

# Recommendations for the use of natriuretic peptides in acute cardiac care<sup>†</sup>

## A position statement from the Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care

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### Introduction

Cardiac biomarkers are integral to the diagnosis and the treatment of acutely ill cardiac patients. The Working Group on Acute Cardiac Care of the European Society of Cardiology has established a Study Group to deal with issues related to cardiac biomarkers in this important area. Biomarkers are used to augment physician skill and judgment. Accordingly, we will outline principles for the application of biomarkers in acute cardiac care in a series of consensus documents; the first was on cardiac troponin (cTn).<sup>1</sup> The present review is on natriuretic peptides (NPs) as markers of cardiac stress and heart failure (HF). Natriuretic peptides help diagnostically and provide prognostic information. Most data have been obtained with assays measuring B-type natriuretic peptide (BNP) or N-terminal proB-type natriuretic peptide (NT-proBNP); therefore, the review focuses on these two markers, and it will mention new markers at the end.<sup>2,3</sup>

### Pathophysiology and biochemistry of natriuretic peptides

The endocrine nature of the heart was first understood with the description of atrial natriuretic peptide (ANP),<sup>4</sup> and later detection of brain (B-type) natriuretic peptide, that is, BNP,<sup>5,6</sup> which is mainly released from the myocardium in humans.<sup>7</sup> B-type natriuretic peptide has similar biological effects to ANP. Both are produced primarily in the atria under normal conditions.<sup>8</sup> Atrial natriuretic peptide is mostly stored in atrial granules and thus available for

ready release; BNP is stored to a limited extent. B-type natriuretic peptide requires *de novo* synthesis to be released in substantial amounts but the BNP gene responds rapidly.<sup>9</sup> The atria contain the highest BNP and ANP concentrations in normals but this is shifted to the ventricles for BNP in HF.<sup>10</sup> Natriuretic peptides promote natriuresis and diuresis, vasodilation, and antagonize the effects of the renin–angiotensin–aldosterone and sympathetic nervous systems (see *Table 1*).<sup>11</sup> In the central nervous system, NPs act as neurotransmitters and decrease sympathetic tone, reduce secretion of arginine-vasopressin and corticotrophin, and inhibit salt appetite and water drinking.<sup>12</sup> Natriuretic peptides modulate myocardial and vascular structure and function via anti-proliferative and cytoprotective effects.<sup>9,11,13</sup>

Of the three known membrane bound natriuretic peptide receptors (NPRs), the guanylyl cyclase–coupled NPR–A and NPR–B receptors are responsible for most biological effects. Natriuretic peptide receptor–C is responsible for clearance and possibly regulation of cell proliferation. B-type natriuretic peptide exerts its activities via binding to NPR-A mediated by its second messenger, cyclic guanosine monophosphate, which regulates ion channels, protein kinases, and phosphodiesterases.

In response to cardiac pathologies with pressure or volume overload, ventricular myocytes re-express foetal genes including ANP and BNP. Then, most of the BNP is released from the ventricles.<sup>8</sup> NPs are increased in all oedematous disorders with salt and fluid overload and those with increased atrial or ventricular wall tension, e.g. in HF and renal failure<sup>9</sup> (*Table 2*). Natriuretic peptides are quantitative markers related to the extent of left ventricular

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**Table 1** Main physiological effects of natriuretic peptides

Inhibition of drinking and sympathetic activity
Natriuresis and diuresis
Inhibition of the rennin–angiotensin aldosterone system
Vascular smooth muscle relaxation, vasodilatation
Increase in endothelial permeability
Pulmonary smooth muscle relaxation
Increased lipolysis in adipose tissue
Inhibition of cardiac and vascular remodelling and cytoprotective effects

**Table 2** Diseases with increase in natriuretic peptides

Acute or chronic systolic or diastolic left and right heart failure
Valvular heart disease
Left ventricular hypertrophy with/without arterial hypertension
Atrial fibrillation
Pulmonary embolism and severe pulmonary hypertension
Inflammatory cardiac disease
Acute or chronic renal failure
Advanced liver cirrhosis with ascites
Anaemia
Sepsis
Endocrine disorders as hyperaldosteronism, Cushing's syndrome, hyperthyroidism
Severe neurological disease, e.g. subarachnoid haemorrhage, stroke, trauma

(LV) dysfunction and the severity of HF, although there is considerable overlap across functional classes. The predominant stimulus for release of BNP is end-diastolic wall stress.<sup>9,14–19</sup> However, BNP is also increased in patients with atrial fibrillation due to atrial distension. In addition, myocardial ischaemia evokes BNP secretion,<sup>19,20</sup> as do paracrine factors, such as angiotensin II, endothelin, and cytokines.<sup>13</sup> B-type natriuretic peptide can also be secreted from myocardial fibroblasts.<sup>21</sup>

## Biochemistry of proB-type natriuretic peptide-derived peptides

Our understanding of the biochemistry of BNP, its processing, and circulating proBNP-derived peptides is incomplete.<sup>14</sup> The gene for BNP encodes a 134-amino acid preproBNP precursor. Removal of a 26-amino acid signal peptide gives rise to a 108-amino acid proBNP.<sup>15</sup> Fragments of this signal peptide are present in blood of normals and patients with acute myocardial infarction (AMI).<sup>22</sup> ProB-type natriuretic peptide is cleaved into BNP 1–32 and NT-proBNP 1–76 mainly upon secretion although some processed BNP is found in cardiomyocytes. Endoproteases and pro-hormone convertases, such as furin and corin, are involved in proBNP processing.<sup>16–18</sup> B-type natriuretic peptide exhibits biological activity, but NT-proBNP has no and proBNP has little.<sup>23</sup>

There are only small amounts of intact BNP 1–32 in blood. ProB-type natriuretic peptide is the major immunoreactive form in patients with HF.<sup>24,25</sup> Thus, HF is characterized by altered NP processing with secretion of less biologically active forms. This may explain the 'NP paradox', where there are beneficial effects of administered BNP despite high concentrations of immunoreactive NPs. N-terminal proB-type natriuretic peptide exists as a monomer.<sup>23</sup> The major circulating forms of BNP are degradation products of BNP 1–32, some have biological activity.<sup>23</sup> N-terminal proB-type natriuretic peptide is degraded at both ends.<sup>26</sup> ProB-type natriuretic peptide and NT-proBNP are glycosylated to a variable degree.<sup>27</sup> The central part of NT-proBNP is the most stable region but glycosylation of the mid-portion of NT-proBNP has been described,<sup>24</sup> which affects binding of the antibodies directed against epitopes 39–50 or 42–46.<sup>28</sup> Glycosylation of amino acid 73 renders proBNP resistant to the effects of convertases.<sup>29</sup> These effects may explain the occasionally low NT-proBNP values. N-terminal proB-type natriuretic peptide concentrations may increase markedly with deglycosylation. Thus, glycosylation explains inter-individual differences in values in patients who are otherwise similar.

## Clearance of B-type natriuretic peptide and N-terminal proB-type natriuretic peptide

The biological half-life of BNP ranges from 13 to 20 min and that of NT-proBNP from 25 to 70 min.<sup>14</sup> B-type natriuretic peptide is cleared via clearance receptors (NP receptor-C) and to a lesser extent by degradation by neutral endopeptidase (EC 3.4.24.11) NT-proBNP is cleared passively by organs with high blood flow (e.g. kidneys, liver, and muscles). B-type natriuretic peptide and N-terminal proB-type natriuretic peptide are extracted renally by 15–20% in healthy individuals. The extraction fraction of both is equally dependent on renal function even with hypertension.<sup>28–30,31</sup> In patients, the proportion of calculated total body NT-proBNP clearance is 55–65% by the kidneys, 20–25% across the liver, 10–15% across the musculoskeletal tissue, and 5–10% across the head and neck.<sup>30</sup> N-terminal proB-type natriuretic peptide renal extraction is maintained in the presence of moderate kidney dysfunction.<sup>30,31</sup> However, in case of severe renal dysfunction [glomerular filtration rate (GFR) <30 mL/min/1.73 m<sup>2</sup>] NT-proBNP/BNP ratios increase for unclear reasons.

## Critical clinical concepts

- (1) Natriuretic peptides are secreted from the heart in response to cardiac haemodynamic stress mediated by volume and/or pressure overload.
- (2) Natriuretic peptides are semi-quantitative markers of cardiac stress and HF, and thus related to the extent of atrial, ventricular, and valvular dysfunction.
- (3) Natriuretic peptides are neither HF nor heart disease specific.
- (4) Heart Failure is characterized by a dysfunctional natriuretic peptide system. Relatively inactive proB-type natriuretic peptide is the major circulating form.

- (5) Under normal circumstances, BNP is processed from proBNP into active BNP and an N-terminal split product, NT-proBNP.
- (6) The major circulating forms of BNP and NT-proBNP appear to be degradation products.
- (7) B-type natriuretic peptide and NT-proBNP are cleared renally to a similar extent; both are increased with renal failure.
- (8) N-terminal proB-type natriuretic peptide values are higher than BNP values due to the longer biological half-life.

## Preanalytical and analytical issues related to B-type natriuretic peptide and N-terminal proB-type natriuretic peptide testing

Detailed recommendations have been published by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Committee on the Standardization of Markers of Cardiac Damage (C-SMCD),<sup>32</sup> and the National Academy of Biochemistry (NACB) and C-SMCD.<sup>33</sup> Clinicians must know how to prepare for blood sampling, how the sample is collected, and some of the analytical fundamentals for proper test interpretation. These are partly method dependent and must be established for each commercially available assay separately. Since there is predominantly one source of antibodies and calibrators for NT-proBNP assays (Roche®), NT-proBNP sample stability is similar for NT-proBNP assays. N-terminal proB-type natriuretic peptide is stable at room temperature for at least 2 days.<sup>34</sup> The long-term stability of frozen samples is at least 4 months at  $-20^{\circ}\text{C}$  and at least 1 year at  $-80^{\circ}\text{C}$ .<sup>35,36</sup> The *in vitro* stability of BNP is assay dependent. Values are stable for at least 4 h at room temperature. There are conflicting reports on the long-term stability of frozen samples and thus must be reported by assay manufacturers. Instability of ethylene diamine tetra acetic (EDTA) plasma samples with high BNP concentrations has been reported even at  $-80^{\circ}\text{C}$ .<sup>37</sup> In order to be safe, a protease inhibitor cocktail including kallikrein- and serine-specific protease inhibitors should be added.<sup>32</sup>

In acute cardiac care situations, blood sampling conditions are less important. N-terminal proB-type natriuretic peptide still is more stable than BNP.<sup>38</sup> For BNP, EDTA whole blood or plasma collected in plastic tubes is the only acceptable specimens. They should be analysed as soon as possible. *In vitro* stability depends on the assay.<sup>39</sup> For NT-proBNP, serum or heparin plasma is specimens of

choice. N-terminal proB-type natriuretic peptide is stable during storage, either glass or plastic tubes are acceptable. Ethylene diamine tetra acetic acid plasma gives a negative bias of 8–10% compared with serum.<sup>34</sup> Current available assays are not standardized, which means that results are not comparable in a given patient. Further, BNP and NT-proBNP values in a given sample may differ between assays using the same antibodies due to matrix effects.

### N-terminal proB-type natriuretic peptide assays

Antibodies and calibrator materials used in routine assays are listed in Table 3 (adapted from [http://www.ifcc.org/pdf/scientificactivities/committees/c-smcd/np\\_assay\\_tablev091209.pdf](http://www.ifcc.org/pdf/scientificactivities/committees/c-smcd/np_assay_tablev091209.pdf)). Assay harmonization is incomplete probably due to matrix effects.<sup>39–41</sup> N-terminal proB-type natriuretic peptide assays concur in classifying patients as having values below or above 125 ng/L, which was the initially proposed cut-off. With all assays a value of 300 ng/L works well for exclusion of acute HF. However, NT-proBNP assays may have a systematic bias at higher concentrations.<sup>39,40</sup> Many manufacturers have switched or are going to switch to monoclonal antibodies. These assays provide almost identical results to polyclonal assays.<sup>42</sup>

### B-type natriuretic peptide assays

There are at least four different antibodies in various combinations and diverse calibrators using recombinant or synthetic BNP 1–32 for BNP assays (see Table 4, adapted from [http://www.ifcc.org/pdf/scientificactivities/committees/c-smcd/np\\_assay\\_tablev091209.pdf](http://www.ifcc.org/pdf/scientificactivities/committees/c-smcd/np_assay_tablev091209.pdf)). Thus, there are substantial differences between methods.<sup>39,41</sup> Even assays using the same antibodies run on different instruments vary markedly. In general, there is good concurrence around values of 100 ng/L, which is the initially proposed cut-off. That value excludes acute HF with high negative predictive value.

### Detection and reference limits

Since NPs manifest high biological variability, analytical sensitivity, and precision are not as critical as for cTn assays. B-type natriuretic peptide and NT-proBNP assays should have a total coefficient of variation of  $\leq 15\%$  at concentrations corresponding to age and gender defined upper reference limits (URL).<sup>32,33</sup> Each assay should report the distribution of values for a gender- and age-matched (by decade) healthy population. This population should be free of symptoms, have normal heart function assessed by imaging, normal renal

**Table 3** Calibrators and antibodies used in commercial NT- pro BNP assays

Manufacturer	Capture antibody	Detection antibody	Standard material
Roche Elecsys, E170, Cobas-POCT	Monoclonal murine	Monoclonal sheep	Synthetic NT-proBNP
Siemens (Dade Behring) RxL, XP and ExL, Vista Stratus CS	Monoclonal sheep	Monoclonal sheep	Synthetic NT-proBNP
Siemens (DPC) Immulite	Polyclonal sheep	Polyclonal sheep	Synthetic NT-proBNP
Ortho Clinical Vitros ECI	Polyclonal sheep	Polyclonal sheep	Synthetic NT-proBNP
bioMerieux Vidas	Polyclonal sheep	Polyclonal sheep	Synthetic NT-proBNP
Mitsubishi Chemical Pathfast	Polyclonal sheep	Polyclonal sheep	Synthetic NT-proBNP
Response Biomedical Ramp	Monoclonal murine	Polyclonal sheep	Synthetic NT-proBNP

**Table 4** Calibrators and antibodies used in commercial BNP assays

Manufacturer	Capture antibody	Detection antibody	Standard material
Inverness (Biosite) Triage	Monoclonal murine (Scios)	Omniconal murine (Biosite)	Recombinant BNP (Scios)
Beckman Coulter Access, Access 2, DxL	Monoclonal murine (Scios)	Omniconal murine (Biosite)	Recombinant BNP (Scios)
Abbott Architect, AxSYM, iSTAT	Monoclonal murine (Scios)	Monoclonal murine	Synthetic BNP (Peptide Institute)
Siemens Advia Centaur, Advia Centaur CP, ACS 180	Monoclonal murine (Shionogi)	Monoclonal murine (Shionogi)	Synthetic BNP (Phoenix Pharmaceutical)

function, a normal haemoglobin, and a normal body mass index (BMI).<sup>43–45</sup> Values often are greatly increased in the acute setting, so a smaller number of decision levels adjusted for age, gender, and renal function can be used to exclude acute HF.

### Serial measurements

Changes over time depend on biological and analytical variability.<sup>46,47</sup> Although NT-proBNP has somewhat lower individual variation, intra-individual biological variability (~30–50%) for all NPs is greater than analytical imprecision.<sup>48</sup> Therefore, changes must be large to be important (>40–50%).<sup>46,49</sup> Only marked deviations from baseline (NT-proBNP >50% and BNP >60%) correlated with haemodynamic improvement in acute HF.<sup>50</sup> Hence, frequent blood sampling is unnecessary. Laboratories should report reference change values based on published biological variation and analytical imprecision. A practical approach is to consider only changes >30% as clinically relevant.

### Critical clinical concepts

- (1) In the acute setting NP blood sampling conditions do not require special considerations.
- (2) B-type natriuretic peptide should be measured as soon as possible (at maximum within 4 h) after the blood sample is obtained. If so, *in vitro* stability is not a problem.
- (3) *In vitro* stability of NT-proBNP is higher than for BNP.
- (4) B-type natriuretic peptide and NT-proBNP assays are not standardized.
- (5) B-type natriuretic peptide assays agree at 100 ng/L. N-terminal proB-type natriuretic peptide assays are similar at 125 ng/L. Other measurements are method dependent.
- (6) A limited number of age, gender, and renal function-adjusted decision levels are sufficient to exclude acute HF.
- (7) Only marked changes from baseline values are related to clinical outcome.

### Clinical use of B-type natriuretic peptide and N-terminal proB-type natriuretic peptide

There are no differences in the diagnostic use of BNP and NT-proBNP except when using nesiritide. B-type natriuretic peptide and NT-proBNP correlate well but NT-proBNP concentrations are higher. B-type natriuretic peptide and NT-proBNP results must be interpreted in the context of the clinical situation

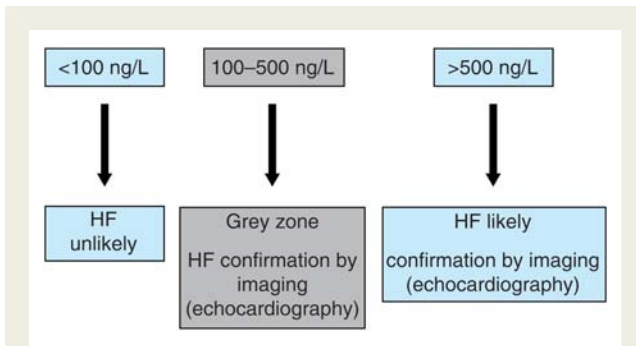
and should be used as continuous variables. The higher the NP level, the higher the likelihood of HF. However; applying a solitary decision limit for all situations is imprudent. Absolute levels are not interchangeable between assays.

### Clinical implications of natriuretic peptide testing in acute heart failure

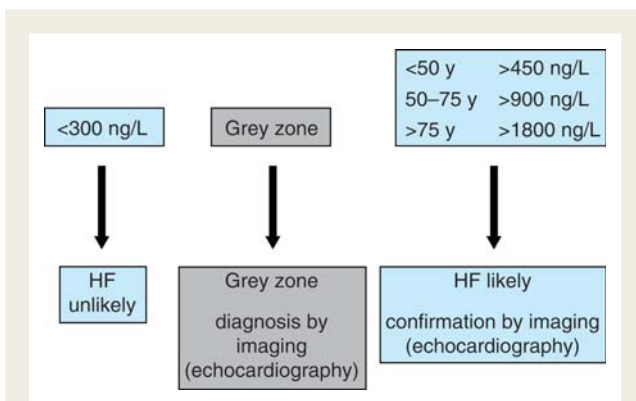
Identifying HF is challenging, especially in the emergency department (ED). Emergency department studies have validated the high diagnostic accuracy of NPs.<sup>2,51–55</sup> B-type natriuretic peptide and NT-proBNP are comparable, with sensitivities of ~90% and specificities ~70%.<sup>56</sup> The Breathing Not Properly (BNP) study of >1500 patients without severe renal failure demonstrated that BNP enhanced the diagnostic accuracy of clinical judgment from 74 to 81%.<sup>52,57</sup> Another study of 600 patients using NT-proBNP showed similar results.<sup>54</sup> Subsequent analyses suggest applying the indicated rule-in and rule-out cut-off values shown in *Figures 1* and *2*.<sup>58</sup> For BNP, 100 and 500 ng/L are valuable rule-out and rule-in cut-points in patients without renal failure.<sup>59</sup> Adjustment is needed for renal disease and obesity. In patients with GFR <60 mL/min/1.73 m<sup>2</sup>, 200–225 ng/L seems a better cut-off to rule-out HF.<sup>60</sup> Obesity requires lower cut-points. In patients with a BMI >35 kg/m<sup>2</sup>, a cut-off of 55 ng/L is recommended.<sup>61</sup>

The International Collaborative for NT-proBNP Study (ICON) established cut-points for NT-proBNP (*Figure 2*). An age-independent cut-point of 300 ng/L had 98% negative predictive value for ruling out HF. Age-related cut-points of 450, 900, and 1800 ng/L for ages <50, 50–75, and >75 years are used to rule-in HF with normal or mildly impaired renal function.<sup>55</sup> If GFR is <60 mL/min/1.73 m<sup>2</sup>, a NT-proBNP value of 1200 ng/L is best for exclusion of HF. Most studies excluded patients with severe renal failure. Despite adjustment, detection and/or exclusion of HF is less accurate in patients with GFR <30 mL/min/1.73 m<sup>2</sup>.<sup>62</sup> Obese patients with HF have lower levels. This may be due to a defect in NP secretion or clearance receptors in adipose tissue. Although, NT-proBNP falls below the cut-points less often, both markers have reduced sensitivity with severe obesity.<sup>63</sup>

Performance of NPs is maximized as continuous variables in patients with an intermediate pre-test probability.<sup>64</sup> Thus, routine use in low- and high-risk groups is controversial. The strongest evidence for NPs in HF is their high negative predictive value. Natriuretic peptides cannot be used to distinguish diastolic from systolic HF although values tend to be lower with diastolic HF.<sup>65</sup>



**Figure 1** Interpretation of BNP values in patients with acute dyspnoea without severe renal failure. In patients with significant renal failure (estimated glomerular filtration rate  $<60$  mL/min/ $1.73$  m<sup>2</sup>) and body mass index  $>35$  kg/m<sup>2</sup> different decision limits must be used (see text). Abbreviations: B-type natriuretic peptide (BNP), heart failure (HF).



**Figure 2** Interpretation of NT-proBNP values in patients with acute dyspnoea without severe renal failure. The use of age-adjusted NT-proBNP cut-off values in the acute setting compensates only for minor renal dysfunction. In case of significant renal failure (estimated glomerular filtration rate  $<60$  mL/min/ $1.73$  m<sup>2</sup>) different decision limits must be used (see text). Abbreviations: N-terminal proBNP (NT-proBNP), heart failure (HF).

There are few situations where NPs are not elevated despite acute haemodynamic compromise and/or severe acute pulmonary congestion. These occur when patients present within the first hour of the onset of pulmonary oedema caused by acute mitral regurgitation because of the need for *de novo* synthesis of NPs, those with preserved ejection fractions and those with constrictive pericarditis without intrinsic heart disease.<sup>66,67</sup>

### Natriuretic peptide testing in patients with acute dyspnoea

The economic benefits in ED patients have been studied.<sup>68–71</sup> Natriuretic peptides result in more rapid initiation of therapy, a reduction in intensive care use, a reduction in the duration of hospitalization, and costs.<sup>68</sup> These findings were partly confirmed in the Improved Management of Patients With Congestive Heart

Failure (IMPROVE-CHF) study using NT-proBNP. Duration of ED visits, readmissions, and medical costs were reduced by better diagnosis.<sup>69</sup> However, these results were not confirmed in a study using BNP<sup>70</sup> or in another with NT-proBNP. The duration of ED stay was unchanged although there was a reduction in the duration of hospitalizations.<sup>71</sup> These moderate results suggest using NPs as an aid to diagnose ED patients, particularly in those at intermediate probability.

### Risk stratification in patients with acute heart failure

Natriuretic peptide measurements on admission or during hospitalization are useful for risk stratification irrespective of the cause.<sup>55,72–77</sup> Natriuretic peptide concentrations help quantify the severity of HF and to predict short- and long-term mortality. An admission NT-proBNP concentration  $>5180$  ng/L is strongly predictive of death by 76 days.<sup>55</sup> The value with the best balance of sensitivity and specificity for 1-year mortality was  $>986$  ng/L.<sup>74</sup> Changes during hospitalization are useful for risk stratification and independent predictors of death or hospital readmission. A predischarge NT-proBNP concentration  $>4137$  ng/L portends a poor prognosis.<sup>75</sup> Similar findings were observed with smaller relative changes in BNP, which were associated with worse outcomes. A high predischarge BNP measurement was an independent marker of death or re-admission,<sup>76</sup> and early treatment lowering BNP level by 30% was associated with improved survival.<sup>77</sup>

### Treatment guidance in acute heart failure

There are no randomized trials using NP guidance in acute HF. B-type natriuretic peptide-guided therapy may reduce all-cause mortality in patients with chronic HF, especially in patients  $<75$  years.<sup>78,79</sup> Other studies mainly reported an increased survival free of hospitalization with this approach.<sup>80</sup> It is reasonable to collect a baseline sample and a second prior to discharge for risk assessment. Patients are at lower risk with reductions  $>30\%$ . These measurements identify those in need of more aggressive management.<sup>81</sup>

### Natriuretic peptides in acute pulmonary embolism

Increased levels identify patients with acute pulmonary embolism (PE) at higher risk. In patients with raised NP values, elevated troponins are an independent prognostic marker.<sup>82</sup> Admission concentrations of NT-proBNP  $<500$ ,  $600$ , or  $1000$  ng/L, respectively, predict better clinical courses.<sup>82–85</sup> Similarly, BNP values  $<50$  or  $90$  ng/L identify low-risk patients; high-risk patients have values  $>500$  ng/L.<sup>86</sup> Reported differences in cut-off values are due to small sample sizes and variation in patient characteristics. Using echocardiography in patients with high values is useful to identify a high-risk subset.<sup>85</sup> Persistent elevations of NT-proBNP (values  $>7500$  ng/L after 24 h or  $<50\%$  decrease) indicate right ventricular dysfunction and a poor prognosis.<sup>87</sup>

## Natriuretic peptides in acute coronary syndrome

Myocardial ischaemia releases BNP,<sup>19,20</sup> and the coherent diastolic and systolic abnormalities release NPs as well. In acute coronary syndromes (ACS) BNP and NT-proBNP values are powerful prognostic markers. Combination with cTn improves risk stratification in non-ST elevation AMI. In ACS trials, admission values of BNP >80 ng/L and NT-proBNP >1170 ng/L for men and >2150 ng/L for women identify high-risk patients.<sup>88,89</sup> N-terminal proB-type natriuretic peptide measurements augment the prognostic information of clinical risk scores.<sup>90</sup> Usually, NP did not predict recurrent AMI or a benefit from an invasive strategy.<sup>89,91,92</sup> Optimal time for risk stratification is uncertain but studies suggest synergism between early and subsequent values.<sup>93</sup> In patients with ST elevation AMI, NPs rise rapidly and values are correlated with infarct size and LV dysfunction.<sup>88,94,95</sup> Patients with AMI and NT-proBNP concentrations <1115 ng/L have a high probability for recovery of LV function.<sup>95</sup> In patients with cardiogenic shock and AMI, NT-proBNP concentrations >12782 ng/L predicted an adverse outcome despite coronary revascularization.<sup>96</sup>

## Natriuretic peptides in intensive care medicine

Severe dyspnoea due to respiratory failure is common in patients in intensive care units (ICUs). The high rate of cardiac and renal dysfunction in ICU patients limits the discriminative role of NPs. B-type natriuretic peptide values <250 ng/L support a diagnosis of acute lung injury. No BNP concentration had a negative predictive value of 100%. Diagnostic accuracy is better if patients with renal dysfunction are excluded.<sup>97</sup> Natriuretic peptides do not correlate with haemodynamic parameters.<sup>50</sup> Patients with acute respiratory problems have elevated NP concentrations due to right heart dysfunction; values are usually lower than with left sided HF.

Patients with sepsis and septic shock have elevated BNP associated with organ and myocardial dysfunction.<sup>98,99</sup> B-type natriuretic peptide >210 ng/L at 24 h after admission is the most significant indicator of increased mortality.<sup>98</sup> An NT-pro-BNP concentration on admission also has prognostic value and thus might facilitate the triage of ICU patients.<sup>100</sup>

## Critical clinical concepts

- (1) Natriuretic peptides in patients with acute dyspnoea can guide the diagnostic investigations and management.
- (2) Natriuretic peptides cannot reliably discriminate systolic from diastolic HF.
- (3) Natriuretic peptides are predictors of morbidity and mortality in acute HF.
- (4) Decreases of NPs >30% in response to HF treatment indicates a good prognosis.
- (5) Natriuretic peptides are prognostic markers in acute PE.
- (6) Natriuretic peptides are predictors of mortality in ACS.
- (7) Natriuretic peptides are risk markers in ICU patients but the therapeutic implications remain to be determined. High

levels in the absence of renal failure suggest possible underlying cardiac disease.

- (8) Renal failure confounds interpretation of NP values.

## Conclusions and outlook

B-type natriuretic peptide and NT-proBNP are markers of cardiac stress but are not cardiac-specific. B-type natriuretic peptide and NT-proBNP have comparable clinical utility, and both help in excluding acute HF. Their use prior to discharge in hospitalized patients aids risk stratification. There is increasing evidence for risk stratification in acute PE and ACS patients. The lower the value, the lower is the risk. A variety of new assays, e.g. mid-regional proANP and proBNP are being developed. So far, these assays are equivalent but no better than other testing.<sup>2,3</sup>

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