

Natriuretic Peptides in Chronic Heart Failure

Hans-Peter Brunner-La Rocca and Sandra Sanders-van Wijk

Department of Cardiology, Maastricht University Medical Center, Maastricht, the Netherlands

Abstract

Normal brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) levels are helpful in excluding chronic heart failure in the ambulatory setting, although they have been studied less well and possibly less accurately than in acute care. They may also be of help in screening patients at risk to intervene and reduce the development of heart failure. Natriuretic peptides are also excellent prognostic markers of chronic heart failure, but the clinical value of such prognostic information is less clear. One possible application for this information is guiding medical therapy in chronic heart failure. Many studies have investigated this approach, but results are mixed and do not clearly show improvement in outcome. Still, it may be that in patients with reduced ejection fraction and few comorbidities, measuring NT-proBNP to uptitrate medication improves prognosis.

Keywords

Natriuretic peptides, chronic heart failure, therapy guidance, prognosis, diagnosis, BNP, NT-proBNP

Disclosure: Both authors receive unrestricted research grants from Roche Diagnostics.

Received: 31 July 2018 **Accepted:** 4 January 2019 **Citation:** *Cardiac Failure Review* 2019;5(1):44–9. **DOI:** <https://doi.org/10.15420/cfr.2018.26.1>

Correspondence: HP Brunner-La Rocca, Department of Cardiology, Maastricht University Medical Center, PO Box 5800, 6202 AZ Maastricht, the Netherlands. E: hp.brunnerlarocca@mumc.nl

Open Access: This work is open access under the CC-BY-NC 4.0 License which allows users to copy, redistribute and make derivative works for non-commercial purposes, provided the original work is cited correctly.

Natriuretic peptides (NPs) are well established in the diagnostic process of heart failure (HF). Low levels of NPs are particularly useful to exclude heart failure (HF). Numerous studies, predominantly in patients presenting with acute onset of symptoms suspected of HF, have convincingly shown the value of NPs in this regard. A meta-analysis published in 2015 clearly summarised the value of brain (B-type) NP (BNP), N-terminal proBNP (NT-proBNP) and mid-regional pro-atrial NP (MR-proANP) in the acute setting, uniformly showing a very high negative predictive value when using low cut-off levels (i.e. BNP <100 pg/ml; NT-proBNP <300 pg/ml, MR-proANP <120 pmol/l).¹

These cut-off values, recommended by the European Society of Cardiology (ESC) guidelines, have an excellent ability to exclude acute HF, missing only a few cases. They help to distinguish HF from non-cardiac causes of dyspnoea.^{2,3} However, the specificity is modest and variable, indicating that confirmatory diagnostic testing by cardiac imaging is required if the result is positive. In addition, the negative predictive value varies quite significantly between studies if higher cut-off values are used.¹

For patients in the outpatient setting not presenting with acute symptoms, the recommended cut-off values are lower, at 35 pg/ml for BNP and 125 pg/ml for NT-proBNP.² Levels above these values are also required as part of the diagnosis of patients with HF and preserved ejection fraction (HFpEF; LVEF ≥50%) or mildly reduced (mid-range; HFmrEF; LVEF 40–49%) left-ventricular ejection fraction (LVEF).² No recommendation is given for MR-proANP as no larger studies in the outpatient setting have been published.

Outpatient cut-off values are less investigated than cut-off values in the acute setting, particularly with respect to BNP. The best cut-off values found in these studies are not as uniform as various guidelines may recommend; only some are in this range, with many of them being higher and more in the range of the values recommended in the acute setting, as well as some being lower.^{4–9}

In addition, the negative predictive value may be less than it is in the acute setting, which possibly relates to diagnostic accuracy reducing with increasing age (i.e. c-statistics decreasing from 0.95 in patients aged <50 years to 0.82 in patients aged >75 years), as shown in a meta-analysis including >5,500 patients from 10 studies to test the diagnostic value of NT-proBNP to detect LVEF≤40%.¹⁰ These authors suggested using an age-specific cut-off value to rule out HF in primary care settings, which would be lower than recommendations in the current US and ESC guidelines for young (<50 years, cut-off value 50 pg/ml) and middle-aged people (50–75 years, 75 pg/ml), but higher for elderly patients (>75 years, 250 pg/ml).¹⁰ Still, this analysis has not been considered by the guidelines and the suggested cut-off values differ between European, US and UK guidelines.^{2,11,12}

While the majority of these studies did not distinguish between HF with reduced ejection fraction (HFrEF; LVEF <40%) and HFpEF, some studies focused on diastolic dysfunction only.¹³ Although NP levels are lower in HFpEF in general, the established thresholds for diagnosing acute HF remain useful in patients with preserved ejection fraction, with only minor loss of diagnostic performance (NPV 90% at a BNP of 100 pg/ml).¹⁴ The distinction may be less relevant in the acute setting, where therapy is largely similar regardless of LVEF. In chronic

HF however, treatment of chronic HF_rEF is well defined, in contrast to that for HF_pEF.² In addition and especially in the elderly, NPs have a much poorer diagnostic performance for HF_pEF.¹⁵

Another study showed the added value of NT-proBNP in diagnosing HF, with increasing levels being added to a score including nine clinical features (age, coronary artery disease, loop diuretics use, pulse rate and regularity, displaced apex beat, rales, heart murmur and elevated jugular vein pressure) to diagnose HF.¹⁶ This score had high c-statistics of 0.86 in the derivation set and higher c-statistics of 0.88 and 0.95 in two external validation sets.¹⁶ The problems with such a score are that it is not easily applicable in clinics and there is a significant zone of uncertainty.

A recent meta-analysis investigated cut-off values using point-of-care devices in both the acute and ambulatory outpatient settings.¹⁷ This analysis may provide the currently most accurate overview of the diagnostic accuracy of NPs in the ambulatory setting. Data from primary care were scarce and ranges of cut-off values varied widely, particularly for BNP. The ESC recommended cut-off level for the non-acute setting (35 pg/ml) was not used in any of the included studies, whereas the value for NT-proBNP (125 pg/ml) was used in four studies.¹⁷ However, results depend on the patient population included and may vary, depending on the prevalence of HF. Additional studies are needed to identify the best cut-off values in the non-acute setting to diagnose HF. In addition, many factors independent of HF may influence NP levels (*Table 1*).

Although there is an obvious overlap of the cardiac causes and HF itself, interpretation of NP levels in individual patients must be done against the background of additional factors influencing these values. For example, in a young patient with no comorbidities, expected NP levels are very low, whereas in elderly patients with reduced renal function and atrial fibrillation levels clearly above the cut-off value are common even in the absence of HF.

Recent data support the application of different thresholds of NT-proBNP for the diagnosis of HF_pEF in patients with AF versus those in sinus rhythm.¹⁸ Importantly, obese patients with HF can have normal values of NPs, even if they are volume overloaded; the Breathing-Not-Propriety study found that the best cut-off value in severely obese subjects is much lower than in lean patients.¹⁹ However, prospective validation of these types of individualised cut-offs is lacking and so is not yet supported by HF guidelines.

Measurement of NPs may also help as screening tool in primary care to stratify patients and reduce risk. The Irish Screening To Prevent Heart Failure (STOP-HF) study randomised patients at risk for developing HF into either usual care or additional measurement of BNP levels.²⁰ If BNP was 50 pg/ml or higher, patients were referred for echocardiography. This resulted in more cardiovascular investigations and more treatment, but less HF and left ventricular dysfunction.²⁰ The measurement of BNP in this setting was likely to be cost effective.²¹ Although these results are promising, confirmation in other populations and healthcare systems is still absent.

The finding that intensifying medical therapy may result in less chronic HF in high-risk patients with elevated NP levels is supported by the Austrian NT-proBNP Selected PreventiOn of cardiac eveNts in a populaTiOn of diabetic patients without A history of Cardiac disease

Table 1: Factors Influencing Natriuretic Peptide Levels Independent of Heart Failure

| Increase in natriuretic peptides |
|--|
| <p><i>Cardiac</i></p> <ul style="list-style-type: none"> • Acute coronary syndromes • Atrial fibrillation • Valvular heart disease • Cardiomyopathies • Myocarditis • Cardioversion • Left ventricular hypertrophy |
| <p><i>Noncardiac</i></p> <ul style="list-style-type: none"> • Age • Female gender • Renal impairment • Pulmonary embolism • Systemic bacterial infections (e.g. pneumonia, sepsis) • Obstructive sleep apnea • Critical illness • Severe burns • Cancer chemotherapy • Toxic and metabolic insults |
| Decrease in natriuretic peptides |
| <ul style="list-style-type: none"> • Obesity |

(PONTIAC) trial in people with diabetes with NTproBNP levels >125 pg/ml but free from any cardiac diseases.²² MR-proANP has not been studied in this regard but was shown to stratify risk for the development of cardiovascular mortality and incident HF in patients with coronary artery disease. In addition, only patients with at least two of three biomarkers elevated – MR-proANP, MR-proADM and CT-proET-1 – showed an improvement in outcome with ACE-inhibition.²³ Obviously, this is no proof that interventions based on MR-proANP levels would result in better outcome, which needs to be prospectively investigated.

Taken together, BNP and NT-proBNP levels are diagnostically useful not only in the acute setting but also in the diagnostic process of chronic HF and possibly in the identification of patients at risk of developing HF. Still, more research is needed in the ambulatory setting. Therefore, cut-off values to exclude HF are not yet clearly defined and their diagnostic value might be less than in the acute setting. In addition, the value of MR-proANP has not yet been tested in this setting. Confirmatory studies are required to define the role of NPs in identifying patients at risk who need advance diagnostics and more aggressive medical therapy.

Prognostic Value of Natriuretic Peptides in Chronic Heart Failure

Without doubt, NPs are strong prognostic markers in patients with chronic HF. This is true for all NPs for which tests are commercially available. However, although NPs may be considered as the most robust prognostic markers in chronic HF, individual studies indicate some variety, showing some other biomarkers having a better prognostic value. Despite this, no single biomarker is clearly prognostically superior to NPs. In many instances, other biomarkers representing different pathophysiological pathways provide additional prognostic information to NPs.²⁴ A 2005 systematic review showed the prognostic value of BNP, including identifying changes over time, in a large number of studies and this number has increased considerably since then.²⁵ It is beyond the scope of this review to discuss these studies and recent reviews discussing the prognostic value of NPs in detail.^{26,27}

Table 2: Some Criteria of Natriuretic Peptide Guided Trials Including Patients with Heart Failure with Reduced Ejection Fraction

| | Troughton et al. ³³ | Beck-da-Silva et al. ³⁴ | STARS-BNP ³⁵ | TIME-CHF ³⁶ | BATTLE-SCARRED ³⁹ | PRIMA ³⁸ | SIGNAL-HF ⁴⁰ | Berger et al. ³⁷ | UPSTEP ⁴² | STARBRITE ⁴³ | PROTECT ⁴¹ | GUIDE-IT ²⁹ |
|--------------------------------|--------------------------------|------------------------------------|-------------------------|---------------------------------|------------------------------|-----------------------------|--------------------------------|-----------------------------|----------------------|-----------------------------|-----------------------|------------------------|
| n | 69 | 41 | 220 | 499 (622) | 134 (364) | 229 (345) | 252 | 177 (278) | 279 | 137 | 151 | 894 |
| Blinded | No | No | No | Single | Double | Single | Single | No | Single | Single | No | No |
| Marker | NT-proBNP | BNP | BNP | NT-proBNP | NT-proBNP | NT-proBNP | NT-proBNP | NT-proBNP | BNP | BNP | NT-proBNP | NT-proBNP |
| Target (pg/ml) | 1,692 | Not stated | 100 | 400/800 | 1,270 | Discharge | 50% reduction | 2,200 | 150/300 | Discharge | 1,000 | 1,000 |
| Control | HF score | HF spec | Usual care | ≤ NYHA class II | Two groups | Usual care | HF spec | Two groups | Usual care | HF spec | Usual care | HF spec |
| Primary endpoint | Death, CV hosp HF | Mean beta-blocker dose achieved | HF death, hosp | Death, all-cause hosp mortality | All-cause mortality | Days alive outside hospital | Days alive outside CV hospital | HF hosp, death | Death, HF hosp/worse | Days alive outside hospital | CV events | CV death, HF hosp |
| Age (mean) | 70 | 65 | 66 | 77 | 76 | 72 | 77 | 71 | 71 | 61 | 63 | 63 |
| NT-BNP/BNP at baseline (pg/ml) | 1,981 | ~600 | 350 | 4,328 | 2,008 | 2,940 | ~2,500 | ~2,350 | 851 | 450 | 2,118 | 2,650 |
| Study duration | 12 months | 90 days | 450 days | 18 months | 3 years | 2 years | 9 months | 18 months | At least 1 year | 90 days | 1 year | 24 months |

The total number of patients included if different is shown in parentheses; differences concern patients with heart failure with preserved ejection fraction or undetermined left ventricular ejection fraction, or two control groups. BNP = B-type natriuretic peptide; CV = cardiovascular; HF = heart failure; HF spec = heart failure specialists; hosp = hospitalisation; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Table 3: Medication Intensification

| | Troughton et al. ³³ | Beck-da-Silva et al. ³⁴ | STARS-BNP ³⁵ | TIME-CHF ³⁶ | BATTLE-SCARRED ³⁹ | PRIMA ³⁸ | SIGNAL-HF ⁴⁰ | Berger et al. ³⁷ | UPSTEP ⁴² | STARBRITE ⁴³ | PROTECT ⁴¹ | GUIDE-IT ²⁹ |
|---------------------|--------------------------------|------------------------------------|-------------------------|------------------------|------------------------------|---------------------|-------------------------|-----------------------------|----------------------|-------------------------|-----------------------|------------------------|
| ACE/ARB | 100% | 100% | 99% | 95% | 82% | 79% | ~90% | 89% | 98% | 86% | 81% | 77% |
| Beta-blocker | 8% | 100% | 98% | 79% | 68% | 77% | 97% | 77% | 94% | ? | 96% | 93% |
| Diuretics | 100% | ? | 100% | 93% | 95% | 96% | 68% | 81% | 90% | 94% | 91% | 49% |
| ACE/ARB ↑ | Yes | ? | Yes | Yes | Yes | (Yes) | (Yes) | Yes | No/Yes | Yes | Yes | No |
| Beta-blocker ↑ | No | No | Yes | Yes | Yes | No | No | Yes | No | Yes | Yes | No |
| Spironolac ↑ | Yes | ? | Yes | Yes | No | No | No | No | No | No | Yes | No |
| Diuretics ↑ | No | ? | No | No | Yes | Yes | No | Decrease | No | No | Decrease | No |
| More adverse events | No | No | No | No | No | No | No | NR | No | No | Trend | No |
| Primary endpoint | Positive | Negative | Positive | Negative | Negative | Negative | Negative | Positive | Negative | Negative | Positive | Negative |
| Mortality | p=0.06 | 2/4 | 7/11, ns | p=0.06 | Identical | p=0.21 | Identical | Identical | Identical | 1/3 | Identical | p=0.37 |

Rows 1–3 show medication at baseline. Rows 4–7 show medication intensification in the natriuretic peptide guided groups as compared to the control group. Rows 8–9 show if more adverse events were present, the primary endpoint was reached and if mortality was changed. ACE = angiotensin-converting-enzyme-inhibitor; ARB = angiotensin receptor blocker; NR = not reported. Mortality: p-value if positive trend; numbers indicate number of deaths in natriuretic peptide group and control group.

More important are the clinical consequences of knowing the prognosis of an individual patient. Guidelines recommend risk assessment by using risk scores to inform management decisions on advanced therapy such as ventricular assist devices and cardiac transplantation, despite no studies showing the clinical value of this recommendation. One may argue that patients at high risk should be monitored more closely. To the best of the authors' knowledge, it has not yet been investigated whether basing frequency of consultations on prognostic markers results in better outcomes and if such an approach would be cost-effective. However, more specialised treatment with scheduled follow-ups does not seem to improve outcome as the NorthStar trial shows.²⁸ Also, the number of visits per se also does not seem to influence outcome.²⁹

Nevertheless, NPs are increasingly used in clinical trials, based on their prognostic value to better predict event rate and to increase the study

power by including patients at higher risk. A prominent recent example is the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, which investigated the effect of sacubitril/valsartan compared to enalapril in chronic HFrEF.³⁰ To meet the inclusion criteria, patients had to have a BNP level of ≥150 pg/ml or NT-proBNP level of ≥600 pg/ml or 100 pg/ml and 400 pg/ml, respectively, if hospitalised within the previous 12 months. Such inclusion criteria based on NPs are not the result of specific underlying pathophysiology but related purely to the strong prognostic value of NPs. In addition, NPs may predict sudden cardiac death and, therefore, might be helpful for indication of ICD implantation.³¹ However, such an approach needs to be prospectively tested before NPs can be recommended as selection criterion. Combining the strong prognostic value of NPs, together with the fact that NP levels change with altered therapy, make them an interesting guide for therapy in HF.³²

Therapy guidance using natriuretic peptides in chronic heart failure

Due to the prognostic power of NPs and because many patients with HF do not meet the target doses of HF drugs as recommended by guidelines, many studies have been conducted to test the hypothesis that therapy guided by repeated measurements of NPs improves outcome compared to usual care.

The first study investigating this hypothesis was published in 2000 but, 19 years and more than a dozen trials later, it has not been established whether this hypothesis is true or not.³³ This is in part related to the fact that none of the NP-guided trials was large enough to convincingly show the effects of this approach. This may be true even for the GUIDE-IT trial, which is the latest and largest study investigating this topic, which was stopped early so did not meet the predefined sample size and follow-up.²⁹ Even more importantly, there is a large variation between the trials^{29, 33-43} with regard to several aspects, including that: the included populations differed significantly; the interventions were not uniform; and follow-up length and the number of time-points to adjust therapy varied (*Tables 2 and 3*).

A recent meta-analysis came to conclusion that NP-guided therapy does not result in any benefit.⁴⁴ However, this meta-analysis did not properly account for the large diversity between the trials, nor did it perform sufficient sensitivity analyses despite including different kind of studies that are not directly comparable. Strikingly, the use of NPs both in the acute setting and in chronic HF was combined in this investigation and studies were included regardless of whether they included patients with HF_{rEF}, HF_{pEF} or both. It is well known that HF_{pEF} does not respond to classic HF therapy, and a previous meta-analysis based on individual patient data showed a different response to NP-guided therapy in HF_{rEF} and HF_{pEF}.^{2,45} In addition, one study (NorthStar) included in this meta-analysis suggested action should be taken only if NT-proBNP levels significantly increased but not if they remained elevated and it included both HF_{rEF} and HF_{pEF}. Not surprisingly, adjustments in therapy were limited and identical in the two treatment arms and, consequently, NT-proBNP hardly changed.⁴⁶ Most other NP-guided trials showed a significant reduction in NP levels in both treatment arms (e.g. Felker, et al, 2017; Pfisterer, et al, 2009).^{29, 36} The only genuinely relevant group of patients in whom NP guidance in chronic HF should be investigated are those with HF_{rEF}. When only results in chronic HF_{rEF} from the previous trials (1,507 in the NP-guided group and 1,516 in the control group) are included, NP-guided therapy – mostly using NT-proBNP, some using BNP – resulted in a significant reduction in mortality (*Figure 1*).^{29,33-43} Overall, 222 (14.7%) patients died in the NP-guided group and 275 (18.1%) in the control group.

As far as we can say, NP-guided therapy seems to be safe, even in elderly patients with significant comorbidities, and may be cost-effective as well.⁴⁷⁻⁴⁹ However, further evidence from more trials on NP-guided therapy is required.

Trials where adjustment in therapy did not differ between the NP-guided versus the clinical guided group, or where increasing loop diuretics was the main difference, usually showed a neutral outcome. In contrast, trials where the focus was mainly on intensifying guideline-recommended medication (e.g. angiotensin-converting enzyme [ACE] inhibition or angiotensin-receptor blockers, beta-blockers or mineralocorticoid receptor antagonists) showed some

positive results although, because of a lack of statistical power, the primary endpoint of the trials was not always reached (*Table 3*). This shows that applying guidelines when managing patients with HF_{rEF} is crucial to improve outcome.

The fact that NP guidance in TIME-CHF resulted in significantly larger uptitration of evidence-based treatment even in patients aged >75 years indicates that, in many patients with HF_{rEF}, the maximum tolerated has not been reached and forced uptitration is feasible.³⁶ Unfortunately, this is often not done in reality and the question arises over what may encourage physicians to do more for these patients. Measuring NPs to indicate the importance of uptitration may help in this regard.

Sacubitril: A Problem for Measuring Natriuretic Peptides?

Among the bioactive peptides, sacubitril reduces the breakdown of the biologically active NPs by inhibiting the enzyme neprilysin, a circulating neutral endopeptidase involved in the degradation of NPs.⁵⁰ This is true for both ANP and BNP, but BNP is a poorer substrate for neprilysin than ANP. Therefore, the increase of BNP may be less.⁵¹ The increase in BNP was only small although significant whereas the increase in urinary cGMP was much larger with sacubitril/valsartan in the PARADIGM-HF study.⁵²

Sacubitril has no direct influence on NT-proBNP because neprilysin has no effect on cleavage of NT-proBNP. However, it might be speculated that an increasing level of BNP results in a negative feedback regarding production of proBNP, thereby reducing NT-proBNP. To the best of our knowledge, this has not been properly tested. In clinical trials, sacubitril/valsartan resulted in a reduction of NT-proBNP, as well as a small increase in BNP as mentioned above.^{52,53} This reduction was accompanied by a better outcome. Therefore, it is likely that the decrease in NT-proBNP is, at least in part, related to more effective treatment of HF. To what extent NT-proBNP levels are influenced by a negative feedback mechanism remains to be determined.

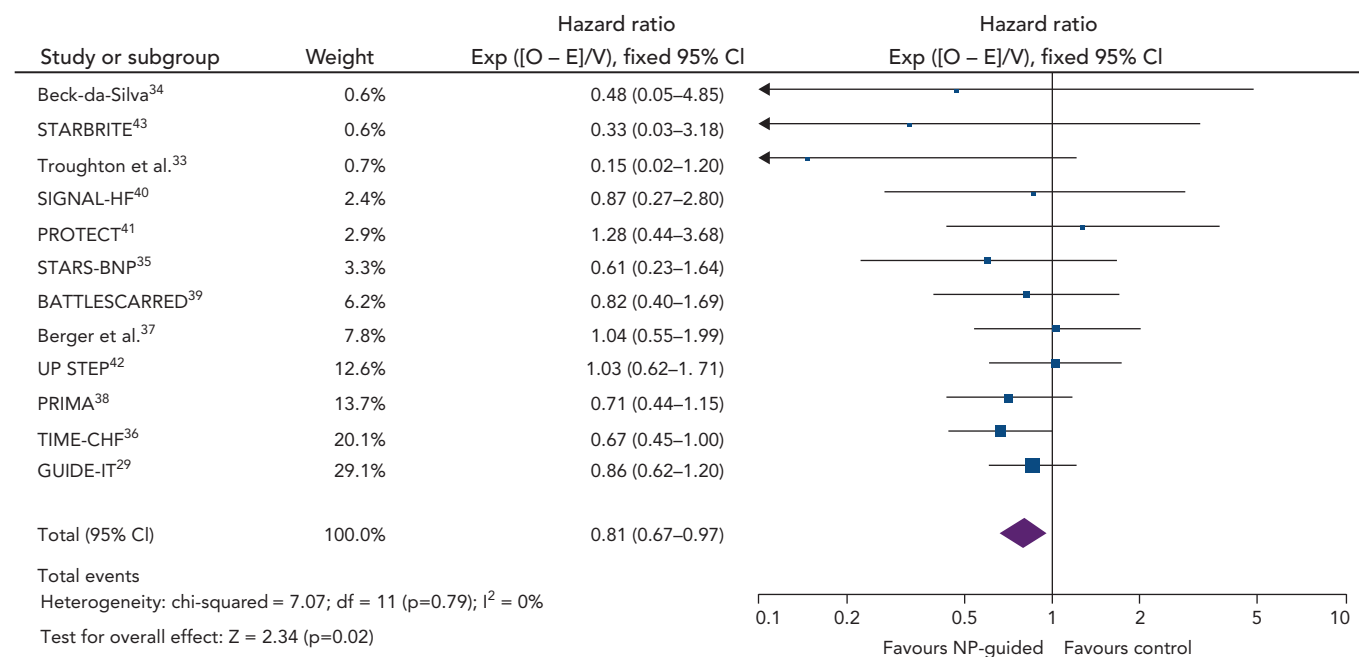
With the more widespread clinical use of sacubitril/valsartan, the measurement of serum NP levels in patients taking this drug may change and a rethinking of their interpretation is required. In patients taking sacubitril/valsartan, levels of BNP may rise because of decreased serum breakdown rather than because of a change in underlying disease state (such as volume overload in AHF), which potentially interferes with the prognostic and diagnostic utility of BNP.²⁷ However, this does not impair the clinical utility of BNP testing to rule out HF rapidly. Also, the clinical interpretation of NT-proBNP levels in patients with HF is probably not affected in a clinically meaningful way by neprilysin inhibition, based on published data.

When to Measure Natriuretic Peptides in Chronic Heart Failure

First, NPs are useful in the initial diagnosis or exclusion of HF. They may also help to identify patients at risk of developing HF where early intervention may reduce risk.

Second, NPs should be used in the outpatient management of HF_{rEF} when deciding whether to start a patient on eplerenone (BNP >250 pg/ml or NT-proBNP >500 pg/ml in men or >750 pg/ml in women, unless they have been hospitalised within the previous 6 months because of HF) or sacubitril/valsartan (BNP >150 pg/ml or NT-proBNP

Figure 1: Mortality in Natriuretic Peptide Guided Trials in Chronic Heart Failure with Reduced Ejection Fraction



Forest plot of mortality among participants in natriuretic peptide (NP) guided trials in chronic HF with reduced EF, showing unadjusted individual and mean hazard ratios with 95% confidence intervals (CIs) for 12 studies (individual patient data in eight studies – Troughton, et al. 2000;³³ Pfisterer, et al. 2009;³⁷ Berger et al. 2010;³⁷ Eurlings, et al. 2010;³⁸ Lainchbury, et al. 2010;³⁹ Persson, et al. 2010;⁴⁰ Januzzi, et al. 2011;⁴¹ Karlstrom, et al. 2011;⁴²) and aggregate data in four studies (Felker, et al. 2017;²⁹ Beck-da-Silva, et al. 2005;³⁴ Jourdain, et al. 2007;³⁵ Shah, et al. 2011³⁶).

>600 pg/ml; in case of a HF, hospitalisation within the previous 12 months, BNP >100 pg/ml or NT-proBNP >400 pg/ml), in line with the ESC HF guidelines, which are based on the inclusion criteria of the respective drug trials.²

Third, despite a lack of sufficient evidence for the superiority of natriuretic guided-therapy overall, NPs can help to decide whether a patient is being treated optimally. This is supported by the American College of Cardiology/American Heart Association guidelines (class IIA level of evidence), although this recommendation might change after the recent GUIDE-IT trial, and is not mentioned in the ESC HF guideline.^{2,11} Based on (pre-stratified) subgroup analyses, we would recommend this approach mainly in patients who have HF with reduced EF and few comorbidities.⁴⁵ Based on trials, it seems best to use a target around normal values, meaning ~125 pg/ml for BNP and ~1,000 pg/ml for NT-proBNP (Table 2).

The focus should be on improving and intensifying drugs that improve outcomes, such as renin-angiotensin system blockers, beta-blockers and mineralocorticoid receptor antagonists in patients whose (NT-pro)BNP levels remain elevated, not on the use of intensified diuretic therapy. This could be done merely to convince patients or their caregivers that (further) uptitration of evidence-based medicine is crucial.

As to whether a lack of elevated NPs means that further uptitration of medication is not required remains to be prospectively tested in a randomised trial. This may be relevant in patients who are most susceptible of side effects (e.g. frail elderly people).

Fourth, NPs may help to distinguish whether an increase in symptoms is related to worsening HF or deterioration of another condition (e.g. chronic obstructive pulmonary disease). When patients are using sacubitril/valsartan, the preferred NP is definitely NT-proBNP. ■

- Roberts E, Ludman AJ, Dworzynski K, et al. The diagnostic accuracy of the natriuretic peptides in heart failure: systematic review and diagnostic meta-analysis in the acute care setting. *BMJ* 2015;350:h910. <https://doi.org/10.1136/bmj.h910>; PMID: 25740799.
- Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129–200. <https://doi.org/10.1093/eurheartj/ehw128>; PMID: 27206819.
- Morrison LK, Harrison A, Krishnaswamy P, et al. 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. [https://doi.org/10.1016/S0735-1097\(01\)01744-2](https://doi.org/10.1016/S0735-1097(01)01744-2); PMID: 11788208.
- Fuat A, Murphy JJ, Hungin AP, et al. The diagnostic accuracy and utility of a B-type natriuretic peptide test in a community population of patients with suspected heart failure. *Br J Gen Pract* 2006;56:327–33. PMID: 16638247.
- Tang WH, Girod JP, Lee MJ, et al. Plasma B-type natriuretic peptide levels in ambulatory patients with established chronic symptomatic systolic heart failure. *Circulation* 2003;108:2964–6. <https://doi.org/10.1161/01.CIR.0000106903.98196.6>; PMID: 14662703.
- 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. [https://doi.org/10.1016/S0140-6736\(97\)06031-5](https://doi.org/10.1016/S0140-6736(97)06031-5); PMID: 119365448.
- Hobbs FD, Davis RC, Roalke AK, et al. Reliability of N-terminal pro-brain natriuretic peptide assay in diagnosis of heart failure: cohort study in representative and high risk community populations. *BMJ* 2002;324:1498. <https://doi.org/10.1136/bmj.324.7352.1498>; PMID: 12077039.
- Wright SP, Doughty RN, Pearl A, et al. Plasma amino-terminal pro-brain natriuretic peptide and accuracy of heart-failure diagnosis in primary care. A randomized, controlled trial. *J Am Coll Cardiol* 2003;42:1793–800. <https://doi.org/10.1016/j.jacc.2003.05.011>; PMID: 14642690.
- Landray MJ, Lehman R, Arnold I. Measuring brain natriuretic peptide in suspected left ventricular systolic dysfunction in general practice: cross-sectional study. *BMJ* 2000;320:985–6. <https://doi.org/10.1136/bmj.320.7240.985>; PMID: 1110753153
- Hildebrandt P, Collinson PO, Doughty RN, et al. Age-dependent values of N-terminal pro-B-type natriuretic peptide are superior to a single cut-point for ruling out suspected systolic dysfunction in primary care. *Eur Heart J* 2010;31:1881–9. <https://doi.org/10.1093/eurheartj/ehq163>; PMID: 20519241.
- Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;62:e147–e239. <https://doi.org/10.1016/j.jacc.2013.05.019>; PMID: 23747642.
- National Institute of Health and Care Excellence. *Chronic heart failure in adults: diagnosis and management*. London: NICE, 2018. Available at: <https://www.nice.org.uk/guidance/ng106> (accessed 16 January 2019).
- McGrady M, Reid CM, Shiel L, et al. N-terminal B-type natriuretic peptide and the association with left ventricular diastolic function in a population at high risk of incident heart failure: results of the SCReening Evaluation of the Evolution of New-Heart Failure Study (SCREEN-HF). *Eur J Heart Fail* 2013;15:573–80. <https://doi.org/10.1093/eurjhf/hft001>; PMID: 23338855.
- 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 Am Coll Cardiol* 2003;41:2010–7. [https://doi.org/10.1016/S0735-1097\(03\)00405-4](https://doi.org/10.1016/S0735-1097(03)00405-4); PMID: 1112798574.
- Mason JM, Hancock HC, Close H, et al. Utility of biomarkers in the differential diagnosis of heart failure in older people: findings from the heart failure in care homes (HFInCH) diagnostic accuracy study. *PLoS One* 2013;8:e53560. <https://doi.org/10.1371/journal.pone.0053560>; PMID: 23326457.
- Kelder JC, Cramer MJ, van Wijngaarden J, et al. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure.

- Circulation* 2011;124:2865–73. <https://doi.org/10.1161/CIRCULATIONAHA.111.019216>; PMID: 22104551.
17. Taylor KS, Verbakel JY, Feakins BG, et al. Diagnostic accuracy of point-of-care natriuretic peptide testing for chronic heart failure in ambulatory care: systematic review and meta-analysis. *BMJ* 2018;361:k1450. <https://doi.org/10.1136/bmj.k1450>; PMID: 29785952.
 18. Lam CS, Rienstra M, Tay WT, et al. Atrial Fibrillation in heart failure with preserved ejection fraction: association with exercise capacity, left ventricular filling pressures, natriuretic peptides, and left atrial volume. *JACC Heart Fail* 2017;5:92–8. <https://doi.org/10.1016/j.jchf.2016.10.005>; PMID: 28017355.
 19. 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;151:999–1005. <https://doi.org/10.1016/j.ahj.2005.10.011>; PMID: 16644321.
 20. Ledwidge M, Gallagher J, Conlon C, et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. *JAMA* 2013;310:66–74. <https://doi.org/10.1001/jama.2013.7588>; PMID: 23821090.
 21. Ledwidge MT, O'Connell E, Gallagher J, et al. Cost-effectiveness of natriuretic peptide-based screening and collaborative care: a report from the STOP-HF (St Vincent's Screening TO Prevent Heart Failure) study. *Eur J Heart Fail* 2015;17:672–9. <https://doi.org/10.1002/ejhf.286>; PMID: 26139583.
 22. Huelsmann M, Neuhold S, Resl M, et al. PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease): a prospective randomized controlled trial. *J Am Coll Cardiol* 2013;62:1365–72. <https://doi.org/10.1016/j.jacc.2013.05.069>; PMID: 23810874.
 23. Sabatine MS, Morrow DA, de Lemos JA, et al. Evaluation of multiple biomarkers of cardiovascular stress for risk prediction and guiding medical therapy in patients with stable coronary disease. *Circulation* 2012;125:233–40. <https://doi.org/10.1161/CIRCULATIONAHA.111.063842>; PMID: 22179538.
 24. Sanders-van Wijk S, van Empel V, Davarzani N, et al. Circulating biomarkers of distinct pathophysiological pathways in heart failure with preserved vs. reduced left ventricular ejection fraction. *Eur J Heart Fail* 2015;17:1006–14. <https://doi.org/10.1002/ejhf.414>; PMID: 26472682.
 25. Doust JA, Pietrzak E, Dobson A, et al. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. *BMJ* 2005;330:625. <https://doi.org/10.1136/bmj.330.7492.625>; PMID: 15774989.
 26. Richards AM. N-terminal B-type natriuretic peptide in heart failure. *Heart Fail Clin* 2018;14:27–39. <https://doi.org/10.1016/j.hfc.2017.08.004>; PMID: 29153198.
 27. Maisel AS, Duran JM, Wettersten N. Natriuretic peptides in heart failure: atrial and B-type natriuretic peptides. *Heart Fail Clin* 2018;14:13–25. <https://doi.org/10.1016/j.hfc.2017.08.002>; PMID: 29153197.
 28. Schou M, Gustafsson F, Videbaek L, et al. Extended heart failure clinic follow-up in low-risk patients: a randomized clinical trial (NorthStar). *Eur Heart J* 2013;34:432–42. <https://doi.org/10.1093/eurheartj/ehs235>; PMID: 22875412.
 29. Felker GM, Anstrom KJ, Adams KF, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA* 2017;318:713–20. <https://doi.org/10.1001/jama.2017.10565>; PMID: 28829876.
 30. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371:993–1004. <https://doi.org/10.1056/NEJMoa1409077>; PMID: 25176015.
 31. Berger R, Huelsman M, Strecker K, et al. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. *Circulation* 2002;105:2392–7. <https://doi.org/10.1161/01.CIR.0000016642.15031.34>; PMID: 12021226.
 32. Brunner-La Rocca HP, Weilenmann D, Kiowski W, et al. Within-patient comparison of effects of different dosages of enalapril on functional capacity and neurohormone levels in patients with chronic heart failure. *Am Heart J* 1999;138:654–62. [https://doi.org/10.1016/S0002-8703\(99\)70179-1](https://doi.org/10.1016/S0002-8703(99)70179-1); PMID: 10502210.
 33. Troughton RW, Frampton CM, Yandle TG, et al. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet* 2000;355:1126–30. [https://doi.org/10.1016/S0140-6736\(00\)02060-2](https://doi.org/10.1016/S0140-6736(00)02060-2); PMID: 1110791374.
 34. Beck-da-Silva L, de Bold A, Fraser M, et al. BNP-guided therapy not better than expert's clinical assessment for beta-blocker titration in patients with heart failure. *Congest Heart Fail* 2005;11:248–53. <https://doi.org/10.1111/j.1527-5299.2005.04239.x>; PMID: 16230866.
 35. 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. <https://doi.org/10.1016/j.jacc.2006.10.081>; PMID: 17448376.
 36. Pfisterer M, Buser P, Rickli H, et al. BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. *JAMA* 2009;301:383–92. <https://doi.org/10.1001/jama.2009.2>; PMID: 19176440.
 37. Berger R, Moertl D, Peter S, et al. N-terminal pro-B-type natriuretic peptide-guided, intensive patient management in addition to multidisciplinary care in chronic heart failure a 3-arm, prospective, randomized pilot study. *J Am Coll Cardiol* 2010;55:645–53. <https://doi.org/10.1016/j.jacc.2009.08.078>; PMID: 20170790.
 38. Eurlings LW, van Pol PE, Kok WE, et al. Management of chronic heart failure guided by individual N-terminal pro-B-type natriuretic peptide targets: results of the PRIMA (Can Pro-brain-natriuretic peptide guided therapy of chronic heart failure improve heart failure morbidity and mortality?) study. *J Am Coll Cardiol* 2010;56:2090–100. <https://doi.org/10.1016/j.jacc.2010.07.030>; PMID: 21144969.
 39. Lainchbury JG, Troughton RW, Strangman KM, et al. N-terminal pro-B-type natriuretic peptide-guided treatment for chronic heart failure: results from the BATTLESCARRED (NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) trial. *J Am Coll Cardiol* 2010;55:53–60. <https://doi.org/10.1016/j.jacc.2009.02.095>; PMID: 20117364.
 40. Persson H, Erntell H, Eriksson B, et al. Improved pharmacological therapy of chronic heart failure in primary care: a randomized Study of NT-proBNP Guided Management of Heart Failure – SIGNAL-HF (Swedish Intervention Study – Guidelines and NT-proBNP Analysis in Heart Failure). *Eur J Heart Fail* 2010;12:1300–8. <https://doi.org/10.1093/eurjhf/hfq169>; PMID: 20876734.
 41. Januzzi JL Jr, Rehman SU, Mohammed AA, et al. Use of amino-terminal pro-B-type natriuretic peptide to guide outpatient therapy of patients with chronic left ventricular systolic dysfunction. *J Am Coll Cardiol* 2011;58:1881–9. <https://doi.org/10.1016/j.jacc.2011.03.072>; PMID: 22018299.
 42. Karlstrom P, Alehagen U, Boman K, et al. Brain natriuretic peptide-guided treatment does not improve morbidity and mortality in extensively treated patients with chronic heart failure: responders to treatment have a significantly better outcome. *Eur J Heart Fail* 2011;13:1096–103. <https://doi.org/10.1093/eurjhf/hfr078>; PMID: 21715446.
 43. Shah MR, Califf RM, Nohria A, et al. The STARBRITE trial: a randomized, pilot study of B-type natriuretic peptide-guided therapy in patients with advanced heart failure. *J Card Fail* 2011;17:613–21. <https://doi.org/10.1016/j.cardfail.2011.04.012>; PMID: 21807321.
 44. Khan MS, Siddiqi TJ, Usman MS, et al. Does natriuretic peptide monitoring improve outcomes in heart failure patients? A systematic review and meta-analysis. *Int J Cardiol* 2018;263:80–7. <https://doi.org/10.1016/j.ijcard.2018.04.049>; PMID: 29685696.
 45. Brunner-La Rocca HP, Eurlings L, Richards AM, et al. Which heart failure patients profit from natriuretic peptide guided therapy? A meta-analysis from individual patient data of randomized trials. *Eur J Heart Fail* 2015;17:1252–61. <https://doi.org/10.1002/ejhf.401>; PMID: 26419999.
 46. Schou M, Gustafsson F, Videbaek L, et al. Adding serial N-terminal pro brain natriuretic peptide measurements to optimal clinical management in outpatients with systolic heart failure: a multicentre randomized clinical trial (NorthStar monitoring study). *Eur J Heart Fail* 2013;15:818–27. <https://doi.org/10.1093/eurjhf/hft037>; PMID: 23507787.
 47. Sanders-van Wijk S, Muzzarelli S, Neuhaus M, et al. Safety and tolerability of intensified, N-terminal pro brain natriuretic peptide-guided compared with standard medical therapy in elderly patients with congestive heart failure: results from TIME-CHF. *Eur J Heart Fail* 2013;15:910–18. <https://doi.org/10.1093/eurjhf/hft079>; PMID: 23666681.
 48. Sanders-van Wijk S, van Asselt AD, Rickli H, et al. Cost-effectiveness of N-terminal pro-B-type natriuretic peptide-guided therapy in elderly heart failure patients: results from TIME-CHF (Trial of Intensified versus Standard Medical Therapy in Elderly Patients with Congestive Heart Failure). *JACC Heart Fail* 2013;1:64–71. <https://doi.org/10.1016/j.jchf.2012.08.002>; PMID: 24621800.
 49. Adlbrecht C, Huelsmann M, Berger R, et al. Cost analysis and cost-effectiveness of NT-proBNP-guided heart failure specialist care in addition to home-based nurse care. *Eur J Clin Invest* 2011;41:315–22. <https://doi.org/10.1111/j.1365-2362.2010.02412.x>; PMID: 21070222.
 50. Mangiafico S, Costello-Boerrigter LC, Andersen IA, et al. Neutral endopeptidase inhibition and the natriuretic peptide system: an evolving strategy in cardiovascular therapeutics. *Eur Heart J* 2013;34:886–93c. <https://doi.org/10.1093/eurheartj/ehs262>; PMID: 22942338.
 51. Mair J, Lindahl B, Giannitsis E, et al. Will sacubitril-valsartan diminish the clinical utility of B-type natriuretic peptide testing in acute cardiac care? *Eur Heart J Acute Cardiovasc Care* 2017;6:321–8. <https://doi.org/10.1177/2048872615626355>; PMID: 26758541.
 52. Packer M, McMurray JJ, Desai AS, et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation* 2015;131:54–61. <https://doi.org/10.1161/CIRCULATIONAHA.114.013748>; PMID: 25403646.
 53. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet* 2012;380:1387–95. [https://doi.org/10.1016/S0140-6736\(12\)61227-6](https://doi.org/10.1016/S0140-6736(12)61227-6); PMID: 122932717.