The ESC Textbook of Intensive and Acute Cardiovascular Care (2 ed.)
Edited by Marco Tubaro, Pascal Vranckx, Susanna Price, and Christiaan Vrints

Latest update

This online textbook has been comprehensively reviewed for the February 2018 update, with revisions made to 28 chapters. Find out more about the updates made.

Publisher: Oxford University Press
Print Publication Date: Feb 2015
DOI: 10.1093/med/9780199687039.001.0001

Biomarkers in acute heart failure

Chapter: Biomarkers in acute heart failure
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DOI: 10.1093/med/9780199687039.003.0037_update_003

Update:

Meta-analyses included confirming the utility of BNP, NT-proBNP, and MR-proANP as negative predictors for acute heart failure and the utility of NT-proBNP-guided outpatient HF management.
Discussion added on a novel therapeutic agent for heart failure with reduced ejection fraction: sacubitril-valsartan (LCZ696).

References added on biomarkers galectin-3, neutrophil gelatinase-associated lipocalin, and procalcitonin.

A model utilizing a panel of biomarkers to assess response to diuretics in acute HF is included as a potential additional role for biomarkers in AHF.

The prognostic value of endothelin in acute HF for short and long-term outcomes was included.

The recently published American Heart Association (AHA) Scientific Statement on Biomarkers in HF was mentioned and cited.

3 new references

Updated on 22 Feb 2018. The previous version of this content can be found here.

Summary

Acute heart failure continues to be a worldwide medical problem, associated with frequent readmissions, high mortality, and a profound economic impact on national health care systems. In the past decade, biomarkers have shifted the way in which acute heart failure is managed by the cardiologist. The search for the ideal biomarker to aid in the diagnosis, prognosis, and treatment of acute heart failure is ongoing. The natriuretic peptides have proved extremely useful in determining whether acute dyspnoea has a cardiac aetiology. In addition, recent trials have demonstrated the use of natriuretic peptides in inpatient and outpatient prognosis, as well as in titrating medications in outpatients with chronic heart failure to prevent acute heart failure hospitalizations. Other emerging acute heart failure biomarkers include mid-regional pro-adrenomedullin, mid-regional proatrial natriuretic peptide, troponin, ST2, and neutrophil gelatinase-associated lipocalin.

Contents
**Introduction**

Acute heart failure (AHF) remains one of the difficult conditions to treat in the spectrum of cardiovascular diseases (CVDs). Biomarkers are essential tools, which help the clinician to quantify the underlying pathophysiological mechanisms and tailor AHF therapy accordingly. With an explosion in biomarker research over the last decade, the role of biomarkers in managing AHF patients is evident. As almost every AHF patient presents through the emergency department (ED), an early diagnosis and early initiation of treatment are key in achieving positive outcomes. A rapid bedside diagnosis allows the clinician to grade the severity of AHF and helps to ‘tailor’ the therapy effectively. Moreover, in circumstances of equivocal radiographical and clinical symptoms, biomarker testing can help clinicians by providing a more accurate diagnostic view, thus preventing a misdiagnosis and aiding an early initiation of treatment, especially in the acute setting.
Biomarkers in acute heart failure

In this chapter we discuss in detail the use of natriuretic peptides, beyond doubt, the most important biomarkers in AHF, but we also address the diagnostic and prognostic utility of other emerging biomarkers that might provide added value for the management of patients with AHF.

The ideal biomarker

A biomarker must contain several characteristics to be considered an ideal AHF biomarker [1]. The ideal AHF biomarker, depending on the nature of the condition being tested, must be highly sensitive or specific. For instance, while screening for asymptomatic left ventricle (LV) dysfunction, a high specificity allowing to ‘rule in’ the disease is required [1, 2], whereas, in diagnosing symptomatic life-threatening conditions such as an acute myocardial infarction (AMI), the biomarker must be highly sensitive in allowing to ‘rule out’ the disease effectively [1, 2]. The other characteristic refers to the biomarkers measurability. In order to achieve this, a biomarker must carry a low coefficient of variation (CV) (<10%), allowing the detection and reflection of even minute changes in the disease state of the patient [2, 3]. Moreover, the technical measurement of the biomarker using assays must be easy to perform and be able to be carried out by the bedside, allowing a faster access to the clinical status of the patient. The ideal biomarker must reflect ongoing pathophysiological changes in the AHF patient, giving a sense of severity of the disease and helping clinicians chart the disease progression. Moreover, biomarker levels must respond to ongoing treatment, allowing the clinician to gauge the effectiveness of the therapy and to titrate the treatment, as needed, to achieve positive outcomes. Ideally, a biomarker or panel of biomarkers would affect clinical management. For example, investigators have demonstrated the potential of a panel of biomarkers to predict poor diuretic response [94]. Specifically, incorporation of biomarkers soluble ST2 (sST2) and neutrophil gelatinase-associated lipocalin (NGAL) along with other clinical indicators are associated with poor diuretic response in an acute HF population. An additional role for an optimal biomarker would be to provide information which affects clinical management. Finally, the ideal biomarker must be cost-effective and applicable across all diverse populations [2, 3].

Thus, an ideal AHF biomarker must be multifaceted, aiding clinicians with not only the diagnosis and prognosis of the diseased state, but also with predicting heart failure recurrence and helping clinicians tailor AHF therapy by monitoring biomarker levels. Over the last decade, the criteria, which the ideal AHF biomarker must fulfil, have certainly evolved. Although natriuretic peptides, as AHF markers, get close, no single biomarker meets all criteria, and researchers have therefore suggested a multimarker approach to maximize AHF treatment and management.
Natriuretic peptides

Natriuretic peptides are circulatory peptide hormones, which are synthesized and released from the myocardial cells, in direct response to ventricular changes in volume and pressure [4]. Natriuretic peptides have gained widespread recognition and are considered benchmark biomarkers in the diagnosis and prognostication of AHF. Natriuretic peptide testing in the ED allows the clinician to accurately diagnose acute decompensated heart failure (ADHF), especially when conventional tests, such as physical examinations and radiographic imaging, have been inconclusive.

Natriuretic peptide biochemistry

Natriuretic peptides belong to a family of structurally similar peptides, consisting of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type and D-type natriuretic peptide [5]. Of these, BNP has widespread clinical applications, due to its in vitro stability, compared to other peptides. The BNP gene is activated as a direct result of several stimuli such as cardiomyocyte stretch, cardiomyocyte injury, and/or death and hypoxia [5, 6]. This gene encodes the 134-amino acid preproBNP precursor molecule. Glycosylation of the preproBNP molecule yields a 26-amino acid signal sequence and the 108-amino acid proBNP molecule [6]. The protein-cleaving enzymes corin and furin cleave this proBNP peptide to produce the biologically active 32-amino acid BNP peptide and the inactive 76-amino acid amino terminal (NT)-proBNP fragment [6, 7] (see Figure 37.1). Once in the circulation, BNP exerts its physiological effects by binding guanylyl cyclase receptors, referred to as natriuretic peptide receptors A and B, and initiating a signalling cascade mediated via cyclic guanosine monophosphate (cGMP). Plasma BNP has a half-life of about 20 min, whereas plasma NT-proBNP has about 70 min [5–7]. BNP is cleared from the circulation by binding natriuretic peptide receptor C and, to some extent, via degradation by neutral endopeptidases. BNP is renally excreted, and, in patients with renal function impairment, BNP levels might be elevated, due to decreased excretion. NT-proBNP, on the other hand, is mainly excreted via the kidneys (55–65%), and the rest via the liver, musculoskeletal tissue, and head and neck [8].
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Figure 37.1
Illustrative representation of AHF pathophysiology, along with biomarker-specific sites of involvement. LVD, left ventricular dysfunction; LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; PCWP, pulmonary capillary wedge pressure; RAAS, renin-angiotensin-aldosterone system; AVP, arginine vasopressin (antidiuretic hormone); ADHF, acute decompensated heart failure; SVR, systemic vascular resistance; HR, heart rate; NGAL, neutrophil gelatinase-associated lipocalin; HS-Troponins, high-sensitivity troponins.

Natriuretic peptide pathophysiology and function

Natriuretic peptides are hormones synthesized in the heart which regulate the water-electrolyte balance in the body. ANP and BNP are released in response to atrial and ventricular wall stretch. Therefore, elevated levels of natriuretic peptides are a result of the body’s response to a volume-overloaded state. The compensatory mechanisms, which are activated in response to a decreased plasma volume, include the RAAS, the sympathetic system, the inflammatory pathway, and the neurohormonal system [9, 10] (see Figure 37.2). Collectively, they work to maintain the plasma volume by affecting Na⁺ and water homeostasis. In healthy individuals, BNP is synthesized in the atria and ventricles, but, in specific conditions, such as HF, associated with volume expansion and pressure overload, BNP gene synthesis occurs mainly in the ventricle [11]. Studies have shown that this synthesis occurs in ‘bursts’, due to the presence of a destabilized nucleic acid sequence in the BNP gene identified as ‘TATTTAT’ [11, 12]. The physiological functions of BNP act to counter the effects caused due a decreasing cardiac output. Once in the circulation, BNP induces vasodilation and promotes natriuresis and kaliuresis; furthermore, it inhibits the actions of
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the sympathetic nervous system, and, more importantly, it inhibits RAAS. Interestingly, BNP has anti-fibrotic and anti-inflammatory effects on the heart, thus exerting an overall cardioprotective effect [11, 12].

Figure 37.2

Clinical utility of natriuretic peptide use in acute heart failure

As a quantitative marker of heart failure, natriuretic peptide levels are best interpreted as a continuous variable. The higher the value, the greater the likelihood that the dyspnoea is due to heart failure. The clinical implications of natriuretic peptide use in AHF revolve around their ability to differentiate cardiac dyspnoea from non-cardiac dyspnoea. BNP levels have been shown to correlate with New York Heart Association (NYHA) functional classes and are inversely related to the calculated EF of the LV [13]. Moreover, BNP levels directly correlate with the measured pulmonary capillary wedge pressures, thus providing an almost accurate estimation of LV systolic dysfunction [14]. Similarly, NT-proBNP levels are fast gaining a stronghold in the management and diagnosis of heart failure patients. With a longer half-life when compared to BNP, NT-proBNP survives longer in the plasma and provides similar information regarding heart failure severity and disease progression [11]. Although natriuretic peptide levels are unable to distinguish systolic from diastolic heart failure, elevated BNP and NT-proBNP reflect a wide array of cardiac pathophysiology such as diastolic function, right ventricular size and function, valvular heart disease, filling pressures, heart rhythm, and coronary ischaemia [15]. Thus, their use has gained widespread acceptance as standard of care for the management of heart failure patients.
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Natriuretic peptide levels are part of the ESC and American College of Cardiology Foundation (ACCF)/AHA heart failure management guideline algorithm, for diagnosing and excluding heart failure [16]. Natriuretic peptide levels aid in the diagnosis, prognosis, and risk stratification of AHF patients. Measuring natriuretic peptide levels also aids the clinician to judge the response to therapy and allows titrating AHF therapy to better improve treatment outcome [17, 18]. A meta-analysis of 37 unique study cohorts described the rule-out thresholds recommended in the 2012 European Society of Cardiology guidelines for heart failure; plasma B type natriuretic peptide, NTproBNP, and MRproANP have excellent ability to exclude acute heart failure [19].

Natriuretic peptide utility in the emergent setting

The Breathing Not Properly study [20] was one of the largest multicentre trials demonstrating the clinical value of using BNP levels in heart failure patients with acute dyspnoea presenting to the ED. In >1500 patients presenting to the ED with acute dyspnoea, adding BNP levels to clinical judgement improved the diagnostic accuracy to 81%. A BNP level of <100 pg/mL was able to rule out heart failure, yielding a 90% sensitivity, 76% specificity, and 90% NPV, whereas a BNP value of >500 pg/mL was able to rule in heart failure, yielding a PPV of 87%. Adding BNP levels to clinical decision making reduced the physician’s indecision rate from 43% to 11%. Finally, a BNP level of 100 pg/mL was found to be the strongest independent predictor of heart failure (83%), proving to be more accurate than the NHANES (67%) and Framingham criteria (73%).

Studies have demonstrated a comparative efficacy of BNP and NT-proBNP levels in discerning heart failure in the acute setting. The PRIDE study [21] established age-stratified NT-proBNP levels in ruling out heart failure. NT-proBNP levels of <300 pg/mL achieved a 99% NPV. Furthermore, NT-proBNP levels were the strongest independent predictor for diagnosing AHF. Table 37.1 provides an overview of NT-proBNP cut-points for diagnosing and ruling out heart failure.

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<th>Table 37.1a Factors increasing natriuretic peptide levels</th>
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<td>Valvular disorders</td>
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<td>Liver disease</td>
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</table>
Sepsis

subarachnoidal haemorrhage (SAH)

Stroke

Trauma

Anaemia

Table 37.1b Factors decreasing natriuretic peptide levels

Obesity

Flash pulmonary oedema

Pericardial tamponade

BNP serves as an excellent surrogate for LV function, particularly the end-diastolic wall stress. In 160 patients with heart failure, there was a significant correlation between BNP levels and LV end-diastolic stress and LV end-diastolic pressure (r = 0.88; r = 0.29, respectively) [22]. In an attempt to assess the diagnostic utility of BNP levels and left ventricle ejection fraction (LVEF), as determined by 2D echocardiography, BNP levels achieved an area under the curve (AUC) of 0.89 vs 0.78 for EF in diagnosing heart failure. Most importantly, a combined knowledge of BNP levels, along with EF, the clinical history, and radiographic imaging correctly classified 97.3% of the patients with heart failure [23].

Despite the reported superiority of natriuretic peptides in diagnosing heart failure, natriuretic peptides do not distinguish systolic heart failure from preserved-EF heart failure, thus natriuretic peptide testing remains an adjunct to conventional testing and must not be used as a stand-alone measure or replace current tools, such as echocardiography or radiographic imaging, in diagnosing heart failure.
Natriuretic peptide utility in the inpatient setting

A review of heart failure databases and registries estimates the in-hospital mortality of AHF to be around 4–7%. The most common causes of acute decompensation, leading to admission, include ACS, arrhythmias such as atrial fibrillation, valvular disorders, impaired renal function, and non-compliance to diet and/or medications [24].

In a subanalysis of the large-scale prospective Euro-Heart Failure Survey II, the characterization of AHF patients and identification of clinical risk predictors revealed that patients with a lower mortality at 1 year were more likely to have new-onset or de novo heart failure, compared to ADHF. Moreover, the use of ACE-Is or ARBs, β-blockers, and lipid-lowering agents was more common among the survivors. Several factors were associated with a worse prognosis, such as a history of previous MI, elevated blood urea nitrogen (BUN) and creatinine, anaemia, and low serum Na+ concentrations. LV systolic dysfunction was found to be a strong independent predictor of short-term and long-term mortality [25].

Inpatient monitoring of BNP levels not only allows the clinician to judge response to therapy, but also provides prognostic information. A >46% reduction in BNP levels from admission, together with an absolute BNP level of <300 pg/mL at discharge, was associated with a significantly lower rate of rehospitalizations and deaths [26]. Results from the I-PRESERVE trial [27] demonstrated that, in patients with preserved-EF heart failure, NT-proBNP levels of >339 pg/mL were associated with an increased rate of AEs. Monitoring BNP levels in AHF can allow a clinician to judge treatment response and appropriately titrate therapy to achieve better outcomes. Moreover, elevated BNP levels may reflect failure to ongoing treatment, warranting the need for more aggressive therapy. The IMPROVE-CHF trial [28] revealed that NT-proBNP testing in acutely dyspnoeic patients presenting to the ED improved diagnostic accuracy when added to clinical judgement. Moreover, it positively impacted direct medical costs of ED visits, rehospitalization over 60 days, and the duration of ED visits. Rapid BNP testing has been shown to reduce the length of stay and thus lower costs of treatment. In a clinical study of participants randomly assigned to standard care vs care utilizing BNP levels, it was found that, in the BNP arm, the total cost of treatment was $5410, compared to $7264 in the standard care arm [29]. That said, serial natriuretic peptide testing is usually discouraged, since only marked deviations from the baseline natriuretic peptide levels (>60% for BNP, and >50% for NT-proBNP) have been shown to be associated with clinical improvement in AHF patients.

In a retrospective analysis of 908 patients hospitalized with ADHF, investigators evaluating the effect of renal function on the prognostic accuracy of NT-proBNP found no interaction between eGFR and NT-proBNP levels in predicting mortality risk at 1 year. They also reported that a single cut-off value of NT-proBNP at 5180 ng/mL was an independent predictor of 1-year mortality, irrespective of the residual
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renal function. Moreover, in patients with acute worsening of renal function, defined as an increase in serum creatinine of >0.3 mg/dL, only patients with persistently elevated NT-proBNP levels, in addition to worsening renal function, were at increased risk of mortality. The study suggests that, in patients hospitalized with ADHF and declining renal function, rising NT-proBNP levels occur not only due to decreased renal clearance, but also due to progressing disease severity [30].

Discharging the AHF patient is often difficult, due to the complex nature of heart failure aetiology and a poor correlation between clinical symptoms and signs and ongoing pathophysiological processes. Moreover, over-aggressive treatment may harm the kidneys and exacerbate renal dysfunction, directly increasing the risk of morbidity and mortality [31]. Diuresis is one of the hallmarks of ADHF treatment but should be carefully undertaken, since aggressive over-diuresis can impair renal function and increase the risk of morbidity and mortality of the patient. The haemodynamic profile of AHF patients can be categorized on the basis of tissue perfusion, providing an estimate of the cardiac output, and congestion referring to the level of fluid overload. On the basis of this categorization, heart failure patients can be classified as ‘warm’ or ‘cold’, depending on the level of perfusion, and as ‘dry’ or ‘wet’, depending on their level of fluid congestion. In inpatient management of heart failure patients, heart failure therapy must be aimed at achieving a dry or euvoalaemic state with adequate perfusion [32]. This is achieved by determining the patient’s ‘dry BNP’ level, which refers to the true BNP level in the absence of fluid overload, also known as the euvoalaemic BNP. The BNP level in the presence of fluid congestion or fluid overload is referred to as ‘wet BNP’. Thus, an adequate diuresis is crucial in the acute decompensated state with fluid overload [32, 33].
Natriuretic peptide utility in the outpatient setting

Natriuretic peptide use to guide outpatient heart failure therapy remains a controversial topic with equivocal results. Almost more than a decade ago, Troughton et al. [34] demonstrated a positive benefit by titrating heart failure therapy to achieve NT-proBNP levels of <1700 pg/mL in patients with newly decompensated heart failure, established after a 9-month follow-up period. Since then, several large multicentre trials have attempted to assess the effects of natriuretic peptide-guided heart failure therapy on future AE rate and cardiovascular mortality. The STARS-BNP trial [35] randomized participants to receive either standard treatment or treatment titrated to achieve a BNP level of <100 pg/mL. Results reported a 50% reduction in deaths due to heart failure in the BNP-guided arm. The multicentre TIME-CHF trial [36] randomized 499 participants, with a mean age of 76 years, to NT-proBNP-guided therapy in order to achieve NT-proBNP levels <400 pg/mL in participants 75 years or younger, and NT-proBNP levels <800 pg/mL in participants 75 years or older, and to symptom-guided therapy. The results reported an improvement in heart failure admissions and the overall mortality in the NT-proBNP arm, only in the 75 years or younger age group and in those with one (or fewer) comorbidity. Similarly, the results from the BATTLESCARRED multicentre trial [37] revealed a reduction in 3-year mortality in participants aged 75 years or less. A meta-analysis of 12 trials published in 2014 demonstrated the use of NT-proBNP-guided therapy reduced all-cause mortality and HF-related hospitalization but not all-cause hospitalization, whereas BNP-guided therapy did not significantly reduce both mortality and morbidity [38].

In conclusion, the use of cardiac NPs to guide pharmacologic therapy significantly reduces mortality and HF-related hospitalization in patients with chronic HF.

The AHF treatment and management paradigm has significantly evolved over the past decade. Figure 37.3 demonstrates a conceptual framework to manage care in HF patients.
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Figure 37.3

While studies suggest the use of serial NP testing as a tool to provide incremental clinical information on risk stratification and prognosis, the use of NP to monitor disease progression and guide HF treatment has shown to be superior to standard care. In a meta-analysis by Troughton et al., NP-guided therapy reduced all-cause mortality in patients aged <75 years with chronic HF and impaired LV systolic function [39].

Although the underlying mechanisms by which natriuretic peptide-guided therapy exerts its beneficial effect remain unclear, authors have alluded to optimization of dosing as a possible role in improving outcomes, rather than just aggressive therapy.
Interpreting natriuretic peptide levels

Certain factors must be considered while interpreting natriuretic peptide levels in the acute setting. First, a thorough clinical examination and a rapid BNP testing to establish the diagnosis and initiate therapy must be considered. Second, a delay in initiating treatment is associated with poor outcomes; thus, treatment should be begun as soon as a diagnosis is made. Finally, markedly elevated BNP levels have been shown to significantly increase the risk of mortality; thus, such patients might benefit from intensive care monitoring, especially in the presence of other organ dysfunction.

Another important caveat to monitoring and interpreting BNP and NT-proBNP levels is recognizing biological variability. In patients admitted with AHF, fluctuation in NP levels are often seen, and studies have shown that a change in BNP levels of >40% and a change in NT-proBNP levels of >25% indicate changing physiological state [40].

Although the natriuretic peptide cut-off values used to diagnose and exclude heart failure have been established, natriuretic peptide values referred to as grey zone values (see Table 37.2) often arise in heart failure patients [41]. Several underlying conditions, such as obesity, renal dysfunction, pulmonary disease, ACS, diastolic dysfunction, sepsis, and valvular disorders, can alter natriuretic peptide levels [41, 42]. Thus, care should be taken while interpreting natriuretic peptide levels in the heart failure patient in the presence of concomitant conditions. Novel therapies such as LCZ-696 (sacubitril-valsartan) have a neprilysin inhibitor component, which decreases degradation of endogenous natriuretic peptides. Preliminary studies have demonstrated that this drug increases circulating levels of BNP, while NT-proBNP levels should not be affected [43]. This drug has recently made international guidelines to be considered in the management of chronic HF. Thus, awareness of its effects on the natriuretic peptide system will be paramount in the management of HF. Table 37.3 provides an overview of conditions associated with increasing or decreasing natriuretic peptide levels.

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<th>Table 37.2 Natriuretic peptide grey zone values</th>
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<td>50–75 years: 300–900 pg/mL</td>
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### Table 37.3 Factors affecting natriuretic peptide levels in patients with heart failure

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**Concomitant conditions seen in the acute heart failure patient**

**Neutrophil gelatinase-associated lipocalin**

AKI in AHF patients is multifactorial, resulting from the administration of nephrotoxic agents to the instillation of IV dye and aggressive diuresis, etc. (see Figure 37.4). In the acute setting, creatinine has been shown to lag behind an insult, thus proving to be an inferior indicator of acute kidney injury (AKI). Neutrophil gelatinase-associated lipocalin (NGAL),
secreted by the renal epithelial cells of the proximal tubules. has shown robust evidence in detecting early AKI.

Figure 37.4
Illustration of factors affecting the interrelationship between the heart and kidney function, and an overview of the nephrotoxic agents most commonly associated with AKI in the AHF patient.

NGAL is a 25 kDa lipoprotein, containing a 178-amino acid structure, and is encoded by the LCN2 gene [44-46]. In humans, NGAL is expressed in neutrophils and, to some extent, in the respiratory and gastrointestinal (GI) tracts, besides being expressed in the kidneys. NGAL functions as part of the innate immunity by binding bacterial siderophores and limiting bacterial growth. In AHF burdened by AKI, NGAL is secreted within 2 hours and is easily detectable in the urine and serum [44-46]. The GALLANT trial [47] assessed the diagnostic and prognostic utility of NGAL, along with BNP, in 188 patients with ADHF presenting to the ED. Results revealed elevated NGAL levels in patients with increased AEs within a 30-day follow-up period. Moreover, NGAL was an independent predictor of adverse events (AEs). Finally, adding BNP testing to NGAL achieved an overall net reclassification improvement of 29.8% patients, with elevated NGAL and BNP levels carrying the highest risk (HR 16.85). The Acute Kidney Injury N-gal Evaluation of Symptomatic heart failure Study (AKINESIS) sought to determine whether NGAL was superior to creatinine for prediction of worsening renal failure in hospitalized patients with acute HF treated with intravenous diuretic agents [48]. This trial demonstrated plasma NGAL was not superior to creatinine for the prediction of worsening renal failure or adverse in-hospital outcomes.

NGAL is an emerging marker of AKI, and a rapid detection of NGAL by the bedside may allow clinicians to avoid kidney injury by avoiding overdiuresis and holding angiotensin-converting enzyme inhibitors (ACE-Is)/angiotensin receptor blockers (ARBs), especially in the presence of normal creatinine levels. Moreover, NGAL may be more than just a marker of tubular dysfunction and may reflect worsening cardiac function.
and increasing disease severity, portending to an increase in short-term mortality.

**Procalcitonin**

Patients with AHF often have an underlying bacterial pulmonary infection, which can be missed due to absent radiographical signs and normal blood counts. Since almost all patients with AHF present to the ED with a chief complaint of dyspnoea, it remains crucial to identify and treat the non-cardiac causes of dyspnoea, if any. Since heart failure is a disease affecting individuals >75 years of age, the burden of mortality is high in this age group in the presence of concomitant infection [49, 50]. Misdiagnosis and inappropriate treatment can further exacerbate the problem and worsen the underlying heart failure. Several mechanisms have been posited to explain a worsening heart failure in the presence of bacterial infection, some of which include an impaired cardiac contractility, due to an increased bacterial uptake by cardiomyocytes, and the activation of the inflammatory cascade, leading to worsening of haemodynamic pressures [51, 52].

The role of procalcitonin (PCT) use in patients with AHF lies in its ability to discern an underlying bacterial pulmonary infection, especially in the absence of radiographic signs and negative blood testing [53]. PCT is a 12.8 kDa peptide with a 116-amino acid structure and is encoded by the CALC 1 gene located on the short arm of chromosome 11 [54, 55]. In the presence of a bacterial infection, PCT messenger RNA (mRNA) upregulation is induced by the bacterial endotoxin, resulting in its release from the neuroendocrine cells of the lungs, intestines, and peripheral mononuclear cells. Moreover, certain pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukin (IL)-1β, and IL-6, mediate PCT release. In non-infective states, PCT is further metabolized to the biologically active calcitonin in the neuroendocrine C cells of the thyroid [55–57].

Maisel et al. [58] demonstrated that using PCT levels can improve the diagnostic accuracy in detecting bacterial pneumonia in AHF patients. Moreover, PCT levels improved the AUC from 0.79 to 0.86 when added to radiographic imaging. In patients with pneumonia, PCT levels ranged from 0.07 to 0.58 ng/mL, compared to 0.05–0.12 ng/mL in patients without pneumonia. PCT was found to be superior to white cell counts in predicting pneumonia. Finally, a survival curve analysis revealed that patients in the lowest quintile (PCT <0.05 ng/mL) had a 92% 90-day survival rate, compared to patients in the fifth quintile (PCT >0.21 ng/mL), achieving an 80.5% 90-day survival rate. The study alluded to the possibility of using PCT levels to guide antibiotic use in AHF patients with bacterial pneumonia.

In a recently published retrospective multicentre analysis of 4 698 patients with varying severity of heart failure, PCT levels were found to be significantly higher in patients with bacterial infection complicated by
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heart failure, compared to those with simple bacterial infections. The study suggested that heart failure may interfere with PCT expression. Results revealed that, in non-infected patients, PCT levels were significantly elevated in patients with increasing severity of heart failure. The study alluded to the consideration and implementation of higher PCT cut-off values in NYHA class II-IV heart failure patients [59]. Other studies have shown that patients with decompensated HF, without clear signs of infection, who have elevated PCT have poorer in-hospital and post-discharge outcomes [60].

Although further trials assessing the utility of PCT levels in infected heart failure patients are needed, natriuretic peptide use, in conjunction with PCT, has been shown to improve the diagnostic accuracy of an underlying bacterial pulmonary infection. Moreover, the study also demonstrated that a BNP level of >400 ng/mL, along with PCT of >0.21 ng/mL, was able to accurately identify all patients with AHF and an underlying bacterial pneumonia.

The role of PCT in the infected heart failure patient is manifold and certainly of high clinical value. PCT testing can not only allow the detection of an underlying bacterial pneumonia, but it can also guide antibiotic therapy in such patients. Randomized clinical trials are needed to further test this hypothesis.

High-sensitivity troponins

High-sensitivity troponins refer to troponins that are measured in the bloodstream, using highly sensitive assays [61]. These assays are able to detect even minute elevations in troponin levels, while maintaining a low coefficient of variation (CV) (<10%) and a diagnostic cut-off at the 99th percentile of the general population [61]. Since several different assays have been utilized, the analytical variability must be considered while interpreting high-sensitivity troponin levels [62]. Myocyte injury, leading to cellular death, can vary from 20 min to 4 hours, depending on several factors such as the infarct size, the condition of the vascular endothelium, etc. Several conditions can cause troponin leaks into the circulation; only a markedly elevated rise (>10%) from the baseline is indicative of MI and warrants intensive cardiac care [62, 63]. High-sensitivity troponin is elevated in the majority of AHF patients and is associated with many markers of disease severity (i.e. prevalence of ischaemic heart disease and worse renal function). Additionally, baseline and peak changes from baseline levels in AHF are associated with poor clinical outcomes, including 6-month mortality [64].

Emerging biomarkers

Galectin-3
Galectin-3 is a protein secreted by activated macrophages, resulting in the proliferation of cardiac fibroblasts and collagen deposition, which ultimately causes cardiac fibrosis [65, 66]. In patients with heart failure, galectin-3 levels have been found to be elevated, denoting its link to cardiac remodelling. Its utility in AHF patients is that of predicting short-term and long-term prognosis [65, 66].

In rodent models, an infusion of galectin-3 led to an increased collagen deposition, and ultimately an impaired cardiac function. Moreover, in rodent models with decompensated heart failure, galectin-3 levels were grossly elevated [67]. In 599 patients presenting to the ED with acute dyspnoea, measured plasma levels of galectin-3, along with NT-proBNP and apelin, revealed that galectin-3 levels were markedly elevated in participants with heart failure, compared to those without. Galectin-3 was the strongest independent predictor of 60-day mortality, yielding an AUC of 0.74 on receiver operator curve (ROC) analysis and an odds ratio (OR) of 10.3; \( P < 0.01 \). Furthermore, in combination with NT-proBNP, elevated galectin-3 levels were a better predictor of mortality [68].

In another interesting analysis of 592 patients hospitalized with heart failure, galectin-3 levels did not provide additive prognostic information at 6 months. However, in patients with preserved-ejection fraction (EF) heart failure, elevated galectin-3 levels were associated with worse prognosis, when compared to those with reduced-EF heart failure [69]. In the cardiac transplant population, serum galectin-3 levels remained significantly elevated the majority of patients after transplantation [70]. Interestingly, elevated levels appear associated with renal dysfunction and this may be not only a model of cardiac remodeling but also systemic dysfunction.

Galectin-3 is a strong prognostic marker and, in the AHF patient, is indicative of ongoing cardiac remodelling. Furthermore, recent trials have further explored the role of galectin-3 in predicting mortality in AHF patients. Data suggest that, although galectin-3 is a robust prognostic marker, elevated levels might be indicative of renal dysfunction, which might be attributed to fibroblast activation, resulting in renal fibrosis. Thus, in AHF patients, elevated galectin-3 levels might not only indicate higher risk, but may also be indicative of an impending renal failure.

**Copeptin**

The role of arginine vasopressin (AVP), also known as the antidiuretic hormone (ADH), in heart failure patients is well established. A decrease in the plasma volume and an increased serum osmolality trigger the release of ADH from the posterior pituitary gland, causing fluid retention [71, 72]. In the most severe cases of heart failure, hyponatraemia is often observed as a direct result of this mechanism. The AVP precursor molecule is synthesized in the hypothalamus and stored in the posterior pituitary gland [57, 58]. Due to its in vitro instability and rapid clearance, AVP is difficult to measure. Copeptin is the more stable and measurable
portion of the AVP molecule. Copeptin is the C-terminal portion of the AVP precursor molecule and is released in equimolar amounts, along with AVP. Copeptin has a 39-amino acid structure and functions similarly to AVP [73].

The role of copeptin in AHF is prognostic in nature. In a subanalysis of the multicentre BACH trial, patients with elevated copeptin levels were found to have the highest risk of mortality and readmissions at 90 days. Patients at the highest quartile of copeptin levels were at an increased risk of 90-day mortality (HR 3.85). On multivariate analysis, copeptin, along with NT-proBNP and Na\(^+\) levels, achieved a net reclassification improvement of 32.7% for the 90-day mortality endpoint. Cox regression analysis revealed that patients with elevated copeptin levels and hyponatraemia were at highest risk for heart failure-related readmissions, heart failure-related ED visits, and death. As mentioned before, in patients with severe heart failure, excess AVP levels result in hyponatraemia. Moreover, excessive diuretic use can also contribute to worsening hyponatraemia. The study alluded to the role of using AVP antagonists to treat hypervolaemic hyponatraemia in such patients with heart failure [74].

RCTs testing the role of using AVP antagonists are needed to better judge their effectiveness in AHF patients. Nevertheless, copeptin serves as an excellent prognostic marker for predicting short-term mortality in AHF patients.

**Mid-regional markers**

Peptides are often immeasurable, due to several factors such as *in vitro* instability and short half-life due to rapid plasma clearance. Mid-regional markers refer to the stable and easily measurable mid-regional fragments of these peptides. The development of newer immunoassays makes it easier to measure these mid-regional epitopes of circulating hormonal peptides [62]. ANP, as mentioned before, performs an array of physiological functions when released into the bloodstream, in direct response to atrial and ventricular volume and pressure [75, 76]. But their instability, coupled with a high plasma clearance, made it difficult to measure ANP. MR-proANP, which refers to the more stable mid-regional fragment of ANP, can now be measured using novel immunoassays directed to the mid segment [62, 63].

A subanalysis of the BACH trial revealed that a cut-point of 130 pmol/L for MR-proANP was non-inferior to BNP at a 100 pg/mL cut-point in diagnosing AHF; furthermore, MR-proANP significantly added to the diagnostic performance of BNP and NT-proBNP. Importantly, MR-proANP was shown to provide additive diagnostic information where natriuretic peptides were inconclusive. In another study, MR-proANP levels assessed in 187 patients with NYHA functional classes III–IV heart failure found that patients with increased MR-proANP levels were at increased risk of cardiovascular mortality (HR 7.6). Clinical trials have thus far
demonstrated both the diagnostic and prognostic utilities of MR-proANP [77]. Recent studies have confirmed similar diagnostic power between MR-proANP, BNP, and NT-proBNP for AHF [78].

The other mid-regional marker in discussion is MR-proADM. Adrenomedullin, first isolated from the phaeochromocytoma extract, is a vasodilatory peptide with a 52-amino acid structure [79]. Adrenomedullin is synthesized in cardiomyocytes and fibroblasts and released into the circulation, in direct response to an increased wall stretch. Other factors stimulating adrenomedullin release are thought to be neurohormonal activation, along with angiotensin II and endothelin-1 [79–81]. But a rapid plasma clearance and a short-half life (22 min) make it unfavourable for clinical use, whereas the mid-regional fragment MR-proADM is a more stable peptide [80, 82]. Recently, endothelin-1 (ET-1) was studied for its prognostic value in the acute HF population from the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial [95]. ET-1, a potent vasoconstrictor, was found to be associated with worsened inpatient and long-term mortality, independent of natriuretic peptides.

In the aforementioned study, MR-proADM proved superior to BNP and NT-proBNP in predicting 90-day mortality in patients with AHF. MR-proADM outperformed troponin in a multivariate analysis. Additionally, MR-proADM has been shown to improve the diagnosis of AHF in elderly patients (>70 years old) when combined with natriuretic peptides [83]. Moreover, MR-proADM, together with copeptin, in predicting 14-day mortality yielded the best AUC of 0.81. Similar results were obtained in a study by Potocki et al. [82], which demonstrated the superior performance of MR-proADM to natriuretic peptides in predicting 30-day mortality.

The diagnostic and prognostic value of mid-regional markers is apparent. With more clinical trials exploring the role of these markers in AHF, their utility in diagnosis and risk stratification of AHF patients seems highly promising.

**ST2**

ST2 is a marker of myocardial remodelling and, at a molecular level, plays a distinct role in promoting myocardial fibrosis [84]. Identified as a member of the IL-1 receptor family, ST2 has two isoforms. The soluble isoform, denoted as sST2, and the membrane-bound receptor form, denoted as ST2L, both of which are expressed in cardiac myocytes. ST2L bind its functional ligand IL-33, and this ST2L/IL-33 interaction exerts a protective effect by preventing ventricular remodelling which occurs in response to mechanical stress [85, 86]. sST2 competes with IL-33, resulting in the loss of this protective effect and promoting myocardial fibrosis. Moreover, sST2 functions as a decoy receptor, limiting the cellular levels of IL-33 [86, 87].
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Studies have alluded to the prognostic nature of sST2. Unlike natriuretic peptides, sST2 is not affected by renal function, age, obesity, or atrial fibrillation [88]. In 593 patients with dyspnoea presenting to the ED, sST2 levels were significantly higher in those with AHF. In patients with systolic heart failure, sST2 levels were higher, compared to patients with non-systolic heart failure (0.67 ng/mL vs 0.42 ng/mL, respectively) [89]. As most patients with systolic heart failure have myocardial remodelling, sST2 levels indicate a poor prognosis. In such patients, therapy may be aimed at suppressing cardiac remodelling and a closer monitoring of such patients. Moreover, when used in conjunction with natriuretic peptides, sST2 adds to the prognostic information. In assessing the association between sST2 levels and the cardiac structure determined by echocardiography, participants with elevated levels of both sST2 and BNP were at five times the risk of 1-year mortality, when compared to neither sST2 nor BNP being elevated [90]. In those hospitalized for AHF, a decrease of this novel biomarker by 15.5% or greater reduces the short-term risk of mortality [91]. Beta-blockers, mineralocorticoid antagonists, and angiotensin receptor antagonists have all shown some evidence in their ability to reduce levels of sST2 [92, 93].

Conclusion

The role of biomarkers in the management and understanding of acute HF continues to evolve. The American Heart Association published a Scientific Statement in 2017 specifically addressing the role of biomarkers in HF [96]. This statement addresses the use of biomarkers in screening, diagnosis, management and prognostic assessment of patients with HF. With respect to acute HF, the use of biomarkers including natriuretic peptides, troponin, copeptin, MRproADM, and sST2 are all mentioned to help better understand the pathophysiology and improve management of this condition.

BNP and NT-proBNP are benchmark biomarkers of cardiac stress and are part of the AHF management guideline algorithm. But certain co-existing conditions, such as pulmonary/systemic infection, valvular dysfunction, renal failure, obesity, etc., can affect biomarker levels. In the presence of ‘grey zone’ biomarker levels, clinicians must look for these comorbid conditions before making a definitive diagnosis of heart failure. AHF treatment should be aimed at lowering the ‘wet BNP’ level, in order to achieve the patient’s ‘dry BNP’ level before discharge. In patients with AHF and superimposed bacterial pneumonia, the use of PCT allows the clinician to identify an underlying bacterial pneumonia when other testing has proved inconclusive. NGAL may help in the detection of early kidney injury, and, in the setting of AHF, elevated NGAL levels may indicate kidney injury due to aggressive diuresis or the use of nephrotoxic agents (ACE-I/ARB, spironolactone, IV dye). Thus, monitoring NGAL levels may allow the clinician to successfully diurese the patient without harming the
Kidneys. Prognostic markers, such as mid-regional peptides, offer additive information on short-term and long-term mortality of the AHF patient.

Troponins are established markers of myocyte death/injury. Although there are several conditions which result in non-specific elevated levels of troponin, high-sensitivity assays, detecting even minute changes in troponins, allow a clinician to gauge the ongoing cellular damage. Newer markers, such as galectin-3, belong to a class of myocyte remodelling markers, and elevated levels suggest ongoing fibrotic change, which requires treatment aimed at preventing further worsening of myocardial remodelling. Copeptin levels are indicative of salt/water homeostatic change, necessitating the use of AVP antagonists to block the effects of ADH and treat hyponatraemia, the electrolyte imbalance most frequently encountered in severe AHF patients. Newer markers, such as mid-regional peptides, are neurohormonal markers. Although current data demonstrate promising diagnostic and prognostic capabilities of these markers in AHF, further research is needed to better define their role in the AHF patient. Finally, ST2 is a marker for myocyte stress, and elevated levels have been shown to favour a poor prognosis.

Table 37.4 provides an overview of the strength of evidence for biomarkers discussed in this section.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Diagnostic capability</th>
<th>Prognostic capability</th>
<th>Biomarker-guided treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natriuretic peptides</td>
<td>++ +</td>
<td>++</td>
<td>++ +</td>
</tr>
<tr>
<td>NGAL</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>++ +</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>High-sensitivity troponins</td>
<td>+ +</td>
<td>++ +</td>
<td>+ +</td>
</tr>
<tr>
<td>Galectin-3</td>
<td>–</td>
<td>+ +</td>
<td>+</td>
</tr>
<tr>
<td>Copeptin</td>
<td>–</td>
<td>++ +</td>
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<tr>
<td>MR-proADM</td>
<td>–</td>
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</table>
Biomarkers in acute heart failure

| ST2 | + | + | + |

The future for AHF biomarkers revolves around a ‘multimarker’ strategy. Moreover, their role in guiding AHF therapy remains controversial but has shown promise. Further randomized clinical trials are needed to better explore this possibility.

**Personal perspectives**

Biomarkers have definitely entered the mainstream in treating and managing patients with heart failure presenting through the emergency department. Their applications in triaging heart failure patients, facilitating early diagnosis, and titrating treatment have been successfully demonstrated. Although there exist certain caveats to their use in the emergent and inpatient setting, the future will certainly see a more integrated approach, utilizing a ‘multimarker strategy’, to better evaluate the heart failure patient. Moreover, emerging biomarkers have provided a more comprehensive understanding of the complex underlying pathophysiology. Finally, the treatment paradigm might see a shift towards a more biomarker-guided therapy.

**Further reading**


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References


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30. Scrutinio D, Mastropasqua F, Guida P, *et al.* Renal Dysfunction and Accuracy of N-Terminal Pro-B-Type Natriuretic Peptide in Predicting
Biomarkers in acute heart failure


Biomarkers in acute heart failure


Biomarkers in acute heart failure


76. Moertl D, Berger R, Struck J, Gleiss A, Hammer A, Morgenthaler NG, Bergmann A, Hulsmann M, Pacher R. Comparison of midregional pro-


Biomarkers in acute heart failure


