Review Article

Circulating biomarkers in heart failure: diagnostic and prognostic importance

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Abstract: Various biological markers are investigated as diagnostic and risk stratification tools for heart failure (HF). However, there is a large body of evidence that natriuretic peptides (NPs), solubilized ST2, galectin-3 and cardiac troponins have been demonstrated a significant relevance to HF advance and mortality rate. Because there is not only ideal biomarker current strategy of biomarker use in HF based on multiple biomarkers' implementation to improve risk stratification and predict risk HF-related death. Consequently, understanding the mechanisms by which the biomarkers reflect several pathophysiological stages of HF is crucial for awareness of optimal personified therapy of different phenotypes of HF. Indeed, personalized risk prediction and nature evolution of HF based on biomarkers' measure in HF patients remains to be challenged. The chapter is depicted the current role and future challenging of biological markers for evolution of HF development and progression. It has discussed the clinical guidelines reported by scientific societies with high levels of scientific reputation regarding HF therapies based on single and serial measurements of biological markers.

Keywords: Acute heart failure; chronic heart failure; biomarkers; prediction; stratification; biomarker guided-therapy

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Introduction

Heart failure (HF) is a major cause of premature death due to cardiovascular (CV) reasons in general population and in individuals with recently established CV disease (1). The prevalence of acute and chronic HF is steadily increasing worldwide, while there is expressive advance in our understanding of basic mechanisms of nature evolution of the disease and principles of prevention and treatment at different stages of the cardiac dysfunction shaping. However, for two past decades in most of developing and developed countries there is growth of economic burden of patients' families and medical care systems and as well as an increase of primary and urgent admission rate of the patients with suspected acute HF and decompensated chronic HF (2). Nevertheless, there are significant differences between sexes, races, and individuals at different ages and numerous comorbidities in prevalence, etiology, and epidemiology, presentation of clinical findings and phenotypes of HF, prognosis, and response to the disease treatment (3). Although contemporary clinical guidelines that were recently published clearly described the main principles of diagnosis, prevention and treatment of acute and chronic HF, a personified risk stratification of the disease remained to be under discussion (4). As a fact, numerous biological markers that are molecular indicators of several pathophysiological stages of nature evolution HF could become a powerful and reliable tool for more exact risk prognostication and accurate predictors of treatment response (5). The aim of the chapter is to summarize

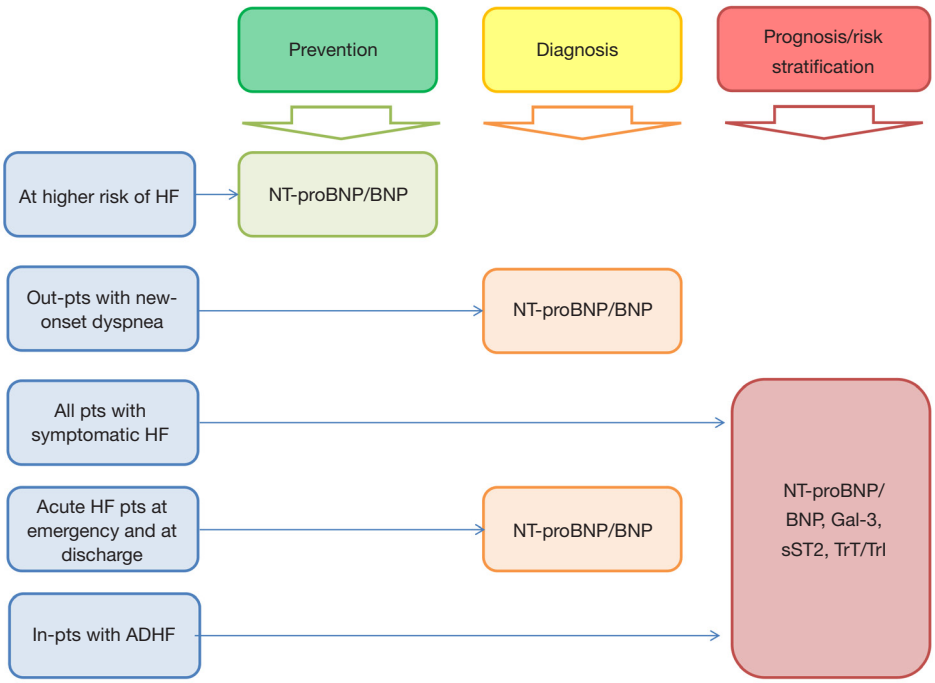

Figure 1 Schema of practical use of various biomarkers along heart failure (HF) development and progression. BNP, brain natriuretic peptide; ADHF, acutely decompensated heart failure.

knowledge regarding the promising role of biological biomarker in diagnosis, risk stratification and personifying treatment strategy in patients with acute and chronic HF.

Conventionally used biomarkers of heart failure

A biomarker is a qualitative and quantitative biological substance/characteristic/parameter(s) that defines a certain pathological condition and may give indications on disease activity or severity and the type of therapy that should be administered to the patient. In 1998, the National Institutes of Health Biomarkers Definitions Working Group defined biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (6). The International Program on Chemical Safety, led by the World Health Organization (WHO) and in coordination with the United Nations and the International Labor Organization, has defined a biomarker as "any substance, structure, or process that can be measured in the body, or its products and influences or predicts the incidence of outcome or disease" (7). The National Academy of Sciences defines a biomarker as an indicator that signals events in biological samples or systems. Finally, experts of FDA (Food and Drug Association, USA) biomarkers can be identified as a broad subcategory of medical signs, which, by accurate measures and reproducibility, can provide an objective suggestion of the medical state examined from outside the patient (7). All these terms, definitions, and characteristics were proposed to describe a biomarker, indicating that it may have the greatest value in early efficacy and safety evaluations, such as *in vitro* studies in tissue samples, *in vivo* studies in animal models, and early-phase clinical trials. Indeed, there are numerous of biomarkers, which reflect several pathophysiological stages of HF and allow stratifying individuals at risk (*Figure 1*).

There has been increasing interest in diagnostic and management strategies of HF based on biomarkers in US and in countries in Europe. Moreover, the real market of these biological markers appears to be extremal growth for last decade. On the one hand, the implementation of biomarkers use in the evidence-based clinical practices can improve efficiency and effectiveness of public health management. On the other hand, all these steps undoubtedly associated with increased cost of new diagnostic and treatment approaches based on biomarker(s) measure. To be able to shape personalized medical care

Table 1 Utility of biomarkers in HF management

Suggestions for use	Patients	COR	LOE	References
NPs				
Rule-in or support of initial working diagnosis	Patients with suspected HF in non-acute setting condition with dyspnea	I	A	(4,9)
	Patients with suspected HF, when the etiology of dyspnea is unclear	I	A	(5,10)
	Patients with suspected HF in acute setting condition	IIb	C	(11)
Exclusion of important cardiac dysfunction	Outpatients with uncertain signs and symptoms of HF	I	A	(10)
Prognosis of HF	Outpatients / inpatients with established HF	I	A	(10)
	Patients who were admitted to the hospital with acute HF	I	A	(10)
	Post-discharged HF patients	IIa	B	(12)
Prevent development of LV dysfunction or new-onset HF	Patients at risk of HF	IIa	B	(10,13)
Target therapy	Outpatients with established HF in euvolemic condition	IIa	B	(10,12,14)
Biomarkers of myocardial injury (cardiac troponins)				
Risk stratification	Patients with established HF	I	A	(10,15,16)
	Patients who were admitted to the hospital with acute HF	I	A	(10,17)
Biomarkers of myocardial fibrosis (galectin-3)				
Risk stratification	Outpatients with established chronic HF	IIb	B	(18,19)
	Inpatients with established acute and chronic HF	IIb	A	(20-22)
	Post-discharged patients	IIa	B	(23)
sST2				
Prognosis of HF	Outpatients / inpatients with established HF	I	A	(23)
	Patients who were admitted to the hospital with acute HF	I	A	(19,24,25)
	Post-discharged patients	IIa	B	(25)

HF, heart failure; NPs, natriuretic peptides; BNP, brain NP; NT-proBNP, N-terminal fragment of brain NP; sST2, soluble suppressor of tumorigenicity-2; MR-proANP, mid-regional pro-atrial NP; COR, classes of recommendations; LOE, level of evidence.

to HF patients, it is extremely important to know which biomarkers are better corresponded to the treatment goals including clinical symptoms, functional status, quality of life, survival and admission to the hospital (8). Contemporary clinical guidelines described what kind of biological markers are necessary to predict most of these goals. The family of natriuretic peptides (NPs) are recommended biomarkers for routine clinical practice to risk stratification and diagnosis of the HF. In contrast, galectin-3, soluble suppressor of tumorigenicity-2 receptor (sST2) and high-sensitivity cardiac troponins can be discussed as promising candidates for improving prediction and risk stratification in HF patients (*Table 1*). Interestingly, recent ESC HF clinical guidelines introduced a new HF phenotype based on measure of left ventricular (LV) ejection fraction (EF) and determined the HF with mid-range EF (HFmrEF). Novel HF phenotype falls between the HF with reduced LVEF (HFrEF) and HF with preserved LVEF (HFpEF) (*Table 2*). The biomarkers' characteristics of the HFmrEF are became uncertain and require to be investigated in details, although

Table 2 Contemporary classification of heart failure according to ESC [2016]

Characteristics of HF	Phenotypes of chronic HF		
	HFrEF	HFpEF	HFmrEF
Symptoms and signs of HF	Symptoms and signs relate to hypervolemic state, fluid retention, diuretics' use		
LVEF	< 40%	>50%	40–49%
NP level(s)	Extremely elevated	Mild-to-moderate elevated	Mild-to-moderate elevated
Relevant structure heart disease	CAD, myocardial infarction, dilated cardiomyopathy, myocarditis, tachycardiomyopathy	LVH, hypertrophic and restrictive cardiomyopathies, CAD, infiltrative diseases,	LVH, CAD, pulmonary hypertension, diabetes-induced cardiomyopathy, tachycardiomyopathy
Relevant systolic dysfunction/ diastolic filling abnormalities	Primary severe systolic dysfunction with diastolic filling abnormalities	Primary diastolic heart failure*	Primary mild systolic dysfunction with diastolic filling abnormalities
Key structural alterations of LA	LAVI >34 mL/m^2	LAVI >34 mL/m^2	LAVI >34 mL/m^2

Notes: NP(s) levels mean BNP >35 pg/mL and/or NT-proBNP >125 pg/mL; *, diastolic dysfunction is determined if four parameters of annular e' velocity are presented their abnormal cutoff values are: septal e' <7 cm/sec, lateral e' <10 cm/sec, average E/e' ratio >14, LA volume index >34 mL/m^2, and peak TR velocity >2.8 m/sec. On the basis of the writing group's collective expert opinion, average E/e' ratio is recommended for simplification. HFrEF, heart failure with reduced left ventricular ejection fraction; HFmrEF, heart failure with mid-range left ventricular ejection fraction; HFpEF, heart failure with preserved left ventricular ejection fraction; CAD, coronary artery disease; LVH, left ventricular hypertrophy; LVEF, left ventricular ejection fraction; LA, left atrial; TR, tricuspidal rout; LAVI, left atrial volume index.

there is suggestion that biomarkers commonly used for risk prediction of HFrEF could be more valuable for HFmrEF prognostication. Commonly available biomarkers primarily help to establish or refute the diagnosis of HF, help to determine the HF severity, and identify adverse consequences of treatment. Overall, in any clinical scenario biological markers as a two/tree steps' algorithm could improve a conventional risk stratification based on clinical criteria and some instrumental parameters in dyspneic individuals with mild diastolic dysfunction (*Table 3*). In fact, the implementation of echocardiographic evaluation of signs/symptoms, resting LVEF and E/e', abnormal diastolic response to exercise followed by the assessment of NPs, galectin-3 and sST2 may improve the diagnosis and prognostic assessment of asymptomatic individuals with HFpEF/HFmrEF and patients with suspected HFpEF who are unable to perform a diagnostic exercise test (9,11). In this context, all these biomarkers deserve to be routinely assessed in subsequent validation studies. However, most evidence of biomarkers as of diagnostic tool with discriminative value has applied for acute and chronic HFrEF individuals as well as chronic HFpEF. In fact, personalized risk prediction based on biomarker measure in acute HF patients remains to be challenged.

NPs

NPs predominantly brain NPs (BNP) and NT-proBNP were recommended by the European Society of Cardiology and American Heart Association for exclusion HF in patients with acute dyspnea, and now they are incorporated into contemporary clinical guidelines as powerful tool for diagnosis, prognosis, risk stratification, and even NPs-guided therapy (1,6). Atrial NP (ANP) and BNP are recognized key regulators of systemic blood pressure, water and salt homeostasis and they are biomarkers of mechanical distress and cardiac wall stretching including acute and chronic fluid overload. Additionally, ANP release from atrial granules upon acute volume overload versus increased synthesis by cardiac myocytes in chronic fluid overload, whereas BNP does not accumulate before any stimuli. In contrast to ANP and BNP, C-type of NP (CNP) is released from endothelial cells and renal cells in response to mechanical stimuli, activation by shear stress and inflammatory cytokines (8).

Both ANP and BNP may counteract renin-angiotensin-aldosterone system, systemic sympathetic activity and other neurohormonal factors including endothelin and vasopressin. ANP and BNP binds with appropriate NP

Table 3 The role of biomarkers in improvement for the conventional methods of heart failure diagnostic and stratification

Predictors	Phenotype of HF	Biomarkers	Diagnostic improvement	Predictive improvement
Clinical signs and symptoms (edema, dyspnea, fatigue, palpitation, low exercise tolerance, fluid retention)	Any	Elevated BNP >35 pg/mL and/or NT-proBNP >125 pg/mL	Increase the likelihood of the diagnosis	Prediction of the risk of admission
		Elevated BNP <35 pg/mL and/or NT-proBNP <125 pg/mL	Ruling-out of the diagnosis	–
	Suspected HFrEF	Elevated galectin-3	Ruling-in of the diagnosis	Prediction of the risk of death
	HFrEF, HFmrEF, HFpEF (?)	Elevated sST2	Ruling-in of the diagnosis	Prediction of the risk of death and admission
Resting LVEF >40%	HFpEF, HFmrEF	BNP >35 pg/mL and/or NT-proBNP >125 pg/mL	Confirm diagnosis	Prediction of cardiovascular death or admission
	Acute HF/ADHF	Elevated tropinin T above 99 percentile of reference range	–	
Resting E/e' <14	HFpEF	Elevated BNP >35 pg/mL and/or NT-proBNP >125 pg/mL	Rule-in of diagnosis	Prediction of cardiovascular death or admission
Abnormal diastolic response to exercise (increase in left ventricular filling pressure)	Asymptomatic mild diastolic dysfunction	Elevated BNP >35 pg/mL and/or NT-proBNP >125 pg/mL	Rule-in of diagnosis	Prediction of cardiovascular admission and death
	HFpEF	Elevated galectin-3 >1.17 ng/mL	Rule-in of diagnosis	Prediction of composite outcome of cardiovascular admission or death

? means lack of data. ADHF, acutely decompensated heart failure; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide; HFpEF, heart failure with preserved ejection fraction; E/e', resting peak early diastolic mitral inflow velocity/peak early diastolic mitral annular velocity ratio.

receptor type A, which are expressed at the surfaces of the target cells and cooperated with cGMP. The main biological effects of NPs are diuresis, natriuresis, increasing glomerular filtration rate, decrease of circulating plasma volume and blood pressure regulation. Moreover, NPs may ensure indirect anti-proliferative activity and mild anti-mutagenic effect that are able to support reversion of hypertrophy of cardiac and vascular walls (7). Therefore, they are produced by cardiac myocytes due to ischemia, necrosis, inflammation, metabolic and toxic damage, and membrane instability (7,8).

Elevated circulating level of NPs particularly BNP and NT-proBNP correlated well with the HF severity and are practically useful biomarkers for the HF diagnosis as well as prognostic markers for CV risk including death due to all causes and HF-related events (14,26). Indeed, in patients with established HFrEF the levels of BNP and NT-proBNP are typically >100 and >250 pg/mL, respectively (12). However, after implementation into routine clinical practice novel drugs—angiotensin receptor blockers/neprilysin inhibitors (ARNI)—this is necessarily indicating the new criterion for NPs' levels with prediction value (10,12). In fact, although NP-based guided therapy of HF has been intensively investigated, but the clinical advantages of the approach requires being studied (13).

Galectin-3

Galectin-3 is a soluble form of the β-galactoside-binding protein that is released from activated mononuclears and other antigen presenting cells due to antigen stimulation. The main biological role of galectin-3 is to activate the fibroblasts and support extravascular accumulation of collagen that lead to fibrosis in target organs including heart and kidney (27). Although the myocardial fibrosis and cardiac injury could be source of cardiac failure, but markers typical of these events are not per se markers of HF. However, galectin-3 appears to be a "cumulative" biomarkers that reflect per se interrelation between inflammation and tissue remodeling including fibrosis.

Indeed, galectin-3 has been served as a prognostic clinical biomarker in HF and other diseases associated with cardiac remodeling and nephropathy, such as atherosclerosis, stroke, diabetes mellitus, vasculitis, and connective tissue diseases (20,21,28). Although galectin-3 was found in elevated concentrations in a serum of the patients with acute and chronic HF regardless of LVEF, there was positive association between galectin-3 level and NT-proBNP level, the estimated glomerular filtration rate but not with age and serum cardiac troponins in individuals with HFrEF (18). In fact, peak concentrations of galectin-3 were related to activity of inflammation, worsening tissue repair and intensity of fibrogenesis in patients with ischemic and non-ischemic chronic HF, but serial repeated measure of the levels of galectin-3 did not exhibit advantages before single measure of this marker in cohort studies (22,23). In contrast, the TRIUMPH (Translational Initiative on Unique and Novel Strategies for Management of Patients with Heart Failure) study serial measurements of galectin-3 levels were a strong independent predictor of clinical outcomes in acute HF patients (24). Interestingly, galectin-3 was not superior to NT-proBNP, sST2, growth differentiation factor (GDF)-15 or high-sensitive C-reactive protein (hsCRP) in prediction of CV mortality and HF-elated clinical outcomes including death, while the combination of both galectin-3 and NT-proBNP was more accurate in predicting HF-related death compared to either of other biomarkers alone (23). Whether galectin-3 is not yet predictive biomarker, but biological target for prevention of HF and extracellular fibrotic remodeling, is not fully understood.

Soluble suppressor of tumorigenicity-2 receptor

Soluble suppressor of tumorigenicity-2 receptor (sST2) belongs to the interleukin (IL)-1 receptor family members. The ST2 consists in two comprising isoforms named membrane-bound (ST2L) and soluble (sST2) isoforms. sST2 binds with its ligand recognized as IL-33 and support production of Th1-related cytokines (such as tumor necrosis factor-alpha) that may play a pivotal role in inflammation, cardiac hypertrophy and remodeling, fibrotic accumulation and necrosis (8). However, there is evidence that sST2 is not just fibrotic and inflammatory biomarkers, but it might be a predictor of the clinical outcomes and nature evolution of HF.

Elevated serum levels of sST2 were found in patients with acute and chronic HF regardless of LVEF. Additionally, levels of sST2 in chronic HF individuals demonstrated close positive association with NYHA HF functional class and both levels of BNP, hs-CRP and GDF15 (19,25). Peak level of sST2 was served as powerful predictor of all-cause mortality, CV death and clinical outcomes in HFrEF/HFpEF and probably in HFmrEF patients (15,17,19). Whether serial measures of sST2 levels are independently predict cardiac fibrosis, vascular remodelling and the progression of HF is not clear.

Biomarkers of myocardial injury

Development and progression of HF strongly relates to direct and indirect damages of cardiac cells by effect of etiology factors of cardiac dysfunction (i.e., ischemia/necrosis, inflammation, hypoxia, hypertrophy, fibrosis) as well as by other factors contributing in pathogenesis of HF (i.e., biomechanical stress due to cardiac remodeling, iron deficiency, oxidative stress/mitochondrial dysfunction). Biomarkers of myocardial injury may be detected in peripheral blood in exaggerated concentration as result in leakage through cardiac cell membranes and due to injury of cells. However, regardless the main cause of cell dysfunction, biomarkers of cardiac cell injury reflect a wide range of pathophysiological process: from instability of lipid layers of membrane due to lipid peroxidation to destroying cell due to necrosis/apoptosis (8).

The wide range of myocardial injury biomarkers, such as cardiac troponins T and I, myoglobin, heart type of fatty acid binding protein, glutathione transferase P1, appeared to be promising predictors of HF-related clinical outcomes and CV death (16). However, high-sensitive cardiac troponins are recommended to improve stratification of the HF patients (29,30).

Interpretative limitations in use of traditional HF biomarkers

There is a large body of evidence regarding the controversial role of NPs in personalized treatment of HF. Indeed, the serum levels of NPs related to age of the patients, co-morbidities, kidney and metabolic clearance (31-35). It is well known that NPs are undergone modifications due to neprilysation, glycosylation, methylation, and oxidation depending on individual particularities (age, kidney clearance, liver function, drug abuse etc.) (32-34) that leads to higher individual biological variability of serum levels of NPs (35-37). Therefore, there

Table 4 The primary causes of changes in circulating NPs' levels

Diseases	Types of changes	Primary causes for NP evolution
Acute and chronic HF	↑↑↑	Over-production due to myocardial wall stretching / fluid overload
MI/ACS	↑↑	Cardiac injury
Atrial fibrillation/atrial flutter	↑↑	Leakage through cardiac myocyte membrane
Myocardities/cardiomyopathy	↑–↑↑↑	Cardiac injury
Cardiac hypertrophy	↑	Leakage through cardiac myocyte membrane
Cardioversion	↑	Cardiac injury
Cancer chemotherapy	↑	Toxic-metabolic myocardial insults
Valvular and pericardial disease	↑–↑↑	Leakage through cardiac myocyte membrane
Pulmonary hypertension	↑–↑↑	Leakage through cardiac myocyte membrane
Cardiac surgery	↑	Leakage through cardiac myocyte membrane
Aging	↑	Lowered kidney clearance
DM	↑–↑↑	Lowered kidney clearance
COPD	↑↑	Myocardial wall stretching
Obesity	↓	Increased degradation by enzymes (glycosylation for NT-poBNP, neprilysin for BNP)
Anemia	↑	Leakage through cardiac myocyte membrane
Renal failure	↑	Lowered kidney clearance
Critical illness, bacterial sepsis, severe burns	↑–↑↑	Lowered kidney clearance

↑, mild increase; ↑↑, moderate increase; ↑↑↑, severe increase; ↓, decrease. NP, natriuretic peptide; HF, heart failure; ACS, acute coronary syndrome; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus.

is a list of the diseases associated with increased level of NPs beyond HF development (*Table 4*).

The main cause of individual variability of serum biomarker concentration is glomerular filtration rate (GFR). Several biomarkers, such as NPs, galectin-3, GDF-15, sST2 and cardiac troponins being independent predictor of all-cause mortality, CV death and HF death, demonstrated close inverse relation to decreased GFR and increased aged (38-40). Consequently, lowered GFR and older age should be paid into account on interpretation of biomarker levels (41). At the same time, galectin-3 was found as biomarker with the lowest individual biological variability (42-44), whereas sST2 was not associated with age, sex and cardiac hemodynamic characteristics (45-48). Thus, there is no biomarker without several limitations for interpretation in practical manner, but multiple biomarker models might have higher accuracy in HF outcomes prediction and lover relation to age, sex, co-morbidities and GFR (48,49).

Novel biomarkers for HF management

The exploration of brand new biomarkers and investigation of novel multiple biomarker models appears to be promising methods to improve diagnostic and predictive value of currently used score of HF stratification (50,51). *Table 5* is reported some promising biomarkers reflected several faces of pathogenesis of HF that could be useful in HF stratification in the future.

Procalcitonin

Procalcitonin is determined a propeptide of calcitonin, which is normally produced by the parafollicular C cells of the thyroid gland (52). Procalcitonin/calcitonin axis is essential for regulation of calcium homeostasis and immunity (53). Recent preclinical and clinical studies have shown that extra-thyroidal production of procalcitonin

Table 5 The promising biomarkers for diagnosis and prognosis of HF

Related pathophysiological processes in HF	HF phenotype	Biomarkers	Relevance to clinical outcomes in HF		
			Mortality	Hospitalization	Risk of HF deterioration
Myocardial biochemical stress	Any	MR-proANP	+	+	+
Neurohumoral activation	HFrEF	Copeptin	+	+	+
	HFrEF	CT-proET-1	–	–	+
	HFrEF	ADM / MR-proADM	+	+	+
Myocardial fibrosis	HFpEF/HFmrEF	PICP	+	+	+
	HFpEF/HFmrEF	CITP	+	+	+
	HFpEF/HFmrEF	PIIINP	+	+	+
	HFpEF, HFmrEF	MMPs	+	+	–
Myocardial necrosis	Any	hFABP	+	+	–
	Any	GSTP1	+	+	–
Vascular remodeling	Any	OPN	+	+	–
	HFpEF/HFmrEF	OPG	+	+	–
	Any	Signature of miRNAs	+	+	+
Inflammation	HFrEF	hs-CRP	+	+	+
	HFrEF	Procalcitonin	+	+	+
	HFrEF	GDF-15	+	+	+
Oxidative stress	HFrEF	Uric acid	+	+	+
	HFrEF	Myeloperoxidase	+	+	+
	HFpEF/HFmrEF	Ceruloplasmin	+	+	+
	HFpEF/HFmrEF	8-OHdG	+	+	+
	HFpEF/HFmrEF	Trx1	+	+	+
Renal dysfunction	HFrEF	Cystatin C	+	+	+
	HFrEF	NGAL	+	+	+
Metabolomic state	HFrEF	Signature of metabolomics (fatty and amine acids, Krebs cycle components, DNAs, lipids, glucose, variable very-long chain carbons, proteins, hormones, enzymes etc.)	+	+	+
Endothelial dysfunction	HFpEF, HFrEF, HFmrEF (?)	Endothelial precursors	+	+	+
	Any	EMVs	+	+	+

+, an effect has now confirmed; –, an effect has not now confirmed; ?, the relation between HF phenotypes and endothelial precursors are not strong investigated. ADHF, acutely decompensated heart failure; MR-proANP, mid-regional pro atrial natriuretic peptide; ADM, adrenomedullin; MR-proADM, mid-regional pro-adrenomedullin; PICP, carboxy terminal propeptide; CT-proET-1, C-terminal-pro-endothelin-1; CITP, carboxy-terminal telopeptide; PIIINP, amino-terminal peptide of procollagen type III; HF, heart failure; hs-CRP, high-sensitive C-reactive protein; hFABP, high-sensitive fatty acid binding protein; GDF, growth differentiation factor; EMPs, endothelial micro vesicles; MMP, matrix metalloproteinase; NGAL, neutrophil gelatinase-associated lipocalin; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; Trx1, thioredoxin 1; GSTP1; glutathione transferase P1

markedly increases in cases of systemic inflammatory reaction, severe infections (viral, bacterial, fungal and parasitic), and shock (54,55). Although serial measurements of procalcitonin are recommended to discriminate of in-hospital mortality in various diseases associated with pro-inflammatory activation (pneumonia, chronic obstructive pulmonary disease, acute respiratory tract infections, sepsis, etc.), lack of strong evidence that the serum procalcitonin levels could be reliable indicator for chronic HF with predictive value (55). The large clinical trials are required to clearly explain the suggestion and fetch more evidence regarding a predictive role of procalcitonin in exacerbated HF individuals.

Copeptin

Copeptin is C-terminal derivate of the arginine vasopressin that normally acts as regulator of water and electrolyte homeostasis (56). Although plasma levels of copeptin are very variable and tightly relate to blood/urine osmolality, copeptin appears to be in higher concentrations in sever hypertension, stroke, acute and chronic HF, myocardial infarction, diabetes mellitus, advanced kidney diseases, and in critical conditions. As quantitative biomarker of endogenous biomechanical stress elevated level of copeptin was found in close positive association with increased CV mortality and CV disease in out-patients and all-cause mortality in critical ill patients (57). There is a large body of evidence regarding that the serial measurements of copeptin level may be provide an important information for discrimination of a risk of all-cause mortality, HF-related outcomes and CV events and diseases (58-61). Although both increased NT-proBNP levels and copeptin levels were recognized significant independent predictors of adverse clinical outcomes in HF, the role of dual markers' contribution in HF risk stratification remains to be challenged (62-65).

The heart type of fatty acid binding protein

The heart type of fatty acid binding protein (hFABP) is normally essential for the long-chain fatty acids re-uptake, regulation of calcium homeostasis in cardiomyocytes and mediating inflammatory reaction (66). Because hFABP is tissue-specific biomarker of myocardial injury and necrosis, it is reserved as predictor of myocardial infarction at the early hours of development of the disease. Recent studies have shown that circulating levels of hFABP are elevated in cardiac dysfunction and closely predicted CV outcomes and HF-related events in in-patients especially in those who had fluid retention and lung congestion (66-68). Although elevated serum level of hFABP exhibited better prognostic information on survival in individuals with acute and advanced HF when compared to NPs, cardiac troponins and even galectin-3 taken alone, there is confusing in improved precision of entire predictive model after incorporating hFABP to NPs and/or galectin-3 (66,68).

GDF-15

GDF-15 is multifunctional cytokine that belongs to the transforming growth factor-β superfamily (69). GDF-15 is normally expressed in various cells including immune cells, fibroblasts, myocardial cells, endothelial cells, and mononuclears. Additionally, GDF-15 is actively secreted into circulation by cardiac myocytes due to stretching and biochemical stress (61,69,70).

Serum levels of GDF-15 associated with increased risk of all-cause death independently to age, clinical signs and symptoms of cardiac dysfunction, LFEF, renal function and NPs in HF (71). Interestingly, in individuals with acute HF the serum levels of GDF-15 were not better to NPs and galectin-3 taken alone in accuracy to predict clinical outcomes including HF-related death and re-admission due to HF decompensation shortly after previous discharge (72). In contrast, GDF-15 could be superior to sST2 in prediction of fatal arrhythmic events and all-cause mortality in non-ischemic CH (9,11). The out-patients with chronic HFrHF/HFpEF/HFmrEF may be candidates to multiple predictive biomarker strategy based on collective measurement of NPs, GDF-15, and galectin-3 (73,74).

Endothelial cell-derived micro vesicles and endothelial precursors

The endothelial dysfunction is established marker and direct player in nature evolution of HF. It is well known that severity of endothelial dysfunction independently associated with complications of HF and the risk of death due to HF-related events and CV death (73). The discoveries of novel biomarkers of endothelial dysfunction with high personalized significance led to determining brand new specific circulating biomarkers, such as endothelial micro vesicles (EMVs) and endothelial progenitor cells (EPCs) also known as endothelial precursors (73,74). Recent

clinical studies have revealed that deficiency of circulating endothelial precursors were independent predictor of HF severity (74-76). Therefore, increased number of apoptotic MVs associated with decreased number activated endothelial cell-derived MVs predicted HF development and advance. This finding became to determine altered or impaired phenotype of MVs and now it is novel HF risk biomarker (77,78). Moreover, risk predictive score based on multiple biomarkers including impaired phenotype of MVs and deficiency of endothelial precursors was significantly superior to traditional biomarkers such as NPs, galectin-3, hs-CRP in HF risk stratification (78,79). However, it is not fully understood whether new HF predictive model would be more reliable in prognostication of HF treatment response. Large clinical trial is needed to clearly understand if personalized therapy of HF under new biomarker model control is better to traditional scores.

Biomarkers of collagen metabolism

Recent clinical studies have shown that impaired collagen metabolism may alter the myocardial collagen network and enable CV remodeling, and mediates HF complications, i.e., atrial fibrillation/flutter, sudden death, and decline LV pump function (80). Additionally, there are findings that BNP could influence on alterations of collagen type I metabolism in HF (77). The OPTIMAL (The Optimizing Congestive Heart Failure Outpatient Clinic trial) was revealed disturbances of collagen type I metabolism that are determined as independent predictor of long-term, all-cause CV mortality in HFrEF patients (81). Although these facts are limited and required to be elucidated carefully, it has been suggested that circulating CITP could be novel independent predictor of survival in HFrEF patients (82).

Matrix metalloproteinases (MMPs)

Development of HF strongly associates with CV remodeling, biomechanical and oxidative myocardial stress, neurohormonal and inflammatory activation that are modulated by MMPs. It has demonstrated that MMPs determine extracellular accumulation of collagen and mediate pro-fibrotic processes (82). Recent pre-clinical and clinical studies have revealed an altered expression of MMPs (MMP-1, MMP-3, MMP-6, MMP-9) and their tissue inhibitors was found in association with severity of cardiac dysfunction (82-86). Probably, the role of these biomarkers requires more future investigations to identify their ability to predict cardiac remodeling and HF-related outcomes.

Biomarkers of oxidative stress

Serum uric acid (SUA)

Recent studies have revealed the elevated level of SUA could be common feature for patients with numerous CV diseases including HF, hypertension, atherosclerosis, obesity, diabetes mellitus and chronic renal disease (87,88). The role of SUA in pathogenesis of HF is controversial. As strong oxidative factor uric acid triggers inflammation and frequently often impairs vascular function (89). In contrast, uric acid in peripheral tissues could act as scavenger of free radicals and protects against an oxidative stress (90,91). In routine clinical practice SUA remains a simple method for detection of HF risk at the early stage of HF advance (92-98). Moreover, serial measures of SUA levels are accurate predictor of clinical outcomes rather in acute HF than in chronic HF (95-97), while SUA undoubtedly remains a risk factor of poor outcomes in HF independently of LVEF (98,99).

Other biomarkers of oxidative stress

Serum levels of oxidative stress biomarkers (myeloperoxidase, vitamin D3, ceruloplasmin and 8-hydroxy-2'-deoxyguanosine) closely correlated with staging chronic HF regardless LVEF and predicted HFrEFm but not HFmrEF or HFpEF (70). Therefore, close link between vascular remodeling (98,99), endothelial dysfunction and CV disease the predictive role of vitamin signature in serum (i.e., vitamin A, B12, D, K, C and E) in HF individuals was found (99-102).

Biomarkers of renal dysfunction in HF

Cystatin C

Cystatin C was found an endogenous inhibitor of cysteine proteases. This biomarker is reported an alternative predictor of CV death in HF (95). The patients with HFrEF exhibited elevated serum levels of cystatin C in association with higher risk of HF-related complications (98,99), whereas in HFpEF patients this fact was not confirmed, while increased cystatin C level was found (100). Despite cystatin C has validated a predictor of kidney injury, the discriminative ability of this biomarker in

chronic HF patients is lower to hs-CRP and NPs (99). In contrast, in acute HF individuals elevated cystatin C levels predicted poor prognosis better than NT-proBNP and SUA (103,104).

Other biomarkers of kidney injury in HF

There are promising biomarkers of kidney injury (stromal cell-derived factor-1, kidney injury molecule-1, exosomes, neutrophil gelatinase-associated lipocalin, interleukin-18) that recently had been used as prognosticators of HF (100,104). Because of all they are non-specific for HF, the implementation of them in routine practice is under fire and probably they could be incorporated into multiple biomarker models rather than single use in HF patients.

Genomic and epigenomic biomarkers

Genomic/epigenomic testing that now incorporated into diagnosis of inherited cardiomyopathies (105,106) appear to be promised method for HF risk stratification. Indeed, DNA methylation, ATP-dependent chromatin remodeling, histone modifications with an involvement of microRNA-related mechanisms are important pathophysiological factors contributing to adverse cardiac remodeling and altered cardiac function (107-110). There are numerous studies depicted the role of single nucleotide polymorphisms of genes encoding enzymes related to oxidative stress (111), genotype of guanine nucleotide-binding proteins beta-3 subunit (106), transcription factor Islet-1 gene (112,113), troponin T (114), CYP2D6 polymorphism (115), cardiac myosin binding protein-C mutations (116), renin-angiotensin-aldosterone system polymorphism (117), bradykinin type 1 receptor gene, angiotensin-II type I receptor gene, the β1-adrenoceptor gene and CYP2D6 polymorphism (118-120) in development of HF. However, encouraging results have not yet received (121-123), whereas controversial data are presented (124,125). Finally, the implementation of genomic/epigenomic markers into real clinical practice to predict HF development is so far future direction (126).

Micro-RNAs

It has been established that microRNAs (miRNA) are widely involved in the development and progression of HF across all pathophysiological stages of the disease (108). miRNA are epigenetic regulators of myocardial response and fibrosis, growth of cardiac myocytes, cardiac and vasculature reparation, immunity, angiogenesis, and inflammation (111). The altered miRNAs' signature was found in patients with asymptomatic and symptomatic HF (127-129). It has suggested the signatures of non-coding RNAs would be candidate to improve diagnosis and prognostication of HF (130).

Mid-regional pro-adrenomedullin (ADM)

Mid-regional pro-adrenomedullin (MR-proADM) is the prohormone of the CV protein ADM and it is well-established neurohumoral marker of cardiac biochemical stress that was raised in patients with infections including sepsis, acute dyspnea, acute HF and severe chronic HFrEF/HFpEF, unstable angina pectoris/myocardial infarction, and throughout the first week after stroke (131). There is evidence regarding that the MR-proADM is an early predictor of in-hospital mortality due to various reasons, i.e. respiratory infections, surgical procedure and CV diseases (132-134). MR-proADM as a marker of biomechanical stress and fibrosis was not better than NPs and did not exhibit equal predictive value to sST2r and galectin-3 in HFrEF/HFpEF (134). Interestingly, sST2 was better to MR-proADM, because it is more closely related to LV remodeling and cardiac fibrosis. Moreover, MR-proADM did not improve a risk stratification based on NPs in patients with chronic HFrEF and moderate anaemia (135). Thus, the role of MR-proADM as a component of biomarker-based stratification is discussable, while the biomarker can contribute to determine the short-term outcomes of critical ill patients with acute severe dyspnea, respiratory infection and acute HF.

Validation of multiple biomarker predictive scores

There are numerous biomarker predictive scores that have approved for chronic HF, whereas predictive models for acute HF have not yet validated (136,137). Current multiple biomarker scores affecting prognostication, risk stratification and diagnosis of HF (*Figure 2*) are based on NPs in combination with biomarkers of myocardial injury and fibrosis (galectin-3 and sST2 receptor). A new score validated by the American Heart Association/American College of Cardiology [2017] is fitted for patients at risk of HF, with established chronic HF (for HFrEF and HFpEF, but not for HFmrEF), with suspected and documented acute HF (at admission), as well as patients with HF at

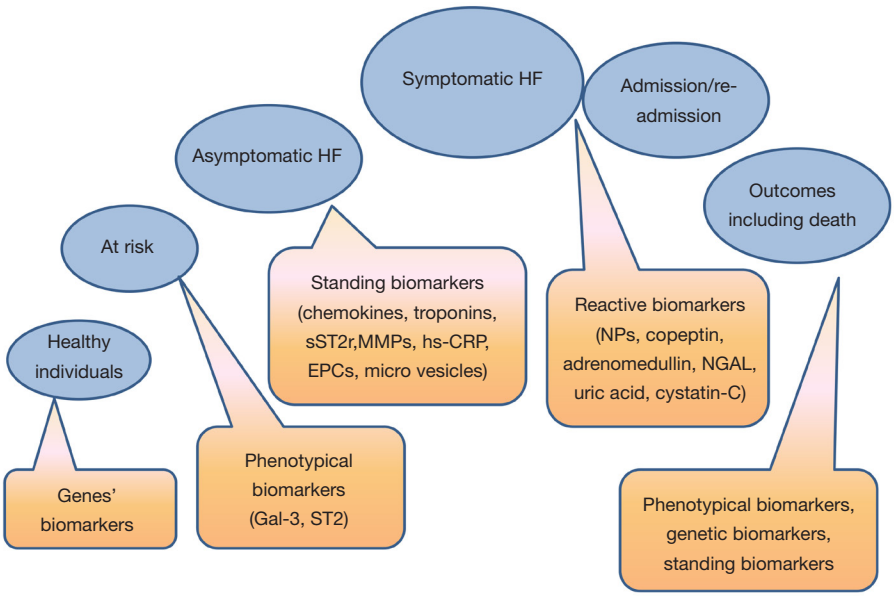

Figure 2 Indications for biomarker use in heart failure (HF) management. ADHF, actually decompensated heart failure; pts, patients; Gal-3, galectin-3; NT-proBNP, NT-pro-brain natriuretic peptide; BNP, brain natriuretic peptide; TrT, troponin T; TrI, troponin I; sST2, soluble suppressor of tumorigenicity-2 receptor.

discharge from the hospital.

Interestingly, there are several attempts regarding use of biomarkers to stratify at risk patients with different phenotypes of HF, such as HFrEF, HFmrEF or HFpEF. Whether add-on biomarkers to based models are needed to improve cumulative predictive value for wide circle of HF individuals with different HF phenotypes, co-morbidities, ages and sex-related particularities is not fully elucidated. It has suggested that sST2 and galectin-3 might sufficiently improve prognosis in HF-related hospitalization and CV death, when they had added to NPs. This strategy is confirmed by experts of various medical associations and the only one is validated now.

Conclusions

There are several controversies regarding the importance of biomarkers as predictors of survival and in diagnosis of HF. Improvement of clinical guidelines for optimizing HF therapy in routine clinical practice under biomarkers' control is required. Obviously, galectin-3 or sST2 would be optimal for improving NPs-based biomarker strategy in HF individuals, while there is large body of evidence that other biomarkers could individualize a risk stratification and predict treatment response. There is need of larger clinical trials in order to direct compare different biomarkers and clarify their role in diagnosis and guided therapy of HF.

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