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Circulating Biomarkers in Heart Failure

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Abstract

Biological markers have served for diagnosis, risk stratification and guided therapy of heart failure (HF). Our knowledge regarding abilities of biomarkers to relate to several pathways of HF pathogenesis and reflect clinical worsening or improvement in the disease is steadily expanding. Although there are numerous clinical guidelines, which clearly diagnosis, prevention and evidence-based treatment of HF, a strategy regarding exclusion of HF, as well as risk stratification of HF, nature evolution of disease is not well established and requires more development. The aim of the chapter is to discuss a role of biomarker-based approaches for more accurate diagnosis, in-depth risk stratification and individual targeting in treatment of patients with HF.

Keywords

Heart failure · Biomarkers · Prediction · Stratification · Biomarker guided-therapy

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Abbreviations

ADM	adrenomedullin
ANP	atrial natriuretic peptide
ARNI	angiotensin receptor neprilysin inhibitors
BNP	brain natriuretic peptide
BRPs	bone related proteins
cGMP	cyclic guanylyl monophosphate
CITP	carboxy-terminal telopeptide
CNP	C-type natriuretic peptide
CRP	C-reactive protein
CT-proET-1	C-terminal-pro-endothelin-1
CV	cardiovascular
EMPs	endothelial microparticles
EPCs	endothelial progenitor cells
Gal-3	galectin-3
GDF-15	Growth differentiation factor-15
HF	heart failure
hFABP	heart type of fatty acid binding protein
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
LV	left ventricular
MMP	matrix metalloproteinase
MPs	micro particles
MR-proANP	mid-regional pro-atrial natriuretic peptide

MR-proADM	mid-regional pro-adrenomedullin
NPs	natriuretic peptides
NT-proBNP	NT-pro-brain natriuretic peptide
PICP	carboxy-terminal propeptide
sST2	soluble suppressor of tumorigenicity-2 receptor

1 Introduction

Heart failure (HF) is a leading cause of premature cardiovascular (CV) death in patients with established CV disease (Ponikowski et al. 2016). Prevalence of HF has been exhibiting a tendency to worldwide, despite the scientific progress in the field of the two past decades. HF is also characterized by an elevated rate of primary and secondary hospitalization and increased economic burden for patients and their families. Although there are numerous clinical guidelines, which clearly indicated diagnosis, prevention and evidence-based treatment of HF, a strategy regarding exclusion of HF diagnosis, as well as risk stratification of HF, nature evolution of disease is not well established and requires more development (Wettersten and Maisel 2016). In this context, biological markers reflected several pathophysiological stages of HF have become a powerful and convenient noninvasive tool for diagnosis of HF, a stratification of HF patients at risk of progression, HF severity, and biomarker-guided therapy (Ledwidge et al. 2013). The aim of the chapter is to discuss a role of biomarker-based approaches for more accurate diagnosis, in-depth risk stratification and individual targeting in treatment patients with HF.

2 Conventionally Used Biomarkers of Heart Failure

According to The Biomarkers Definitions Working Group Biomarkers are defined 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 (Biomarkers Definitions Working Group (National Institutes of Health) 2001).There are numerous of biomarkers, which reflect several pathophysiological stages of HF and allow stratifying individuals at risk (Fig. 1). Currently updated clinical recommendations have been reported that the natriuretic peptides (NPs), including brain NP (BNP), mid-regional pro-atrial NP (MR-proANP), NT-pro-brain NP (NT-proBNP), mid-regional pro-brain NP (MR-proBNP), are the most frequently used biomarkers in clinical practice to stratify patients at risk of cardiac dysfunction, a risk of admission/readmission to the hospital due to HF-related reasons, and a risk of death (Pouleur 2015), while galectin-3, high-sensitivity cardiac troponins and soluble suppressor of tumorigenicity-2 (sST2) receptor are thought to be promising biomarkers in this respect (Table 1). Most data on cardiac biomarkers have been derived from chronic HF individuals. In contrast, risk prediction in patients admitted to hospital with acute HF remains a challenge.

2.1 Natriuretic Peptides

First NPs were recommended by the European Society of Cardiology and American Heart Association for exclusion HF, and then they were discussed as a tool for risk stratification, and NPs-guided therapy (Ponikowski et al. 2016; Wettersten and Maisel 2016). The majority of NPs' family members (Atrial NP [ANP] and brain [BNP] apart from C-type of NP [CNP]) are mechanical stress-related markers. They are actively released by cardiomyocytes as a result in fluid overload, cardiac stretching, as well as due to exposure to other causes, e.g. ischemia/ necrosis, metabolic and toxic damage, membrane stability loss, and inflammation (Berezin 2017a). ANP is released from atrial granules upon acute volume overload, whereas BNP is stressed-related peptide that does not accumulate before stimulation. In contrast, CNP is secreted from activated endothelial cells and renal cells in response to cytokine activation and through endothelium-dependent

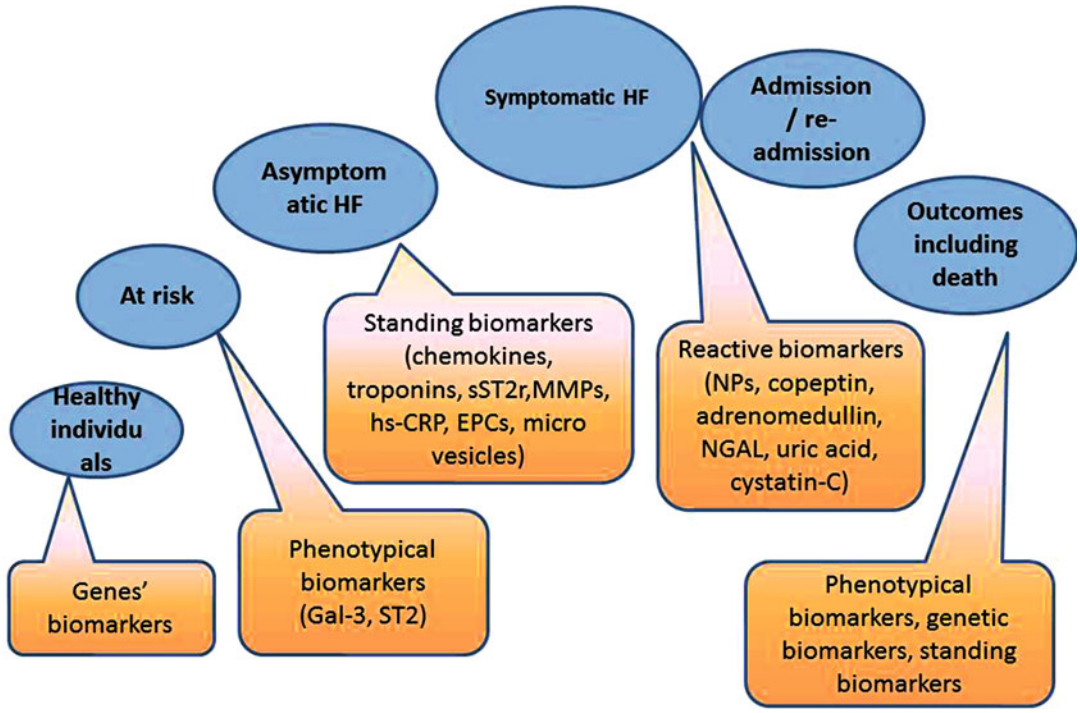

Fig. 1 Schema of practical use of various biomarkers in HF development and progression

agonists, e.g. acetylcholine (Berezin 2017a). The biological effects of ANP and BNP are mediated by binding with appropriate NP receptor type A (NPRA). NPRA are expressed at the surfaces of the target cells and are linked with cGMP mediating water/electrolyte homeostatic effects, i.e. diuresis/natriuresis, increasing glomerular filtration rate, volume of circulating plasma, suppressing systemic sympathetic activities, maintenance of cardiac output and regulation of blood pressure. NPs may demonstrate anti-proliferative activity and anti-mutagenic effect, mediate vascular dilatation and prevent vascular wall hypertrophy (Berezin 2017a). Additionally, NPs show modest anti-aldosterone and endothelin-1 effects.

In patients with HF the plasma levels of BNP and NT-proBNP are typically >100 pg/ml and >250 pg/mL, respectively, while there is high individual biological variability of both biomarkers irrespective of presentation of HFrEF or HFpEF (Felker et al. 2017). Elevated levels of NPs are well correlated with clinical status and severity of HFrEF/HFpEF patients, a risk of developing acute HF regardless etiology of the disease, risk of hospital admission/re-admission, as well as all-cause mortality, CV and HF death in individuals with established HF including at discharge from the hospital after treating HF decompensation (Feng et al. 2017). More recent evidence suggests that NPs along with the next generation of CV biomarkers could provide added predictive value to drug therapy of HF, which could potentially lower HF-related risk of outcomes (Fonarow 2017; Chow et al. 2017).

2.2 Biomarkers of Myocardial Fibrosis

2.2.1 Galectin-3

Galectin-3 is a soluble β-galactoside-binding protein, which is actively secreted by activated mononuclears and macrophages due to inflammatory stimulation. The main biological function

Table 1 Utility of biomarkers in HF management

Suggestions for use	Patients	COR	LOE
NPs (BNP, NT-proBNP or MR-proANP)			
Rule-in or support of initial working diagnosis	Patients with suspected HF in non-acute setting condition with dyspnea	I	A
	Patients with suspected acute and chronic HF, when the etiology of dyspnea is unclear	I	A
	Patients with suspected HF in acute setting condition	IIb	C
Exclusion of important cardiac dysfunction	Outpatients with uncertain signs and symptoms of HF	I	A
Prognosis of HF	Outpatients/inpatients with established HF	I	A
	Patients who were admitted to the hospital with acute HF	I	A
	Postdischarged patients	IIa	B
Prevent development of LV dysfunction or new-onset HF	Patients at risk of HF development	IIa	B
Target therapy	Outpatients with established HF in euvolemic condition	IIa	B
Biomarkers of myocardial injury (cardiac troponins)			
Risk stratification	Patients with established HF	I	A
	Patients who were admitted to the hospital with acute HF	I	A
Biomarkers of myocardial fibrosis (galectin-3)			
Risk stratification	Outpatients with established chronic HF	IIb	B
	Inpatients with established acute and chronic HF	IIb	A
	Post-discharged patients	IIa	B
sST2			
Prognosis of HF	Outpatients/inpatients with established HF	I	A
	Patients who were admitted to the hospital with acute HF	I	A
	Post-discharged patients	IIa	B

Abbreviations: *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

of galectin-3 is to activate the fibroblasts for further collagen synthesis (Yancy et al. 2017). Recent pre-clinical and clinical studies have revealed the pivotal role of galectin-3 in progressive accumulation of extracellular matrix leading to cardiac fibrosis, cardiac remodeling, and worsening cardiac performances associated with impaired cardiac systolic and diastolic function, dilation of cardiac cavities, and induction of cardiac arrhythmias (Boulogne et al. 2017a; Souza et al. 2017). Galectin-3 in elevated concentrations was measured in a serum of the patients at risk of HF and CV disease (Lala et al. 2017). In patients with acute HF galectin-3 associated with NT-proBNP levels and the estimated glomerular filtration rate but not with age and serum cardiac troponins (Imran et al. 2017). Galectin-3 was not superior to NT-proBNP, sST2 receptor, Growth Differentiation Factor (GDF)-15 or high-sensitive C-reactive protein (hsCRP) in prediction of CV mortality and HF death, while the combination of galectin-3 and NPs was more accurate in predicting HF death compared to either of the biomarkers alone (Besler et al. 2017a).

2.2.2 Soluble Suppressor of Tumorigenicity-2 Receptor

Soluble suppressor of tumorigenicity-2 receptor (sST2) belongs to the interleukin (IL)-1 receptor family members, which has two isoforms, i.e. membrane-bound (ST2L) and soluble (sST2) isoforms. sST2 interacts with its ligand IL-33 and through myocardial mRNA expressions of Th1-related cytokines (tumor necrosis factor-alpha) may directly enhance

cardiac hypertrophy, fibrosis, cavity dilation with impaired cardiac function (Berezin 2017a).

The serum levels of sST2 in acute HF were dramatically increased on admission and appeared to be decreased rapidly depending on clinical improvement. Therefore, sST2 in HF has well correlated with BNP and GDF15 levels (Srivatsan et al. 2015). sST2 levels at discharge were better predictor of HF re-admission than ones at admission (Boulogne et al. 2017b). Although both biomarkers of myocardial fibrosis (sST2 receptor and galectin-3) are predictive of HF-related admission to the hospital and CV death (Billebeau et al. 2017), direct head-to-head comparison of sST2 and galectin-3 revealed superiority of sST2 over galectin-3 in HF risk stratification (Bayes-Genis et al. 2014).

2.3 Biomarkers of Myocardial Injury

Development and progression of HF strongly relates to direct and indirect damages of cardiac cells by effect of etiological factors of cardiac dysfunction (i.e. ischemia/necrosis, inflammation, hypoxia, hypertrophy, fibrosis) as well as by other factors contributing to the 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 elevated concentration as a result of leakage through cardiac cell membranes and due to injury of cells. However, regardless of 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 (Berezin 2017a).

There are some biomarkers of myocardial injury and necrosis (cardiac troponins T and I, myoglobin, heart type of fatty acid binding protein, glutathione transferase P1), which are investigated in details as potential predictors of HF onset and HF-related outcomes (Anguita 2017). Since last two decades high-sensitivity cardiac troponins had been suggested to be prognosticators of high risk of CV mortality and combined adverse CV outcomes in HF (Nagarajan et al. 2012; Masson et al. 2010).

3 Biomarker-Guided Therapy of HF

It had been found that NP guided HF therapy improved titration of medications (Feng et al. 2017; Fonarow 2017), but did not lead to better HF clinical outcomes (Wettersten and Maisel 2016; Berezin 2017a). Meanwhile, serial measurements of NPs could be useful for determining the severity of HF for decision about ambulatory and in-hospital medical care. Additionally, NT-proBNP, but not BNP, is better suited during HF therapy based on the new angiotensin-receptor-neprilysin-inhibitor (ARNI) (Malek and Gaikwad 2017). The clinical trials have shown that neprilysin inhibition together with chronic renin-angiotensin system blockage with Sacubitril/Valsartan may increase the bioavailability of NPs and promotes additional cardio-renal benefits and thereby reduce all-cause mortality, CV mortality and HF death (Wong et al. 2017). Because biologically active BNP is degraded by neprilysin, in HF patients treated with ARNI circulating level of BNP sufficiently increases, whereas NT-proBNP concentration declines dramatically. In such situations the principles of NPs-based HF guided therapy are become complicated. Apparently, monitoring of BNP levels is not suitable for risk stratification and HF adjusted medical care, when ARNIs are used, however, NT-proBNP remains useful for risk assessment and HF stratification regardless drug prescriptions (Luchner et al. 2017; Aspromonte et al. 2016; Skaf et al. 2017; Nakanishi et al. 2017). Finally, majority of experts believe that a combination of biomarkers may ultimately prove to be more informative in their predictive ability than single biomarker (Nymo et al. 2017).

4 Limitations in Use of Conventional Biomarkers in HF

Confusingly, the role of NPs in modification of treatment considerably relates to aging, CV disease, metabolic co-morbidities, kidney clearance, metabolism (neprilysin for BNP, glycosylation, methylation, oxidation for other NPs), toxic effect (cardiotoxicity) (Berezin 2016a). Therefore, higher individual biological variability of these biomarkers may impair interpretation of the measured results (Favresse and Gruson 2017). There is a big list of diseases associated with increased level of NPs beyond HF development (Table 2).

Although galectin-3 is an independent predictor of all-cause mortality, CV death and occurrence of HF, there is an inverse relationship

Table 2 The potential causes of changes in circulating NPs' levels

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

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

between serum galectin-3 level and estimated glomerular filtration rate (Besler et al. 2017b). Accordingly, lowered kidney clearance should be taken into consideration, when data of galectin-3 measurement are interpreted. Therefore, older patients contributed to higher galectin-3 concentrations than younger individuals (Krintus et al. 2017). Amongst other biomarkers (NPs, GDF-15, high-sensitivity troponin T, sST2, aldosterone, phosphate, parathyroid hormone, plasma renin, and creatinine), galectin-3 had the lowest individual biological variability, whereas NPs and GDF-15 had the highest ones (Meijers et al. 2017). In contrast to NPs serum galectin-3 levels did not appear to be significantly related to circulating level of cardiac troponins, left ventricular (LV) ejection fraction and LV mass index (Agnello et al. 2017). However, there was a positive correlation between galectin-3 levels and NT-proBNP in HF individuals. Thus, galectin3 and NPs might be considered as the best markers for both short- and long term death prediction in HF regardless kidney function and age. Unfortunately, no biomarker predicted the short-term composite HF endpoints in acute HF (Miró et al. 2017). Additionally, there are controversial findings related to the lack of association of galectin-3 concentration with adverse outcomes in chronic HF (Wojciechowska et al. 2017).

Even sST2 was not associated with age, female sex, LV structure or LV systolic or diastolic function (Maisel and Di Somma 2016; Berezin 2016b; AbouEzzeddine et al. 2017). Thus, these findings confirmed that the sST2 is a marker of systemic inflammation and fibrosis with predictive ability regarding all-cause and CV death in HF (AbouEzzeddine et al. 2017; Aimo et al. 2017).

5 Novel Biomarkers for HF Management

The discovery of new biomarkers is promising, but rarely novel molecules prove to be significantly better in diagnostic and predictive value than the established biomarkers. In addition to the various types of NPs, galectin-3, sST2, high-sensitive cardiac troponins, several other biomarkers have been investigated to be better predictors in HF (Table 3).

5.1 Procalcitonin

Procalcitonin is propeptide of calcitonin, which is normaly produced and actively secreted by the parafollicular C cells of the thyroid gland (Ryu et al. 2015). Procalcitonin/calcitonin axis is essential for regulation of calcium homeostasis and immunity (Berezin 2017a). The preclinical and clinical studies have shown that extrathyroidal production of procalcitonin markedly increases in cases of systemic inflammatory reaction, severe infections (viral, bacterial, fungal and parasitic), and shock (Reiner et al. 2017; Hayashida et al. 2017; Simon et al. 2004). 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.), there is evidence that the serum procalcitotin levels might be a predictive biomarker for chronic HF (Simon et al. 2004). Large clinical trials are required to obtain evidence for a predictive role of procalcitonin in exacerbated HF individuals.

5.2 Copeptin

Copeptin is C-terminal derivative of the arginine vasopressin that normally acts as regulator of water and electrolyte homeostasis (Morgenthaler 2006). 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,

Table 3 The promising novel biomarkers for HF depending on HF phenotypes

Related pathophysiological processes in HF	HF phenotype	Biomarkers	Relevance to clinical outcomes in HF
Myocardial biochemical stress	Any	MR-proANP	All-cause, CV and HF-related mortality, risk of hospital re-admission at discharge, risk of HF deterioration
Neurohumoral activation	HFrEF	Copeptin	All-cause and HF-related death, CV mortality, hospital admission rate
	HFrEF	CT-proET-1	NYHA stage
	HFrEF	ADM/MR-proADM	All-cause mortality, CV mortality and HF-related death in acute HF
Myocardial fibrosis	HFpEF/ HFmrEF	PICP	AF, CV mortality, MI, HF-related death
	HFpEF/ HFmrEF	CITP	AF, CV mortality, MI, HF-related death
	HFpEF/ HFmrEF	PIIINP	All-cause mortality, CV mortality, MI, HF-related death
	HFpEF, HFmrEF	MMPs	All-cause, CV and HF-related mortality in acute HF, ADHF, risk of HF admission in HF
Myocardial necrosis	Any	hFABP	CV and HF-related mortality
	Any	GSTP1	MI mortality, CV events and HF admission
Vascular remodeling	Any	OPN	CV mortality, MI, HF onset
	HFpEF/ HFmrEF	OPG	CV mortality, MI, HF onset
	Any	Signature of miRNAs	All-cause and CV mortality, MI, HF onset, HF progression
Inflammation	HFrEF	hs-CRP	NYHA stage of HF, risk of death in ADHF
	HFrEF	Procalcitonin	ADHF, acute HF, CV death, readmission rate
	HFrEF	GDF-15	CV mortality, HF deterioration
Oxidative stress	HFrEF	Uric acid	All-cause and CV mortality
	HFrEF	Myeloperoxidase	All-cause and CV mortality in ADHF, acute HF, HF-related outcomes in chronic HF
	HFpEF/ HFmrEF	Ceruloplasmin	Risk of HF deterioration, NYHA-stage
	HFpEF/ HFmrEF	8-OHdG	
	HFpEF/ HFmrEF	Trx1	
Renal dysfunction	HFrEF	Cystatin C	All-cause and CV mortality, HF-related death, HF readmission in acute HF
	HFrEF	NGAL	HF-related death in acute HF and ADHF
Metabolomic state	HFrEF	Signature of metabolomics (fatty and amine acids, Krebs cycle components, DNAs, lipids, glucose, variable very-long chain carbons, proteins, hormones, enzymes ets.)	HF-related death, CV mortality, hospital re-admission rate

(continued)

Table 3 (continued)

Related pathophysiological processes in HF	HF phenotype	Biomarkers	Relevance to clinical outcomes in HF
Endothelial dysfunction	HFpEF, HFrEF, HFmrEF (?)	EPCs	All-cause mortality, CV mortality, HF-related death, admission/ readmission rate
	Any	EMPs	

Abbreviations: *ADHF* acutely decompensated heart failure, *AF* atrial fibrillation, *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, *EPCs* endothelial progenitor cells, *EMPs* endothelial cell-derived micro particles, *MI* myocardial infarction, *MMP* matrix metalloproteinase, *NGAL* neutrophil gelatinase-associated lipocalin, *8-OHdG* 8-hydroxy-2′-deoxyguanosine, *Trx1* thioredoxin 1, *GSTP1* glutathione transferase P1

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 states (Remde et al. 2016). There is a large body of evidence 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 (Moayedi and Ross 2017; Krane et al. 2017; Yan et al. 2017a; Berezin 2015a). Although both increased NT-proBNP levels and copeptin levels were recognized significant independent predictors of adverse clinical outcomes in HF, the role of dual marker contribution in HF risk stratification remains to be clarified (Savic-Radojevic et al. 2017; Smaradottir et al. 2017; Sahin et al. 2017; Herrero-Puente et al. 2017).

5.3 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 (Chmurzynska 2006). 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 (Savic-Radojevic et al. 2017; Chmurzynska 2006; Qian et al. 2016; Kitai et al. 2017). Although elevated serum level of hFABP yielded 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 confusion about the improved precision of entire predictive model after incorporating hFABP to NPs and/or galectin-3 (Savic-Radojevic et al. 2017; Qian et al. 2016; Kitai et al. 2017).

5.4 Growth Differentiation Factor-15

Growth differentiation factor (GDF)-15 is multifunctional cytokine that belongs to the transforming growth factor-β superfamily (Kempf and Wollert 2009). 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 (Berezin 2015a; Kempf and Wollert 2009; Chan et al. 2016).

Serum levels of GDF-15 are associated with increased risk of all-cause death independent of age, clinical signs and symptoms of cardiac dysfunction, LVEF, renal function and NPs in HF (Hage et al. 2017). Interestingly, in in-patients with acute HF the serum levels of GDF-15 were not better to NPs and galectin-3 taken alone in accuracy to predict HF-related outcomes including death and re-admission to the hospital after discharge (Demissei et al. 2017). In contrast, out-patients with chronic HFrHF/HFpEF may be candidates to multiple predictive biomarker strategy based on collective measurement of NPs, GDF-15, and galectin-3 (Berezin et al. 2015a; Berezin 2015b).

5.5 Endothelial Cell-Derived Micro Particles and Endothelial Progenitor Cells

Impaired endothelial function plays a pivotal role in HF development and HF-related complications and also associates with an appearance in the peripheral blood of specific circulating biomarkers, i.e. endothelial microparticles (EMPs) and endothelial progenitor cells (EPCs) (Berezin et al. 2015a; Berezin 2015b; Berezin at al. 2016). Recent clinical studies have shown that an ability of mature endothelial cells and their precursors to release of secretom progressively worse depended on HF stage and severity (Berezin 2015b, c; Berezin et al. 2014a, 2015b, 2016c). There is novel HF risk prediction score created by means of biomarkers, e.g. NPs, galectin-3, high sensitive CRP and estimated ratio between both numbers of apoptotic EMPs and EPCs (Berezin et al. 2015b; Berezin 2015d). However, it is not clear whether new predictive models would be effective in HF treatment. More clinical trials are required to improve our understanding in the field of individualized therapy of HF under biomarker control.

5.6 Biomarkers of Collagen Metabolism

Recent studies have shown that impaired collagen metabolism may alter the myocardial collagen network, enable cardiovascular remodeling, and mediates HF complications, i.e. atrial fibrillation/flutter, sudden death, and decline in LV pump function (Löfsjögård et al. 2014). Interestingly, there is evidence regarding causative role of BNP in alterations in collagen type I metabolism in HFrEF (Berezin 2016c). The OPTIMAL (The Optimizing Congestive Heart Failure Outpatient Clinic trial) revealed that disturbances of collagen type I metabolism are independent predictors of long-term, all-cause mortality and CV mortality in HFrEF individuals (Löfsjögård et al. 2017). Therefore, circulating CITP is probably an independent predictor of survival in patients with HFrEF (Tziakas et al. 2012).

5.7 Matrix Metalloproteinases

Development of HF strongly associates with CV remodeling, biomechanical and oxidative myocardial stress, neurohormonal and inflammatory activation that are modulated by matrix metalloproteinases (MMPs). It has demonstrated that MMPs determine extracellular accumulation of collagen and mediate pro-fibrotic processes (Berezin and Samura 2013). Recent pre-clinical and clinical studies have shown that an impairment of cardiac function may relate to the collagen accumulation due to an imbalance between expression of MMPs, predominantly MMP-1, MMP-3, MMP-6, MMP-9, and suppression of their tissue inhibitors (Collier et al. 2011; Hutchinson et al. 2010; Berezin et al. 2015c). However, the predictive value of these biomarkers was not confirmed and requires more future investigations.

5.8 Biomarkers of Oxidative Stress

5.8.1 Serum Uric Acid

Observational and clinical studies have shown that the elevated level of serum uric acid (SUA) is a common feature in patients with HF, hypertension, atherosclerosis, obesity, diabetes mellitus and chronic renal disease (Grassi et al. 2013; Borghi et al. 2015). The role of SUA in pathogenesis of CV disease is controversial. On the one hand, SUA induces an oxidative stress through over-production of reactive oxygen species. SUA often impairs vascular function via enhancement of inflammatory damage, inducing vascular calcification and directly via cell membranes deterioration effect (Grassi et al. 2013). On the other hand, low-grading inflammation that is frequently found in HF may cause xanthine oxidase over-activity and leads to increased tissue SUA accumulation, which acts as scavenger of free radicals and protects against an damaging effect of oxidative stress (Berezin and Kremzer 2013; Berezin 2014). Additionally, an increase of SUA may be an attribute of lowered kidney clearance in a progress of HF. Therefore, there is evidence regarding the regulatory role of SUA in EPC differentiation that allow discussing uric acid as a mediator of reparation of tissues in HF (Berezin et al. 2014b).

Numerous clinical studies have emphasized the predictive role of baseline SUA for early post-discharge HF outcomes (Amin et al. 2017; Okazaki et al. 2016, 2017). Interestingly, the activity of xanthine oxidoreductase that is a key rate-limiting enzyme of purine degradation may be more accurate predictor of HFrEF severity and HF clinical outcomes than SUA (Otaki et al. 2017; Huerta et al. 2016; Kim et al. 2013). Consequently, SUA remains an established risk factor of clinical outcomes in acute HF (Berezin 2017b), while poor prognosis in patients with chronic HF is not elucidated (Berezin 2017c).

5.8.2 Other Biomarkers of Oxidative Stress

Serum levels of myeloperoxidase, vitamin D3, ceruloplasmin and 8-hydroxy-2-′-deoxyguanosine correlate with staging of chronic HF regardless of LVEF and predict a development of HFrEF, while the role of these biomarkers of oxidative stress remains under discussion (Chan et al. 2016; Mozos et al. 2017). Although there is evidence regarding the close link between vascular remodeling (Berezin 2017d; Mozos and Marginean 2015), 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 is not still clear and requires to be investigated (Berezin 2017c).

5.9 Biomarkers of Renal Dysfunction in HF

5.9.1 Cystatin C

Cystatin C is an endogenous inhibitor of cysteine proteases and this biomarker is discussed as an alternative predictor of CV events in acute and chronic HF patients with any types of cardiorenal syndrome (Kim et al. 2013). The patients with HFrEF demonstrated elevated serum cystatin C, especially in cases with serious risk of CV complications (Kim et al. 2013). Additionally, increased cystatin C level in hypertensive patients with HFpEF was found (Berezin 2017d). It appears to be associated with LV diastolic dysfunction and alterations in collagen metabolism regardless of estimated GFR (Berezin 2017d). Although cystatin C has now validated a powerful predictor of CV outcomes and kidney injury, its sensitivity in patients with chronic HF is inferior to that of hs-CRP and NPs (Berezin 2017c). In contrast, in acute HF Cystatin C provided an incremental value for prognosis more than NT-proBNP and uric acid (Kim et al. 2015; Taub et al. 2012).

5.9.2 Other Biomarkers of Kidney Injury in HF

There are many perspective biomarkers of kidney injury that could be useful for stratification of HF at risk, i.g. stromal cell-derived factor-1, exosomes, MPs, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1, interleukin-18 and miRNAs (Berezin 2017d; Taub et al. 2012). Although they are at the early stages of renal dysfunction prior to any elevations in serum creatinine, the prognostication of clinical outcomes in acute HF and chronic HF require more investigations.

5.10 Genetic Biomarkers

By now, genetic testing has incorporated as a part of patient evaluation for suspected inherited cardiomyopathies (Teekakirikul et al. 2013; Teo et al. 2015). It turns out the epigenetic modifications through DNA methylation, ATP-dependent chromatin remodeling, histone modifications with an involvement of microRNA-related mechanisms might be sufficient pathophysiological factors contributing to adverse cardiac remodeling and altered cardiac function (Hershberger and Siegfried 2011). In this context, the novel risk scores reflecting variabilities in genetic and epigenetic features in HF development appear to be promising (Berezin 2016d; Yang et al. 2015; Lopes and Elliott 2013). Indeed, some early studies have reported interesting results with respect to genetic precursors of HFpEF and HFrEF (Berezin 2016e; Fazakas et al. 2016; McNamara et al. 2014; Friedrich et al. 2013; Hofman et al. 2010; Sutter et al. 2013; Kolder et al. 2012). There are numerous studies depicted the role of single nucleotide polymorphisms (SNPs) of genes encoding enzymes related to oxidative stress (Berezin 2016e), genotype of guanine nucleotide-binding proteins (G-proteins) beta-3 subunit (GNB3) (Fazakas et al. 2016), transcription factor Islet-1 gene (McNamara et al. 2014), troponin T (Friedrich et al. 2013), CYP2D6 polymorphism (Hofman et al. 2010), cardiac myosin binding protein-C mutations (Sutter et al. 2013), renin-angiotensin-aldosterone system polymorphism (Kolder et al. 2012) etc. in HF development and progression. It is well known that angiotensin-converting enzyme (ACE) I/D gene D allele was associated with higher overall mortality as compared with the I allele in HF patients and that the effect could be modified by ACE inhibitors' given (Wu et al. 2010). Additionally, ACE DD and angiotensin-1-receptor 1166 CC genotypes may synergistically increase the predisposition to HFpEF (Kolder et al. 2012; Wu et al. 2009, 2010).

The ARIC (Atherosclerosis Risk in Communities) study reported that none of the metabolite SNPs including pyroglutamine, dihydroxy docosatrienoic acid were individually associated with incident HF, whereas a genetic risk score created by summing the most significant risk alleles from each metabolite determined 11% greater risk of HF per allele (Yu et al. 2013). (Ganna et al. 2013) have reported that amongst 707 common SNPs associated with 125 diseases including HF it would not be easy to obtain explainable results by common genetic variants related to HF development. Consequently, a close gene-gene interaction may determine an individual's risk of HF through different pathways including epigenetic modifications. All these findings lead to the assumption that genes score might be a powerful tool for prediction of HF development.

More successful genome-wide linkage studies toward genes-related contribution in HF have been done by incorporating SNPs of several genes (i.g. the bradykinin type 1 receptor gene, angiotensin-II type I receptor gene, the β1-adrenoceptor gene and CYP2D6 polymorphism) in predictive score to benefit and suffer harm from HF therapy. Although these pharmacogenetic studies have focused on promised topics, the obtained results have not been absolutely consistent (Ganna et al. 2013; Yip and Pirmohamed 2013; Nelveg-Kristensen et al. 2015). In contrast, there is evidence that the gene expression profiles might be useful rather for risk prediction in HF than for choosing HF treatment regime (Bondar et al. 2014; Berezin

2016f). Thus, the clinical implementation of the HF therapy based on genes scoring remains uncertain and requires more evaluation in the future (Poller et al. 2017).

5.11 Micro-RNAs

It has been established that microRNAs (miRNA) are involved in the development and progression of HF across all pathophysiological stages of the disease (Berezin 2016d). miRNA are epigenetic regulators of myocardial response and fibrosis, growth of cardiac myocytes, cardiac and vasculature reparation, immunity, angiogenesis, and inflammation (Berezin 2016e). The altered miRNA' signature was found in patients with asymptomatic and symptomatic HF (Jin et al. 2017; Vegter et al. 2017; Yan et al. 2017b). It has suggested the signatures of non-coding RNAs would be candidate to improve diagnosis and prognostication of HF (Wong et al. 2014).

5.12 Mid-Regional pro-Adrenomedullin

Mid-regional pro-adrenomedullin (MR-proADM) is the prohormone of the CV protein adrenomedullin and it is well-established neurohumoral marker of cardiac biochemical stress that is raised in patients with infections, acute dyspnea, acute HF, severe chronic HFrEF/HFpEF, unstable angina pectoris/myocardial infarction, and throughout the first week after stroke (Bustamante et al. 2017). There is evidence 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 (Odermatt et al. 2017; Dres et al. 2017; Lopes and Menezes Falcão 2017). 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 (Lopes and Menezes Falcão 2017). Interestingly, sST2 was better to MR-proADM, because it is more closely related to left ventricular remodeling and cardiac fibrosis. Moreover, MR-proADM did not improve a risk stratification based on NPs in patients with chronic HFrEF and moderate anaemia (Welsh et al. 2017). Thus, the role of MR-proADM as a component of biomarker-based stratification is discussable, may contribute to determine the short-term outcomes of critical ill patients with acute severe dyspnea, respiratory infection and acute HF.

6 Validation of Multiple Biomarker Predictive Scores

Despite several predictive scores based on biomarkers' measurement and approved for chronic HF, predictive scores for acute HF have not been validated (Bayes-Genis and Ordonez-Llanos 2015; Cohen-Solal et al. 2015). Current multiple biomarker scores for prognostication, risk stratification and diagnosis of HF (Fig. 2) are based on NPs in combination with biomarkers of myocardial injury and fibrosis (galectin-3 and sST2 receptor). A new score was validated by the American Heart Association/American College of Cardiology (2017), suitable for patients at risk of HF, with established chronic HF (for both HFrEF and HFpEF), with suspected and documented acute HF (at admission), as well as patients with HF at discharge from the hospital.

Interestingly, there are several attempts regarding use of biomarkers to stratify at risk patients with HFrEF and HFpEF. Whether add-on biomarkers are needed to improve cumulative predictive value for wide spectrum of HF individuals with different HF phenotypes, co-morbidities, ages and sex-related peculiarities is not fully clear. There is no clarity and consistent evidence for multiple biomarker strategy in improvement in CV mortality and CV outcomes. It has been suggested that sST2 and galectin-3 could improve prognosis in HF-related hospitalization and CV death, when added to NPs. This strategy is confirmed by experts of various

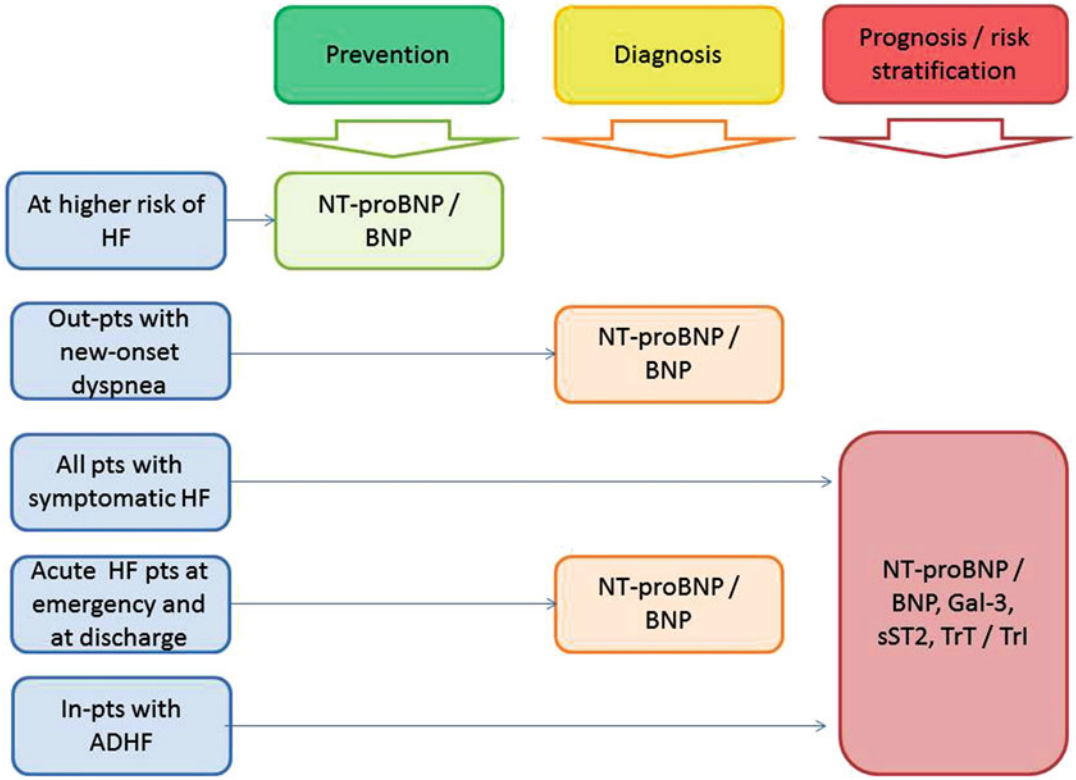

Fig. 2 Practical use of various biomarkers in HF development and progression
Abbreviations: *ADHF* actually decompensated heart failure, *pts* patients, *Gal-3* galectin-3, *NT – proBNP* NT-pro-brain natriuretic peptide, *BNP* brain natriuretic peptide, *TrT* troponin T, *TrI* troponin I, *sST2* soluble suppressor of tumorigenicity-2 receptor

medical associations and is the only one that is validated now (Chow et al. 2017).

7 Conclusions

There are many controversies regarding the importance of biomarkers as predictors of survival and in diagnosis of HF. Improvement of clinical guideline recommendations for optimizing HF therapy in routine clinical practice under biomarkers' control is required. Obviously, galectin-3 or sST2r would be optimal for improving NPs- based biomarker strategy in HF individuals, while there is evidence regarding other biomarkers that could individualize stratification of risk and treatment. There is need of larger clinical trials in order to head-to-head compare different biomarkers and clarify their role in diagnosis and guided therapy of HF.

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