The Role of B-TYPE NATRIURETIC PEPTIDE (BNP) AND N-terminal pro brain natriuretic peptide (NT-pro BNP) in Cardiology

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Abstract:

In recent years biomarkers have emerged as important tools for diagnosis, risk stratification and therapeutic decision making in cardiovascular diseases. Currently, several promising new biomarkers are under scientific investigation. Most of these new biomarkers, however, are not yet suitable for clinical application, with the exception of B-type natriuretic peptide (BNP) and its N- terminal fragment (NT-pro BNP). Both markers have proven their diagnostic usefulness in a great number of studies and thus have progressed from bench to clinical application. The aim of this article is to concisely review the diagnostic and prognostic role of BNP and NT-pro BNP in different cardiac diseases.

Key words: BNP, biomarkers, cardiology, NT-pro BNP, diagnostic, natriuretic peptide

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INTRODUCTION

Natriuretic peptides (NPs) are substance that induces natriuresis, which is the excretion of sodium by the kidneys. It is made by the cardiac organ. It is controlled in partly by enzymes such as neprilysin and corin, a transmembrane serine protease expressed by cardiomyocytes. The NP plays a central role in cardiac disorder [1]. The NPs are a group of peptide hormones that play important roles in the control of renal, cardiovascular, endocrine, and skeletal homeostasis. NPs is classified into four groups; atrial NP (ANP), brain-type NP (BNP), C-type NP and dendroaspis NP, a D-type NP, each with its own characteristic roles [2]. The BNP and N-terminal pro BNP (NT-pro BNP) are found in the bloodstream normally, only in small levels. High levels can be regarded as the heart is not pumping as much blood as the body requires. NP tests measure the levels of BNP or NT-pro BNP in the blood. The NP tests are both useful in diagnosing heart failure, but rely on different types of measurements [3]. NP tests are most often used to diagnose or rule out heart failure. If it has already been diagnosed with heart failure, the test may be used to: Find out the severity of the condition, plan treatment and find out if treatment is working. The test may also be used to find out whether or not your symptoms are due to heart failure [4]. Hence, a NP test may be needed when there are symptoms of heart failure such as: Difficulty breathing, coughing or wheezing, fatigue, swelling in abdomen, legs, and/or feet and loss of appetite or nausea [5].

PHYSIOLOGICAL ACTIONS OF NPs

NP is a set of unique hormones that are primarily produced by tissues of the cardiovascular system. They have a peculiar 17 amino acid residue ring structure that significantly contributes to their bioactivity and specificity. Their production in the heart is triggered by sympathetic nerve activity, angiotensin II, endothelin, and cardiac chamber distension [6]. Larger peptide precursors are used in the cardiomyocytes that perform this synthesis. These NPs circulate to their target tissues after being released by the cells, where they bind to NPR-A receptors linked to guanylyl cyclase and the production of cGMP.

ANP is a peptide with 28 amino acids. Atrial myocytes create, store, and release it. As a result, increased blood volumes are associated with increased ANP levels. BNP is a peptide with 32 amino acids. It is initially located in the brain. The heart's ventricular tissue produces the majority of it. It is known that during heart failure, there is an increase in the synthesis and release of BNP. A circulating enzyme that breaks down NPs is called neutral endopeptidase (neprilysin). The circulation levels of NP are increased and their actions become active when this enzyme is inhibited [7].

Synthesis and Structural of BNP & NT-pro BNP

B-type natriuretic peptide, which is also called brain-type natriuretic peptide (BNP), was first described in 1988 after isolation from porcine brain. However, it was soon found to originate mainly from the heart, representing a cardiac hormone. BNP belongs to the natriuretic peptide family together with other structurally similar peptides, namely atrial natriuretic peptide (ANP), C-type natriuretic peptide (CNP), and urodilatin. The natriuretic peptides have in common a characteristic biochemical structure which consists of a 17 amino-acid ring and a disulfide bridge between two cysteine molecules. The major source of BNP synthesis and secretion is the ventricular myocardium. Whereas ANP is stored in granules and can be released immediately after stimulation, only small amounts of BNP are stored in granules and rapid gene expression with de novo synthesis of the peptide is the underlying mechanism for the regulation of BNP secretion. BNP is synthesised as a prehormone (pro BNP) comprising 108 amino acids. Upon release into the circulation it is cleaved in equal proportions into the biologically active 32 amino acid BNP, which represents the C-terminal fragment, and the biologically inactive 76 amino acid N-terminal fragment (NT-pro BNP). Both molecules are constantly released and can be detected in the blood. The main stimulus for increased BNP and NT-pro BNP synthesis and secretion is myocardial wall stress. Furthermore, factors such as myocardial ischaemia and endocrine (paracrine) modulation by other neurohormones and cytokines are also of importance. In the systemic circulation BNP mediates a variety of biological effects by interaction with the natriuretic peptide receptor type A (NPR-A) causing intracellular cGMP production. The physiological effects of BNP are manifold and comprise natriuresis/diuresis, peripheral vasodilatation, and inhibition of the renin– angiotensin–aldosterone system (RAAS) and the sympathetic nervous system (SNS). BNP is cleared from plasma by binding to the natriuretic peptide receptor type C (NPR-C) and through proteolysis by neutral endopeptidases. In contrast, NT-pro BNP is mainly cleared by renal excretion. However, recent studies suggest that there might also be other important clearing mechanisms for NT-pro BNP. The half-life of BNP is 20 mins whereas NT-pro BNP has a half-life of 120 mins, which explains why NT-pro BNP serum values are approximately six times higher than BNP values, even though both molecules are released in equimolar proportions (figs 1 and 2) [8]

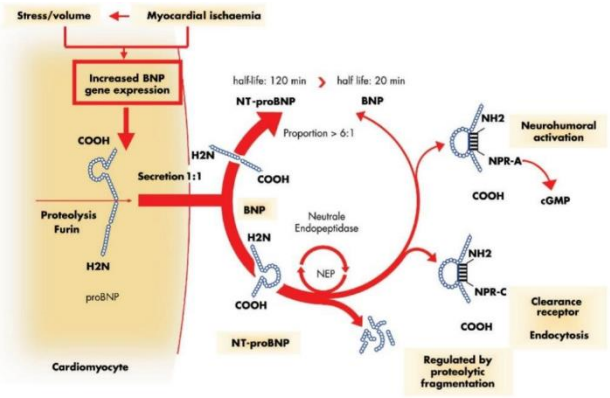

Figure 1 shows a schematic representation of the synthesis, release, and receptor interaction of B-type natriuretic peptide (BNP) and NT-pro BNP. The cardiomyocytes produce BNP as a prohormone. Pro BNP is split into BNP and the N-terminal fragment (NT proBNP) in equimolar amounts as soon as it is released into the bloodstream. The rise in intracellular cGMP caused by the interaction between BNP and the natriuretic peptide receptor type A (NPR-A) mediates the biological effects. Reproduced with E. Spannuth's permission.

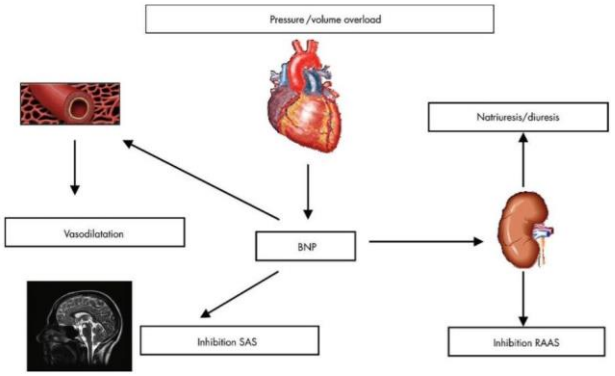

Figure 2 Physiological effects of B-type natriuretic peptide (BNP). Volume or pressure overload leads to ventricular wall stress and BNP release. The systemic biological effects of BNP are peripheral vasodilatation, increase in natriuresis and diuresis, and inhibition of the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system (RAAS).

Biological determinants of BNP & NT-pro BNP concentrations

Blood levels of natriuretic peptides are affected by several physiological factors such as circadian rhythm, age, exercise, and body posture. The factors that contribute to increased concentrations of the peptide due to the aging process are cardiac and renal functions typical of senescence, reduced degradation of peptides and development of resistance to the action of peptides in the target organs, namely kidney, leading to a significantly higher production of BNP **[9]**. Furthermore, the most common cardiac alterations in the elderly, namely left atrial enlargement, increased afterload and presence of diastolic dysfunction, may interfere in peptide plasma levels **[10,11]**. Several drugs, including diuretics, angiotensin-converting enzyme (ACE) inhibitors, adrenergic agonists as well as sex, thyroid and glucocorticoid hormones may modify the circulating levels of natriuretic peptides **[12]**. Serum concentrations of BNP are higher in women than in men in the absence of cardiac dysfunction **[13]**. This increase could be related to estrogen levels, since it was observed higher peptide levels in women who underwent hormone replacement therapy. Another study suggested that there would be a partial suppression of BNP secretion and of inactive N-terminal pro-BNP (NT-pro- BNP) associated with levels of free teststerona, substantiating lower peptide levels in men. It is suggested that specific reference values for age and gender should be applied to the interpretation of BNP values.

Comorbidities that influence the interpretation of BNP concentrations

The presence of obesity may interfere in BNP levels, inasmuch as adipose tissue is closely related to receptors that participate in the degradation of circulating natriuretic peptides **[14]**. Higher cut-off values are recommended for the diagnosis of heart failure (HF) in obese patients **[15].** The presence of renal failure may increase BNP values and higher cutoff values should be adopted for the detection of HF in advanced chronic renal patients **[16]**. Patients with chronic renal disease are prone to an increase in atrial pressure, systemic pressure and ventricular mass, situations in which a rise in the synthesis and secretion of BNP would be expected **[16]**. Renal excretion of BNP has been described, but alterations in the circulating levels in renal disease patients are more likely related to the reduction of clearance by natriuretic peptide receptor C (NPR- C) and neutral endopeptidase (NEPs) **[17]**. Concomitant lung disease does not diminish the usefulness of distinguishing patients with or without HF. However, it is important to consider that BNP is elevated in one third of cases of pulmonary embolism. This rise accounts for the increase in right ventricular pressure and indicates a worse prognosis for pulmonary embolism **[18]**. In cases of chronic pulmonary hypertension without cardiac volume overload, expected BNP values range from 100 to 500 pg/ml **[19]**.

BNP and NT-pro-BNP in the assessment of cardiac function

BNP is synthesized as pre-pro-BNP, especially in the ventricular myocardium. In the myocyte, pre-pro-BNP is cleaved by enzymatic action on pro-BNP and released as BNP (active form) and NT-pro BNP (inactive form). Both BNP and NT-pro-BNP levels indicate the severity of heart failure, but there are differences between the two tests as to the influence of age and renal function. BNP is cleared from the plasma by glomerular filtration and also by endopeptidase degradation. In contrast, NT-pro-BNP may be eliminated exclusively by glomerular filtration, hence the strong influence of renal function on NT-pro-BNP

concentrations. As a decrease in glomerular filtration rate occurs with age, the diagnostic cutoff value for NT-pro-BNP is age dependent. The same applies to BNP, but with lower intensity **[20]**. Both peptides are usually higher in patients on hemodialysis treatment even in the absence of circulating volume overload **[21]**. Despite these limitations, a study evaluating the effectiveness of natriuretic peptides in clinical practice demonstrated that both BNP and NT-pro-BNP are useful tools in the management to heart failure **[22].** Many studies have assessed BNP concentration values in order to aid HF diagnosis in patients with dyspnea. A study measuring ANF and BNP in emergency patients with dyspnea demonstrated that plasma BNP at admission had a higher accuracy than the ejection fraction of the left ventricle and ANF for the diagnosis of HF [23]. In this study, the authors defined HF based on clinical findings, conventional tests, response to treatment and assessment of the ejection fraction of the left ventricle by angiography. Another study, assessing BNP in 250 patients who were admitted to the emergency room with dyspnea as the chief complaint, identified a significant discrepancy between BNP values in patients with and without HF diagnosis [24]. BNP value of 80 pg/ml was highly specific and sensitive for the diagnosis of HF. The negative predictive value of BNP < 80 pg/ml was 98%, thus excluding HF. A major multicenter trial evaluated 1,586 patients with acute dyspnea in order to verify whether BNP may be deployed to differentiate patients with HF from those with other causes of shortness of breath [25]. The final results showed that BNP had good specificity and high negative predictive value to exclude the diagnosis of HF, with an area under the receiver operating characteristic curve (ROC) of 0.91, indicating excellent accuracy. The results also demonstrated an association between BNP plasma levels and severity of heart failure, in accordance with the functional classification of the New York Heart Association (NYHA). The same study corroborated that a simple BNP assessment was more accurate for the diagnosis of HF than Framingham criteria for HF and the American National Health and Nutrition Examination scale (NHANES) [25]. Thus, the assessment of BNP may be deployed to exclude the diagnosis of HF, mainly if the symptoms and signs are equivocal or mild and when they occur associated with comorbidities such as lung disease or obesity [26].These diseases cause dyspnea, hindering the definition of cardiac etiology on clinical examination. There is a positive correlation between BNP levels and end diastolic pressure of the left ventricle and an inverse correlation with left ventricular function. One study indicated that these levels represent an independent assessment of ventricular function, precluding the need for any further costly tests [27]. An investigation was conducted with ambulatory elderly population in order to establish reference intervals and concentration limits for decision making based on BNP and NT-pro- BNP assessment. It comprised 218 normal elderly patients and 474 with symptoms associated with HF. The upper limit of BNP reference range for healthy elderly was ≤ 97 pg/ml. The cutoff value for decision making based on cardiovascular mortality following the HF population was approximately 170 pg/ml [28]. BNP levels above 400 pg/ml characterize the clinical manifestations resulting from HF, whereas values below 100 pg/ml practically exclude HF as the cause of symptoms. For values between 100 and 400 pg/ml, clinical and other methods should be deployed for differential diagnosis [29]. BNP assessment has proved to be cost-effective, inasmuch as the rapid diagnosis of HF obtained with its assessment decreases the time to initiate therapy, length of hospitalization and care costs. Once HF is diagnosed, it becomes essential to characterize the type and degree of the cardiac involvement. In the elderly, numerous heart diseases, mainly coronary artery disease and aortic valve stenosis, may progress silently, therefore their identification is fundamental to a suitable approach. Thus, a two-dimensional echocardiography is recommended for all elderly patients with HF for diagnostic, etiologic, prognostic and functional comparison [30]. A study investigated the use of BNP as a risk stratification strategy for cardiovascular disease by evaluating 10 biomarkers in 3,219 patients participating in the Framingham Heart Study: C-reactive protein (CRP), BNP, NT-pro-BNP, aldosterone, renin, fibrinogen, D-dimer, plasminogen activator inhibitor type 1, homocysteine and serum albumin/urinary creatinine. After seven years observing cardiovascular events, five biomarkers were predictors of death (BNP, CRP, serum albumin/urinary creatinine, homocysteine and

renin) and two markers (BNP and serum albumin/urinary creatinine) were predictors of both death and cardiovascular risk [31]. NT-pro-BNP has also been used for cardiovascular risk stratification in patients with acute coronary syndrome without ST segment elevation. It was confirmed that higher baseline NT-pro BNP was associated with severe coronary artery disease and death in 1,141 patients with high troponin T [32]. For the diagnostic approach of HF with an ejection fraction of the normal left ventricle, the European Consensus of Cardiology (2007) recommends the association of BNP assessment and E/E' ratio with echocardiography, hence increasing the area under the ROC curve of 83% to 95% diagnostic accuracy [33]. High BNP or NT-pro-BNP levels are not sufficient evidence for the diagnosis of heart failure with ejection fraction of the normal left ventricle, thus requiring additional noninvasive exams. B-type natriuretic peptide in the evaluation of cardiac function 245 For exclusion of HF with an ejection fraction of the normal left ventricle, a high negative predictive value would be below 120 pg/ml for NT-pro-BNP and 100 pg/ml for BNP. For diagnosis, a high positive predictive value of NT-pro-BNP would be as from 220 pg/ml and 200 pg/ml for BNP [33]. Natriuretic peptides are especially recommended for exclusion of HF with an ejection fraction of the normal left ventricle, and not for diagnosis. Nevertheless, it should be complemented with other noninvasive investigation when applied for diagnostic purposes [33]. The use of serial BNP measurements to monitor the treatment of HF is not well established. Caution should be exercised when interpreting the variation in 50% concentration as related to medical therapy, insofar as there is a consistently high biological variation for both BNP and NT- pro-BNP [34]. A systematic review study indicates that the groups of patients with chronic HF monitored with NT-pro-BNP during therapy received more intensive care, more aggressive therapy and progressed with better quality of life, improvement in echocardiographic parameters and a few adverse events [35]. The risk assessment of cardiovascular disease in the setting of primary prevention with BNP or NT-pro-BNP is unjustified. The increase in the concentrations of BNP or NT-pro-BNP is associated with higher mortality in the following 2-7 years in the studied populations. However, the benefits of therapy based on these assessments are uncertain [36]. For early diagnosis of HF, plasma BNP or NT-pro-BNP may be helpful in patients with recent onset of dyspnea, improving diagnostic accuracy with a high negative predictive value [37].

CLINICAL APPLICATIONS

Heart failure

The diagnostic value of BNP and NT-pro BNP is best investigated in patients with heart failure. In a large number of studies it has been consistently found that BNP and N- pro BNP are elevated in patients with heart failure, and values were found to be related to disease severity as assessed by New York Heart Association (NYHA) functional class (fig 3), left ventricular systolic ejection fraction, and left ventricular diastolic function [8].

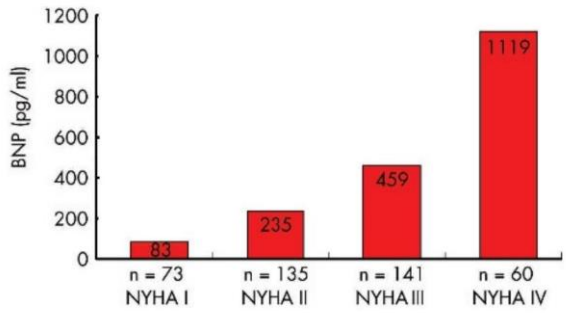

Figure 3 Median B-type natriuretic peptide (BNP) in patients with heart failure according to New York Heart Association (NYHA) functional status. Adapted from Wieczorek etal.[38]

Guiding and monitoring heart failure treatment

Even though there is a large body of evidence demonstrating the association of elevated BNP or NT-pro BNP values with disease severity and prognosis in heart failure patients, there are limited data available which focus on the therapeutic implications derived from BNP and NT-pro BNP assessment. It has been reported that BNP and NT-pro BNP can be attenuated by treatment with drugs such as angiotensin receptor blockers or b blockers. Furthermore, several studies have been able to demonstrate changes of BNP and NT-pro BNP values during

recompensation therapy in acute heart failure related to an improvement in invasively measured haemodynamic parameters[39]. Subsequently, it was also shown that a decrease in BNP during the initial hospital stay was associated with a favourable clinical outcome, whereas no change or an increase in BNP values was associated with an unfavourable outcome [40]. In a small pilot study by Troughton et al involving 79 patients with clinically overt heart failure and an ejection fraction below 40%, patients were randomly assigned either to clinically guided therapy or a combination of clinical parameters and BNP measurement to guide therapy. The event-free survival rate over 180 days was significantly lower in the BNP guided group [41]. In another study, a substudy of the Australia-New Zealand heart failure trial, 297 patients with ischaemic heart disease and an ejection fraction below 45% were randomised to placebo or carvedilol treatment. Patients with NT- pro BNP values on admission above the median had a significant risk reduction if they were treated with carvedilol, whereas in the group of patients with BNP values below the median, the clinical outcome was identical for both the carvedilol and placebo treatment groups. This suggests that NT-pro BNP might help to identify those heart failure patients who derive benefit from active treatment with carvedilol (fig 4) [42]. These results are in contrast to the COPERNICUS trial, which enrolled 2289 patients with severe chronic heart failure (NYHA class III or IV) and an ejection fraction below 25%. The overall one year mortality of 14.9% in this study was extremely high and it was found that patients receiving active treatment with carvedilol had a better outcome than placebo treated patients. In a substudy of this trial including 1011 European patients, NT-pro BNP values were obtained at study entry. Even though NT-pro BNP was highly predictive for an unfavourable outcome in those patients, the treatment effect of carvedilol did not differ between patients with high NT-pro BNP values (above the median) and those with low NT-pro BNP values[43]. Therefore, the data from these studies are promising and suggest that BNP and NT-pro BNP might be linically useful for determining the optimal treatment for patients with heart failure and for monitoring treatment effects. The results of ongoing larger prospective trials, however, are awaited before definite conclusions can be reached.

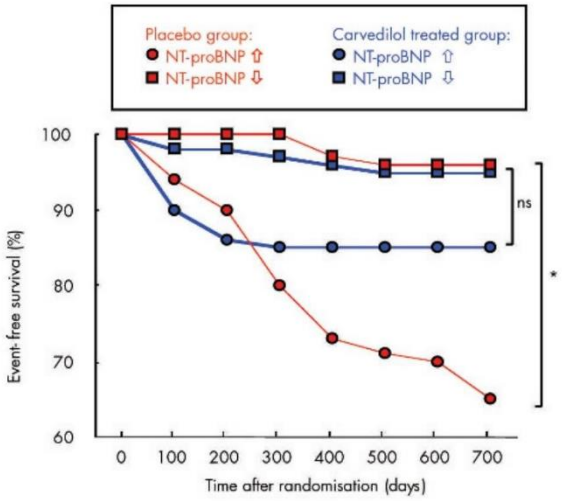

Figure 4: Kaplan–Meier curves for event-free survival of patients with ischaemic left ventricular dysfunction treated with carvedilol (blue line) or placebo (red line), with NT-pro BNP below the median (circles) and NT-pro BNP above the median (squares). ns, not significant; *p < 0.001. Modified from Richards et al [42].

Coronary artery disease

Originally BNP and NT-pro BNP were considered biomarkers for heart failure only. More recently, however, there has been a growing body of data on the relevance of both markers in coronary artery disease. It is widely believed that the underlying pathophysiological process for an increase in BNP and NT-pro BNP values is left ventricular systolic or diastolic dysfunction caused by myocardial ischaemia leading to an increased wall stress. Nevertheless, data derived from experimental studies suggest a direct release of BNP and NT-pro BNP from cardiomyocytes in response to myocardial ischaemia independent of ventricular wall stress. It has also been demonstrated that BNP even rises after temporary myocardial ischaemia induced by balloon inflation during coronary intervention.

Acute coronary syndromes (ACS)

Substudies of large scaled clinical trials (OPUS-TIMI 16, TACTICS-TIMI 18, FRISC II, GUSTO IV, PRISM)[44,45] have evaluated the prognostic

value of BNP and NT-pro BNP in patients presenting with non-ST elevation acute coronary syndromes (NSTE-ACS). In all studies elevated values of BNP and NT-pro BNP have consistently been found. Furthermore, both markers were highly predictive for an adverse outcome independently of other biomarkers, especially troponins and C reactive protein (CRP). However, it must be emphasised that BNP and NT- pro BNP were predictive for mortality and heart failure after an ACS but not for recurrent ischaemic events. Similar results were reported for the predictive value of BNP and NT-pro BNP after ST elevation myocardial infarction (STEMI) [46]. Different studies evaluated whether serial assessment of NT-pro BNP is superior to a one time point assessment at admission. Jernberg et al studied 755 patients with an ACS and observed no difference in the predictive value as indicated by the AUC of the ROC curve for NT-pro BNP on admission and after 6 h [44]. In a substudy of the PRISM trial Heeschen et al demonstrated an incremental prognostic value of serial NT-pro BNP assessment on admission and a second measurement 72 h later. In the FRISC-II trial serial NT-pro BNP analyses were evaluated during the acute and the chronic phase of ACS and disclosed that the predictive value of NT-pro BNP value measured three and six months after the index event is a better predictor for two year mortality than early NT-pro BNP determination at admission or at 48 h after the acute event. However, the best time to take a sample for BNP or NT-pro BNP assessment still remains to be fully established. In addition, the therapeutic benefits that can be derived from BNP and NT-pro BNP assessment in ACS are not clear. The only published study to date which investigated the usefulness of NT-pro BNP for identifying patients who might benefit from an early invasive strategy is a substudy of the FRISC-II trial. In this study a trend towards a better outcome of patients with NT-pro BNP values in the highest tertile was observed. However, in combination with elevated interleukin (IL)-6 concentrations, NT-pro BNP values in the third tertile indicated a significant treatment benefit from early invasive therapy[47]. In the substudy of the PRISM trial, Heeschen et al analysed the effect of glycoprotein IIb/IIIa inhibition with tirofiban with respect to NT-pro BNP values [46]. Even though they found that patients with high NT-pro BNP values had a lower event rate with tirofiban treatment compared to placebo at 48 h, they found no significant interaction between NT-pro BNP values and the clinical benefit of tirofiban treatment at 30 days. Several matters need to be addressed before BNP and NT-pro BNP can be recommended for application in clinical routine in patients with ACS. Different cut-off values have been applied in the various studies, but to date no clearly defined cut-off value has been established. Moreover, further studies are needed to assess the therapeutic benefits that can be derived from BNP and NT-pro BNP assessment.

Stable coronary artery disease

Recent studies have evaluated the relevance of BNP and NT-pro BNP in patients with stable angina pectoris. It could be demonstrated that NT-pro BNP serum concentrations show a close relation to the extent of coronary artery disease and inducible myocardial ischaemia [48,49]. Furthermore, three independent studies have indicated that BNP and NT-pro BNP provide prognostic information on long term mortality and adverse cardiovascular events superior to that provided by traditional risk factors [50]. However, no cut-off values are clearly defined and therapeutic consequences remain open.

Valvular heart disease

Valvular heart diseases lead to either volume or pressure overload of the left ventricle. Thus it is reasonable to expect that BNP and NT-pro BNP could be useful in evaluating the severity and prognosis of valve diseases. However, data are sparse. For patients with valvular aortic stenosis it has been shown in several small studies that both BNP and NT-pro BNP are related to disease severity, functional status and disease progression, with a decline of elevated values after successful valve replacement. Furthermore, the values provide prognostic information for an unfavourable postoperative outcome [51,52]. The therapeutic implications of these findings are uncertain, but it can be speculated that BNP or NT-pro BNP assessment might help to decide upon the optimal timing for valve surgery. Data on the diagnostic utility of BNP and NT-pro BNP in patients with aortic regurgitation and mitral regurgitation are very limited, demonstrating that both markers are elevated in relation to

disease severity. However, there are no data available concerning the prognostic value. Generally, there is good evidence that BNP and NT-pro BNP assessment might play a role in the future diagnostic work up of patients with valvular heart diseases, but the clinical benefits that can be derived have not yet been established. Thus, further studies are warranted.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

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CONCLUSIONS

BNP and NT-pro BNP have emerged as powerful biomarkers in various cardiovascular diseases. Both markers can be detected in serum plasma using commercially available assays. The diagnostic performance of BNP and NT-pro BNP is comparable and there is no meaningful difference between them. They reflect haemodynamic myocardial stress independent of the underlying pathology, thus they are not specific for a distinct pathology such as heart failure but for cardiovascular diseases in general. Their particular strength is to rule out heart failure in patients presenting to the emergency department with shortness of breath. They provide strong and independent prognostic information in patients with heart failure, stable coronary artery disease, acute coronary syndromes, and valvular aortic stenosis.

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