern Med 2007;167:400–7.
[52] Maisel AS, McCord J, Nowak RM, et al. Bedside B-type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. Results from the Breathing Not Properly Multinational Study. J Amer Coll Cardiol Jun 4 2003;41(11):2010–7.
[53] Cleland JG, Taylor J, Tendera M. Prognosis in heart failure with a normal ejection fraction. N Engl J Med Aug 23 2007;357(8):829–30.
[54] Leya FS, Arab D, Joyal D, et al. The efficacy of brain natriuretic peptide levels in differentiating constrictive pericarditis from restrictive cardiomyopathy. J Am Coll Cardiol 2005;45:1900–2.
[55] Babuin L, Alegria JR, Oh JK, Nishimura RA, Jaffe AS. Brain natriuretic peptide levels in constrictive pericarditis and restrictive cardiomyopathy. J Am Coll Cardiol 2006;47:1489–91.
[56] Yoshimura M, Yasue H, Okumura K, et al. Different secretion patterns of atrial natriuretic peptide and brain natriuretic peptide in patients with congestive heart failure. Circulation 1993;87:464–9.
[57] Fonarow G. How well are chronic heart failure patients being managed? Rev Cardiovasc Med 2006;7(Suppl 1):S3–S11.
[58] Fonarow GC, Stough WG, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol 2007.
[59] Dokainish H, Zoghbi WA, Lakkis NM, et al. Optimal noninvasive assessment of left ventricular filling pressures: a comparison of tissue Doppler echocardiography and B-type natriuretic peptide in patients with pulmonary artery catheters. Circulation 2004;109:2432–9.
[60] J. O'Neill, C. Bott-Silverman, A. McRae, et al., B-type natriuretic peptide levels are not a surrogate marker for invasive hemodynamics during management of patients with severe heart failure. Am Heart J, 149:2, 363–369.
[61] M. Shah, V. Hasselblad, G. Tasissa, et al., Rapid assay brain natriuretic peptide and troponin I in patients hospitalized with decompensated heart failure (from the evaluation study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness Trial). Am J Cardiol, 100:9, 1427–1433.
[62] Kazanegra R, Cheng V, Garcia A, et al. A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study. J Card Fail 2001;7:21–9.
[63] Chen HH. Heart failure: a state of brain natriuretic peptide deficiency or resistance or both! J Am Coll Cardiol 2007;49:1089–91.
[64] Shimizu H, Masuta K, Aono K, et al. Molecular forms of human brain natriuretic peptide in plasma. Clin Chim Acta 2002;316:129–35.
[65] Lam CS, Burnett Jr JC, Costello-Boerrigter L, Rodeheffer RJ, Redfield MM. Alternate circulating pro-B-type natriuretic peptide and B-type natriuretic peptide forms in the general population. J Am Coll Cardiol 2007;49:1193–202.
[66] Dokainish H, Zoghbi WA, Lakkis NM, et al. Incremental predictive power of B-type natriuretic peptide and tissue Doppler echocardiography in the prognosis of patients with congestive heart failure. J Am Coll Cardiol 2005;45:1223–6.
[67] Logeart D, Saudubray C, Beyne P, et al. Comparative value of Doppler echocardiography and B-type natriuretic peptide assay in the etiologic diagnosis of acute dyspnea. J Am Coll Cardiol 2002;40:1794–800.
[68] Mebazaa A, Nieminen MS, Packer M, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. JAMA 2007;297:1883–91.
[69] M. Costanzo, M. Guglin, M. Saltzberg et al., Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. JACC, 49:6, 675–683.
[70] Cowie MR, Jourdain P, Maisel A, et al. Clinical applications of B-type natriuretic peptide (BNP) testing. Eur Heart J Oct 2003;24(19): 1710–8.
[71] McLean AS, Tang B, Nalos M, Huang SJ, Stewart DE. Increased B-type natriuretic peptide (BNP) level is a strong predictor for cardiac dysfunction in intensive care unit patients. Anaesth Intensive Care 2003;31:21–7.
[72] Karmpaliotis D, Kirtane AJ, Ruisi CP, et al. Diagnostic and prognostic utility of brain natriuretic peptide in subjects admitted to the ICU with hypoxic respiratory failure due to noncardiogenic and cardiogenic pulmonary edema. Chest 2007;131:964–71.
[73] Charpentier J, luyt CE, Fulla Y, et al. Brain natriuretic peptide: a marker of myocardial dysfunction and prognosis during severe sepsis. Crit Care Med 2004;32:660–5.
[74] Forfia PR, Watkins SP, Rame JE, Stewart KJ, Shapiro EP. Relationship between B-type natriuretic peptides and pulmonary capillary wedge pressure in the intensive care unit. J Am Coll Cardiol 2005;45:1667–71.
[75] Tung RH, Garcia C, Morss Am, et al. Utility of B-type natriuretic peptide for the evaluation of intensive care unit shock. Crit Care Med 2004;32:1643–7.
[76] Mekontso-Dessap A, de Prost N, Girou E, et al. B-type natriuretic peptide and weaning from mechanical ventilation. Intensive Care Med 2006;32:1529–36.
[77] Hutfless R, Kazanegra R, Madani M, et al. Utility of B-type natriuretic peptide in predicting postoperative complications and outcomes in patients undergoing heart surgery. J Am Coll Cardiol 2004;43:1873–9.
[78] Phua J, Lim TK, Lee KH. B-type natriuretic peptide: issues for the intensivist and pulmonologist. Crit Care Med 2005;33:2094–103.
[79] O'Hanlon R, O'Shea P, Ledwidge M, et al. The biologic variability of B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide in stable heart failure patients. J Card Fail Feb 2007;13(1): 50–5 Review. Erratum in: J Card Fail. 2007.
[80] Bruins S, Fokkema MR, Römer JW, Dejongste MJ, van der Dijs FP, van den Ouweland JM. Muskiet FA High intraindividual variation of B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with stable chronic heart failure. Clin Chen Nov 2004;50(11): 2052–8 Electronic publication ahead of print 2004 Sep 2.
[81] Wu AH. Serial testing of B-type natriuretic peptide and NTpro-BNP for monitoring therapy of heart failure: the role of biologic variation in the interpretation of results. Am Heart J Nov 2006;152(5):828–34.
[82] Iwanaga Y, Nishi I, Furuichi S, et al. B-type natriuretic peptide strongly reflects diastolic wall stress in patients with chronic heart failure: comparison between systolic and diastolic heart failure. J Am Coll Cardiol 2006;47:742–8.
[83] Nohria A, Givertz MM. B-type natriuretic peptide and the stressed heart. J Am Coll Cardiol 2006;47:749–51.
[84] Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Lancet 2000;355:1126–30.
[85] Jourdain P, Jondeau G, Funck F, et al. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. J Am Coll Cardiol 2007;49:1733–9.
[86] Miller WL, Hartman KA, Burritt MF, et al. Serial biomarker measurements in ambulatory patients with chronic heart failure. The importance of change over time. Circ 2007;116:249–57.
[87] Lainchbury JG, Troughton RW, Frampton CM, et al. NTproBNP-guided drug treatment for chronic heart failure: design and methods in the "BATTLESCARRED" trial. Eur J Heart Fail 2006;8(5):532–8.

[88] Benedict CR, Francis GS, Shelton B, et al. Effect of long-term enalapril therapy on neurohormones in patients with left ventricular dysfunction. Am J Cardiol 1995;75:1151–7.
[89] Yoshimura M, Mizuno Y, Nakayama M, et al. B-type natriuretic peptide as a marker of the effects of enalapril in patients with heart failure. Am J Med 2002;112:716–20.
[90] Richards A, Doughty R, Nicholls M. Neurohumoral prediction of benefit from carvedilol in ischaemic left ventricular dysfunction. Circulation 1999;99:786–92.
[91] Tsutamoto, Wada A, Maeda K, et al. Effect of spironolactone on plasma brain natriuretic peptide in patients with congestive heart failure. J Am Coll Cardiol 2001;37:1228–33.
[92] Anand IS, Fisher LD, et al. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). Circulation 2003;107(9):1278–83.
[93] Fruhwald FM, Fahrleitner-Pammer A, Berger R, et al. Early and sustained effects of cardiac resynchronization therapy on N-terminal pro-B-type natriuretic peptide in patients with moderate to severe heart failure and cardiac dyssynchrony. Eur Heart J Jul 2007;28(13): 1592–7 Electronic publication ahead of print 2007 Feb 13.
[94] Olsson LG, Swedberg K, Cleland JG, et al. Prognostic importance of plasma NT-pro BNP in chronic heart failure in patients treated with a beta-blocker: results from the Carvedilol Or Metoprolol European Trial (COMET) trial. Eur J Heart Fail 2007;9(8):795–801.
[95] Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett Jr JC. Plasma brain natriuretic peptide concentration: impact of age and gender. J Am Coll Cardiol 2002;40:976–82.
[96] Wang TJ, Larson MG, Levy D, et al. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. Am J Cardiol 2002;90:254–8.
[97] McDonagh TA, Morrison CE, Lawrence A, et al. Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population. Lancet 1997;350:829–33.
[98] Redfield MM, Jacobsen SJ, Burnett Jr JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194–202.
[99] Daniels LB, Maisel A. B-type natriuretic peptide: time to incorporate natriuretic peptides in our practice. J Cardiovasc Med (Hagerstown) 2006;7:414–5.
[100] Vasan RS, Benjamin EJ, Larson MG, et al. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham heart study. JAMA 2002;288:1252–9.
[101] Vanderheyden M, Goethals M, Verstreken S, et al. Wall stress modulates brain natriuretic peptide production in pressure overload cardiomyopathy. J Am Coll Cardiol 2004;44:2349–54.
[102] SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685–91.
[103] Nakamura M, Endo H, Nasu M, Arakawa N, Segawa T, Hiramori K. Value of plasma B type natriuretic peptide measurement for heart disease screening in a Japanese population. Heart 2002;87:131–5.
[104] Nielsen OW, McDonagh TA, Robb SD, Dargie HJ. Retrospective analysis of the cost-effectiveness of using plasma brain natriuretic peptide in screening for left ventricular systolic dysfunction in the general population. J Am Coll Cardiol 2003;41:113–20.
[105] Heidenreich PA, Gubens MA, Fonarow GC, Konstam MA, Stevenson LW, Shekelle PG. Cost-effectiveness of screening with B-type natriuretic peptide to identify patients with reduced left ventricular ejection fraction. J Am Coll Cardiol 2004;43:1019–26.
[106] McDonagh TA, Robb SD, Murdoch DR, et al. Biochemical detection of left-ventricular systolic dysfunction. Lancet 1998;351:9–13.
[107] Luchner A, Burnett Jr JC, Jougasaki M, et al. Evaluation of brain natriuretic peptide as marker of left ventricular dysfunction and hypertrophy in the population. J Hypertens 2000;18:1121–8.
[108] Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett Jr JC. Plasma brain natriuretic peptide to detect preclinical ventricular systolic or diastolic dysfunction: a community-based study. Circulation 2004;109:3176–81.
[109] Nakamura M, Endo H, Nasu M, Arakawa N, Segawa T, Hiramori K. Value of plasma B type natriuretic peptide measurement for heart disease screening in a Japanese population. Heart 2002;87:131–5.
[110] Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 2004;350:655–63.