

# The integration of BNP and NT-proBNP into clinical medicine

Christian Mueller, Tobias Breidhardt, Kirsten Laule-Kilian, Michael Christ, André P. Perruchoud

## Summary

B-type natriuretic peptide (BNP) and NT-proBNP have been shown to be extremely helpful in the diagnosis and management of patients with heart failure (HF). These neurohormones are predominantly secreted from the left and the right cardiac ventricle in response to volume and pressure overload. BNP and NT-proBNP can be seen as quantitative markers of HF summarizing the extent of systolic and diastolic left ventricular dysfunction. Research data from clinical studies and six years of clinical experience with BNP allow us

to provide clear recommendations regarding the integration of BNP/NT-proBNP into clinical medicine. With multiple additional indications in prospect, current evidence clearly supports the use of BNP and NT-proBNP in three clinical settings: patients with acute dyspnoea, prior to discharge in patients hospitalised with acute HF, and the long-term management of patients with HF.

*Key words: dyspnoea; diagnosis; B-type natriuretic peptide; heart failure*

## Introduction

Since our last review on the use of B-type natriuretic peptide (BNP) in this journal [1], research in Switzerland and worldwide provided further data improving our understanding of this exciting marker. This review summarises clinical situations with sufficient evidence to support the use of BNP or NT-proBNP in clinical practice. For some indications, the question is no longer “should I use it”, but rather “how can I make best use of it”? Therefore, we will also provide detailed recommendations on the most appropriate cut-off values for clinical decisions.

The clinical importance of a specific disease marker is related to the overall importance of the disease, availability of alternative methods to reliably diagnose the disease and quantify disease severity, and of course the performance of the marker. The clinical impact of BNP and NT-proBNP, as quantitative markers of heart failure (HF), stems from the fact that HF is a major public health problem, the difficulty in the clinical diagnosis of HF, and their excellent diagnostic accuracy in patients with dyspnoea.

## Heart failure epidemic

HF is common, associated with very high morbidity and mortality, extremely expensive, and often difficult to diagnose [1–4]. Currently, there are nearly 1.5 million new cases of HF in Europe and North America every year [2–4]. HF is characterised by frequently recurrent decompensation leading to worsening dyspnoea finally requiring hospitalisation. Moreover, 5 years after the diagnosis of HF, 50% of HF patients will have died from the disease. It is estimated that in Europe,

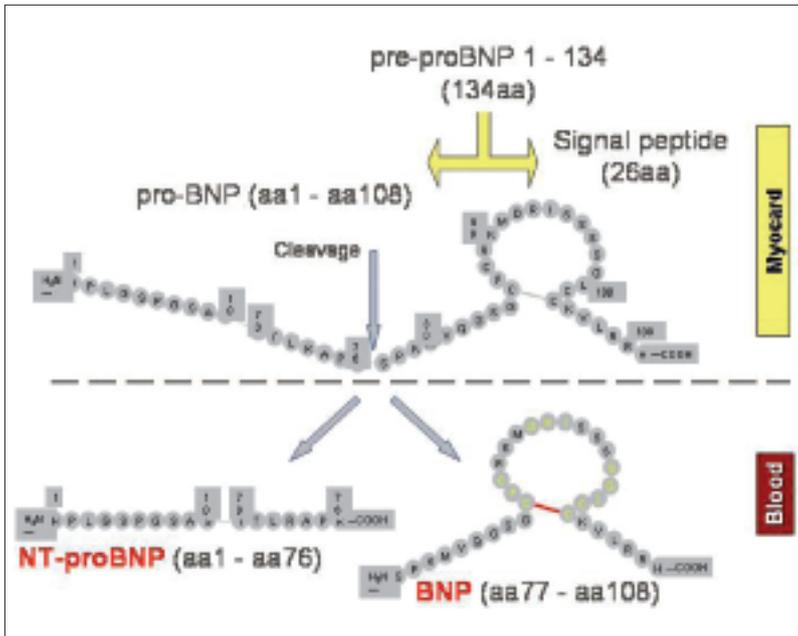
total cost of HF exceeds 50 billion € every year [2–4]. HF is difficult to diagnose because symptoms are non-specific, and typical physical signs are present in less than half of patients with HF. Our record in the diagnosis of HF is poor with less than 50% of patients being correctly identified during the initial consultation [5, 6]. Misdiagnosis of HF causes morbidity, and increases time to discharge and treatment cost.

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## BNP and NT-proBNP are quantitative markers of HF with high diagnostic accuracy

BNP and NT-proBNP can be seen as quantitative markers of HF that summarise the extent of systolic and diastolic left ventricular dysfunction. In general, levels of BNP and NT-proBNP are directly related to the severity of HF symptoms and to the severity of the cardiac abnormality. BNP is

actual cut-off values are very different (figure 1 and 2). The largest validating study included more than 1500 patients and found a high diagnostic accuracy for BNP in determining the correct diagnosis (HF versus no HF). Adding BNP to clinical judgement would have enhanced diagnostic accuracy from 74% to 81%. In those participants with an intermediate (21% to 79%) clinical probability of HF, BNP at a cut-off value of 100 pg/ml correctly classified 74% of the cases. The areas under the receiver operating characteristic curve were 0.86, 0.90, and 0.93 for clinical judgement, for BNP at a cut-off of 100 pg/ml, and for the 2 in combination, respectively ( $P < 0.0001$  for all pair-wise comparisons) [14, 15]. These data led to the conclusion that the use of BNP increases the accuracy of the clinical evaluation in patients presenting with acute dyspnoea. Moreover, a randomised comparison of a strategy of making NT-proBNP results available to primary care physicians, in addition to the ECG, chest radiography, and echocardiographic data, has reported a substantial increase in diagnostic accuracy for patients with new symptoms that might be caused by HF [20]. The main impact of NT-proBNP measurement on diagnostic accuracy was the general practitioner correctly ruling out HF. In summary, BNP and NT-proBNP as single tests outperform all other variables available in the ED. Moreover, when used in conjunction with other clinical information, BNP and NT-proBNP significantly increase diagnostic accuracy. There are certain pitfalls when HF may present with low BNP or NT-proBNP levels that need to be kept in mind. These include HF secondary to causes upstream from the left ventricle including mitral stenosis and acute mitral regurgitation.

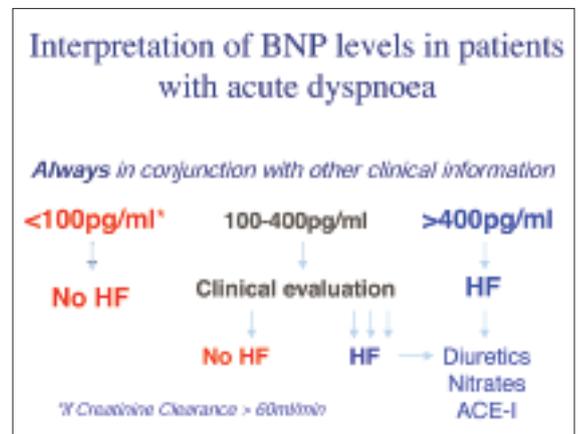


**Figure 1**

BNP and NT-proBNP are quantitative markers of cardiac stress that are released into blood after cleavage of precursors.

a 32-amino acid polypeptide (figure 1) that is co-secreted with the inactive aminoterminal proBNP (NT-proBNP) from the left and the right cardiac ventricle in response to ventricular volume expansion and pressure overload [7-13]. Recent data suggest that left ventricular enddiastolic wall stress and wall stiffness may be the predominate triggers of BNP release [11, 12]. The severity of left ventricular diastolic dysfunction, right ventricular dysfunction, and mitral regurgitation in addition to left ventricular systolic dysfunction determine plasma BNP levels in the individual patient [13].

Numerous observational studies including patients presenting with symptoms suggestive of HF – mainly acute dyspnoea – that validated BNP and NT-proBNP against a gold standard diagnosis of HF have convincingly demonstrated that BNP and NT-proBNP as single tests outperform all other variables available in the emergency department (ED) [14-20]. Overall, BNP and NT-proBNP seem to have similar test characteristics for the diagnosis of HF in patients presenting with acute dyspnoea. However, it is important to note that the



**Figure 2**

Interpretation of BNP levels in patients presenting with acute dyspnoea

## The use of BNP improves medical and economic outcome

Although the diagnostic potential of BNP in patients with acute dyspnoea was already described more than 10 years ago [9], producing assay results cost several days. This obviously limited its use in clinical practice. The development of a rapid fluorescence immunoassay (Biosite, San Diego, California, US) allowed BNP levels to become available within 20–30 minutes. The central question remained whether the availability of a simple and rapid blood test that increases the diagnostic accuracy in fact translates in improved patient management when used in clinical practice? This important issue was addressed in the BNP for Acute Shortness of Breath Evaluation (BASEL) study [21]. The median time from presentation at the emergency department to the initiation of the ap-

propriate therapy according to the final discharge diagnosis was 90 minutes in the control group and 63 minutes in the BNP group ( $p = 0.03$ ). The use of BNP levels significantly reduced the need for hospital admission (75% versus 85%) or intensive care (15% versus 24%). Time to discharge was significantly reduced in the BNP group (median 8 days versus 11 days in the control group). Total cost of treatment was \$5,410 in the BNP group compared to \$7,264 in the control group, a significant reduction of 26%. These data support the conclusion that used in conjunction with other clinical information, rapid measurement of BNP in the ED improved medical and economic outcome.

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## BNP should be measured in all patients presenting with acute dyspnoea

The BASEL study included unselected consecutive patients presenting with acute dyspnoea. Recent data suggested that BNP levels might be most useful in patients with an intermediate clinical probability of HF [15, 16]. Whether restricting BNP measurements to patients in this subgroup would yield similar medical and economic benefits as those observed in the BASEL study is unknown. Moreover, the approach used in the BASEL study has obvious logistical advantages. Delaying the venipuncture for BNP until the physician has collected all clinical data -and chest x-ray in most occasions- to determine whether the individual

patient has an intermediate clinical probability of HF would beyond doubt significantly increase the time to the correct diagnosis and accordingly the time to appropriate treatment in those patients, who might benefit the most from BNP testing. As BNP testing is non-invasive, simple, and cost-effective, measuring BNP directly at presentation at the time of venipuncture for routine blood tests in all patients with acute dyspnoea seems to be reasonable. Moreover, in addition to the diagnostic utility, BNP levels do provide valuable prognostic information in patients with HF.

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## The cost-effectiveness of BNP is maintained at 6 months

In the BASEL study we also assessed the cost-effectiveness of BNP testing during long-term follow-up. To address the fact that tailoring of resources may very well be cost-effective initially, but may result in large secondary costs due to recurrent symptoms, cost-effectiveness analyses were performed at 180 days follow-up. As our major finding we reported that BNP testing was cost-effective also at 180 days follow-up. Analysis of incremental 180-day cost-effectiveness showed that BNP guidance resulted in lower mortality and lower cost in 80.6%, in higher mortality and lower cost in 19.3%, and in higher or lower mortality and higher cost in both below 0.1%. The use of BNP

levels significantly reduced total treatment cost. This reduction was driven by significantly fewer days spent in-hospital in the BNP group. Large part of this reduction in days in-hospital and cost occurred during the initial presentation and was fully maintained at 180 days. Sensitivity analyses demonstrated that this observation is robust to changes in most variables, but sensitive to changes in re-hospitalisation with BNP-guidance. Subgroup analysis revealed that the benefit of BNP testing was particularly evident in patients with a history of either coronary artery disease or pulmonary disease [22].

## BNP or NT-proBNP – point of care or central laboratory?

BNP and NT-proBNP are two different peptides that show a high correlation in patients with acute dyspnoea [16, 23–25]. It is important to note that the correlation is only moderate when more heterogeneous patient cohorts are examined (unpublished data). The rapid point of care BNP assay was available three years earlier than the first clinical assay for NT-proBNP (Roche Diagnostics, Basel, Switzerland). Therefore, not surprisingly more clinical experience is available for BNP compared to NT-proBNP. However, due to intense ongoing research on both peptides, novel information regarding BNP and NT-proBNP still becomes available every month.

The International Collaborative for NT-proBNP Study helped defining the most appropriate cut-off values for NT-proBNP by pooling data from several single centre studies that had each suggested excellent accuracy but a wide range of optimal cut-off values (with differences in baseline characteristics including age, which was most likely responsible for this fact) [16, 17, 19, 26].

Recently, BNP and NT-proBNP have been directly compared against a gold standard diagnosis in four studies including patients with acute dyspnoea [16, 23–25]. Both peptides showed similar accuracy in three studies, and BNP was superior to NT-proBNP in one study. This study exclusively enrolled patients above the age of 65 years [25]. Therefore, BNP seems to have an advantage in elderly patients. This observation may be related to the fact that renal dysfunction, which is prevalent in the elderly, is associated with a more pronounced increase in NT-proBNP levels as compared to BNP levels [25, 26, 29].

The importance of the clinical experience available in an individual institution with one specific marker cannot be overemphasized. Particularly, as there is no fixed equation that reliably allows the conversion of BNP to NT-proBNP levels or vice-versa. Therefore, from the clinical point of view, changing from one marker to the other should be discouraged once the clinicians have become familiar with either BNP or NT-proBNP. Should a change become inevitable, close cooperation and intense bilateral communication between laboratory and clinical staff is mandatory.

Several limitations regarding statements concerning the preferred marker have to be kept in mind. Firstly, BNP and NT-proBNP have nearly exclusively been compared in patients with acute dyspnoea. As BNP and NT-proBNP are increasingly being used in other clinical settings, including pre-discharge evaluation of HF patients, outpatient management of patients with chronic HF, the detection of left ventricular systolic dysfunction, risk-stratification in healthy individuals, and patients with coronary artery disease, many additional studies directly comparing both peptides in these individual scenarios are necessary. Secondly, meanwhile additional assays for BNP (Abbott, Bayer, Beckman-Coulter) and NT-proBNP (Dade Behring) have become available. In contrast to the Biosite point-of-care test, all three novel BNP assays and both NT-proBNP assays are laboratory based. Therefore, the question is not only whether to use BNP or NT-proBNP, but also whether to use a point-of-care test or a laboratory based test. Although a detailed discussion of the advantages and disadvantages of point-of-care testing is beyond the scope of this review, logistic issues will play a major role in the decision for a specific assay. Thirdly, the three novel BNP assays have been “harmonised” to the Biosite test. However, they are different tests using different antibodies, with the exception of the Beckmann-Coulter test that uses the licensed Biosite antibody. Initial experience with these novel BNP assays shows a high correlation ( $r > 0.9$ ) with the Biosite BNP assay [27, 28]. However, there is a need for further studies comparing these assays individually with a clinical gold standard diagnosis and correlating them with the Biosite assay in order to definitely confirm that the identical cut-off values can be used with these novel assays as validated with the Biosite assay [14, 15, 21, 29, 30]. The same is true for the Dade Behring test that uses the licensed NT-proBNP antibody from Roche. Fourthly, given our current knowledge of BNP, NT-proBNP, and the limitations of the adjudicated “gold standard diagnosis” in the studies comparing BNP and NT-proBNP, one has to stress that ultimately only clinical outcome studies will be able to definitely answer the question, whether BNP or NT-proBNP is superior for any individual clinical setting.

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## What cut-off values to use in patients with acute dyspnoea?

In order to make best use of the diagnostic information of BNP and NT-proBNP levels, the clinician needs to understand that both are quantitative markers of HF. The higher the BNP or NT-proBNP level, the higher the likelihood that the dyspnoea in the individual patient is caused by HF. In order to make BNP and NT-proBNP lev-

els easy to use in the ED, it has become common to use two cut-off values: a lower one with a high negative predictive value to reliably exclude HF as the cause of acute dyspnoea, and a second higher one with a high positive predictive value to “rule in” HF as the cause of dyspnoea. As shown in figure 2, for BNP 100 pg/ml and 400 pg/ml should

be used. These cut-off values apply irrespective of age and sex [29–31]. However, two clinical conditions require adjustment: kidney disease and obesity. In patients with kidney disease and an estimated glomerular filtration rate of less than 60 ml/min, 200–225 pg/ml rather than 100 pg/ml is the most appropriate cut-off value to rule out HF [29, 32]. In contrast, the presence of obesity requires the use of lower cut-off values. In patients with severe obesity and a body mass index above 35, we

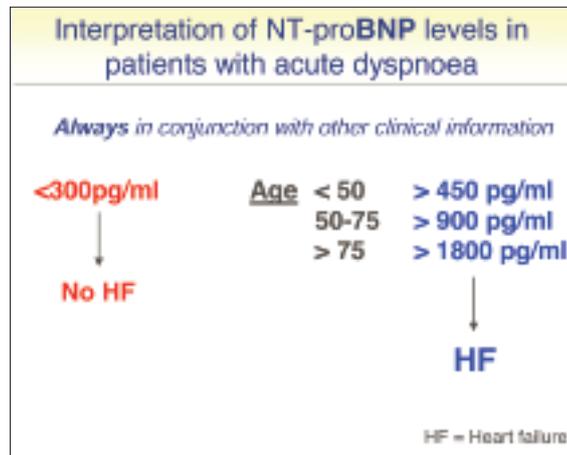
recommend a BNP cut-off value of 60 pg/ml to rule out and 200 pg/ml to rule in HF as the cause of acute dyspnoea [33, 34].

About 75% of patients with acute dyspnoea will present with either low (<100 pg/ml) or high (>400–500 pg/ml) BNP levels [14, 15]. In these, the BNP level is extremely helpful and quickly leads to the correct diagnosis. In the other 25% of patients, the BNP level is in a gray zone. Although most patients with intermediate BNP levels do have mild HF, BNP is less helpful in this range due to considerable overlap with BNP levels in pulmonary embolism, pneumonia, and other disorders

The International Collaborative for NT-proBNP Study defined the most appropriate cut-off values for NT-proBNP [16, 17, 19, 26]. As shown in figure 3, 300 pg/ml should be used to “rule out” HF. Depending on age, 450 pg/ml, 900 pg/ml, or 1800 pg/ml should be used to “rule in” HF. Again, NT-proBNP levels below the lower cut-off or above the upper cut-off value are extremely helpful, whereas NT-proBNP levels in the gray zone are less helpful. Of note, obesity is also associated with significantly lower NT-proBNP levels [35].

**Figure 3**

Interpretation of NT-proBNP levels in patients presenting with acute dyspnoea. The cut-off value to rule in HF is age-dependent.



## ED versus primary care versus private practice

Most of our knowledge regarding the value and performance of BNP and NT-proBNP testing is derived from studies including patients presenting with acute dyspnoea to the ED. However, most patients with novel or increasing dyspnoea will present to their doctor in private practice rather than the ED. In general, doctors in private practice are more experienced as compared to their colleagues in the ED, and often have detailed knowledge regarding medical and social history of their patients. However, their access to specialist consultation and additional testing including chest x-ray, pulse oximetry, spirometry, and echocardiography is more restricted as compared to the ED. In addition, disease severity may be less and mean age may be higher in patients presenting in private practice, with both variables further increasing the diagnostic challenge.

It is currently an unresolved question whether the use of BNP and NT-proBNP for the evaluation of patients presenting to doctors in private practice requires specific cut-off values or whether the cut-off values validated in studies in the ED can be applied. Five major limitations contribute to this uncertainty: 1) only a small number of studies have evaluated the use of BNP and NT-proBNP in private practice, 2) some of the studies performed in the primary care setting applied other BNP assays than currently in clinical use [5], 3) the definition of a gold standard diagnosis, already a major challenge in the ED setting, is even more difficult in primary care, 4) the detection of left ventricular systolic dysfunction is methodologi-

cally distinct from the identification of HF as the cause of dyspnoea [10] and, 5) case selection impacts on cut-off values. Most of the pioneer studies in primary care were performed in the UK and New Zealand [5, 20]. Differences in public health systems between these countries and other countries in Europe as well as the US will obviously influence baseline characteristics of patients presenting in private practice

It is important to note that despite these methodological limitations, initial experience in primary care is very promising [5, 20]. In our experience the severity of symptoms is more important than the site of presentation. In patients presenting with severe dyspnoea (NYHA III or IV) we recommend to use the cut-off values validated in the ED studies (figure 1+2). In patients presenting with mild dyspnoea (NYHA II) slightly lower values should be used. As shown in a randomised comparison of a strategy of making NT-proBNP results available to primary care physicians, the main impact of BNP or NT-proBNP measurement on diagnostic accuracy might be the general practitioner correctly ruling out HF. Given the importance of dyspnoea in primary care, additional randomised controlled trials are desperately needed in this setting. Some of these are already under way, including BASEL III – Private Practice, an international, multi-centre, randomised, controlled study on the impact of rapid BNP testing on patient outcome and resource utilisation in patients presenting with acute dyspnoea to doctors in private practice.

## Intensive care unit

Respiratory failure is an important reason for admission of patients to an intensive care unit (ICU), and also a common reason for the deterioration of patients already treated in the ICU [36–39]. It is a very serious condition associated with significant mortality. HF is a common cause of respiratory failure in both circumstances. Unfortunately, the rapid and accurate differentiation of HF from other causes of respiratory failure in the ICU is perhaps even more difficult as the identification of HF in patients presenting with acute dyspnoea to the ED. Although our knowledge on the use of BNP and NT-proBNP in the ICU is still limited, two distinct lessons have been learned. Firstly, although BNP levels may very well be helpful in the detection of myocardial dysfunction, therapeutic consequences heavily rely on the underlying cause of myocardial dysfunction [39]. Respiratory failure secondary to severe sepsis due to pneumonia or other infections is often associated with high BNP and NT-proBNP levels [40]. Although the increase in BNP/NT-proBNP most likely is due to myocardial dysfunction and the

term “HF” may well be appropriate for the condition, management consists of volume replacement rather than diuretics as would be the case for patients with conventional HF. Secondly, the use of higher cut-off values seems warranted. As described previously for other settings, BNP and NT-proBNP levels in the ICU should be interpreted as quantitative markers of HF in conjunction with all other information pertaining to the individual patient. Existing data suggests a lower cut-off of 150 pg/ml to rule out HF as the cause of respiratory failure and 600 pg/ml as a reasonable higher cut-off value to rule in HF [36, 37, 41]. Clearly, more studies are necessary before definite conclusions regarding the value of BNP or NT-proBNP in the management of ICU patients can be drawn. Among others, BASEL II – Intensive Care Unit, a multi-centre, randomised, controlled study including patients with respiratory failure from seven Swiss ICUs is currently evaluating the impact of rapid BNP testing on medical and economic outcome.

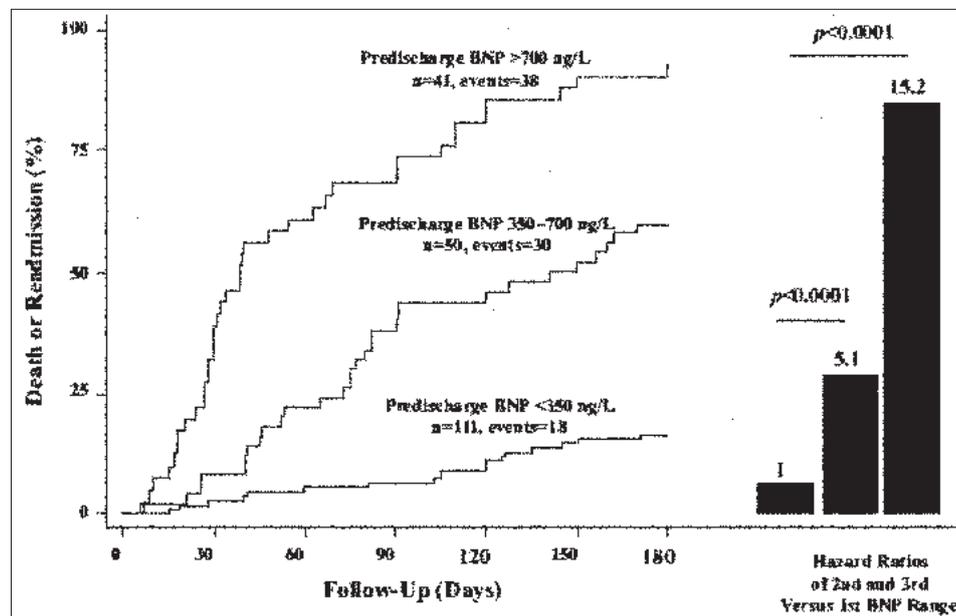
## Risk-stratification prior to discharge in patients admitted for acute HF

Patients admitted for acute decompensated HF are at high risk for death or re-hospitalisation for recurrent HF within the next months. The measurement of BNP or NT-proBNP prior to discharge can reliably identify those patients at highest risk (figure 4). There is consistent evidence from two independent studies that we should try to achieve pre-discharge BNP levels below 350–400 pg/ml [42, 43]. If this level is not achieved at the time of planned discharge, intensification of acute HF therapy with up-titration of nitrates and

diuretics is warranted. Patients with a pre-discharge BNP level of 350–700 pg/ml had a five times increased mortality or readmission for HF risk as compared to patients with a pre-discharge BNP below 350 pg/ml. Once the pre-discharge BNP was above 700 pg/ml, mortality or readmission for HF risk increased by a factor 15 and reached a rate of 90% [42]. Obviously, in some elderly patients it may not be possible to achieve BNP levels below 350 pg/ml. Similar results were reported for NT-proBNP [44].

**Figure 4**

Predischarge BNP levels are a powerful predictor of death or readmission within 180 days. (Used with permission from Logeart et al. [42])



## Management of patients with chronic HF

In patients with chronic HF, high levels of BNP or NT-proBNP have consistently been associated with poor outcome [45–49]. Therefore, it is intriguing to monitor HF patients with regular assessment of these sensitive and specific markers of HF. This approach allows the identification of impeding decompensation on the one hand, and reassurance and identification of non-cardiac causes of symptoms with an easy obtainable objective marker on the other hand. HF medication is titrated to achieve a maximal reduction of BNP/NT-proBNP levels.

Two randomised controlled trials have confirmed the superiority of BNP/NT-proBNP guidance as compared to standard guidelines based management [50, 51]. Troughton et al. [50] randomised 69 patients with impaired systolic function (left-ventricular ejection fraction <40%) and symptomatic HF (NYHA class II–IV) to receive treatment guided by either plasma NT-proBNP concentration determined by a local assay (BNP group) or standardised clinical assessment (clinical group). During follow-up (median 10 months), there were fewer total cardiovascular events (death, hospital admission, or heart failure decompensation) in the BNP group than in the clinical group (19 versus 54,  $p = 0.02$ ). At 6 months, 27% of patients in the BNP group and 53% of patients in the clinical group had experienced a first cardiovascular event ( $p = 0.03$ ). Changes in left-ventricular function, quality of life, renal function, and adverse events were similar in both groups. The authors concluded that NT-proBNP-guided treatment of HF reduced total cardiovascular events, and delayed time to first event compared with intensive clinically guided treatment. This finding has recently been confirmed by a French multi-centre study (STARS-BNP) [51]. Patrick Jourdain and his fellow STARS-BNP investigators on behalf of the working group on HF of the French Society of Cardiology randomised 220 patients with stable chronic HF and systolic left ventricular dysfunction on optimal medical therapy to receive either treatment guided by plasma BNP concentration (BNP group) or treatment adapted to standardised clinical assessment without BNP measurement (clinical group). Medical therapy had to include ACE-inhibitors, diuretics and beta-blockers at “optimal” daily dose according to investigators and ESC guidelines. Daily diuretic dose had to be stable for at least one month. Out-patient visits were scheduled every month for 3 months (titration phase) and every 4 months thereafter. The target in the clinical group was the clinical improvement of the patient, whereas the target in the BNP group was to decrease BNP to 100 pg/ml. BNP was measured using the Biosite point-of-care assay. The primary endpoint was emergency transplantation, death or hospitalisation related to HF. Mean age was 64 years, mean

follow-up was 15 months. The primary composite endpoint rate was markedly lower in the BNP group with a 54% relative risk reduction during follow-up. Event-free survival was also significantly better in the BNP group (84.3% in the BNP group versus 73.3% in the clinical group;  $p < 0.001$ ).

Two patients in the BNP group and ten patients in the clinical group were hospitalised twice or more for acute HF decompensation ( $p < 0.05$ ). One fourth of treatment modifications in BNP group was related to patient's symptoms and three fourths were related only to BNP level. Interestingly, only 40% of patients reached the BNP target of 100 pg/ml at the end of titration phase in BNP group. The STARS-BNP investigators concluded from their data that in HF patients treated according to guidelines, the use of BNP plasma levels to guide medical therapy reduced death and hospital admission for HF, and delayed the time to first event compared to clinically guided treatment.

Beyond doubt, the use of BNP or NT-proBNP has the potential to significantly improve our management of patients with chronic HF. However, some questions and concerns remain. Firstly, several studies demonstrated variation of intra-individual BNP/NT-proBNP concentrations of >30% (ranging from 30% to 50%) with reference change values at the 95% confidence interval (ie the estimated critical difference) ranging from 99% to 130% in healthy subjects and heart failure patients despite identical clinical status. According to this estimated confidence interval, only a great change in plasma BNP levels should be considered significant in an individual patient (for example, a decrease of >50% or an increase of more than two-fold). However, many recent clinical studies have demonstrated that BNP variations below this estimated critical difference could also have clinical relevance. Like the concentration of other neuro-hormones, levels of plasma BNP/NT-proBNP fluctuate widely and rapidly along with heart rhythm and blood pressure variations in response to physiological stimuli. However, biological variation of BNP should not be interpreted strictly as random fluctuation around a homeostatic set-point, as assumed by the common model used in all studies on biological variation of BNP reported in the literature. Most likely, most of the variation of intra-individual BNP/NT-proBNP concentrations reflects true biological variation that we fail to detect with our common insensitive clinical tools [52, 53]. Evidence from endpoint studies suggests that in HF patients a change in BNP/NT-proBNP >30% is clinically meaningful [44]. Secondly, the BNP target pursued in the STARS-BNP study was very low. The benefit regarding the combined endpoint of death or HF hospitalisation was counterbalanced by a

higher rate of hospitalisations due to non-HF reasons. These most likely included hypovolaemia, renal failure, and falls associated with the aggressive treatment regime. Therefore, a slightly higher BNP target may be more appropriate in many patients, particularly the elderly. The results of other

ongoing randomised trials on BNP/NT-proBNP guidance in chronic HF patients will demonstrate, whether improvements in outcome can also be achieved in elderly patients with predominately diastolic HF [54, 55].

## Future indications

The list of potential future indications for the measurement of BNP and NT-proBNP is long. Numerous studies have established that BNP and NT-proBNP levels provide independent and powerful prognostic information in various additional settings. These include healthy volunteers, patients with stable coronary artery disease, acute coronary syndrome, primary pulmonary hypertension, sepsis, community-acquired pneumonia, and renovascular hypertension [56]. Moreover, the measurement of BNP and NT-proBNP has been suggested as a marker of myocardial ischaemia [57-61].

These future indications have in common that they currently still lack an established therapeutic or prophylactic consequence in response to the information obtained by the BNP or NT-proBNP level. Therefore, additional research is necessary to define the role of BNP and NT-proBNP in these clinical situations.

In conclusion, our HF patients are in desperate need for better medical care. The introduction of BNP and NT-proBNP represents a major advance in the diagnosis and management of HF. The use of these quantitative markers of HF is cost-effective in the diagnosis of HF and allows us to improve medical and economic outcomes. We should take advantage of these simple tests to improve the management of our HF patients, and other conditions presenting with acute dyspnoea.

### Correspondence:

Prof. Dr. Christian Mueller  
Department of Internal Medicine  
University Hospital  
Petersgraben 4  
CH-4031 Basel  
Switzerland  
E-Mail: [chmueller@ubbs.ch](mailto:chmueller@ubbs.ch)

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