

# Natriuretic peptides (BNP and NT-proBNP): measurement and relevance in heart failure

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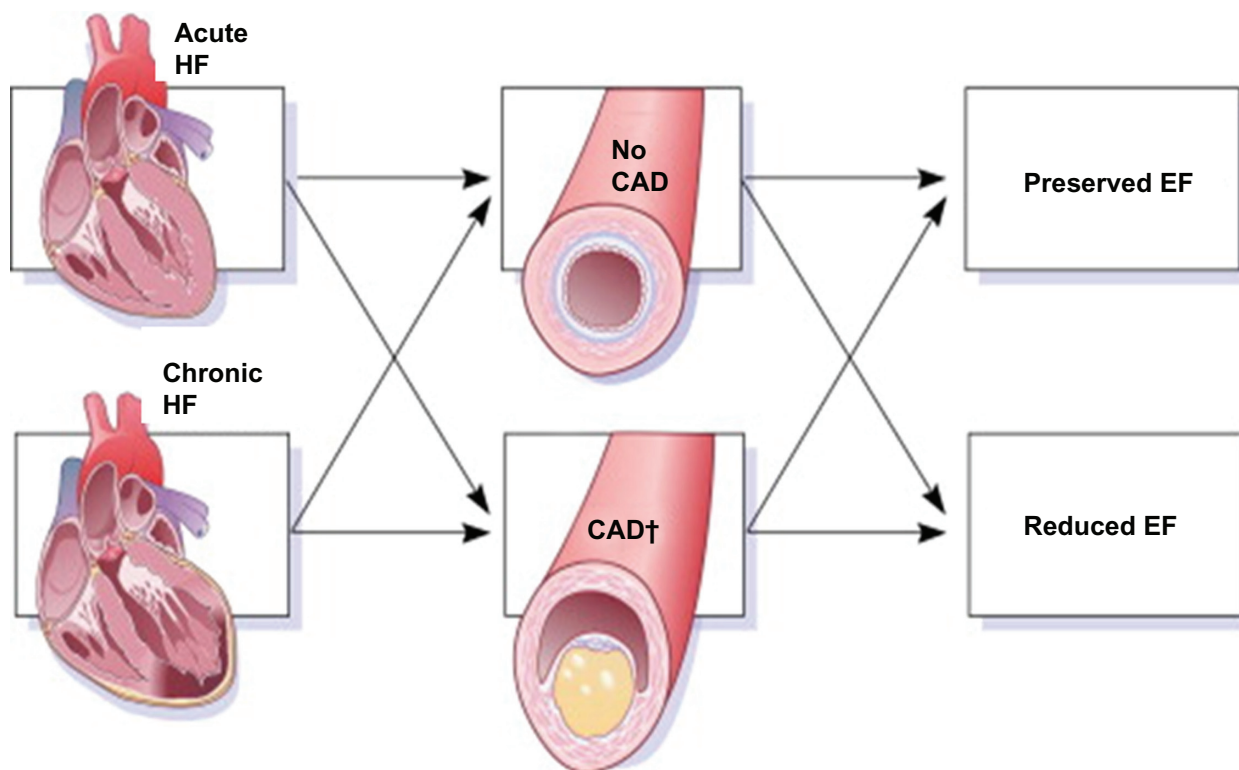
**Abstract:** For patients presenting with acute dyspnea, an incorrect diagnosis could increase the mortality risk. When used in the evaluation of patients with acute symptoms, brain natriuretic peptide and N-terminal pro-brain natriuretic peptide (BNP and NT-proBNP, respectively) testing is highly sensitive for the diagnosis or exclusion of acute or chronic decompensated heart failure (HF). It has been demonstrated that BNP and proBNP levels can facilitate diagnosis and guide HF therapy. Natriuretic peptide (NP) levels are strictly related with HF severity; they are particularly increased in more advanced New York Heart Association (NYHA) classes and in patients with poor outcome. Therefore elevated NP levels were found to correlate with the severity of left ventricular systolic dysfunction, right ventricular dysfunction and pressures, and left ventricular filling alterations. However, the optimal use of NP determination agrees with patient history, physical examination, and all other diagnostic tools. There are some clinical conditions (ie, obesity, renal insufficiency anemia) for which the NP measurement is not diagnostic. Algorithm building taking into consideration all clinical and echocardiographic parameters, as well as NP measurements, may lead to the earlier identification and better risk stratification of patients with chronic HF, independently from etiology.

**Keywords:** heart failure, diagnosis, echocardiography, natriuretic peptides

## Introduction

Chronic heart failure (CHF) is a condition occurring with increased frequency and particularly in older patients >75 years old. Its prevalence is between 0.8% and 2% in the general population.<sup>1</sup> Patients may be classified as having heart failure (HF) when presenting for the first time (*de novo*) with acute heart failure (AHF) or in decompensated worsening CHF. In both groups the presence and extent of coronary artery disease (CAD) may determine the initial, in-hospital, and post-discharge management. Low blood pressure, renal impairment, and/or signs and symptoms refractory to standard therapy characterize advanced HF. *De novo* HF represents the remainder of patients presenting with AHF and may be classified further by dividing them into those with pre-existing risk for HF (eg, hypertension, CAD) without evidence of prior left ventricular (LV) dysfunction or structural abnormalities, and those with pre-existing cardiac structural abnormalities (eg, reduced ejection fraction [EF]) (Figure 1).<sup>2</sup> Early diagnosis and categorization is very important for an effective therapy optimization and prognosis improvement. However, categorization is often difficult because of nonspecific symptoms and the lack of a gold standard protocol for correct diagnosis. After traditional

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**Figure 1** Classification of acute and chronic heart failure on the basis of coronary diseases and systolic dysfunction presence.

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**Abbreviations:** HF, heart failure; CAD, coronary artery disease; EF, ejection fraction.

first-line examinations (ECG, thorax radiography and clinical examination) echocardiography is the technique recommended for patients affected by HF, because of its diagnostic and etiologic capability.

European Guidelines (2008) emphasized the role of natriuretic peptides (NP) as potential markers for HF.<sup>3</sup> Therefore, NPs seem to be independent mortality predictors in patients with CHF. Although most studies showed that brain natriuretic peptide (BNP) is a marker with a higher sensitivity and specificity; however the application of this analysis in clinical practice is often limited by the absence of a universally accepted normal range. A single determination of BNP at any time during the progression of chronic HF is a clinically useful tool for risk stratification.<sup>4</sup> The hypothesis that repeated measurements could carry prognostic information beyond a single measure was confirmed in different settings. The importance of repeated determinations is in monitoring the progression of disease and in evaluating the clinical effects of medical therapy.<sup>5</sup> In the near future, algorithm building will take into consideration clinical and echocardiographic parameters as well as NP measurements, and this may better ensure the correct diagnosis and categorization for patients with worsening prognosis.

## Natriuretic peptides and heart failure diagnosis

BNP is a hormone that is secreted predominantly by the ventricles, and reaches very high plasma concentrations in subjects with congestive HF or AHF. BNP is synthesized in the heart as a reaction to cardiac wall distension and stretching, and neurohormonal activation. The cardiomyocytes synthesize a pre-propeptide (preproBNP 134 amino acids) which is split into a signal peptide and a propeptide (proBNP 108 amino acids). During secretion from the cardiomyocytes, proBNP is split at a ratio of 1:1 into the physiologically active BNP (32 amino acids) which corresponds to the C-terminal fragment, and the biologically inactive N-terminal fragment (NT proBNP, 76 amino acids).<sup>6</sup> Secreted NP leads to natriuresis and vasodilation activation with a concomitant inhibition of the renin–angiotensin system and adrenergic activity.<sup>7</sup> An increase in plasma BNP concentration results in improved myocardial relaxation and has an important regulatory role in response to acute increases in ventricular volume by opposing vasoconstriction, sodium retention, and the antidiuretic effects of activated renin–angiotensin–aldosterone system. However, plasma NP levels are elevated in patients with acute myocardial infarction

and LV dysfunction; this increase persists during late phases of cardiac remodeling.<sup>8</sup> Elevated peptide levels are directly correlated with prognosis, NYHA score, intra-ventricular pressure, pulmonary pressure, and inversely proportional to cardiac output.<sup>9</sup> Increased plasma BNP concentrations have also been observed in hypertrophic cardiomyopathy, diastolic dysfunction and LV hypertrophy. In these circumstances, BNP levels appear related to the myocardial mass index, interventricular and posterior wall thickness.<sup>10</sup> Several studies have confirmed the effectiveness of determining plasma BNP concentrations in patients presenting with acute dyspnea. Initial research led by Dao et al studied 250 subjects that were admitted to the department of emergency medicine with acute dyspnea, they demonstrated that patients diagnosed with cardiac dyspnea had significantly elevated plasma BNP concentrations while patients with non cardiogenic dyspnea they were significantly lower. This is perhaps the differential key in patients who present with acute dyspnea as they showed that plasma BNP concentrations of less than 80 pg/mL had a 98% predictive negative value.<sup>11</sup> In a second, larger study, BNP levels were measured in 321 patients: the authors confirmed that patients with HF had higher BNP levels than patients with dyspnea due to respiratory diseases.<sup>12</sup> The first multicenter study, Breathing not Properly Study, enrolled 1586 emergency-department patients that presented with acute dyspnea and were all submitted to BNP measurement. The gold standard for congestive HF was adjudicated by two independent cardiologists (blind to the laboratory results), who reviewed all clinical data and standardized scores. BNP values directly correlated with the NYHA functional class: a linear correlation was seen among patients in NYHA I (197 pg/mL) compared to patients in NYHA IV (978 pg/mL).<sup>13</sup> In the same way, Lainchbury et al showed that concentrations of proBNP were considerably higher among patients with acute HF compared with those who had a dyspnea due to other causes.<sup>14</sup> Importantly, in this and in subsequent trials of patients with acute symptoms, the optimal proBNP concentration for diagnosis of acute HF was found to be considerably higher than those observed in studies of outpatient evaluation. In this study, investigators compared the proBNP assay (Roche Diagnostics, Indianapolis, IN) with the Biosite BNP assay (San Diego, CA, USA) and demonstrated identical areas under the receiver operating characteristic (ROC) curve (0.89 for both), demonstrating significant comparability of the two assays for the evaluation of the patient with acute symptoms.<sup>14</sup> Although the population sample was different some common data emerged and the diagnosis of HF was confirmed by clinical

history. Several parameters like high venous pressure recruitment, increase of LV dimension, and interstitial edema detected using chest radiogram were evaluated. None of these procedures showed a similar diagnostic accuracy as plasma BNP analysis. BNP is not only a good marker for the diagnosis of HF but is also an excellent indicator of the severity of CHF as BNP values increase linearly in relation to the stage.<sup>3</sup>

## Natriuretic peptide and outcome

In CHF patients NP measurement appears very important for risk stratification as high levels are associated with recurrent hospitalization and risk of sudden death.<sup>15</sup> Studies using natriuretic peptides have suggested that predischARGE BNP measurement appears a strong predictor for identifying subsequent death or hospital admission at 6 months.<sup>16,17</sup> In patients with coronary disease and preserved ventricular function, BNP provides strong and incremental prognostic information to traditional risk factors.<sup>18</sup> Although “hard targets” for proBNP values are not entirely defined, morbidity and mortality in CHF appear to increase markedly with a proBNP concentration >500 pg/mL. The best evidence of the prognostic value of BNP in CHF comes from statistically robust controlled clinical trials that include a large number of clinically well-characterized patients from different sites. The first data on proBNP from such a trial came from the Australia–New Zealand Heart Failure Group.<sup>19</sup> In approximately 300 patients with well-characterized chronic HF of ischemic etiology (LV ejection fraction [LVEF] < 0.45) randomized to receive carvedilol or placebo, levels of proBNP above the median were associated with increased risks for new decompensated HF events (relative risk [RR], 4.7; 95% confidence interval [CI], 2.2–10.3) and all-cause mortality (RR, 4.7; 95% CI, 2.0–10.9) during 18 months of follow-up, independently of age, NYHA functional class, LVEF, previous myocardial infarction, or previous HF admission. The most important Valsartan Heart Failure (Val-HeFT) trial, 5010 patients (85% with blood samples collected at study entry) with mild-to-moderate chronic HF receiving recommended medical therapy, were randomized to an angiotensin II type 1 receptor blocker or placebo.<sup>20</sup> An increment of 500 ng/L above the baseline concentration of proBNP carried an increased adjusted risk of 3.8% for mortality and 3.0% for hospitalization for HF. On multivariate analysis, proBNP ranked as the first prognostic factor in these patients – independent of and more powerful than traditional risk factors, such as NYHA class, age, LV dilation, or renal dysfunction.<sup>21</sup> A single determination of proBNP at any time during the

progression of chronic HF provides a clinically useful tool for risk stratification. The Val-HeFT study showed NP to be prognostically superior to several other recognized neurohormonal markers of risk in HF, including norepinephrine, renin activity, aldosterone, and endothelin. In a head-to-head comparison of BNP and proBNP including Val-HeFT study participants, baseline BNP and proBNP were powerfully and similarly related to both mortality and risk of admission with decompensated HF independent of, and more strongly than, any of a range of pertinent predictive demographic, clinical, and echocardiographic variables.<sup>21</sup> As with acute HF, the hypothesis that repeated measurements could lead to more precise prognostic information respect to a single measurement has been confirmed in different settings.<sup>9,10</sup> The value of repeated determinations of NP levels appears to be very important for monitoring the progression of heart disease and may help in evaluating the clinical effects of medical therapy. For instance, changes in NP levels during hospitalization were independent predictors of hospital readmission within 6 months and the death of patients hospitalized for decompensated HF. This result appears more relevant with respect to the improvement of some echocardiographic parameters (ejection fraction, diastolic volume).<sup>22</sup> For the above reasons some authors propose BNP analysis for the clinical evaluation and therapy guidance of HF.<sup>23,24</sup>

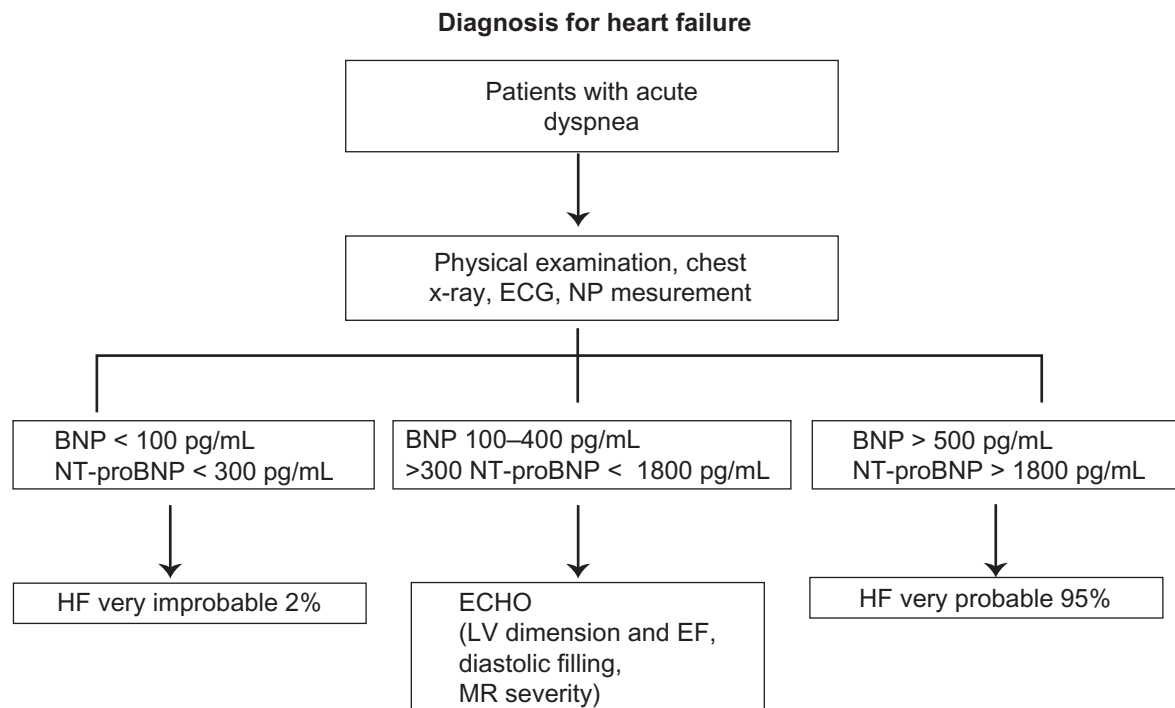
## Natriuretic peptides in CHF with preserved systolic function

LV systolic function is preserved in 40% to 50% of patients with CHF. The plasma levels of BNP correlate with echocardiographic measurements of both ventricular systolic and diastolic dysfunction.<sup>25–30</sup> Whereas the prognostic value of BNP in patients with impaired LV systolic function is well documented, there are less data for patients with CHF and preserved systolic function. In a prospective study that included 161 patients, the probability of death within 12 months after hospital admission was predicted by plasma levels of proBNP in patients with systolic dysfunction as well as in patients with preserved systolic function.<sup>31</sup> Similarly, proBNP values at discharge or changes in proBNP concentration during hospitalization were strong prognostic predictors of mortality, regardless of systolic function, in 244 patients admitted for decompensated HF and followed for 6 months.<sup>32</sup> Upcoming prospective trials will clarify the utility of NP in the prognosis and management of HF with preserved LVEF. It may be speculated that the association of high plasma NP levels and adverse outcomes could be simply a reflection of elevated filling pressures due to diastolic

dysfunction. NP levels have been shown to correlate closely with LV end-diastolic wall stress, mitral E wave velocity and early diastolic wave tissue velocity ratio ( $E/e'$ ) in the setting of HF and preserved systolic function.<sup>33–35</sup> Arterial hypertension is accompanied by higher levels of BNP, a reliable indicator of LV pressure and/or volume overload.<sup>34</sup> BNP levels are closely associated with LV hypertrophy and filling impairment and may be used to facilitate the diagnosis of LV diastolic dysfunction in hypertensives.<sup>35</sup> Wall thickness during arterial hypertension is the major compensatory mechanism to pressure overload and it is often associated with myocardial fibrosis collagen deposition and reduction in LV relaxation and distensibility.<sup>36</sup> Experimental studies demonstrated that the genetic expression of BNP in myocardial tissue is one of the most important early indicators of LV pressure overload and it occurs before LV hypertrophy (LVH) development.<sup>37–39</sup> However not all studies carried out on patients with high blood pressure showed the same results: while some researchers revealed that patients with LVH had high BNP levels, other researchers did not show a similar trend.<sup>40,41</sup> Such a discordance may be due to the different biases and populations enrolled in the studies. We believe that LVH alone is not a specific stimulus for BNP increase, increased NP levels could be firstly due to diastolic filling alterations independently from cardiac hypertrophy presence. In fact, the strongest correlations have been reported for BNP with LV diastolic wall stress which follows the stretch-mediated BNP secretion.<sup>33</sup> BNP levels increase with the greater severity of overall diastolic dysfunction, independently of LVEF, age, sex, body mass index, and renal function, and the highest levels are seen in subjects with restrictive filling patterns.<sup>42–44</sup> BNP levels correlate with indexes of filling pressure, including transmitral early filling velocity (E) and its ratio to early diastolic annular velocity ( $E/E_a$ ) – as well as with indexes of compliance and myocardial relaxation.<sup>43,44</sup> In subjects with normal LVEF, elevated proBNP (600 pg/mL) or BNP (100 pg/mL) are the strongest independent predictors of severe diastolic dysfunction; low BNP levels (140 pg/mL) exhibit a very high, negative predictive value (90%) for diastolic dysfunction.<sup>43,44</sup>

## Natriuretic peptide and right ventricular (RV) function

The right ventricle contributes to plasma levels of BNP or proBNP, with either normal or impaired LVEF. Levels of both peptides correlate with measures of RV size and function, increasing with greater dilatation and systolic dysfunction,



**Figure 2** Decisional algorithm for HF diagnosis on the basis of NP measurement: in case of NP values in the gray zone it is necessary to confirm or exclude diagnosis by echocardiography

**Abbreviations:** ECG, electrocardiogram EF, ejection fraction; NP, natriuretic peptide; BNP, brain natriuretic peptide; NT-proBNP, N-terminal probrain natriuretic peptide; HF, heart failure; LV, left ventricle; MR, mitral regurgitation; ECHO, echocardiogram.

and with increasing RV pressure estimates.<sup>43,44</sup> Few patients with pulmonary disease have a BNP levels >100 pg/mL, or proBNP levels > 350 pg/mL. In patients with pulmonary hypertension and RV dysfunction (eg, chronic obstructive pulmonary disease, pulmonary interstitial fibrosis or primary pulmonary hypertension) NP levels are often in a gray (unclear) zone or in a diagnostic zone for HF.<sup>45</sup> The accuracy of NP to diagnose HF is unchanged in the presence of pre-existing pulmonary disease. NP levels may also be increased in the setting of acute RV strain as a result of a pulmonary embolism. NP levels should not replace the standard diagnostic process when this condition is foreseen as these levels are higher in more than 30% of patients and they are associated with a worse outcome particularly when they occur with an increase in RV pressure and volume.<sup>46,47</sup>

Although the left ventricle is considered the most important contractility chamber, several recent studies have shown the pivotal importance of RV function. RV systolic dysfunction is an independent prognostic factor in patients with moderate to severe HF, and it is strictly related to reduced effort tolerance and exercise training. Although initial studies showed that increased NP levels were associated with the severity of LV dysfunction some authors have recently shown that patients with both RV and

LV dysfunction have increased levels.<sup>48–51</sup> Again, studies conducted by magnetic resonance and tomography confirmed a negative correlation between right systolic function and BNP levels in patients affected to post-ischemic cardiomyopathy.<sup>52</sup>

### Natriuretic peptides and gray zone: where echo is superior to the laboratory

Plasma BNP levels are a useful test in the diagnosis of HF with high sensitivity and specificity and strong positive predictive values. However, in some circumstances, BNP measurements without clinical interpretation and knowledge are not best able to differentiate cardiogenic or other dyspnea. There are a few confounding factors that could potentially alter plasma BNP levels such as; gender, females have higher levels do males. Thus increased BNP levels have a greater predictive value for adverse events in women.<sup>53</sup> NP also changes on the basis of the race: African-American and Hispanic subjects have higher levels than Caucasians in the same NYHA class.<sup>54</sup> Renal insufficiency also leads to augmented BNP levels independent to HF presence. In the same way patients with anemia have higher BNP levels. Significantly



increased levels have also been detected in patients with cardio-renal syndrome.<sup>55-57</sup> Contrarily, obesity is associated with lower BNP levels even with concomitant hypertension or LV dysfunction.<sup>58</sup> Finally supraventricular arrhythmia such as atrial fibrillation is related to higher BNP levels, suggesting that a more elevated normal range should be considered in patients with atrial fibrillation for HF diagnosis.<sup>59</sup> The lack of only one set of normal range values, due to the different idiopathic levels and commercially available analysis kits, make for further confusion for their clinical application. While some researchers state values of >100 pg/mL indicate HF, others suggest a value of >200 pg/mL. The ADHERE study, which included more than 48,000 patients, indicated the prognostic mortality values of 430 pg/mL.<sup>60</sup> In all the cited conditions a careful clinical examination together with an echocardiographic examination evaluating systo-diastolic function should be complementary to BNP analysis for diagnostic strategy and treatment implementation.

A diagnostic “score” incorporating NP results with patient history and physical examination has been described.<sup>61</sup> Although they are more complex than the recommended 1-step pathways for use of BNP testing, the algorithms for NT testing are clearer, providing much more information to the clinicians in clinical practice<sup>62</sup> (Figure 2).

## Conclusions

In CHF, measurement of BNP is among the strongest independent predictors of all relevant clinical outcomes and is useful across the whole spectrum of HF disease severity. High BNP levels are related to ventricular dysfunction severity and more advanced HF stages. Confusing factors (including obesity and renal dysfunction) may complicate the clinical interpretation of circulating BNP levels in patients with chronic and stable HF and should be considered when patients are evaluated. Serial measurements of BNP in the chronic outpatient setting appear to convey additional prognostic value for relevant adverse outcomes, including death or destabilization of HF requiring hospitalization, and they are thus recommended in every clinical approach.

NP can facilitate diagnosis and guide HF therapy. Their increase is directly related to more advanced NYHA classes and to poor prognosis. A complete algorithm including clinical, echocardiographic, and laboratory examinations will lead to a better stratification in the setting of HF.

## Disclosures

The authors disclose no conflicts of interest.

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