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# Biomarkers in Heart Failure: From Research to Clinical Practice

Alexander E. Berezin, M.D., Ph.D. and Alexander A. Berezin, M.D.
Internal Medicine Department, Zaporozhye Medical Academy of Postgraduate Education, Zaporozhye, Ukraine

The aim of this narrative review is to summarize contemporary evidence on the use of circulating cardiac biomarkers of heart failure (HF) and to identify a promising biomarker model for clinical use in personalized point-of-care HF management. We discuss the reported biomarkers of HF classified into clusters, including myocardial stretch and biomechanical stress; cardiac myocyte injury; systemic, adipocyte tissue, and microvascular inflammation; cardiac fibrosis and matrix remodeling; neurohumoral activation and oxidative stress; impaired endothelial function and integrity; and renal and skeletal muscle dysfunction. We focus on the benefits and drawbacks of biomarker-guided assistance in daily clinical management of patients with HF. In addition, we provide clear information on the role of alternative biomarkers and future directions with the aim of improving the predictive ability and reproducibility of multiple biomarker models and advancing genomic, transcriptomic, proteomic, and metabolomic evaluations.

**Key Words:** Heart failure, Cardiac Biomarkers, Multiple Biomarker Models, Prediction, Management

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**Corresponding author:**
Alexander E. Berezin, M.D., Ph.D.
Senior Consultant of Therapeutic Unit, Internal Medicine Department, Zaporozhye State Medical University, 26 Mayakovsky Avenue, Zaporozhye, 69035, Ukraine
Tel: +380-61-272-9607
E-mail: aeberezin@gmail.com

**Co-corresponding author:**
Alexander A. Berezin, M.D.
Internal Medicine Department, Zaporozhye Medical Academy of Postgraduate Education, 20, Vinter blvd, Zaporozhye, 69000, Ukraine
E-mail: lunik.mender@gmail.com



## INTRODUCTION

Heart failure (HF) remains the leading cause of premature death in patients with established cardiovascular disease (CVD) worldwide, regardless of the specific clinical phenotype [1]. Although the prevalence of HF with reduced ejection fraction (HFrEF) has stabilized in the majority of developed Western countries and has even decreased in some populations, an increasing prevalence of HF with preserved (HFpEF) and HF with mildly reduced ejection fraction (HFmrEF) has been found in both developed and developing countries [2]. This alarming opposite trend in the prevalence of different HF phenotypes may be a result of an increase in the occurrence of conventional CV risk factors, including hypertension, abdominal obesity, dyslipidemia, and diabetes mellitus, in relatively young individuals [3]. Another explanation is the affordability of medical care and continuously increasing economic burden on patients and the medical care system [4]. However, the reduction in mortality among HF patients with different HF phenotypes is regarded to be occurring at a less rapid pace than expected, thus pointing to an era of endless HF epidemic [5]. A recent systematic review established that the estimated prevalence of preclinical stages of HF (stages

A and B) reached up to 43% among high-risk patients with hypertension and in men [6]. The 7-year risk of incidence of symptomatic HF (stages C and D) and all-cause mortality reached up to 9.8% and 5.4%, respectively [6]. Early diagnosis and intervention are considered to slow or even stop the progression of HF from the asymptomatic to symptomatic stages. In this regard, HF management requires a clear understanding of screening, risk stratification, diagnostic algorithms, and personalized point-of-care (POC) strategies informed by validated and evidence-based models [7].

Biomarker-guided management of HF as part of the POC HF platform, comprising personal consultation, optimal comorbidity care, and concise HF diagnostic and treatment algorithms, seems to be a promising strategy as well as an effective tool that has been partially implemented in current HF guidelines [8]. The new 2021 guidelines of the European Society of Cardiology (ESC) for the diagnosis and treatment of acute and chronic HF and the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) guidelines report strong agreement in the use of natriuretic peptides (NPs) in the diagnosis, prediction, and management of HF, although only the 2022 AHA/ACC/HFSA guidelines provide alternative biomarkers (galectin-3, soluble suppressor tumorigenisity-2) for risk stratification and prediction of outcomes [9, 10]. Findings regarding alternative biomarkers are highly conflicting, reflecting several stages of natural HF evolution that may be useful in risk stratification and management of different phenotypes of HF.

The purpose of this narrative review is to elucidate the contemporary evidence regarding the use of circulating cardiac biomarkers in HF and to evaluate a promising biomarker model in the POC management of HF.

## NATURAL EVOLUTION OF HF AND CIRCULATING CARDIAC BIOMARKERS

Recognition of the utility of biological indicators to reflect certain pathogenic processes contributing to the natural evolution of HF has become widespread in the current century [11]. However, the clinical utility of biomarkers may be overvalued given the complexity of the pathogenesis of HF, which frequently relates to its etiology (primary ischemic/non-ischemic), initial direct cause, and phenotype [12]. Moreover, an overlap between various pre-existing comorbidities (chronic kidney disease, diabetes mellitus, and chronic obstructive pulmonary disease), conventional cardiovascular risk factors (hypertension, dyslipidemia, smoking, and obesity), age- and gender-related conditions, and profile of complications deeply interfere with the natural evolution of HF, transition of its phenotypes, and the therapeutic response [13]. For instance, ischemia/necrosis due to acute myocardial infarction leads to cardiac myocyte loss, whereas expanding fibrosis, cardiac hypertrophy, and microvascular complications play a pivotal role in the progression of adverse cardiac remodeling and development of HF, referred to as the HFrEF/HFmrEF phenotype rather than the HFpEF phenotype. In contrast, HFpEF is a result of cardiac hypertrophy, myocardial fibrosis, disproportional changes in the space architecture of the cavities, and cardiac arrhythmias [14]. There is also strong evidence that a signature of the complication profile or comorbidities may replicate their impact on HF progression [15].

One of the most illustrative examples is the occurrence of atrial fibrillation during the clinical course of HFpEF, which is regarded as the most powerful predictor of the transformation into HFrEF and an increased risk of poor outcomes [16]. The next example includes type 2 diabetes mellitus (T2DM), which was found to be either a common risk factor for HFpEF or a consequence of its natural progression [17]. Regardless of its onset, T2DM has a negative impact on premature death through a large number of pathogenetic pathways interfering with adverse cardiac remodeling, such as microvascular inflammation, accelerating atherosclerosis, impaired ability of endogenous repair, oxidative stress and mitochondrial dysfunction, neurohumoral activation, and target organ damage (diabetes-induced nephropathy, skeletal myopathy, adipose tissue dysfunction, and angiopathy) [18].

The early hypothesis of the linear evolution of HF from HFpEF to HFrEF is considered unrealistic because each HF phenotype demonstrates a unique logical trend of its progression and transformation into other phenotypes from the impact of the disease itself or the therapy [19]. Previous clinical studies have shown that the mortality rate in patients with HF seems to invariantly correspond to the HF phenotype, but there was no significant difference in CV mortality and HF hospitalization between patients with HFrEF and HFpEF [20]. These parameters in patients with HFmrEF are also regarded to have been nearly similar to those in patients with HFrEF, but not to those in patients who demonstrated a trend of improving left ventricular ejection fraction (LVEF) over time [21].

These findings indicate that potential biomarkers could contribute to the diagnosis and treatment of HF in connection with numerous mutually corresponding factors that are involved in the pathogenesis of different phenotypes of HF. These conceptual clusters of cumulative pathogenetic factors include myocar-


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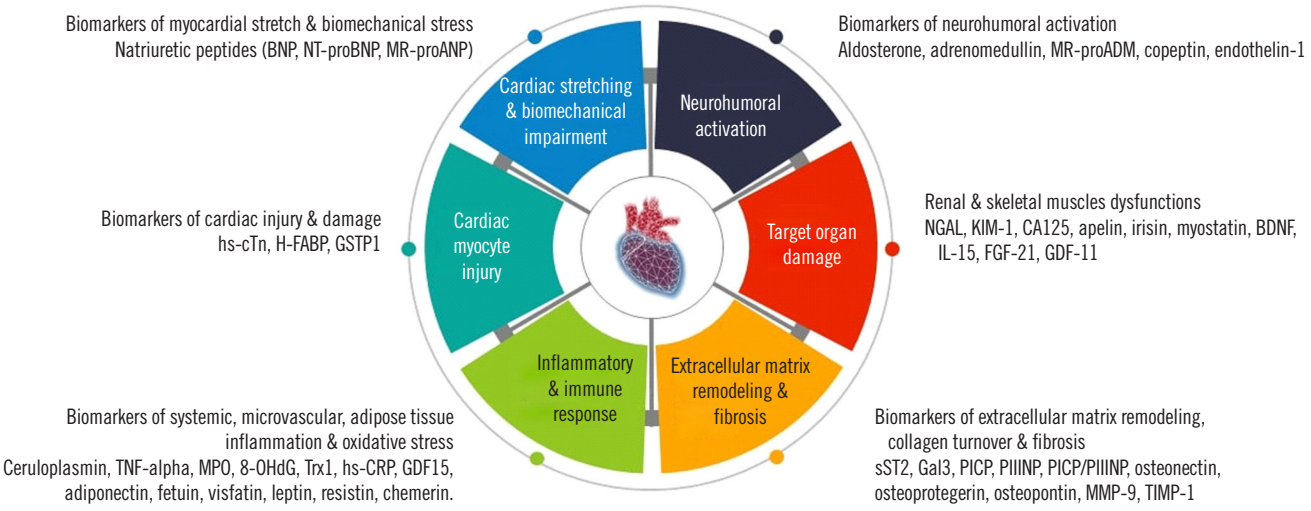


**Fig. 1.** Circulating biomarkers of the most important conceptual clusters influencing the natural evolution of heart failure (HF).
Abbreviations: BDNF, brain-derived neurotrophic factor; hs-cTn, high-sensitivity cardiac troponins; H-FABP, heart-type fatty acid-binding protein; FGF, fibroblast growth factor; Gal3, galectin-3; GDF, growth differentiation factor; GSTP1, glutathione transferase P1; IL, interleukin; KIM-1, kidney injury molecule-1; MR-proANP, mid-regional atrial natriuretic pro-peptide; MR-proADM, mid-regional pro-adrenomedullin; MPO, myeloperoxidase; sST2, soluble isoform of suppression of tumorigenicity 2; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; NT-proBNP, N-terminal brain natriuretic pro-peptide; NGAL, neutrophil gelatinase-associated lipocalin; PICP, procollagen type I carboxyterminal peptide; PIIINP, pro-collagen type III aminoterminal peptide; PICP/PIIINP; MMP-9, matrix metalloproteinase 9; TIMP-1, tissue inhibitor of matrix metalloproteinase; TNF, tumor necrosis factor; Trx1, thioredoxin 1.

dial stretch and biomechanical stress; cardiac myocyte injury; systemic, adipocyte tissue, and microvascular inflammation; cardiac fibrosis and matrix remodeling; neurohumoral activation and oxidative stress; impaired endothelial function and integrity; and renal and skeletal muscle dysfunction (Fig. 1).

The number of potential circulating biomarkers reflecting these relationships among clusters has exponentially increased over the last two decades [22]. Although each biomarker should ideally correspond to a single point of HF pathogenesis, in reality, receiving an exact clinical interpretation of peak concentrations is challenging due to the changes seen in the majority of current biomarkers due to wide overlap with conceptual clusters. However, these biomarkers do not exhibit predictive ability accurate enough to aid in the management of any phenotypes of HF.

## NATRIURETIC PEPTIDES

The first molecules recognized as powerful tools to manage HF are NPs, which continue to be emphasized in current HF guidelines [9, 10]. NPs are referred to as circulating cardiac biomarkers of myocardial stretch and biomechanical stress and mainly include several types of molecules, such as brain natriuretic peptide (BNP), N-terminal brain natriuretic pro-peptide (NT-proBNP), and mid-regional atrial natriuretic pro-peptide (MR-proANP), along with other subsets of NPs, such as C-type NP [9]. Stretching of the myocardium, elevated intracardiac filling pressures, increased intracardiac volumes, and fluid overload are considered the most influential factors for the synthesis and release of NPs. However, other causes, including systemic inflammatory reaction, myocardial ischemia and necrosis, hypoxia, brain trauma, infections, and adipose tissue dysfunction, are considered to be involved in the production, secretion, clearance, and bioavailability of NPs [23]. According to well-established classic considerations, NPs are defined as physiological antagonists of the sympathetic nervous system and renin-angiotensin-aldosterone systems, with primary biological roles of diuresis/water uresis, electrolyte homeostasis, fluid retention, blood pressure, and vasodilation [23, 24]. A broad spectrum of pleiotropic effects of NPs on target tissues has been described, including anti-proliferative, anti-apoptotic, anti-inflammatory, tissue-protective, and angiopoietic capabilities [24].

Although NPs have higher negative than positive diagnostic value for HF in the general population, there are different cut-off points for NPs in numerous populations, including patients of older/senior age, female sex, and residents of nursing homes [25]. Moreover, there is a wide spectrum of CV (atrial fibrillation/flutter, acute coronary syndrome/myocardial infarction, hypertension, cardiac hypertrophy, acute pulmonary embolism, and valvular heart disease) and non-CV (shock, obesity, diabetes mellitus, pneumonia, chronic obstructive pulmonary disease,

**Table 1.** Recommended NP cut-offs for acute HF diagnosis*

| Cut-off to make a decision | Cut-off points | | | | |
|---|---|---|---|---|---|
| | BNP, pg/mL | NT-proBNP, pg/mL | | | MR-proANP, pmol/L |
| | All ages | Aged <50 yr | Aged 50–75 yr | Aged >75 yr | All ages |
| Acute/acutely decompensated HF | | | | | |
| Rule out HF | <100 | <300 | <300 | <300 | <40 |
| Mild probability ("grey" zone) | 100–400 | 300–450 | 300–900 | 300–1,800 | 40–120 |
| Rule in HF | >400 | >450 | >900 | >1,800 | >120 |
| Stable HF | | | | | |
| Rule out HF | <35 | <125 | <125 | ≥125 | <40 |
| Mild probability ("grey" zone) | 35–150 | 125–600 | 125–600 | 125–600 | 40–120 |
| Rule in HF | >150 | >600 | >600 | >600 | >120 |

*Data were obtained from references [25-29].
Abbreviations: NP, natriuretic peptide; HF, heart failure; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MR-pro-ANP, mid-regional pro-atrial natriuretic peptide.

and sepsis) conditions that may modify the circulating concentrations of NPs, regardless of the presence of HF. Aortic stenosis, atrial fibrillation, acute pulmonary embolism, or severe pulmonary hypertension interfere with increasing NP concentrations, whereas other conditions such as obesity are associated with reduced NP concentrations.

Although BNP, NT-proBNP, and MR-proANP show comparable diagnostic and prognostic accuracy, all of these factors often lead to underdiagnosis or misdiagnosis of HF; therefore, different cut-off points of NPs should be determined for diagnostic purposes (Table 1). NT-proBNP concentrations are more closely related to age, sex, and renal clearance than BNP and MR-proANP concentrations, and age-dependent cut-offs to rule-in HF are preferred over NT-proBNP. MR-proANP did not exhibit a significant correlation with gender and age in patients with acute and chronic HF [26, 27], but was prominently associated with newly diagnosed acute HF [28]. NT-proBNP showed higher diagnostic accuracy of asymptomatic cardiac dysfunction than MR-proANP in older people with multiple risk factors for HF (diabetes mellitus, chronic kidney disease, vascular disease, atrial fibrillation, and hypertension) [29, 30]. In this context, the diagnostic accuracy of NPs is considered to increase through a serial evaluation of NP concentrations.

It remains unclear whether this approach is useful for all phenotypes of HF because fluid accumulation in the pleural space is regarded a common sign of acute/acutely decompensated HFrEF and HFmrEF [31]. Implementation of angiotensin receptor neprilysin inhibitors (ARNIs) as a component of the optimal strategy of HFrEF care put into question the use of BNP for serial measures, highlighting the value of NT-proBNP in POC therapy of HF [32]. NPs have been thoroughly evaluated as promising surrogate indicators of the risk of HF progression and compensation, along with a prediction of the response to guide-based HF therapy [33]. Although NP-guided management of HF has been assessed in numerous clinical trials and rigorously evaluated in several meta-analyses, its role in improving clinical outcomes in HF patients with different phenotypes remains controversial [34, 35]. The predictive abilities of peak concentrations and even a trend of NPs in ambulatory follow-up have been found to be sufficiently reliable and accurate for all-cause mortality [36].

There is serious concern about the strict resemblance of NP predictive values among patients with HFrEF/HFmrEF to those with HFpEF [37]. The DIAST-CHF trial revealed that NT-proBNP was a better predictor of incident atrial fibrillation than HF among stable outpatients with CV risk factors [38]. Importantly, clinical use of NPs has a well-established economic benefit when compared with other cardiac and non-cardiac biomarkers. Therefore, POC management of HF based on NP measures seems to be the most cost-effective strategy [39, 40]. There is strong evidence that integration of NP in the optimal guide-based management of HF may help cardiologists to (1) detect high-risk HF patients, (2) recognize whether these patients are in a stable condition or if there is a tendency to progress toward decompensated HF, (3) optimize HF management, (4) improve prognosis assessment, (5) reduce all-cause and HF-related mortality and re-admission to hospital, and (6) save costs per year of life. All of these benefits of various NPs along with some disadvantages are summarized in Table 2.


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**Table 2.** Advantages and disadvantages of current biomarkers in HF

| Biomarker | Correspondence to basic pathophysiological mechanism/triggers | Current role in HF | Advantages | Disadvantages |
|---|---|---|---|---|
| NPs | Biomechanical stress, ischemia/necrosis/reperfusion damage, fluid overload | Rule out HF.<br>Risk stratification of HF.<br>Prediction of all-cause and CV mortality.<br>POC management. | Independent predictor of high risk of HF, HF occurrence and progression, HF outcomes and death.<br>Available for POC management and consequent measures in follow-up.<br>Cost-effective diagnostic workup of newly suspected HF | Respectively high biological variability.<br>Renal clearance.<br>Different cut-off points for various HF populations depending on CV risk factor presentation, age, and gender.<br>Dependence of diagnostic reliability from co-existing CV and non-CV conditions |
| hs-cTn | Myocardial necrosis | Prediction of HF occurrence.<br>Prediction of all-cause and CV mortality. | Independent predictor of poor clinical outcomes.<br>Available for continuous monitoring.<br>Able to improve predictive value of NPs.<br>Available for multiple-marker strategy for risk stratification. | No relation between an effect of OGBM and changes of hs-cTn.<br>Optimal plasma cut-off point under question.<br>Gender-specific effects. |
| H-FABP | Myocardial necrosis | Independent predictor of all-cause and CV mortality. | Peak concentrations independently predict HF occurrence. | No strong evidence in large clinical trials. |
| GSTP1 | Myocardial necrosis, inflammation, apoptosis | Independent predictor of ACR. | Peak concentrations independently associated with susceptibility of cardiac dysfunction. | No strong evidence in large clinical trials. |
| Galectin-3 | Extracellular fibrosis and inflammation | Alternative stratification at higher risk of CV death and HF manifestation. | Peak concentrations independently associated with elevated risk of all-cause mortality, CV mortality, and HF-related outcomes. | Lack of dynamics during therapy.<br>Low diagnostic accuracy for HF.<br>Predictive value for readmission lower than that of NT-proBNP.<br>Cut-off depends on age and gender. |
| sST2 | Extracellular fibrosis and inflammation | Alternative stratification at higher risk of all-cause mortality, CV death, and HF manifestation. | Peak concentrations independently associated with elevated risk of all-cause mortality, CV mortality, and HF-related outcomes.<br>Available for serial measures and guided therapy. | The concentrations at discharge exert higher predictive potency than at admission. |

Abbreviations: ACR, adverse cardiac remodeling; HF, heart failure; CV, cardiovascular; hs-cTn, high-sensitivity cardiac troponin; H-FABP, heart-type fatty acid-binding protein; GSTP1, glutathione transferase P1; NPs, natriuretic peptides; NT-proBNP, N-terminal brain natriuretic pro-peptide; OGBM, optimal guide-based management; POC, point-of-care; sST2, soluble isoform of suppression of tumorigenicity 2.

## BIOMARKERS OF CARDIAC MYOCYTE INJURY

### Cardiac troponins

Although the implementation of high-sensitivity (hs) analytical methods to detect circulating cardiac troponins (cTn) I and T resulted in sufficient improvement in diagnostic accuracy in the setting of myocardial necrosis for acute coronary syndromes (ACS) and acute myocardial infarction (AMI) [41], the changes in even very low concentrations of these biomarkers in acute/acutely decompensated HF patients enable their use as predictive indicators of all-cause and CV mortality [42]. There is a large amount of evidence showing that the measurement of hs-cTn concentrations can be a powerful tool for predicting the occurrence of systolic and diastolic cardiac dysfunction and clinical conditions at high risk for developing HF, including aortic stenosis, stable coronary artery disease, and cardiac hypertrophy [43].

Clinical studies and numerous meta-analyses have shown that elevated baseline concentrations of hs-cTns allow cardiologists to effectively stratify chronic HF patients at a higher risk of CV mortality and poor CV outcomes, regardless of HF phenotypes and NP concentrations [44, 45]. HFrEF patients with the most elevated hs-cTnT concentrations, which were 3–5-fold higher than those of patients with normal biomarker concentrations, demonstrated increased risks of CV death and HF hospitalization [46]. A model including hs-cTnT and hs-cTnI along with NT-proBNP and clinical features significantly improved the risk prediction of clinical outcomes in patients with acute and chronic HF, regardless of etiology, phenotype, and presence of renal dysfunction [47, 48]. The newly updated four-pillar strategy of HFrEF management was found to significantly reduce the concentrations of hs-cTnT in connection with improved survival, but SGLT2 inhibitors (mainly empagliflozin and dapagliflozin) exerted favor-

able effects on HFrEF/HFpEF and renal outcomes, independent of baseline hs-cTnT concentrations [46]. These facts lead us to consider whether thorough monitoring of the serum concentrations of hs-cTn should be incorporated in routine optimal guide-based management (OGBM) of HF, whereas peak concentrations of hs-cTn retain their discriminative potency in acute and chronic HF. Data from HF patients included in the Biomarkers in Heart Failure Outpatient Study (BIOS) Consortium showed a significant difference in prognostic cut-offs of hs-cTnT between male and female patients with HF, whereas there was no difference with respect to NT-proBNP concentrations [49].

### Heart-type fatty acid-binding protein

Other biomarkers of myocardial necrosis, such as heart-type fatty acid-binding protein (H-FABP) and glutathione transferase P1 (GSTP1), which are not included in the contemporary diagnostic strategy for ACS/AMI, are promising predictors of acute HF. H-FABP reflects myocardial injury and has several putative advantages over hs-cTn [50]. First, H-FABP is rapidly released from myocardial cells within 1 hour of damage due to ischemia/necrosis, allowing reliable stratification of patients with low concentrations of hs-cTn. Second, there is no need to recheck hs-cTn, which reduces the total cost of diagnosis [51]. There is still no clear consensus for the routine implementation of H-FABP in OGBM for HF, although strong algorithms for risk stratification for acute pulmonary embolism have already been developed [52]. It remains unclear whether H-FABP surpasses hs-cTn in its discriminative potency among HF patients without ACS, which requires further investigation.

### Glutathione transferase P1

Decreased levels of GSTP1 contribute to the susceptibility to impairment of cardiac function and adverse cardiac remodeling via regulation of oxidative stress, systemic and microvascular inflammation, and endothelial dysfunction in HF [53]. There is limited evidence that polymorphisms in glutathione transferases, which are engaged in direct antioxidant defense and indirect modulation of apoptosis-related signaling pathways in the myocardium, are indicators of HF manifestations [54].

## BIOMARKERS OF FIBROSIS AND INFLAMMATION

### Galectin-3

Galectin-3 is a β-galactoside-binding lectin that regulates myocardial and microvascular inflammation, mononuclear migration, and extracellular accumulation of collagen matrix through overproduction of collagen and fibroblast proliferation, leading to adverse cardiac remodeling and cardiac dysfunction [55]. The main stimulus for macrophage secretion of galectin-3 is suggested to be aldosterone, which translates autocrine and paracrine signals from transforming growth factor-β and cyclin D1 in fibroblasts to attenuate myofibroblast proliferation, immune cell recruitment, and extracellular collagen matrix deposition [56]. Pro-inflammatory cytokines such as interferon-gamma and interleukin-6 were found to induce galectin-3 mRNA expression in the myocardium and vasculature [57]. In fact, galectin-3 has been considered the most upregulated protein in cardiac hypertrophy, the transformation of HFpEF into HFrEF, and malignant arrhythmia related to electrophysiological remodeling due to fibrotic changes in the myocardium [58].

Recent research progress has revealed the pivotal role of galectin-3 in CVD and for HF diagnosis and management. When compared with other HF biomarkers, galectin-3 provides information about the myocardial fibrotic state and the risk of adverse cardiac remodeling and its progression [59]. Among patients at higher risk of HF, there was no association between dynamic changes in galectin-3 and incident HF or atrial fibrillation [60]. Although peak concentrations of galectin-3 were independently associated with an elevated risk of all-cause mortality, CV mortality, and HF hospitalization for all HF phenotypes [61], there was no significant impact of HF medications on galectin-3 concentrations [62]. Thus, galectin-3 remains an alternative biomarker that may add discriminative value to NPs but does not meet serial measures.

### Soluble isoform of suppression of tumorigenicity 2

Soluble isoform of suppression of tumorigenicity 2 (sST2) is a biomarker of cardiac fibrosis and inflammation, which has been thoroughly investigated during the last decade; therefore, there are numerous high-quality narrative and systematic reviews of sST2 in HF [63, 64]. The concentration of sST2 predicted the risk of cardiac remodeling, HF occurrence, and death regardless of common comorbidities, including coronary artery disease, renal failure, chronic obstructive pulmonary disease, and hypertension [65]. Elevated concentrations of sST2 >35 ng/mL were also found to be reliable and specific biomarkers of all-cause death, CV death, and HF hospitalization in patients with HFrEF and HFpEF, whereas NPs seem to be more sensitive in stratifying patients with HFrEF than those with HFpEF [66, 67]. Overall, sST2 exerts the most important characteristics of ideal biomarkers, including high accuracy in a single measure, possibil-


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ity of being repeatedly measured and incorporated into a multiple-biomarker approach for risk stratification, and availability in clinical practice at a reasonable cost [68]. Although sST2 retains predictive potency as a biomarker, it also provides additional information for risk stratification similar to NPs.

## BIOMARKERS OF EXTRACELLULAR MATRIX REMODELING

Abundant molecules are considered to be responsible for the structural modification of the extracellular matrix (ECM) and the binding between cardiac myocytes and their surroundings, including fibrillar compounds of the ECM (collagen type I and type III); products of their degradation (pro- or telopeptides); glycoproteins, proteoglycans, and some proteins (fibronectin, laminin, fibrillin, and elastin); as well as bone-related peptides, including osteonectin, osteoprotegerin, and osteopontin. Under physiological conditions, these molecules take part in the regulation of cardiac ECM arrangement, the alteration of which plays a pivotal role in adverse cardiac remodeling in HF. Elucidating the role of each of these molecules warrants comprehensive and thorough investigation, because they are heavily involved in the pathogenesis of myocardial fibrosis and are related to arrhythmogenesis [69, 70]. Although numerous clinical trials have been performed in the last two decades to evaluate the utility of these molecules as diagnostic or prognostic biomarkers in patients with HF, collagen turnover biomarkers and bone-related proteins have been found to be closely associated with all-cause and CV mortality and HF hospital admission [71, 72]. These markers are not highly specific for detecting adverse cardiac remodeling, and abnormal concentrations have often been found in acute and stable coronary artery disease, valvular heart disease, cardiac hypertrophy, and cardiomyopathy (Table 3). Nevertheless, there is a large amount of evidence that collagen turnover biomarkers, mainly telopeptides such as serum carboxy-terminal telopeptide of collagen type-I and osteoprotegerin, rule out HF rather than confirm this condition [73, 74]. It remains unclear whether these are reliable biomarkers for a multiple-biomarker strategy, because they are considered surrogate markers of vascular calcification, coronary artery disease, and severity of HF, but can also be overexpressed in acute decompensated HF [75].

**Table 3.** Advantages and disadvantages of plausible biomarkers without proven value in current HF management

| Biomarker | Correspondence to basic pathophysiological mechanism/triggers | Advantages | Disadvantages |
|---|---|---|---|
| Pro- or telopeptides of collagen type-I | ECM remodeling | Independent predictor of high risk of HF, HF outcomes, and death.<br>Additive prognostic value when compared with the concentrations of NT-proBNP.<br>Available for a multi-marker approach for risk stratification. | Unavailable for serial measures.<br>Low diagnostic value |
| Bone-related proteins | ECM remodeling | Independent of NPs' predictive value for CV mortality, HF hospitalization, and arrhythmia.<br>Available for a multi-marker approach for risk stratification. | Unavailable for serial measures.<br>Low diagnostic value |
| GDF15 | Inflammation | Predicts ischemia-induced HF and AF.<br>Available for a multi-marker approach for risk stratification.<br>Available for biomarker-guided therapy | Not available for prediction of newly diagnosed HF and non-ischemic cardiomyopathy. |
| Renal dysfunction biomarkers | Renal injury | Available for serial monitoring.<br>Association of HF-related outcomes | No relation to change of HF management. |
| Biomarkers of neurohumoral activation | Neurohumoral activation | Available for mortality prediction regardless of HF phenotypes. | Strict similarity in predictive abilities with those of NPs.<br>Available for acute HF rather than chronic HF. |
| Oxidative stress biomarkers | Mitochondrial injury | Relatively low-cost measures. | Low accuracy, predictive ability, reproducibility, and reliability. |
| Skeletal muscles dysfunction biomarkers | Muscles injury | Available for mortality prediction regardless of HF phenotypes.<br>Association of HF-related outcomes.<br>Available for biomarker-guided therapy. | No validated scores to use. |

Abbreviations: AF, atrial fibrillation; ECM, extracellular matrix; CV, cardiovascular; HF, heart failure; GDF-15, growth differentiation factor-15; NPs, natriuretic peptides.

## BIOMARKERS OF INFLAMMATION

Growth differentiation factor-15 (GDF15) belongs to the transforming growth factor-beta superfamily and regulates the inflammatory response and tissue repair [76]. The direct molecular targets of GDF-15 are c-Jun N-terminal kinase, Bcl-2-associated death promoter, and epidermal growth factor receptor suppression, along with activation of Smad/eNOS. The PI3K/AKT signaling pathways are considered crucial elements in tissue protection progenitor and mature endothelial cells. In animal models, overexpression of GDF15 was found to be a conductor of a lean phenotype, insulin sensitivity, hypophagia, and other metabolic parameters, which may explain the link between T2DM and cardiac dysfunction via the orphan glial-derived neurotrophic factor (GDNF) family receptor α-like (GFRAL) [77]. Overall, GDF15 exerts a cardioprotective effect that connects to its spectrum of autocrine/paracrine properties, including anti-inflammatory, antioxidative, and antiapoptotic properties [78]. Cardiomyocyte expression of GDF15 was highly induced by ischemia and reperfusion injury and was associated with cardiac fibrosis after inflammation due to AMI and HF. Elevated concentrations of GDF15 predicted newly onset atrial fibrillation [79], cardiac thrombosis [80], cardioembolic stroke, and AMI, but not HF and non-ischemic cardiomyopathy [81]. GDF15 is considered a promising biomarker or a potential therapeutic target for the management of HF; however, models based on GDF15 have not yet been validated and are frequently based on retrospective investigations.

Classic biomarkers of inflammatory activation, such as tumor necrosis factor-alpha and its soluble receptor I, interleukin-6, YKL-40, disintegrin and metalloprotease 17 (ADAM-17), cluster of differentiation 146 (CD146), and high-sensitivity C-reactive protein, failed to show independent predictive value from clinical findings, echocardiographic characteristics, and NPs. In addition, these markers have renal clearance, which is considered a setback rather than a neutral particularity for patients with HF. Therefore, their diagnostic potency was found to be sufficiently reduced compared with that of BNP and NT-proBNP [82].

The multicenter Prevalence of Microvascular Dysfunction in Heart Failure With Preserved Ejection Fraction (PROMIS-HFpEF) study provided data on 248 circulating inflammatory proteins, including tumor necrosis factor receptor 1 (TNFR1), urokinase plasminogen activator receptor (UPAR), insulin-like growth factor binding protein 7 (IGFBP7), and GDF15, from 228 patients with HFpEF [83]. This study strongly confirmed that inflammatory markers were upregulated in HFpEF patients when compared with those of healthy volunteers, and that the profile constructed from these biomarkers mediated the association between comorbid conditions and echocardiographic characteristics of left and right ventricular function [83].

There are numerous renal dysfunction biomarkers, including albumin in urine, albumin:creatinine ratio, and estimated glomerular filtration rate based on serum creatinine and cystatin C, neutrophil gelatinase-associated lipocalin, and kidney injury molecule-1. These markers only exhibit limited usefulness in HF management in routine clinical practice with no modifications in HF strategy depending on the trend of changes in biomarker concentrations [84]. However, these markers improved the prediction of 10-year HF risk based on conventional CV risk factors [85].

Conventional biomarkers of neurohumoral activation (adrenomedullin, mid-regional pro-adrenomedullin, copeptin) seem to be informative for predicting mortality in patients with different phenotypes of HF, but their circulating concentrations proportionally increase in connection with disease severity, mainly among patients with acute decompensated HF [86]. Clinical features showed similar accuracy as the circulating concentrations of biomarkers of neurohumoral activation in patients with HF, mainly in hypervolemic conditions. Moreover, these biomarkers exerted strict similarity in their predictive abilities when compared with BNP and NT-proBNP for all-cause mortality in acute HF [87].

Oxidative stress biomarkers were extremely popular two decades ago because their measurements did not require sophisticated techniques, and an understanding of their interplay in HF pathogenesis was quite clear. However, numerous biomarkers affecting various aspects of oxidative stress and mitochondrial injury, such as ceruloplasmin, myeloperoxidase, 8-hydroxy-2′-deoxyguanosine, and thioredoxin 1, do not demonstrate sufficiently high accuracy, predictive ability, reproducibility, and reliability to be incorporated into clinical practice. In addition, novel oxidative stress biomarkers (α1-antitrypsin and lectin-like oxidized low-density lipoprotein receptor-1) appear to represent promising targets for HF management [88].

A large number of circulating biomarkers of skeletal myopathy (myostatin, irisin, brain-derived neurotrophic factor, interleukin-15, fibroblast growth factor-21, and growth differential factor-11) have been widely evaluated to improve the predictive ability of NPs in HFpEF and HFrEF in combination with several metabolic conditions. Although these biomarker models are promising, their main setbacks include the retrospective design of the studies, small sample size, and lack of validation using conventional scores [89]. Apelin and irisin seem to yield precise predictive information when added to NPs in patients with any HF phe-


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notype. Although the serial measures of these biomarkers appeared quite useful in terms of modification of HF management in patients with HFrEF, there are limited data supporting this finding [90, 91].

## MULTI-MARKER PREDICTIVE MODEL

The current approach for searching for new biomarkers is based on common principles of machine learning, which enables judgment of fewer variants of biomarkers of the risk of all-cause death or HF-related hospitalization. For instance, Chirinos, *et al*. (2020) [92] evaluated the concentrations of 49 plasma biomarkers in HF patients included in the Treatment of Preserved Cardiac Function Heart Failure With an aldosterone Antagonist (TopCat) trial and found that the model composed of fibroblast growth factor-23, osteoprotegerin, tumor necrosis factor-alpha and its soluble receptor I, interleukin-6, YKL-40, fatty acid binding protein-4, GDF15, angiopoietin-2, matrix metalloproteinase-7, sST-2, and NT-proBNP predicted outcomes in patients with HFpEF. The incorporation of sST2 into the Penn HF Study, Barcelona Study, and ProBNP Outpatient Tailored Chronic Heart Failure (PROTECT) biomarker sub-study exhibited an increase in the discriminative potency of the whole model, although the optimal panel of markers remained uncertain and requires further investigation [93]. Thus, a biomarker-driven strategy in HF care is argued to better match the patient's metabolic profile than conventional HF management [94].

## FUTURE DIRECTIONS

Although the biomarker-guided approach to predict the natural evolution of HF and detect vulnerable populations in terms of all-cause mortality, CV death, and HF hospitalization appears promising, there is uncertainty in the optimal number of biomarkers selected in multi-marker scores, economic burden after implementation of the strategy, and impact of biomarker measures on the modification of HF management [93, 94]. Preference for genomic, transcriptomic, proteomic, and metabolomic evaluation in comparison with a single biomarker determination is not specified and requires more data for evaluation [95]. In this regard, cell-free and packaged microRNAs, circulating extracellular vesicles, and precursors of various cells (endothelial progenitor cells and mononuclear precursors), which are engaged in cardiac and vascular repair, are regarded as interesting options for future investigations of improving personalization in HF management [96].

## CONCLUSION

NP remains the most practically useful circulating biomarker for HF; however, its predictive potency may vary depending on the HF phenotype and signature of comorbidities. Alternative biomarkers such as galectin-3 and sST2 seem to add prognostic information to NPs, especially among patients at higher risk of HF. Other biomarkers and methods for their clinical implementation are under question and require thorough examination in the future. The multiple-biomarker approach has been tested, but it remains unclear whether its economic burden and reproducibility are suitable for practical utilization.

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## AUTHOR CONTRIBUTIONS

Both authors contributed to the conception and design of the study, evaluated the quality of the reviewed studies, interpreted the findings, and drafted the manuscript. Both authors have read and approved the final version of the manuscript.

## CONFLICTS OF INTEREST

The authors do not have any conflict of interest.

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## ORCID

Alexander E. Berezin https://orcid.org/0000-0002-0446-3999
Alexander A. Berezin https://orcid.org/0000-0002-0660-9082

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