Chapter 2

Biomarkers for Risk Prediction in Acute Decompensated Heart Failure

AR van der Velde
WC Meijers
RA de Boer

*Current Heart Failure Reports (2014); 11: 246-259*
ABSTRACT

Risk prediction in patients admitted with acute decompensated heart failure (ADHF) remains a challenge. Biomarkers may improve risk prediction, which in turn may help to better inform patients regarding short-term and long-term prognosis, therapy and care. Most data on biomarkers have been derived from patient cohorts with chronic heart failure. In ADHF, currently, risk tools largely rely on common clinical and biochemical parameters. However, ADHF is not a single disease. It presents in various manners and different etiologies may underlie ADHF, which are reflected by different biomarkers. In the last decade, many studies have reported the prognostic value of these biomarkers. These studies have attempted to describe a value for statistical modeling, e.g., reclassification indices, in an effort to report incremental value over a clinical model or the “gold standard”. However, the overall incremental predictive value of biomarkers has been modest compared to already existing clinical models. Natriuretic peptides, e.g., (NT-pro)BNP, are the benchmark, but head-to-head comparisons show that there are novel biomarkers with comparable prognostic value. Multimarker strategies may provide superior risk stratification. Future studies should elucidate cost-effectiveness of single or combined biomarker testing. The purpose of this review was to provide an update on current biomarkers and to identify new promising biomarkers that can be used in prognostication of acute heart failure.
INTRODUCTION

Heart failure (HF) is a complex disease, and its underlying pathophysiology is multifactorial. Patients who are hospitalized for a rapid worsening of preexistent HF or acute decompensated heart failure (ADHF), are difficult to treat, their mortality rate remains high [1••], and it remains a challenge to predict the risk of individual patients [2]. ADHF is associated with a number of individual characteristics including clinical, biochemical, demographic variables and comorbidity [3•]. For risk prediction after admission for ADHF, biomarkers may be of additional value to assess risk. “Biomarkers” can be any objectively measured biological marker that reflects normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic interventions [4•]. It is difficult to identify the perfect biomarker, primarily because HF has various different causes, which may be reflected by an array of different biomarkers. Thus, it remains a challenge to identify individual prognostic variables to guide clinical decision making. Nevertheless, biomarkers may be used as a tool, which can help doctors to better inform patients regarding therapy and care options. Accurate prognostic evaluation may aid in identifying patients who are at high risk and need more intensive monitoring, while those estimated lower risk, may be monitored less intensively. The purpose of this review is to provide an update on current biomarkers as predictors for outcome in ADHF, and to discuss new promising biomarkers, including HE4/WAP4C, syndecan-1 and urinary C-type natriuretic peptide, and also a new technique called bioelectrical impedance vector analysis (BIVA).

BIOMARKERS FOR HF RISK STRATIFICATION: MARKERS OF UNDERLYING PATHOPHYSIOLOGY

Several biomarkers for ADHF reflect the underlying pathophysiology of HF. Commonly, incident HF is preceded by a cardiovascular event. This event may happen suddenly as in myocardial infarction (MI), or may be slow and progressive, as in hypertension. Over time, the heart becomes progressively damaged due to maladaptive changes, often referred to as cardiac remodeling. In the end, the sequelae of events will impair the contractile function resulting in reduced cardiac output. Before this point, the human body will try to compensate, predominantly with neurohormonal activation [5]. Activation of the sympathetic nervous system with increased release of epinephrine leads to increased contractility and increased vascular resistance. Similarly, activation of the renin-angiotensin-system (RAAS) and increased release of antidiuretic hormone (ADH) leads to vasoconstriction and increased cardiac output. However, prolonged increase in angiotensin II also induces deleterious effects such as fibrosis via aldosterone, while norepinephrine induces cardiac remodeling and hypertrophy. In concert with apoptosis
of cardiac cells, this (mal)adaptive response on the long term contributes to adverse cardiac remodeling [6]. Once the delicate balance in the failing heart is disturbed, it will lead to congestion by fluids, which is clinically reflected as acute decompensated heart failure. This is accompanied by volume overload of the left ventricle (LV) leading to increased myocardial wall stretch. Each step of progression to heart failure is reflected by different kinds of biomarkers (Fig. 1).

**MARKERS OF NEUROENDOCRINE ACTIVATION**

**MR-proADM**
In response to increased ventricular wall stress and hemodynamic changes, adrenomedullin (ADM), a peptide hormone, is secreted by myocardial tissue and endothelial cells [7]. ADM stimulates natriuresis and vasodilatation, which is mediated by cAMP and nitric oxide, thereby decreasing afterload and increasing cardiac output [8, 9•]. Elevated levels of this peptide hormone have been associated with the severity of HF [10]. However, ADM is difficult to measure due to its short half-life, instability in plasma and fast clearance from circulation [11, 12]. Midregional pro-adrenomedullin (MR-proADM) is a stable precursor of ADM and its levels mirror those of ADM [12]. Elevated levels of MR-proADM have also shown to be predictive for adverse outcome in ADHF patients [13–15, 16•], and some studies even suggest that MR-proADM is superior in predicting mortality, compared to BNP or NT-proBNP in patients with ADHF (Table 1) [16•, 17].

**Copeptin**
As a result of changes in osmolality and decreases in circulatory pressures, arginine vasopressin (AVP, also known as ADH) is chronically released by the posterior pituitary gland in patients with HF in order to preserve cardiac output [18•]. AVP interacts with renal collecting ducts (via the V2-receptor) and maintains vascular tonus (via the V1a-receptor), thereby regulating blood pressure. Higher levels of AVP are related to severity of disease in patients with HF [19]. However, AVP is difficult to measure due to its instability and fast clearance rate [20]. Copeptin is the C-terminal segment of the AVP-prohormone and is a stable surrogate marker for AVP [21]. It is also released by the hypothalamus, in the same amounts as AVP [22] and is a sensitive marker for HF progression [23]. In patients with acute decompensated HF, copeptin was found to be predictive for all-cause mortality at 1-year [24•] and also at 24 months [25]. The predictive value was similar to MR-proADM, C-terminal endothelin-1 precursor fragment, midregional proatrial natriuretic peptide (MR-proANP), and B-type natriuretic peptide (BNP) [16•]. Serial measurement of copeptin was found to be an independent predictor for death
Figure 1: Pathophysiology of heart failure, which is reflected by different biomarkers.
<table>
<thead>
<tr>
<th>Biomarker</th>
<th>AUC</th>
<th>NRI</th>
<th>Incremental Value Over: (Model)</th>
<th>Endpoint</th>
<th>Follow-up</th>
<th>Author</th>
<th>Study</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiomyocyte stretch</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR-proANP</td>
<td>0.75</td>
<td>7.4 %</td>
<td>Clinical prediction model</td>
<td>All-cause mortality</td>
<td>1 year</td>
<td>Lassus J et al. [125••]</td>
<td>MOCA study</td>
<td>5306</td>
</tr>
<tr>
<td></td>
<td>0.67</td>
<td>23 %*</td>
<td>Clinical model</td>
<td>All-cause mortality</td>
<td>5 year</td>
<td>Seronde MF et al. [82••]</td>
<td>Biomarcoeurs, FINN-AKVA</td>
<td>306</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>0.84</td>
<td>12.9 %</td>
<td>Clinical model</td>
<td>All-cause mortality</td>
<td>1 year</td>
<td>Scrutinio D et al. [152]</td>
<td>MOCA study</td>
<td>5306</td>
</tr>
<tr>
<td></td>
<td>0.75</td>
<td>9.1 %</td>
<td>Clinical prediction model</td>
<td>All-cause mortality</td>
<td>1 year</td>
<td>Lassus J et al. [125••]</td>
<td>MOCA study</td>
<td>5306</td>
</tr>
<tr>
<td></td>
<td>0.81</td>
<td>7 %</td>
<td>Clinical risk factors</td>
<td>All-cause mortality</td>
<td>90 days</td>
<td>Lassus J et al. [125••]</td>
<td>MOCA study</td>
<td>5306</td>
</tr>
<tr>
<td></td>
<td>0.56</td>
<td>11 %*</td>
<td>Clinical model</td>
<td>All-cause mortality</td>
<td>5 year</td>
<td>Scrutinio D et al. [152]</td>
<td>MOCA study</td>
<td>5306</td>
</tr>
<tr>
<td>BNP</td>
<td>0.75</td>
<td>5.5 %</td>
<td>Clinical prediction model</td>
<td>All-cause mortality</td>
<td>1 year</td>
<td>Lassus J et al. [125••]</td>
<td>MOCA study</td>
<td>5306</td>
</tr>
<tr>
<td></td>
<td>0.60</td>
<td>4 %*</td>
<td>Clinical model</td>
<td>All-cause mortality</td>
<td>5 year</td>
<td>Scrutinio D et al. [152]</td>
<td>MOCA study</td>
<td>5306</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>0.75</td>
<td>5.3 %</td>
<td>Clinical prediction model</td>
<td>All-cause mortality</td>
<td>1 year</td>
<td>Lassus J et al. [125••]</td>
<td>MOCA study</td>
<td>5306</td>
</tr>
<tr>
<td>HE4</td>
<td>0.75</td>
<td>31 %*</td>
<td>Clinical model + BNP</td>
<td>All-cause mortality + HF rehospitalization</td>
<td>18 months</td>
<td>De Boer RA et al. [138•]</td>
<td>COACH</td>
<td>567</td>
</tr>
<tr>
<td><strong>Cardiac remodeling</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galectin-3</td>
<td>0.70</td>
<td>42.6 %*</td>
<td>Clinical model + BNP</td>
<td>HF Rehospitalization</td>
<td>30 days</td>
<td>Meijers WC et al. [53]</td>
<td>COACH, PRIDE, UMD H-23258</td>
<td>902</td>
</tr>
<tr>
<td></td>
<td>0.82</td>
<td>19 %</td>
<td>Clinical risk factors</td>
<td>All-cause mortality</td>
<td>90 days</td>
<td>Lassus J et al. [125••]</td>
<td>MOCA study</td>
<td>5306</td>
</tr>
<tr>
<td>ST-2</td>
<td>0.77</td>
<td>25.5 %</td>
<td>Clinical prediction model</td>
<td>All-cause mortality</td>
<td>30 days</td>
<td>Lassus J et al. [125••]</td>
<td>MOCA study</td>
<td>5306</td>
</tr>
<tr>
<td></td>
<td>0.77</td>
<td>10.3 %</td>
<td>Clinical prediction model</td>
<td>All-cause mortality</td>
<td>1 year</td>
<td>Lassus J et al. [125••]</td>
<td>MOCA study</td>
<td>5306</td>
</tr>
<tr>
<td>Syndecan-1</td>
<td>N.A.</td>
<td>48.5 %*</td>
<td>Clinical risk factors</td>
<td>All-cause mortality + HF rehospitalization in HFPEF</td>
<td>18 months</td>
<td>Tromp J et al. [144•]</td>
<td>COACH</td>
<td>567</td>
</tr>
<tr>
<td><strong>Neuroendocrine activation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copeptin</td>
<td>0.83</td>
<td>37 %</td>
<td>Adjusted model + NT-proBNP</td>
<td>All-cause mortality</td>
<td>30 days</td>
<td>Potocki M et al. [127]</td>
<td>BACH trial</td>
<td>287</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR-proADM</td>
<td>N.A.</td>
<td>8.9 %</td>
<td>Best clinical model</td>
<td>All-cause mortality</td>
<td>90 days</td>
<td>Maisel A et al. [153]</td>
<td>BACH trial</td>
<td>557</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Biomarkers for Risk Prediction in Acute Decompensated Heart Failure (continued)

<table>
<thead>
<tr>
<th>AUC</th>
<th>NRF (%)</th>
<th>Incremental value over: (Model)</th>
<th>Endpoint</th>
<th>Follow-up</th>
<th>Author</th>
<th>Study</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.80</td>
<td>28.7 %</td>
<td>Clinical model</td>
<td>All-cause mortality</td>
<td>30 days</td>
<td>Lassus J et al. [125••]</td>
<td>MOCA study</td>
<td>5306</td>
</tr>
<tr>
<td>0.76</td>
<td>9.1 %</td>
<td>Clinical model</td>
<td>All-cause mortality</td>
<td>1 year</td>
<td>Lassus J et al. [125••]</td>
<td>MOCA study</td>
<td>5306</td>
</tr>
</tbody>
</table>

**Renal injury**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Clinical model</th>
<th>All-cause mortality + HF rehospitalization</th>
<th>30 days</th>
<th>Maisel A et al. [123•]</th>
<th>GALLANT trial</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NGAL</td>
<td>0.73</td>
<td>29.8 %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
or transplantation in an univariate analysis. However, after adjustment for troponin T in multivariate analysis, this association was diminished [26•].

**Chromogranin A**

Chromogranin A is believed to reflect the activity of the central nervous system [27•] and is produced by adrenergic and neuroendocrine cells [28]. Chromogranin A is a prohormone, which is cleaved after posttranslational modification in vasostatins and catestatin. These peptides negatively regulate neuroendocrine function of the adjacent cells: vasostatin inhibits vasoconstriction and catestatin inhibits the release of catecholamines [29]. Patients with HF have higher levels of chromogranin A and these levels are associated with severity of HF and were found to be an independent predictor for mortality in patients with ADHF [30•].

**MARKERS OF CARDIAC REMODELING**

Cardiac remodeling is about the process of cellular changes of the myocardium and includes myocyte hypertrophy, fibrosis and apoptosis or necrosis [31, 32••]. Biomarkers of cardiac remodeling with established prognostic value include: ST2, galectin-3, and GDF-15.

**(Soluble) ST2**

Following volume overload and mechanical strain, more ST2 mRNA is released from cardiomyocytes and fibroblasts [33, 34, 35••]. ST2 exists in multiple isoforms including ST2L; a transmembrane receptor, and soluble ST2 (sST2); a circulating form of ST2 [36]. ST2L exerts its effect via IL-33, a ligand of ST2, and has antifibrotic and antihypertrophic effects [37]. However, sST2 can bind IL-33, acting as a decoy receptor, and blocks the antihypertrophic and antifibrotic effects of IL-33 [38]. In this way, sST2 is the component of ST2 with deleterious effects. The sST2 levels are higher in patients with heart failure and have been shown to be associated with poor prognosis in patients with ADHF [39, 40] and add prognostic value to NT-proBNP and hsTropT [41•]. The sST2 levels are also significantly correlated with left ventricular end systolic volumes and dimensions and left ventricular ejection fraction (LVEF) [42]. Moreover, elevated levels of sST2 identify patients with a more decompensated profile and more progressive cardiac remodeling [43]. Serial measurements of sST2 add prognostic information to baseline measurements [44, 45•].
Galectin-3
In response to cardiac stress (e.g., pressure overload), galectin-3 is released by activated macrophages in the heart to stimulate production of collagens, causing fibrosis and subsequent ventricular dysfunction [46, 47•, 48•]. A key feature of galectin-3 is cell-cell adhesion [49], and, therefore, it also plays an important role in tumor growth, metastasis [50], and inflammation [51]. The prognostic value of galectin-3 has been extensively studied and galectin-3 was found to be an independent predictor for mortality [52] and rehospitalization [53] in patients with ADHF. ROC analysis for predicting mortality was superior to NT-proBNP and apelin [54•]. However, some studies did not find this association in multivariate analysis after correction for eGFR or NT-proBNP [54•, 55]. Serial measurements in patients with ADHF also provide additional prognostic value [56]. Galectin-3 is not only an interesting biomarker because of its prognostic value; interestingly, it may also serve as a potential target for therapy. Experimental studies have shown that pharmacological inhibition of galectin-3 attenuates cardiac fibrosis in animal models [48•, 57••]. These two features render galectin-3 a promising biomarker and protein for further study in HF biology.

GDF-15
Cardiovascular events, like ischemia, pressure overload or atherosclerosis, induce a rapid upregulation of GDF-15 in cardiomyocytes [58•, 59], although GDF-15 may also colocalize in macrophages [60]. However, circulating GDF-15 is produced mostly outside the heart and, therefore, is not cardio-specific. GDF-15 is a member of the TGF-β superfamily and has shown to have anti-inflammatory and antihypertrophic effects [58•, 59]. This cardioprotective factor has shown to be a promising predictor for outcome in chronic heart failure patients [45•, 61–64]. GDF-15 has also shown to be a predictor in HF patients with a preserved ejection fraction (HFpEF) [65]. Serial measurements show that increasing levels of GDF-15 over time predict adverse outcomes [63]. However, data in ADHF patients are lacking.

MARKERS OF MYOCARDIAL STRETCH
In ADHF, increased filling pressures induce myocardial stretch, and, as a result, natriuretic peptides (NPs) are released from cardiomyocytes into the plasma. NPs have been extensively studied in both acute and chronic heart failure, and have been shown to be powerful predictors of outcome [66••]. NPs include atrial natriuretic peptide (ANP), which is mainly released from atrial cardiomyocytes, and B-type natriuretic peptide (BNP), mainly released from ventricular cardiomyocytes. Both ANP and BNP have natriuretic, diuretic, and vasodilatory effects. Secondary functions include inhibition of the
RAAS system and endothelin-1 secretion [67]. ANP and BNP are the biologically active peptides but their prognostic performance is less strong compared to their precursor peptides. N-terminal pro B-type natriuretic peptide (NT-proBNP) is a part of the precursor peptide BNP and is more stable and has a longer half-life [68]. The same applies for ANP. ANP has a short half-life and measurements are unreliable [69•]. N-terminal pro atrial natriuretic peptide (NT-proANP) is more stable but also prone to degradation [69•]. Another precursor of ANP, midregional pro atrial-type natriuretic peptide (MR-proANP) is a more stable alternative and has also shown its predictive value [69•, 70].

For diagnosis of ADHF, BNP and NT-proBNP are equally effective [71]. However, this is different for prognosis. Compared to clinical assessment (history taking and physical examination) or New York Heart Association (NYHA) symptoms, NT-proBNP is superior in predicting outcome [72, 73]. Serial measurements of NT-proBNP have also been shown to have incremental prognostic value, both the relative change as well as the absolute value [74].

However, the percent change in NT-proBNP seems to be more important than the absolute value at discharge [75]. The PROTECT study also showed that biomarker-guided therapy in patients with acute heart failure was useful: a 50 % reduction in NT-proBNP was associated with almost 50 % reduction of events [76]. Future studies should confirm this in an acute HF cohort. For patients with chronic heart failure, NT-proBNP guided therapy remains controversial. Some suggested that adding serial measurements of NT-proBNP to optimal clinical management may not improve outcome [77•]. Furthermore, posttreatment or discharge values of NTpro-BNP are more predictive for adverse outcome compared to NT-proBNP levels at hospital admission [75, 78]. The ongoing Guiding Evidence Based Therapy Using Biomarker Intensified Treatment (GUIDE-IT; ClinicalTrials.gov Identifier: NCT01685840) trial is expected to provide more definite answers if natriuretic peptide guided therapy is helpful in systolic heart failure. In conclusion, both absolute values as well as relative changes of NT-proBNP during hospitalization are informative.

When NPs are used for risk prediction, certain confounders have to be taken into account. Renal failure will increase NP levels [79] and obese patients tend to have lower levels of NPs [80]. Because of the beneficial effects of NPs, it was hypothesized that systemic infusion of NPs will have favorable effects in patients. However, recombinant NPs as a therapeutic did not lead to less mortality [81•].

MR-proANP is a relatively new player and has shown strong prognostic value at least comparable to NT-proBNP or BNP [24•]. For long-term prognosis, MR-proANP seems to be more predictive than NT-proBNP or BNP [82••]. Serial measurements of MR-proANP added prognostic information, also in a multivariate analysis after adjustment for cofactors [26•]. Further investigation is warranted to assess if MR-proANP indeed outperforms NT-proBNP, which is the gold standard nowadays.
MARKERS OF INFLAMMATION

Heart failure is considered as a proinflammatory state, and furthermore, infection is an important precipitating factor for ADHF, especially in the elderly. Therefore, markers of infection have been considered as predictors for prognosis [83].

C-Reactive Protein (CRP)

Progression of heart failure occurs, at least in part, by the effect of proinflammatory cytokines like IL-6 and TNF-alpha [84]. IL-6 induces release of CRP, synthesized by the liver [85]. CRP is recognized as one of the best markers reflecting inflammation and has a function in the activation of the complement system [86]. Levels of high sensitivity (hs)CRP are higher in patients with HF and are associated with mortality and rehospitalization in patients with ADHF [87, 88]. However, CRP is less reliable as a predictor for prognosis in the treatment of HF patients with secondary infections, and more reliable as a predictor for outcomes in noninfected patients [89•].

Procalcitonin

In infective states, especially bacterial infections, procalcitonin is upregulated by endotoxin stimuli but it can also be triggered in a noninfective inflammatory state by proinflammatory cytokines, such as IL-6 or TNF [90, 91]. This implies that procalcitonin levels are not only increased in pneumonia or sepsis, but can also be elevated in cardiogenic shock and acute coronary syndrome (ACS) [92, 93]. Procalcitonin is a precursor peptide of calcitonin, and is released from the liver and peripheral blood mononuclear cells [91]. Following (bacterial) infection, procalcitonin levels reach a fast peak (within eight hours), even before C-reactive protein [94]. Procalcitonin has been shown to be an independent predictor for 30-day mortality in ADHF [95•]. However, another study did not find this association with all-cause mortality [96]. Whether procalcitonin is a strong predictor for outcome in acute heart failure remains uncertain and more studies are needed to answer this question. Procalcitonin can be helpful to identify patients with pneumonia [97] and elevated levels (>0.5 ng/ml) have a specificity of 0.99 for diagnosis of systemic infection [98], so that current procalcitonin studies in HF primarily address the coexistence of pneumonia.

IL-6

IL-6 is a proinflammatory cytokine, released in response to infection [99•]. IL-6 can bind IL-6R, a membrane receptor. This complex activates gp130, which induces intracellular inflammatory signaling pathways [100]. IL-6 is an important mediator of the acute phase response and induces release of CRP [101]. IL-6 is significantly correlated with 180-day mortality [102] and is predictive for mortality in patients with ADHF [103, 104•, 105].
MARKERS OF MYOCYTE INJURY

Troponin
During admission for ADHF, increased myocardial wall stress and elevated left ventricular end diastolic pressure exist, which lead to decreased myocardial perfusion and subsequent myocyte necrosis and apoptosis [106•]. As a result of this (subclinical) myocardial injury, troponin can be released from the cytosol of cardiomyocytes into the circulation [107]. Troponin is a cardiac regulatory protein and controls actin-myosin interaction [108]. The troponin complex consists of an I, T, and C complex, which can be found on the actin filament [109]. Troponin C is not specific for the heart; however, troponin T & I are specific markers for myocardial injury [108] and can be used to confirm the diagnosis of ACS [110] and to estimate infarct size [111]. Troponin has a high specificity; however, there are certain factors that can interfere with circulating levels of troponin, such as renal failure, sex, age, and LV hypertrophy [112]. Troponin I and T were both found to be important prognostic factors in patients with ADHF [113••]. Patients with elevated levels of troponin had lower (systolic) blood pressure, lower LV ejection fraction, and higher in-hospital mortality (8.0 % vs 2.7 %) [113••]. In comparing high sensitivity troponins, troponin T was found to be a better predictor for outcome compared to troponin I [114•]. Serial measurements of troponin were also found to be predictive for outcome. Poor outcomes were observed in patients with increasing troponin levels after hospital admission and treatment for ADHF [115].

MARKERS OF RENAL INJURY

Renal insufficiency is common in patients with acute heart failure. Worsening renal function and acute kidney injury are both being associated with a worse prognosis [116], and acute kidney injury occurs in 30-50 % of patients hospitalized for ADHF and is associated with prolonged length of stay, increased hospitalization costs, and increased mortality [117•, 118]. For this reason, markers of renal injury like cystatin C and Neutrophil Gelatinase-Associated Lipocalin (NGAL) may be useful in identifying high-risk patients.

Cystatin C
Cystatin C is a cysteine protease inhibitor that is released from all functioning cells. It is constantly produced and is freely filtered by the glomerulus. Because it is not actively secreted by renal tubules, it is considered an ideal endogenous marker of renal (glomerular) function [119, 120]. It has been reported that high cystatin C levels are associated with a higher risk for mortality and/or HF readmission, and also after multivariate adjustments [121]. A prospective, observational, multicenter study conducted in hospitalized
patients with acute heart failure showed that cystatin C remained a significant predictor for outcome after adjustment for established biochemical predictors of adverse events such as creatinine, estimated glomerular filtration rate (Cockcroft-Gault), hemoglobin, sodium, and NT-proBNP [122]. Cystatin C levels of ADHF patients were much higher in these patients compared to ambulatory patients with chronic HF. It was speculated that these findings probably reflect a more advanced kidney dysfunction in patients with ADHF, resulting in a poor prognosis in this population.

**NGAL**

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25-kDa protein secreted by renal tubular cells, leucocytes, and epithelial cells. It is released in response to ischemic or toxic injury and is a measure of acute kidney injury and precedes creatinine elevation [123•]. ADHF patients with elevated serum NGAL levels at admission have a higher risk that is associated with the development of worsening renal function [124]. NGAL has been shown to be a strong prognostic indicator of 30 days outcome at discharge for patients admitted to the hospital for ADHF [123•]. NGAL improved reclassification over BNP with 29.8 %, but in a model containing only BNP without clinical variables (Table 1).

**HEAD-TO-HEAD COMPARISONS AND MULTIMARKER APPROACHES**

Nowadays, a large number of biomarkers is available for estimating prognosis after ADHF. Comparing these biomarkers for risk prediction might be difficult, because each of them is reflecting a different pathophysiology, but they may help to identify which marker, or which combination of markers, provides most incremental value. Several studies have examined the prognostic value of multiple biomarkers in the same study.

The MOCA trial studied the incremental value of biomarkers in a multinational observational cohort on ADHF and was comprised of 5,306 patients [125••]. Several biomarkers provided incremental value in risk prediction compared to the clinical prediction model (age, gender, blood pressure, estimated glomerular filtration rate, heart rate, and sodium and hemoglobin levels). For prediction of 30-day mortality, MR-proADM showed the highest incremental value in risk prediction (NRI: 28.7 %) (Table 1). For 1-year prognosis, sST2 was found to be the best predictor (NRI: 10.3 %). Also dual biomarker combinations were studied. For 30-day mortality, the combination of CRP and MR-proADM yielded the highest incremental value in predicting prognosis (NRI: 36.8 %) and for 1-year mortality the combination of CRP and sST2 was found to be the best predictor (NRI: 20.3 %).

In the BACH trial, a prospective, multicenter study of 1,641 patients presenting with dyspnea at the emergency department, MR-proADM again was found to be the best
predictor for mortality at several time points compared to BNP and NT-proBNP. However, for prediction of rehospitalization, BNP was still superior [16•].

Two large cohorts, Biomarcoeurs and FINN-AKVA, studied the prognostic value of natriuretic peptides of patients with ADHF [82••]. MR-proANP was found to be the best predictor for 5-year mortality (NRI: 23 %). Gegenhuber et al., measured several promising biomarkers for risk prediction in 137 patients with ADHF [24•]. For the prediction of 1-year mortality, MR-proANP had the highest predictive value (AUC: 0.73), before BNP (AUC: 0.72), MR-proADM (AUC: 0.71), and copeptin (AUC: 0.69).

The GALLANT trial showed that the renal marker NGAL was a significant predictor for events in multivariable analyses while neither eGFR nor creatinine reached significance. Furthermore, NGAL improved reclassification over BNP by a net 10.3 % [123•].

Zairis et al., studied 577 patients with ADHF. Cox regression modeling showed that BNP was the best predictor, compared to cardiac troponin I and hs-CRP. The combination of these biomarkers improved C-statistics from 0.70 to 0.82 [126•]. Potocki et al., performed a prospective, observational cohort study in 287 patients with acute dyspnea [127]. AUC was highest for copeptin (0.83), followed by NT-proBNP (0.76), and BNP (0.63). After inclusion of copeptin to the adjusted model (including NT-proBNP), NRI was 37 %. Finally, a small study of 79 patients reported BNP to be the best predictor for mortality in univariate analysis, compared to proinflammatory cytokines, including IL-6 [128].

**GENDER DIFFERENCES**

In biomarkers for acute heart failure, sex based differences have been described. For instance, levels of natriuretic peptides are higher in healthy women, compared to healthy men [129]. This may partly be explained by estrogen-mediated stimulation and androgen-mediated suppression [130, 131] and; therefore, it was suggested to use sex specific reference limits [129]. However, in decompensated state, these sex based differences are not significantly different. This may be explained by the higher percentage of women with HFpEF, which is accompanied by lower values of natriuretic peptides [132]. Besides natriuretic peptides, levels of biomarkers that are related to cardiac remodeling or inflammation (syndecan-1, CRP, GDF-15, IL-6) are found to be significantly lower in women compared to men [133•]. However, the fibrosis marker galectin-3 generally shows higher values in healthy women [132, 134•]. In contrast, another fibrotic marker, sST2, is significantly lower in women, which might be due to the effects of sex hormones [135]. Recently, a new intriguing biomarker was also discovered with prognostic value specifically for women [136]. Proneurotensin was found to be associated with development of cardiovascular disease and cardiovascular mortality, but only in women. Proneurotensin
is a stable precursor of neurotensin, and regulates satiety, but more research is needed to establish its role in development of cardiovascular disease in women.

NEW DEVELOPMENTS

HE4/WAP4C
Recently, human epididymis protein 4 (HE4) or whey acidic protein four-disulphide core (WAP4C) was identified as one of the most upregulated genes in cultured myofibroblasts. HE4 is an established biomarker for epithelial ovarian cancer and is known for its antiprotease and anti-inflammatory function [137]. HE4 is not cardiospecific and is associated with GDF-15, and in this regard may play a role in the immune response. In an analysis of the COACH trial, a multicenter randomized study with 567 patients admitted for ADHF, HE4 was associated with HF severity and outcome. Furthermore, HE4 was shown to be an independent predictor for HF outcome and improved risk classification (NRI: 31 %, over clinical model + BNP) [138•]. A recent animal study showed that administration of HE4-neutralizing antibodies had protective effects in preventing fibrosis [139••]. These results show that HE4 could be a potential new biomarker for (acute) heart failure, and may serve as a new therapeutic target to prevent fibrosis.

Urinary C-type Natriuretic Peptide
In HF, renal dysfunction is common and also an independent predictor of outcome in patients with ADHF [140]. However, the prognostic value of renal tubular injury is not reflected in current estimates of kidney function. Recently, urinary C-type natriuretic peptide was discovered as a biomarker for HF. This urinary peptide is produced both in the kidney as well as in the endothelium of renal tubules and plasma levels of a specific isoform are elevated in patients with ADHF [141]. Urinary C-type natriuretic peptide is a venodilator and undergoes downstream cleavage into NT-proCNP and CNP53, which is further processed to NT-CNP53. NT-CNP53 has a longer half-life and is more stable compared to the active CNP [142]. In a study of 58 patients with ADHF, urinary NT-CNP53 excretion was found to be predictive for mortality and all-cause rehospitalization or death [143•], even after adjustment for age, urinary protein/creatinine ratio and plasma NT-proBNP. In the same study, urinary KIM-1 and NGAL excretion were no significant predictors for outcome. Additionally, NT-CNP53 showed incremental prognostic value to plasma NT-proBNP for the combined endpoint of death and rehospitalization.

Syndecan-1
Syndecan-1 is a transmembrane receptor and a member of the proteoglycan family. It is associated with fibrotic and inflammatory diseases and is involved in matrix-matrix inter-
actions. In a recent study, syndecan-1 was found to be a predictor for clinical outcome in patients HFpEF, but not in patients with reduced ejection fraction (HFrEF), independent of other known heart failure risk factors [144•]. Multivariable regression analysis showed a positive correlation with markers of fibrosis and remodeling (galectin-3, ST2, periostin) but not with markers for inflammation. Syndecan-1 also improved risk classification in patients with HFpEF after adding to the established model of clinical risk factors (NRI: 48.5 %). Syndecan-1 could serve as a potential predictor for outcome specifically in patients with HFpEF, but clearly more studies are needed to confirm this.

Bioelectrical Impedance Vector Analysis (BIVA)

In healthy individuals, total body water (TBW) comprises approximately 60 % of body weight and can be found intracellular and extracellular. One third of TBW is extracellular, both in interstitial fluid and in intravascular fluid. Estimation of body fluid status was found to be important for risk stratification in ill patients [145], but it is often difficult to assess. Bioimpedance analysis is a noninvasive technique to estimate volume status and body composition. This is measured by bioelectrical impedance, where resistance was found to be inversely related to TBW. BIVA is now considered to be the superior method to assess TBW and was recently tested in 270 patients with acute heart failure. BIVA showed significant prognostic value in univariate and multivariate analysis for a 30-day follow-up of cardiac events and improved prognostic value to BNP, particularly in the BNP ‘grey zone’ (100-400 pg/ml) [146, 147•]. BIVA is a promising new technique for risk prediction in acute heart failure. More and larger studies on this topic should elucidate if BIVA could serve as a new prognostic marker in acute heart failure.

CONCLUSION

Numerous studies have demonstrated the clinical utility of different biomarkers in acute and chronic HF. Currently, NPs are routinely used in HF care, but there are several novel biomarkers. Biomarkers should be critically reviewed and should fulfill certain criteria [148]. Baseline and repeated measurements should be possible and at reasonable cost. Secondly, the biomarker should provide information that is not already available from clinical assessment. During the last decade, (NT-pro) BNP was the benchmark as prognostic biomarker for outcome in patients with ADHF. However, recent head-to-head comparisons show that MR-proANP and MR-proADM are promising biomarkers that could maybe replace (NT-Pro) BNP as the benchmark.

Novel biomarkers should demonstrate at least comparable diagnostic or prognostic value over currently available assays [149]. Multiple studies nowadays report a net reclassification index, which make it easy to report the incremental prognostic value of
a biomarker (Table 1). Nevertheless, it remains difficult to find a single biomarker that fulfills all the needs for the evaluation of prognosis in patients with ADHF. Some biomarkers have shown their predictive value, however this remains limited over already existing clinical parameters [125••]. This also accounts for multimarker studies where only modest prognostic improvements were found compared to only traditional risk factors [150]. A good clinical prediction model often has high prognostic value with corresponding high AUC values [125••] so that improving above and beyond a good model by adding a biomarker is difficult. Therefore, current studies are focusing on combinations of biomarkers for risk prediction in acute heart failure. Ultimately, multimarker strategy may provide superior risk stratification compared to single biomarker measurement [55], particularly when biomarkers from distinct pathophysiologic pathways are combined, providing ‘orthogonal’ information to one another.

In the future, discovery of novel biomarkers may be achieved by proteomics and metabolomics, although these omics-based techniques have yet to yielded new biomarkers of acute heart failure. There are promising results in cardiac transplantation [151•], and; hence, future studies could yield new interesting biomarkers for acute heart failure. Future research should also elucidate if a multimarker strategy is cost-effective. Furthermore, biomarker guided trials are underway. If monitoring of biomarkers are of incremental value in patients with acute heart failure, they should provide more clarity.
REFERENCES

Papers of particular interest have been highlighted as:
- Of importance
-• Of major importance


ALARM-HF was a large survey among 4,953 patients with AHF in 9 different countries and described characteristics and management of acute heart failure in these patients.


The EuroHeart Failure Survey (EHFS) II evaluated 3- and 12-month mortality in 2,981 patients with acute heart failure from 30 different countries and identified clinical risk markers.


The Biomarkers Definitions Working Group defined biomarkers as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention.


This article describes the hemodynamic effects of systemic infusion of adrenomedullin up to pathophysiological plasma levels in healthy volunteers.


   The BACH trial was a prospective, multicenter, international study of 1,641 ADHF patients presenting with dyspnea at the emergency department and studied the diagnostic and prognostic value of various biomarkers.
   This review focuses on the different components of neurohormonal activation in heart failure.
22. Struck J, Morgenthaler NG, Bergmann A. Copeptin, a stable peptide derived from the vasopressin precursor, is elevated in serum of sepsis patients. Peptides 2005,26:2500-2504
   This study compares the prognostic value of different novel biomarkers and concludes some have similar predictive properties compared with BNP for 1-year all-cause mortality.
   The authors studied serial monitoring of MR-proANP and copeptin and concluded this was useful for detecting the highest-risk outpatients with HF.
   This is an extensive review about the functions and mechanisms of the chromogranin-secretogranin family.


In 137 patients with acute destabilized heart failure, increased chromogranin A and CT-proET-1 plasma concentrations add independent prognostic information to NT-proBNP.


This review discusses the molecular pathways that are involved in myocardial fibrosis.


The ADHERE registry describes characteristics and outcome of 100,000 patients hospitalized for acute decompensated heart failure.


This study investigated the use of ST2 and hs-Troponin and conclude these markers provide superior risk stratification over NT-proBNP.
Biomarkers for Risk Prediction in Acute Decompensated Heart Failure

Chapter 2

42. Shah RV, Chen-Tournoux AA, Picard MH, van Kimmenade RR, Januzzi JL. Serum levels of the interleukin-1 receptor family member ST2, cardiac structure and function, and long-term mortality in patients with acute dyspnea. Circ Heart Fail 2009;2:311-319


54. van Kimmenade RR, Januzzi JL, Jr, Ellinor PT, et al. Utility of amino-terminal pro-brain natriuretic peptide, galectin-3, and apelin for the evaluation of patients with acute heart failure. J Am Coll Cardiol 2006;48:1217-1224 This substudy of the PRIDE demonstrated the clinical utility of galectin-3 for the first time, showing that galectin-3 was the best predictor for 60-day mortality.


Chapter 2

This article showed that galectin-3 could also serve as a “target for therapy”. Inhibition of galectin-3 resulted in attenuation of fibrosis in animal models of heart failure.


The authors identified GDF-15 as a novel antagonist of hypertrophic response.


This systematic review concludes that BNP is a strong prognostic factor in patients with heart failure.


MR-proANP was found to be a better predictor for death in patients with chronic heart failure, compared to BNP and NT-proBNP.


When serial measurements of NT-proBNP were added to optimal clinical management, this was not associated with improved outcome.


Infusion of nesiritide in a randomized controlled trial in 7,141 patients did not affect the rate of death or hospitalization.


This study of 710 patients evaluated the diagnostic and prognostic value of 4 natriuretic peptides and concluded that MR-proANP had the best prognostic value at 5 years.


CRP has prognostic value in acute decompensated heart failure patients without infection but not in patients with infectious complications.


94. Meisner M, Adina H, Schmidt J. Correlation of procalcitonin and C-reactive protein to inflammation, complications, and outcome during the intensive care unit course of multiple-trauma patients. Crit Care 2006,10:R1


This review describes the different components of the inflammatory response following myocardial infarction.


Pro- and anti-inflammatory cytokines were measured in 423 patients with acute decompensated heart failure. IL-6, IL-10 and TNF-a provided important prognostic information in these patients.

This review describes heart failure in different clinical model systems, like a cardiorenal model, a hemodynamic model and a neurohormonal model.


Troponin levels were measured in 84,872 patients who were hospitalized for acute decompensated heart failure. A positive troponin test was associated with higher in-hospital mortality.

In a head-to-head comparison between troponin T and troponin I, troponin T showed better performance and was a better predictor for death.


This systematic review and meta-analysis concludes that worsening renal function predicts substantially higher rates of mortality and hospitalization in patients with heart failure.


In this study, NGAL was measured in 186 patients with acute decompensated heart failure. Plasma NGAL was found to be a strong predictor for 30-days outcome and improved reclassification over BNP.


In the MOCA study, 5,306 patients with acute decompensated heart failure were included. Biomarkers including sST2, MR-proADM, natriuretic peptides and CRP added prognostic value to clinical risk factors for predicting mortality.


This multimarker study concluded that an increasing number of elevated biomarkers, increased the risk of cardiac death gradually.


Female patients presenting with heart failure have a different clinical presentation and better outcome compared to male patients.


In this large community-based cohort, galectin-3 was associated with age and various risk factors of cardiovascular disease, with a strong gender interaction.


In the COACH trial, HE4 improved net reclassification when it was added to the clinical model and was correlated with markers of heart failure severity.


HE4 was found to be a new potential biomarker of (renal) fibrosis and could serve as a new therapeutic target.


Urinary C-type natriuretic peptide was detected in patients with heart failure and may have clinical utility as a biomarker.

144. Tromp J, van der Pol A, Klip IT, et al. The Fibrosis Marker Syndecan-1 and Outcome in Heart Failure Patients with Reduced and Preserved Ejection Fraction. Circ Heart Fail 2014, Syndecan-1 levels correlate with biomarkers of fibrosis and was a predictor for outcome in patients with HfPEF but not in HFrEF.


Proteomics has led to discovery of new biomarkers for various diseases, providing new treatments and diagnostics. This proposed computational pipeline is applicable to other biomarker proteomic studies.

