



Role of biomarkers in the heart failure clinic

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Heart failure (HF) is a common cardiovascular disease that has a complex pathophysiology. Because it is the final stage of many cardiovascular diseases, proper diagnosis and treatment are crucial for prolonging patients' survival and improving their well-being. Several biomarkers have been identified in HF, and their roles in diagnosis and prognostication have been widely investigated. Among them, natriuretic peptides are key for diagnosing HF, predicting its prognosis, and monitoring the effectiveness of HF treatment. Moreover, natriuretic peptides can also be used to treat HF. In addition to natriuretic peptides, several other biomarkers were included in the most recent HF management guidelines. Thus, we reviewed the role of the biomarkers included in these guidelines and discussed future perspectives.

Keywords: Biomarker; Galectin-3; Natriuretic peptides; Soluble ST2; Troponin

Introduction

Heart failure (HF) is a complex cardiovascular disease with multiple pathophysiologic mechanisms, so it is considered the final stage of many cardiovascular diseases. The prevalence of HF continues to increase over time due to the aging and the increase of comorbid cardiovascular diseases. The estimated prevalence of HF is 1% to 2% of the general adult population [1], and approximately 6,000,000 American adults over the age of 20 have experienced HF according to US data between 2015 and 2018 [2]. Prompt diagnosis and treatment of HF can reduce its associated socioeconomic burden. However, the diagnosis of HF usually relies on symptoms, physical examination, serum concentration of natriuretic peptides, and left ventricular systolic and diastolic function assessed by echocardiography. Recent

treatment guidelines for HF include natriuretic peptides in support of the diagnosis, prediction of prognosis, and management of HF patients. As the coronavirus disease 2019 (COVID-19) pandemic has expanded, physical examination has become challenging, with difficulties to diagnose HF in patients presenting with dyspnea and chest discomfort. Therefore, the importance of biomarkers has increased, especially in patients with restricted physical examinations [3]. Besides natriuretic peptides, several other biomarkers have been introduced to support the understanding of the pathophysiology of HF, improving personal care through better individual HF phenotyping [4].

In this review article, we will discuss the current use of biomarkers in the diagnosis and management of HF and their future perspectives.

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Biomarkers of the pathophysiology of heart failure

There are many biomarkers involved in the pathophysiological mechanisms of HF, which can be classified into four categories: myocardial damage, neurohormonal activation, myocardial remodeling, and biomarkers of inflammation and oxidative stress (Table 1). Although there are many biomarkers involved in the development of HF, only a few are currently available in clinical practice. B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) not only play an important pathophysiological role in the HF development, but also increase as the disease progresses, so they can be used for the diagnosis or monitoring of HF. BNP and NT-proBNP are major biomarkers widely used in the HF clinic because they can reflect the clinical status of patients aiding clinical judgment for the diagnosis, management, and prognosis of HF.

Biomarkers recommended in recent heart failure treatment guidelines

The 2021 European Society of Cardiology (ESC) guidelines for HF have been updated to reflect recent clinical studies, and notable changes have been made in HF management [5]. These focus on BNP/NT-proBNP as biomarkers for diagnosis and treatment of HF [5], emphasizing their role in the diagnostic process of chronic HF, acute HF, HF with preserved ejection fraction (HFpEF), and advanced HF. The role of most other biomarkers has not been highlighted; only troponin is recommended to rule out acute coronary syndrome (ACS) in the acute HF setting (Table 2).

The 2017 ACC/AHA/HFSA focused update guideline for the management of HF also emphasized BNP/NT-proBNP for HF prevention, diagnosis, and prognosis (as added risk stratification) [6]. In these treatment guidelines, biomarkers other than natriuretic peptides are mentioned. Biomarkers such as soluble suppression of tumorigenicity 2 (sST2) and galectin-3 are acknowledged to predict death and hospitalization and also provide prognostic value over natriuretic peptide levels for HF patients as class IIb recommendations (Table 3).

Although the 2021 ESC guideline is the most recently updated, the fact that it does not include the biomarkers mentioned in the 2017 American College of Cardiology guideline

suggests that there is little clinical evidence in their support.

BNP and NT-proBNP

1. Synthesis and excretion of BNP/NT-proBNP

BNP and NT-proBNP are biomarkers indicating myocardial stretch, it has sufficient evidence for HF diagnosis [4]. BNP gene expression increases as a result of myocardial ischemia or myocardial stretch [7]. BNP is synthesized as proBNP with 108 amino acids in cardiomyocytes. When proBNP is released into the circulation, it is cleaved into inactive NT-proBNP with 76 amino acids and active BNP with 32 amino acids. BNP has various biological effects, including vasodilatation, natriuresis and inhibition of the renin-angiotensin-aldosterone system and sympathetic nervous system

Table 1. Biomarkers of pathophysiologic pathways contributing to heart failure development

| Mechanism | Biomarkers |
|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Myocyte stretch | Atrial natriuretic peptide (ANP), mid-regional proANP B-type natriuretic peptide (BNP), N-terminal proBNP Growth differentiation factor (GDF) Neuregulin Soluble suppression of tumorigenicity 2 (sST2) |
| Neurohumoral activation | Norepinephrine Renin Angiotensin II Aldosterone Arginine vasopressin Endothelin-1 Chromogranin A and B Adrenomedullin |
| Myocardial damage | Cardiac troponins (TnT, TnI, and hsTn) Creatinine kinase-MB (CK-MB) Heart-type fatty acid-binding protein Soluble Fas cell surface death receptor (sFAS) Heat shock protein 60 Soluble TNF-related apoptosis-inducing ligand (sTRAIL) Pentaxin 3 |
| Biomarkers of comorbidity | Inflammation: C-reactive protein (CRP), tumor necrosis factor- α (TNF- α), lipoprotein-associated phospholipase A2 (LP-PLA2), IL-1, IL-6, IL-10, IL-18 Adipokines, polacininonin, cytokines Oxidative stress: Myeloperoxidase, oxidized low-density lipoproteins, plasma malondialdehyde |

Table 2. Biomarkers for heart failure recommended by the European Society of Cardiology 2021 guidelines

| Clinical setting | Biomarker | Class of recommendation | Level of evidence | Reference value |
|--------------------------------------------------------|--------------------------|-------------------------|-------------------|---------------------------------------------------------------------------------------------|
| Chronic HF | | | | |
| Diagnostic test for suspected chronic HF | BNP, NT-proBNP | I | B | NT-proBNP ≥ 125 pg/mL BNP ≥ 35 pg/mL |
| To rule out HF | MR-proANP | None | None | <40 pmol/L |
| Objective evidence of serologic abnormalities in HFpEF | BNP/NT-proBNP | None | None | NT-proBNP >125 pg/mL (SR) or 365 pg/mL (AF) BNP >35 pg/mL (SR) or 105 pg/mL (AF) |
| Advanced HF | | | | |
| Criteria for advanced HF | BNP/NT-proBNP | None | None | Persistently high (or increasing) BNP or NT-proBNP value |
| Acute HF | | | | |
| Diagnostic test for acute HF (to rule out AHF) | BNP/NT-proBNP, MR-proANP | Ia | None | BNP ≥ 100 pg/mL, NT-proBNP ≥ 300 pg/mL ^{a)} , MR-proANP ≥ 120 pg/mL |
| To exclude ACS | Troponin | I | None | None |

HF, heart failure; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal proBNP; MR-proANP, mid-regional pro-atrial natriuretic peptide; HFpEF, heart failure with preserved ejection fraction; SR, sinus rhythm; AF, atrial fibrillation; AHF, acute heart failure; ACS, acute coronary syndrome.

^{a)}Rule-in values for the diagnosis of acute HF: >450 pg/mL for age <55 years, >900 pg/mL for 55–75 years, and >1,800 pg/mL for age >75 years.

Table 3. Biomarker indications according to 2017 ACC/AHA/HFSA focused update [6]

| Clinical setting | Biomarkers | Class of recommendation | Level of evidence | Comments |
|------------------------------------------------------|--------------------------------------------------------------------------------------------------------|-------------------------|-------------------|-----------------------------------------------------------------------------------------------------|
| HF prevention | | | | |
| Patients at risk of developing HF | BNP, NT-proBNP | Ia | B | Can be useful to prevent LV dysfunction (systolic or diastolic) or new-onset HF |
| HF diagnosis | | | | |
| Patients with dyspnea | BNP, NT-proBNP | I | A | Useful to support diagnosis or exclude HF |
| Prognosis of added risk stratification | | | | |
| Chronic HF | BNP, NT-proBNP | I | A | Useful for establishing prognosis or disease severity |
| Baseline measurement at hospital admission | BNP, NT-proBNP, and cardiac troponin | I | A | Useful to establish prognosis in acutely decompensated HF |
| During HF hospitalization, pre-discharge measurement | BNP, NT-proBNP | Ia | B | Can be useful to establish post-discharge prognosis |
| Chronic HF | Biomarkers of myocardial injury or fibrosis (soluble ST2, galectin-3, hs-cardiac troponin, and others) | Ib | B | Predictive of hospitalization and death in HF patients and also additive to NP levels ^{a)} |

ACC/AHA/HFSA, American College of Cardiology/American Heart Association/Heart Failure Society of America; HF, heart failure; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal proBNP; LV, left ventricle; ST2, suppression of tumorigenicity 2; NP, natriuretic peptide.

^{a)}A combination of biomarkers may be more informative than single-biomarker measurements.

through interaction with natriuretic peptide receptor type A, resulting in increased production of intracellular cyclic guanosine monophosphate. BNP binds to the natriuretic peptide type C and is eliminated through proteolysis by neutral endopeptidase, with a half-life of approximately 20 minutes. And NT-proBNP, the inactive form, is mainly cleared by renal excretion, and its half-life is approximately 120 minutes.

2. Clinical relevance of BNP and NT-proBNP

After BNP was discovered to be secreted during myocardial stretch and to have favorable effects such as natriuresis, it was initially used for the treatment of HF patients [8]. Yoshimura et al. [8] reported that infusion of synthetic human BNP improves left ventricular function in heart failure reduced ejection fraction (HFrEF) through natriuretic effects and vasodilation. However, BNP and NT-proBNP were

found to be related to symptoms assessed by the New York Heart Association, the functional class, hemodynamic status in the setting of volume expansion or pressure overload, and left ventricle (LV) diastolic and systolic function [9,10]. Thus, these have been widely used to diagnose and monitor HF.

According to a randomized controlled trial, amino-terminal proBNP testing significantly improved the accuracy of HF diagnosis in the general population [11], and other studies support the use of BNP/NT-proBNP testing in primary care to evaluate HF in non-acute settings [12-14]. In an acute HF setting, the NT-proBNP level is the standard clinical assessment with a very high negative predictive value to identify or rule out acute HF [15]. A meta-analysis acknowledged that testing the NT-proBNP level in suspected acute HF patients enables prompt and precise exclusion of the diagnosis [16]. Especially for patients who require a rapid evaluation for potential HF and who cannot undergo echocardiography in an emergency department, BNP and NT-proBNP testing can provide meaningful information or differential diagnosis of HF. And it is highly probable that the symptoms and signs of a patient with normal BNP or NT-proBNP are not related to HF, and further investigation should be performed to identify other causes of these signs and symptoms [17].

In addition, natriuretic peptides can be useful not only for diagnosing HF but also for predicting prognosis. Therefore, to measure the BNP or NT-proBNP level is clinically relevant to estimate not only the presence but also the severity of HF, indicating clinical improvement in response to medical treatment [18-20]. Several clinical trials have used natriuretic peptide levels to evaluate the effectiveness of medical treatment and indicate clinical improvement, and some have shown that biomarker-guided treatment can improve the outcomes of HF [21,22]. In the STOP-HF (St Vincent's Screening To Prevent Heart Failure) study, treatment with BNP-based screening and collaboration reduced the rates of events of HF and LV systolic dysfunction, diastolic dysfunction [23]. According to a study that compared the prognostic value of NT-proBNP in advanced HF with that of other parameters, NT-proBNP measurement alone was a better prognostic meaning than LV ejection fraction (LVEF), peak VO_2 , and HF survival score [24].

Another important point is that BNP/NT-proBNP have been used worldwide for a long time and have recognized cutoff values. In the non-acute setting, the upper normal

limits are 35 pg/mL for BNP and 125 pg/mL for NT-proBNP [25-27].

Various studies have reported that natriuretic peptide levels can be used as a parameter of clinical improvement in response to medical care. However, the associated prognoses have been inconsistent. The TIME-CHF trial (Trial of Intensified vs. Standard Medical Therapy in Elderly Patients With Congestive Heart Failure) showed that HF therapy guided by NT-proBNP did not enhance composite clinical outcomes or quality of life than symptom-guided treatment [28]. Also, in the GUIDE-IT study (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure), treatment with NT-proBNP-guide did not improve first HF hospitalization or cardiovascular death [29]. Consistent evaluation is difficult due to differences in the target patient groups and study designs; however, it does appear that natriuretic peptide-guided treatment does not always show better outcomes than symptom-guided treatment. Since GUIDE-IT is a large-scale, multicenter, randomized trial, its results should not be overlooked.

3. Limitations of using BNP and NT-proBNP

Although structural cardiac and non-cardiac diseases are associated with increased BNP/NT-proBNP levels, a single measurement can reduce the confidence of HF diagnosis. Clinicians should be aware of the caveats of testing. First, elevated BNP or NT-proBNP levels could be due to various causes, including non-cardiac factors, which can reduce diagnostic accuracy [5]. However, levels are usually lower than those in acute decompensated HF patients [4]. Also, BNP or NT-proBNP levels can increase with age. The ESC practical guidelines for natriuretic peptide concentrations suggest different cutoff values for acute and chronic settings and age groups [9]. Age in particular increases the cutoff value of the gray zone and increases the need for cautious interpretation. Second, chronic kidney disease patients usually have higher BNP or NT-proBNP levels. Accumulation of these natriuretic peptides in chronic kidney disease patients occurs because of their decreased secretion accompanied by an increased release of these peptides due to hypertension and chronic volume overload comorbidities. Thus, the cutoffs of BNP at 200 pg/mL and NT-proBNP at 1,200 pg/mL provide an appropriate diagnostic performance in patients with renal insufficiency defined as decreased estimated glomerular filtration rate <60 mL/min per 1.73 m²

[4]. Third, obesity is known to be associated with lower BNP levels than traditional cutoff values used in the diagnosis of HF due to a variety of physiological and metabolic mechanisms [30,31]. Fourth, low BNP concentration may also be detected in patients with advanced end-stage HF or right HF [9]. Therefore, the BNP levels of patients with relatively stable HF should be interpreted with care [32]. Fifth, among others, lung disease and atrial arrhythmias can also affect the BNP and NT-proBNP levels, so their interpretation must take these factors into consideration [9]. These particular comorbidities are very common in HF patients, and may limit interpreting the value of BNP and NT-proBNP levels in clinical practice.

Mid-regional pro-atrial natriuretic peptide

Atrial natriuretic peptide (ANP) is produced in the atrium in response to increased wall stress secondary to intravascular volume increase [33,34]. Mid-regional pro-ANP (MR-proANP) is another biomarker of myocardial remodeling, and its diagnostic role has been established [35]. The serum level of MR-proANP is not influenced by anemia and obesity [35,36]. The 2021 ESC guidelines suggest the use of MR-proANP to rule out HF in the diagnosis of new-onset acute HF. In a large, multicenter, prospective, trial of patients presenting to an emergency department with dyspnea, MR-proANP showed that it was not inferior to BNP for the diagnosis of acute HF [37]. Another study also showed that MR-proANP had a value comparable to that of NT-proBNP in the diagnosis of acute HF [38]. Heining et al. [39] showed that MR-proANP achieved an AUC of 0.83 in the diagnosis of acute HF. Their study applied a cutoff value of 120 pmol/L, produced a sensitivity of 91.1% and a negative predictive value of 92.1%.

However, increased MR-proANP levels have been found in conditions such as atrial arrhythmia [40,41], sepsis, respiratory tract infections, ventilator-associated pneumonia [42,43], and renal dysfunction [44]. And most studies using MR-proANP have focused on the acute HF setting, only few studies have looked at the early stages of HF. In addition to most of these considered the prognostic (not diagnostic) role of MR-proANP. Therefore, its diagnostic use in patients with symptoms suggestive of HF has not been established in non-acute HF settings [45]. More research is needed in

the future.

Cardiac biomarkers other than natriuretic peptides

1. Cardiac troponins

Cardiac troponins are biomarkers indicating myocardial damage and their measurement is the gold standard to diagnose acute myocardial infarction [46]. In the updated 2021 ESC guidelines, cardiac troponin is recognized as having a limited role. Among laboratory tests, cardiac troponins are useful for detecting ACS, although elevated levels are detected in the majority of patients with acute HF [5]. Troponins can be elevated for a variety of reasons, including renal failure, stroke, pulmonary thromboembolism, sepsis, cardiac causes such as cardiac surgery, cardioversion, LV hypertrophy, and arrhythmia, all of which can increase the risk of HF [47]. However, according to a previous review article, about 20% of acutely symptomatic patients admitted to an emergency room had elevated levels of cardiac troponins, and most of them did not have ACS [48]. A post-hoc analysis of another cohort reported that high-sensitivity (hs)-troponin I was elevated in the vast majority of hospitalized patients and more than 50% of outpatients with HFpEF [49]. The usefulness of troponin seems to be underestimated not only in the HF guidelines, but also in clinical practice.

Troponin T and troponin I release can occur in patients with HF in the absence of an ACS event [50]. The mechanism of troponin elevation is explained by myocardial oxygen demand-supply mismatch and abnormal microvascular growth patterns [51]. Other mechanisms leading to increased troponin level in HF remain elusive in many cases, but they prominently include supply-demand inequity, associated with coronary artery obstruction and endothelial dysfunction, anemia, or subendocardial injury [52]. Sato et al. [53] showed that persistently increased troponin concentrations in dilated cardiomyopathy suggest ongoing subclinical myocyte degeneration, which is associated with deterioration of patient clinical status.

Cardiac troponins were found to be helpful in diagnosing both HF and ACS in the large-cohort ADHERE study (Acute Decompensated Heart Failure National Registry). Troponins are good predictors of short-term in-hospital mortality in acute decompensated HF patients, and cardiac troponin I and T have identical predictive value [54]. In both

acute HF and chronic stable HF, troponin is a significant prognostic factor. Tentzeris et al. [55] evaluated the complementary role of copeptin and cardiac troponin T in the identification of high-risk chronic HF, and the combination of hs-troponin T and copeptin may predict clinical outcome. Also, troponins are useful surrogate markers in chemotherapy-induced cardiomyopathy. A cardio-oncology working group proposed using periodic troponin measurements to detect chemotherapy-induced cardiotoxicity [56]. In addition, measuring changes in troponin levels helps predict the prognosis of HF [52].

Most hospitals use either troponin I or troponin T, but there is no evidence that either is superior. In the general population, troponin I and T levels show some statistical differences in predicting CVD, but both are significant indicators for HF prediction [57]. However, most studies using troponin have used retrospective designs, and many of them did not completely exclude factors that could affect troponin levels.

2. Soluble ST2

ST2 is a member of the interleukin (IL)-1 receptor family with transmembrane and soluble isoforms (soluble ST2, sST2), and is a biomechanically-derived protein synthesized primarily by cardiac fibroblasts. IL-33-ST2 signaling plays an important role in the mechanistically-activated cardioprotective fibroblast-myocardial paracrine system. Thus, IL-33 may have therapeutic potential for treating the myocardial response to overload. sST2, a biomarker of myocardial stretch, blocks the anti-hypertrophic effects of IL-33, and measuring sST2 provides useful information as a biomarker for HF [58].

The clinical trials measuring sST2 in patients with HF are summarized in Table 4. sST2 has been shown to discriminate HF and predict its prognosis in various clinical settings, acute and chronic HF in particular. A previous meta-analysis of sST2 has shown that it has prognostic value in predicting composite outcomes in acute HF [59]. In a relatively large-cohort study (HF-ACTION), sST2 was independently associated with clinical outcomes after adjusting for NT-proBNP in the multivariable models, and higher sST2 was associated with both poor functional capacity and poor prognosis [60]. Another study reported that sST2 was associated with cardiac abnormalities prevalent in echocardiography, including increased LV end-systolic dimension/

volume and decreased LVEF [61]. In a head-to-head comparison (PROTECT trial) of serial sST2, hs-troponin T measurements and growth differentiation factor-15, only sST2 approved to add prognostic information to the baseline levels and predict changes in LV function in a chronic HF setting [62].

Unlike natriuretic peptides, sST2 is not significantly related to age, heart rhythm, or body mass index (BMI) [63]. The relative independence of sST2 from common comorbidities is a potential advantage. In terms of biological variability, sST2 is a good biomarker for HF. Piper et al. [64] examined patients with HF to determine the biological variability of sST2 by collecting blood samples at different time points. Compared with NT-proBNP, sST2 demonstrated significantly lower coefficients of variation and reference change values. The serum concentration of sST2 is not influenced by sex, age, BMI, renal function, atrial fibrillation, or prior HF diagnosis [65]. Therefore, sST2 may be a good biomarker for monitoring patients with such comorbidities.

However, there are several limitations to the use of sST2 in the clinical setting. First, there are no large, well-designed, prospective studies using sST2. Although many animal experiments have validated sST2, the number of clinical trials is small and most studies have enrolled only a small number of patients. Second, no clear standard value of the sST2 level has been accepted worldwide, with the reference value varying from study to study. In an analysis of the data from the HF-ACTION study, an sST2 cutoff value of 35 ng/dL well predicted short-term all-cause death, cardiovascular death, and HF hospitalization [60]. In the PRIDE study, a multivariable analysis showed that an sST2 concentration above 20 mg/dL strongly predicted 1-year mortality in dyspneic patients [66]. Because the enrolled patients and listed values vary widely from study to study, it is difficult to determine a specific value for use in clinical practice. In addition, the standard values vary widely with sex, being much higher in males than females [67]. Third, sST2 is associated with measures of inflammation, such as leukocyte count, and C-reactive protein, unlike natriuretic peptides [63]. sST2 also exhibits a circadian rhythm and is usually low in the morning and high in the late afternoon, so values may vary depending on the time the blood sample is taken [68].

3. Galectin-3

Galectin-3 is produced by macrophages that stimulates the

Table 4. Clinical trials using sST2

| Author | Study population | Aim of study | Implication |
|-------------------------------|----------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chronic HF | | | |
| Ahmad et al. [69] | (HF-ACTION trial) Chronic HF with LVEF below 35% (n=813) | To determine whether biomarkers improve prediction of the mode of death in patients with chronic HF | Predictor of pump failure risk |
| Gaggin et al. [62] | Chronic HF with LV systolic dysfunction (LVEF <40%) (n=151) | To perform head-to-head comparison of 3 biomarkers (sST2, GDF-15, hs-troponin T) | Only serial measurement of sST2 appeared to add prognostic information to the baseline concentration and predict change in LV function |
| O'Meara et al. [70] | (PARADIGM-HF trial) HFREF (LVEF <40%) (n=1,758) | To determine the relationship between sST2 and outcomes and the prognostic utility of various sST2 partition values | Baseline sST2 remained an independent predictor of outcomes. Changes in sST2 from baseline to one month were independently associated with outcome risks |
| Felker et al. [60] | (HF-ACTION trial) Chronic HF with LVEF below 35% (n=910) | To evaluate ST2 levels and their association with functional capacity and long-term clinical outcomes | ST2 was modestly associated with functional capacity and significantly associated with outcomes |
| Acute HF | | | |
| Manzano-Fernandez et al. [71] | ADHF (n=447) | To determine whether the risk of mortality associated with sST2 concentration differs in ADHF patients with HFpEF compared with patients with systolic HF | sST2 was an independent predictor of mortality, regardless of LVEF |
| Shah et al. [61] | Acute dyspneic patients with/without decompensated HF (n=139) | To evaluate the associations between sST2 and cardiac structure and function To determine whether sST2 retains prognostic meaning | sST2 was associated with cardiac abnormalities, a more decompensated hemodynamic profile, and long-term mortality |
| Mueller et al. [72] | ADHF patients in the emergency department (n=137) | To evaluate the value of sST2 as a prognostic marker in patients with ADHF | Increased sST2 levels were independently and strongly associated with 1-year all-cause mortality |
| Rehman et al. [63] | Patients with acute HF (n=346) | To examine patient-specific characteristics of ST2 in acute HF | As a myocardial-specific response to stretch, ST2 showed strong clinical and biochemical correlations in patients with acute HF. Prognostically, ST2 is powerful in acute HF |
| Kim et al. [73] | Patients hospitalized with ADHF and renal insufficiency (n=66) | To investigate the role of sST2 as a prognosticator in patients hospitalized with acute HF and renal insufficiency | The pre-discharge sST2 measurement can be helpful in predicting short-term outcomes in ADHF with renal insufficiency |

HF, heart failure; LV, left ventricular; LVEF, LV ejection fraction; sST2, soluble suppression of tumorigenicity 2; GDF-15, growth differentiation factor-15; hs-troponin, high-sensitivity troponin; PARADIGM-HF trial, Prospective Comparison of ARNI (Angiotensin Receptor–Neprilysin Inhibitor) with ACEI (Angiotensin–Converting–Enzyme Inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure trial; HFREF, heart failure reduced ejection fraction; HF-ACTION trial, heart failure: a controlled trial investigating outcomes of exercise training trial; ADHF, acute decompensated heart failure; HFpEF, heart failure with preserved ejection fraction.

profibrotic pathway, leading to proliferation of fibroblast and consequent collagen deposition [74]. In the inflammatory response and wound healing process, pro-inflammatory cytokines released by cardiomyocytes lead to macrophage activation, and activated macrophages release galectin-3, which binds to myofibroblasts, activating them and triggering collagen synthesis. Collagen deposition causes myocardial scarring, long-term remodeling, and dilatation of the LV [75]. Galectin-3 thus promotes the differentiation of fibroblasts into myofibroblasts through both

the transforming growth factor- β 1-dependent and -independent pathways [76].

Since galectin-3 reflects cardiac function and is a good indicator of HF prognosis, it can be a useful biomarker for HF. Among dyspneic patients with and without acute decompensated HF, elevated galectin-3 are associated with E/Ea ratio, a lower right ventricular function, higher right ventricular systolic pressure, and more severe valvular regurgitation [77]. In a recent study of large population-based cohort, galectin-3, BNP, and sST2, galectin-3 showed the

highest discrimination value for preclinical diastolic dysfunction [78].

Compared with the biological variability of biomarkers between patients with stable HF and healthy adults, galectin-3 showed lower intraindividual biological variability than other biomarkers [74]. In terms of serial measurements, galectin-3 also has advantages over other biomarkers. Serial measurements of biomarkers (NT-proBNP, troponin, sST2, and galectin-3) at different time points in patients with acute HF showed that only galectin-3 was constant over time [79]. Therefore, alterations in galectin-3 level can indicate underlying pathophysiological changes that could lead to a poor prognosis. A previous meta-analysis assessed the usefulness of galectin-3 in predicting short-term all-cause and cardiovascular mortality in patients with HF. The results showed that increased galectin-3 was associated with higher short-term all-cause mortality and cardiovascular mortality, even after adjusting for other well-established risk factors [80]. In a sub-study of the Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure trial, higher galectin-3 identified HF patients at low risk for 1-month and 6-month mortality and HF rehospitalization after an episode of acute HF [81]. In another large-scale cohort analysis (Framingham Offspring Cohort), a higher concentration of galectin-3 was associated with an increased risk of incident HF and short-term mortality [82]. Galectin-3 measurements repeatedly appeared to be a powerful predictor for outcomes in acute HF patients and was independent of NT-proBNP. Galectin-3 might also be useful in clinical practice for prognosis development and treatment monitoring [83]. In HFpEF patients, galectin-3 is also an independent predictor for the outcome of HF and appears to be particularly useful [84].

However, no randomized controlled trials have demonstrated that galectin-3 can be used to accurately diagnose HF or evaluate its prognosis. Although studies differ, galectin-3 seems to have a relatively low diagnostic value in predicting death and HF-readmission [84]. In a community-based cohort, this protein was associated with new-onset HF in the high-risk but not in the low-risk group [85]. Therefore, its usefulness as a biomarker to discriminate HF in outpatients is limited. In addition, no clear standard cutoff value for galectin-3 levels has been accepted worldwide. Galectin-3 levels also correlate with age, BMI, sex, diabetes mellitus, renal dysfunction, and hypertension [86].

In particular, the effect of renal function is significant, and care must be taken in interpretation. According to animal studies, galectin-3 is markedly upregulated in acute tubular injury and the subsequent regeneration [87] as well as in progressive renal fibrosis [88].

Future directions for biomarkers for HF

1. Emerging biomarkers in HF

Given the trend of combining biomarkers, the discovery of novel biomarkers is important. Many HF biomarkers have already been established or are emerging according to multiple pathophysiologic processes [89]. Given the complexity, combining biomarkers that reflect various mechanisms could theoretically offer an improved picture of the myocardial status. Inflammation is thought to play a crucial role in the complex etiology of HFpEF, and the use of biomarkers that reflect inflammation is expected to be key in the future. New biomarkers such as GDF-15, myeloperoxidase, copeptin, and tumor necrosis factor lack clinical validation, but are soon expected to play a role as HF biomarkers.

2. Multiple biomarker approach

Regardless of the type of biomarker, combining biomarkers can improve the accuracy of diagnosis, prognostication, and assessment of treatment effects. Most biomarkers maximize their usefulness when used in combination with NT-proBNP levels. In particular, the combination of ST2 and NT-proBNP has been shown to be an excellent predictor of prognosis [63]. Troponin T also showed good results when measured together with NT-proBNP. The risk of HF is significantly greater when there is an increase in both biomarkers compared with an increase of either NT-proBNP or troponin T alone [90]. Even without BNP, combinations of biomarkers have a considerable value. In chronic stable HF, elevated sST2 and galectin-3 had a significantly higher hazard ratio together than alone, regardless of the BNP level, suggesting that simultaneous sST2 and galectin-3 elevation is associated with poor prognosis [91]. In addition, hs-C-reactive protein, which represents inflammation, can be used as a parameter for HF, and research on this has been reported recently [92]. Strategies that combine multiple biomarkers may ultimately give benefits in guiding HF therapy, but additional validation is needed [93,94].

3. Serial measurements of biomarkers

Although biomarkers can differ between patients, it is important to check whether a particular patient's levels increase compared with the baseline level. Serial measurements of biomarkers are important for the diagnosis of HF in the community. According to an observational study (Cardiovascular Health Study), the frequency of biomarker increase per year in the HF-free population is 14.8% for troponin T and 13.2% for NT-proBNP. After 10 years, the cumulative HF incidence is 50.4% when there is an increase in both biomarkers, and 12.2% when neither biomarker is increased [90]. Therefore, even if at a particular time HF was not diagnosed because of normal biomarker levels, a diagnosis becomes more likely in follow-up biomarker measurements.

Serial biomarker follow-up is important for predicting HF outcomes. It was found that serial measurements of natriuretic peptides provide strong prognostic information in chronic HF, not only in HF with reduced EF but also in HF with mid-range EF and HF with preserved EF [95-97]. A previous study analyzing two independent randomized controlled trials of chronic HF (Val-HeFT and GISSI-HF trials, a total of 5,284 patients) reported that changes in hs-troponin T concentration over time were a robust predictor of future cardiovascular events in patients with chronic HF [98]. In addition, changes in biomarkers over time in chronic HF can predict the risk of adverse events or outcomes, as well as changes in cardiac structure or LV function [99]. Changes in the concentration of biomarkers are likely to reflect the presence of ongoing cardiac pathophysiology, and could offer a mechanism to differentiate preclinical HF phenotypes.

4. For healthcare providers

To increase the efficiency of biomarker measurement, physicians must select appropriate biomarkers that represent each patient's clinical characteristics. In addition, the type of biomarker and cutoff value implemented by each center may be different. In particular, in the case of natriuretic peptides, BNP, proBNP, and NT-proBNP have different clinical implications, so care must be taken not to confuse them. Biomarkers that reflect myocardial injury will be helpful to evaluate the degree of myocardial damage caused by acute events. After HF progresses, biomarkers that reflect cardiac remodeling, such as hypertrophy or fibrosis, might provide the most information. However, discovering clinically ap-

propriate biomarkers is difficult because of the many mechanisms involved in the various HF phenotypes. Physicians should consider the confounding aspects of biomarkers and interpret their values with caution. All biomarkers can be significantly affected by various factors, and the severity of HF, general condition, and comorbidities must be carefully considered. Particularly, in cases of acute HF with hemodynamic instability, the timing of laboratory tests can greatly affect the results. Within a single patient, biomarker levels can vary with time, depending on the use of diuretics, hemodialysis, mechanical ventilation, etc. The multi-marker approach to HF management and decision-making is useful in the emergency room and offers various cutoff values for each biomarker [3].

5. Future directions in clinical trials

Several biomarkers are recommended in the current guidelines. However, while BNP and NT-proBNP are employed, the clinical use of other biomarkers is still limited owing to a lack of adequate clinical trials. In addition, the clinical setting of the enrolled patients varies among the few available studies, and the number of enrolled patients is too small. The reference value can also vary depending on the equipment used to analyze the samples, so inter-equipment validation is required. Therefore, further large-scale biomarker studies are warranted.

Currently, in Korea, a large-scale registry (KorHF III Registry, under the leadership of the Korea HF Society) that includes various biomarkers (BNP, NT-proBNP, ST2, cardiac troponin I, and cardiac troponin T) is in progress and is likely to provide important information.

However, the combination of biomarkers from different pathophysiological processes remains unknown. Moreover, we do not know when and how often these biomarkers should be measured for appropriate management of patients with HF. An increased number of biomarker tests correlates with a better HF diagnosis, but physicians must consider cost-effectiveness in clinical practice. Thus, it is difficult to conduct multiple biomarker tests that are not included in the guidelines. We should study which biomarkers to combine, when to measure, and how often to measure. In addition, we should consider their cost-effectiveness, balancing the cost of testing and their benefit in appropriate HF management.

Conclusions

Despite several limitations, BNP/NT-proBNP are the only biomarkers included in the current guidelines. Cardiac troponins, sST2, and galectin 3 are independent prognostic biomarkers of HF and can be used as supplementary measurements. Although clinical trials are needed to reasonably apply these biomarkers in clinical practice, it is essential to add new biomarkers to the guidelines to assist and support healthcare providers in managing HF.

Future research should adopt a multi-marker approach to improve the risk prediction models, diagnosis, and management of HF. When using biomarkers for HF, it is also important to establish a setting for multiple tests to evaluate risk stratification or predict prognosis, rather than relying on a single test. To better use cardiac biomarkers, physicians must select appropriate biomarkers for HF and exert caution when interpreting their values considering variable clinical profiles.

Article information

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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References

1. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. *Eur J Heart Fail* 2020;22:1342–56.
2. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart disease and stroke statistics-2021 update: a report from the American Heart Association. *Circulation* 2021;143:e254–743.
3. Aleksova A, Sinagra G, Beltrami AP, Pierri A, Ferro F, Janjusevic M, et al. Biomarkers in the management of acute heart failure: state of the art and role in COVID-19 era. *ESC Heart Fail* 2021;8:4465–83.
4. Ibrahim NE, Januzzi JL Jr. Established and emerging roles of biomarkers in heart failure. *Circ Res* 2018;123:614–29.
5. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;42:3599–726.
6. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 2017;136:e137–61.
7. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. *Heart* 2006;92:843–9.
8. Yoshimura M, Yasue H, Morita E, Sakaino N, Jougasaki M, Kurose M, et al. Hemodynamic, renal, and hormonal responses to brain natriuretic peptide infusion in patients with congestive heart failure. *Circulation* 1991;84:1581–8.
9. Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JG, Kozhuharov N, et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. *Eur J Heart Fail* 2019;21:715–31.
10. Wiecek SJ, Wu AH, Christenson R, Krishnaswamy P, Gottlieb S, Rosano T, et al. A rapid B-type natriuretic peptide assay accurately diagnoses left ventricular dysfunction and heart failure: a multicenter evaluation. *Am Heart J* 2002;144:834–9.
11. Wright SP, Doughty RN, Pearl A, Gamble GD, Whalley GA, Walsh HJ, et al. Plasma amino-terminal pro-brain natriuretic peptide and accuracy of heart-failure diagnosis in primary care: a randomized, controlled trial. *J Am Coll Cardiol* 2003;42:1793–800.
12. Mueller C, Maeder MT, Christ A, Reichlin T, Staub D, Noveanu M, et al. B-type natriuretic peptides for the evaluation of exercise intolerance. *Am J Med* 2009;122:265–72.
13. Burri E, Hochholzer K, Arenja N, Martin-Braschler H, Kaestner L, Gekeler H, et al. B-type natriuretic peptide in the evaluation and management of dyspnoea in primary care. *J Intern Med* 2012;272:504–13.
14. Booth RA, Hill SA, Don-Wauchope A, Santaguida PL, Oremus

- M, McKelvie R, et al. Performance of BNP and NT-proBNP for diagnosis of heart failure in primary care patients: a systematic review. *Heart Fail Rev* 2014;19:439–51.
15. Januzzi JL Jr, Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *Am J Cardiol* 2005;95:948–54.
 16. Roberts E, Ludman AJ, Dworzynski K, Al-Mohammad A, Cowie MR, McMurray JJ, et al. The diagnostic accuracy of the natriuretic peptides in heart failure: systematic review and diagnostic meta-analysis in the acute care setting. *BMJ* 2015;350:h910.
 17. Kim MS, Lee JH, Kim EJ, Park DG, Park SJ, Park JJ, et al. Korean guidelines for diagnosis and management of chronic heart failure. *Korean Circ J* 2017;47:555–643.
 18. Bayes-Genis A, Santalo-Bel M, Zapico-Muniz E, Lopez L, Cotes C, Bellido J, et al. N-terminal probrain natriuretic peptide (NT-proBNP) in the emergency diagnosis and in-hospital monitoring of patients with dyspnoea and ventricular dysfunction. *Eur J Heart Fail* 2004;6:301–8.
 19. Berger R, Huelsman M, Strecker K, Bojic A, Moser P, Stanek B, et al. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. *Circulation* 2002;105:2392–7.
 20. Taub PR, Daniels LB, Maisel AS. Usefulness of B-type natriuretic peptide levels in predicting hemodynamic and clinical decompensation. *Heart Fail Clin* 2009;5:169–75.
 21. Januzzi JL Jr, Rehman SU, Mohammed AA, Bhardwaj A, Barajas L, Barajas J, et al. Use of amino-terminal pro-B-type natriuretic peptide to guide outpatient therapy of patients with chronic left ventricular systolic dysfunction. *J Am Coll Cardiol* 2011;58:1881–9.
 22. Jourdain P, Jondeau G, Funck F, Gueffet P, Le Helloco A, Donal E, et al. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. *J Am Coll Cardiol* 2007;49:1733–9.
 23. Ledwidge M, Gallagher J, Conlon C, Tallon E, O'Connell E, Dawkins I, et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. *JAMA* 2013;310:66–74.
 24. Gardner RS, Ozalp F, Murday AJ, Robb SD, McDonagh TA. N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. *Eur Heart J* 2003;24:1735–43.
 25. Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, et al. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997;350:1349–53.
 26. Zaphiriou A, Robb S, Murray-Thomas T, Mendez G, Fox K, McDonagh T, et al. The diagnostic accuracy of plasma BNP and NTproBNP in patients referred from primary care with suspected heart failure: results of the UK natriuretic peptide study. *Eur J Heart Fail* 2005;7:537–41.
 27. Kelder JC, Cramer MJ, Verweij WM, Grobbee DE, Hoes AW. Clinical utility of three B-type natriuretic peptide assays for the initial diagnostic assessment of new slow-onset heart failure. *J Card Fail* 2011;17:729–34.
 28. Pfisterer M, Buser P, Rickli H, Gutmann M, Erne P, Rickenbacher P, et al. BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. *JAMA* 2009;301:383–92.
 29. Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA* 2017;318:713–20.
 30. Madamanchi C, Alhosaini H, Sumida A, Runge MS. Obesity and natriuretic peptides, BNP and NT-proBNP: mechanisms and diagnostic implications for heart failure. *Int J Cardiol* 2014;176:611–7.
 31. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Wilson PW, et al. Impact of obesity on plasma natriuretic peptide levels. *Circulation* 2004;109:594–600.
 32. Tang WH, Girod JP, Lee MJ, Starling RC, Young JB, Van Lente F, et al. Plasma B-type natriuretic peptide levels in ambulatory patients with established chronic symptomatic systolic heart failure. *Circulation* 2003;108:2964–6.
 33. Yoshibayashi M, Saito Y, Nakao K. Brain natriuretic peptide versus atrial natriuretic peptide: physiological and pathophysiological significance in children and adults: a review. *Eur J Endocrinol* 1996;135:265–8.
 34. McMurray J, Pfeffer MA. New therapeutic options in congestive heart failure: part I. *Circulation* 2002;105:2099–106.
 35. Han X, Zhang S, Chen Z, Adhikari BK, Zhang Y, Zhang J, et al. Cardiac biomarkers of heart failure in chronic kidney disease. *Clin Chim Acta* 2020;510:298–310.
 36. Kube J, Ebner N, Jankowska EA, Rozentryt P, Ciccoira M, Filipatos GS, et al. The influence of confounders in the analysis of mid-regional pro-atrial natriuretic peptide in patients with chronic heart failure. *Int J Cardiol* 2016;219:84–91.
 37. Maisel A, Mueller C, Nowak R, Peacock WF, Landsberg JW,

- Ponikowski P, et al. Mid-region pro-hormone markers for diagnosis and prognosis in acute dyspnea: results from the BACH (Biomarkers in Acute Heart Failure) trial. *J Am Coll Cardiol* 2010;55:2062–76.
38. Darche FF, Baumgartner C, Biener M, Muller-Hennessen M, Vafaie M, Koch V, et al. Comparative accuracy of NT-proBNP and MR-proANP for the diagnosis of acute heart failure in dyspnoeic patients. *ESC Heart Fail* 2017;4:232–40.
39. Heining L, Giesa C, Ewig S. MR-proANP, MR-proADM, and PCT in patients presenting with acute dyspnea in a medical emergency unit. *Lung* 2016;194:185–91.
40. Gegenhuber A, Struck J, Poelz W, Pacher R, Morgenthaler NG, Bergmann A, et al. Midregional pro-A-type natriuretic peptide measurements for diagnosis of acute destabilized heart failure in short-of-breath patients: comparison with B-type natriuretic peptide (BNP) and amino-terminal proBNP. *Clin Chem* 2006;52:827–31.
41. Richards M, Di Somma S, Mueller C, Nowak R, Peacock WF, Ponikowski P, et al. Atrial fibrillation impairs the diagnostic performance of cardiac natriuretic peptides in dyspneic patients: results from the BACH Study (Biomarkers in ACute Heart Failure). *JACC Heart Fail* 2013;1:192–9.
42. Muller B, Suess E, Schuetz P, Muller C, Bingisser R, Bergmann A, et al. Circulating levels of pro-atrial natriuretic peptide in lower respiratory tract infections. *J Intern Med* 2006;260:568–76.
43. Seligman R, Papassotiropoulos J, Morgenthaler NG, Meisner M, Teixeira PJ. Prognostic value of midregional pro-atrial natriuretic peptide in ventilator-associated pneumonia. *Intensive Care Med* 2008;34:2084–91.
44. Vickery S, Price CP, John RI, Abbas NA, Webb MC, Kempson ME, et al. B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with CKD: relationship to renal function and left ventricular hypertrophy. *Am J Kidney Dis* 2005;46:610–20.
45. Gohar A, Rutten FH, den Ruijter H, Kelder JC, von Haehling S, Anker SD, et al. Mid-regional pro-atrial natriuretic peptide for the early detection of non-acute heart failure. *Eur J Heart Fail* 2019;21:1219–27.
46. Latini R, Masson S, Anand IS, Missov E, Carlson M, Vago T, et al. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. *Circulation* 2007;116:1242–9.
47. Mahajan VS, Jarolim P. How to interpret elevated cardiac troponin levels. *Circulation* 2011;124:2350–4.
48. Giannitsis E, Katus HA. Cardiac troponin level elevations not related to acute coronary syndromes. *Nat Rev Cardiol* 2013;10:623–34.
49. Fudim M, Ambrosy AP, Sun JL, Anstrom KJ, Bart BA, Butler J, et al. High-sensitivity troponin I in hospitalized and ambulatory patients with heart failure with preserved ejection fraction: insights from the Heart Failure Clinical Research Network. *J Am Heart Assoc* 2018;7:e010364.
50. Chow SL, Maisel AS, Anand I, Bozkurt B, de Boer RA, Felker GM, et al. Role of biomarkers for the prevention, assessment, and management of heart failure: a scientific statement from the American Heart Association. *Circulation* 2017;135:e1054–91.
51. De Boer RA, Pinto YM, Van Veldhuisen DJ. The imbalance between oxygen demand and supply as a potential mechanism in the pathophysiology of heart failure: the role of microvascular growth and abnormalities. *Microcirculation* 2003;10:113–26.
52. Januzzi JL Jr, Filippatos G, Nieminen M, Gheorghide M. Troponin elevation in patients with heart failure: on behalf of the third Universal Definition of Myocardial Infarction Global Task Force: Heart Failure Section. *Eur Heart J* 2012;33:2265–71.
53. Sato Y, Yamada T, Taniguchi R, Nagai K, Makiyama T, Okada H, et al. Persistently increased serum concentrations of cardiac troponin t in patients with idiopathic dilated cardiomyopathy are predictive of adverse outcomes. *Circulation* 2001;103:369–74.
54. Peacock WF 4th, De Marco T, Fonarow GC, Diercks D, Wynne J, Apple FS, et al. Cardiac troponin and outcome in acute heart failure. *N Engl J Med* 2008;358:2117–26.
55. Tentzeris I, Jarai R, Farhan S, Perkmann T, Schwarz MA, Jakl G, et al. Complementary role of copeptin and high-sensitivity troponin in predicting outcome in patients with stable chronic heart failure. *Eur J Heart Fail* 2011;13:726–33.
56. Zamorano JL, Lancellotti P, Rodriguez Munoz D, Aboyans V, Asteggiano R, Galderisi M, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2017;19:9–42.
57. Welsh P, Preiss D, Hayward C, Shah AS, McAllister D, Briggs A, et al. Cardiac troponin T and troponin I in the general population. *Circulation* 2019;139:2754–64.
58. Sanada S, Hakuno D, Higgins LJ, Schreiter ER, McKenzie AN, Lee RT. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. *J Clin Invest* 2007;117:1538–49.
59. Aimo A, Vergaro G, Ripoli A, Bayes-Genis A, Pascual Figal DA, de Boer RA, et al. Meta-analysis of soluble suppression of tumori-

- genicity-2 and prognosis in acute heart failure. *JACC Heart Fail* 2017;5:287–96.
60. Felker GM, Fiuzat M, Thompson V, Shaw LK, Neely ML, Adams KF, et al. Soluble ST2 in ambulatory patients with heart failure: association with functional capacity and long-term outcomes. *Circ Heart Fail* 2013;6:1172–9.
 61. 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;2:311–9.
 62. Gaggin HK, Szymonifka J, Bhardwaj A, Belcher A, De Berardinis B, Motiwala S, et al. Head-to-head comparison of serial soluble ST2, growth differentiation factor-15, and highly-sensitive troponin T measurements in patients with chronic heart failure. *JACC Heart Fail* 2014;2:65–72.
 63. Rehman SU, Mueller T, Januzzi JL Jr. Characteristics of the novel interleukin family biomarker ST2 in patients with acute heart failure. *J Am Coll Cardiol* 2008;52:1458–65.
 64. Piper S, deCoursey J, Sherwood R, Amin-Youssef G, McDonagh T. Biologic variability of soluble ST2 in patients with stable chronic heart failure and implications for monitoring. *Am J Cardiol* 2016;118:95–8.
 65. Aleksova A, Paldino A, Beltrami AP, Padoan L, Iacoviello M, Sinagra G, et al. Cardiac biomarkers in the emergency department: the role of soluble ST2 (sST2) in acute heart failure and acute coronary syndrome: there is meat on the bone. *J Clin Med* 2019;8:270.
 66. Januzzi JL Jr, Peacock WF, Maisel AS, Chae CU, Jesse RL, Baggish AL, et al. Measurement of the interleukin family member ST2 in patients with acute dyspnea: results from the PRIDE (Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department) study. *J Am Coll Cardiol* 2007;50:607–13.
 67. Nah EH, Cho S, Kim S, Cho HI. Reference interval and the role of soluble suppression of tumorigenicity 2 (sST2) in subclinical cardiac dysfunction at health checkups. *J Clin Lab Anal* 2020;34:e23461.
 68. Crnko S, Printezi MI, Jansen TP, Leiteris L, van der Meer MG, Schutte H, et al. Prognostic biomarker soluble ST2 exhibits diurnal variation in chronic heart failure patients. *ESC Heart Fail* 2020;7:1224–33.
 69. Ahmad T, Fiuzat M, Neely B, Neely ML, Pencina MJ, Kraus WE, et al. Biomarkers of myocardial stress and fibrosis as predictors of mode of death in patients with chronic heart failure. *JACC Heart Fail* 2014;2:260–8.
 70. O'Meara E, Prescott MF, Claggett B, Rouleau JL, Chiang LM, Solomon SD, et al. Independent prognostic value of serum soluble ST2 measurements in patients with heart failure and a reduced ejection fraction in the PARADIGM-HF Trial (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure). *Circ Heart Fail* 2018;11:e004446.
 71. Manzano-Fernandez S, Mueller T, Pascual-Figal D, Truong QA, Januzzi JL. Usefulness of soluble concentrations of interleukin family member ST2 as predictor of mortality in patients with acutely decompensated heart failure relative to left ventricular ejection fraction. *Am J Cardiol* 2011;107:259–67.
 72. Mueller T, Dieplinger B, Gegenhuber A, Poelz W, Pacher R, Haltmayer M. Increased plasma concentrations of soluble ST2 are predictive for 1-year mortality in patients with acute destabilized heart failure. *Clin Chem* 2008;54:752–6.
 73. Kim MS, Jeong TD, Han SB, Min WK, Kim JJ. Role of soluble ST2 as a prognostic marker in patients with acute heart failure and renal insufficiency. *J Korean Med Sci* 2015;30:569–75.
 74. Schindler EI, Szymanski JJ, Hock KG, Geltman EM, Scott MG. Short- and long-term biologic variability of galectin-3 and other cardiac biomarkers in patients with stable heart failure and healthy adults. *Clin Chem* 2016;62:360–6.
 75. Suthahar N, Meijers WC, Sillje HH, Ho JE, Liu FT, de Boer RA. Galectin-3 activation and inhibition in heart failure and cardiovascular disease: an update. *Theranostics* 2018;8:593–609.
 76. Li M, Yuan Y, Guo K, Lao Y, Huang X, Feng L. Value of galectin-3 in acute myocardial infarction. *Am J Cardiovasc Drugs* 2020;20:333–42.
 77. Shah RV, Chen-Tournoux AA, Picard MH, van Kimmenade RR, Januzzi JL. Galectin-3, cardiac structure and function, and long-term mortality in patients with acutely decompensated heart failure. *Eur J Heart Fail* 2010;12:826–32.
 78. Huttin O, Kobayashi M, Ferreira JP, Coiro S, Bozec E, Selton-Suty C, et al. Circulating multimarker approach to identify patients with preclinical left ventricular remodelling and/or diastolic dysfunction. *ESC Heart Fail* 2021;8:1700–5.
 79. Demissei BG, Cotter G, Prescott MF, Felker GM, Filippatos G, Greenberg BH, et al. A multimarker multi-time point-based risk stratification strategy in acute heart failure: results from the RELAX-AHF trial. *Eur J Heart Fail* 2017;19:1001–10.
 80. Chen A, Hou W, Zhang Y, Chen Y, He B. Prognostic value of serum galectin-3 in patients with heart failure: a meta-analysis. *Int J Cardiol* 2015;182:168–70.
 81. Meijers WC, de Boer RA, van Veldhuisen DJ, Jaarsma T, Hillege

- HL, Maisel AS, et al. Biomarkers and low risk in heart failure: data from COACH and TRIUMPH. *Eur J Heart Fail* 2015;17:1271–82.
82. Ho JE, Liu C, Lyass A, Courchesne P, Pencina MJ, Vasan RS, et al. Galectin-3, a marker of cardiac fibrosis, predicts incident heart failure in the community. *J Am Coll Cardiol* 2012;60:1249–56.
83. van Vark LC, Lesman-Leegte I, Baart SJ, Postmus D, Pinto YM, de Boer RA, et al. Prognostic value of serial galectin-3 measurements in patients with acute heart failure. *J Am Heart Assoc* 2017;6:e003700.
84. de Boer RA, Lok DJ, Jaarsma T, van der Meer P, Voors AA, Hillege HL, et al. Predictive value of plasma galectin-3 levels in heart failure with reduced and preserved ejection fraction. *Ann Med* 2011;43:60–8.
85. Brouwers FP, van Gilst WH, Damman K, van den Berg MP, Gansevoort RT, Bakker SJ, et al. Clinical risk stratification optimizes value of biomarkers to predict new-onset heart failure in a community-based cohort. *Circ Heart Fail* 2014;7:723–31.
86. Sciacchitano S, Lavra L, Morgante A, Ulivieri A, Magi F, De Francesco GP, et al. Galectin-3: one molecule for an alphabet of diseases, from A to Z. *Int J Mol Sci* 2018;19:379.
87. Nishiyama J, Kobayashi S, Ishida A, Nakabayashi I, Tajima O, Miura S, et al. Up-regulation of galectin-3 in acute renal failure of the rat. *Am J Pathol* 2000;157:815–23.
88. Henderson NC, Mackinnon AC, Farnworth SL, Kipari T, Haslett C, Iredale JP, et al. Galectin-3 expression and secretion links macrophages to the promotion of renal fibrosis. *Am J Pathol* 2008;172:288–98.
89. Sarhene M, Wang Y, Wei J, Huang Y, Li M, Li L, et al. Biomarkers in heart failure: the past, current and future. *Heart Fail Rev* 2019;24:867–903.
90. Glick D, deFilippi CR, Christenson R, Gottdiener JS, Seliger SL. Long-term trajectory of two unique cardiac biomarkers and subsequent left ventricular structural pathology and risk of incident heart failure in community-dwelling older adults at low baseline risk. *JACC Heart Fail* 2013;1:353–60.
91. Barutaut M, Fournier P, Peacock WF, Evaristi MF, Dambrin C, Caubere C, et al. sST2 adds to the prognostic value of Gal-3 and BNP in chronic heart failure. *Acta Cardiol* 2020;75:739–47.
92. Feng J, Tian P, Liang L, Chen Y, Wang Y, Zhai M, et al. Outcome and prognostic value of N-terminal pro-brain natriuretic peptide and high-sensitivity C-reactive protein in mildly dilated cardiomyopathy vs. dilated cardiomyopathy. *ESC Heart Fail* 2022 Mar 4 [Epub]. <https://doi.org/10.1002/ehf2.13864>.
93. Ky B, French B, Levy WC, Sweitzer NK, Fang JC, Wu AH, et al. Multiple biomarkers for risk prediction in chronic heart failure. *Circ Heart Fail* 2012;5:183–90.
94. Sabatine MS, Morrow DA, de Lemos JA, Omland T, Sloan S, Jarolim P, et al. Evaluation of multiple biomarkers of cardiovascular stress for risk prediction and guiding medical therapy in patients with stable coronary disease. *Circulation* 2012;125:233–40.
95. Zile MR, Claggett BL, Prescott MF, McMurray JJ, Packer M, Rouleau JL, et al. Prognostic implications of changes in N-terminal pro-B-type natriuretic peptide in patients with heart failure. *J Am Coll Cardiol* 2016;68:2425–36.
96. Kubanek M, Goode KM, Lanska V, Clark AL, Cleland JG. The prognostic value of repeated measurement of N-terminal pro-B-type natriuretic peptide in patients with chronic heart failure due to left ventricular systolic dysfunction. *Eur J Heart Fail* 2009;11:367–77.
97. Savarese G, Hage C, Orsini N, Dahlstrom U, Perrone-Filardi P, Rosano GM, et al. Reductions in N-terminal pro-brain natriuretic peptide levels are associated with lower mortality and heart failure hospitalization rates in patients with heart failure with mid-range and preserved ejection fraction. *Circ Heart Fail* 2016;9:e003105.
98. Masson S, Anand I, Favero C, Barlera S, Vago T, Bertocchi E, et al. Serial measurement of cardiac troponin T using a highly sensitive assay in patients with chronic heart failure: data from 2 large randomized clinical trials. *Circulation* 2012;125:280–8.
99. Weiner RB, Baggish AL, Chen-Tournoux A, Marshall JE, Gaggin HK, Bhardwaj A, et al. Improvement in structural and functional echocardiographic parameters during chronic heart failure therapy guided by natriuretic peptides: mechanistic insights from the ProBNP Outpatient Tailored Chronic Heart Failure (PROTECT) study. *Eur J Heart Fail* 2013;15:342–51.