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Biomarkers in heart failure: the past, current and future

Michael Sarhene[1,2,3] · Yili Wang[1,2,3] · Jing Wei[1,2,3] · Yuting Huang[1,2,3] · Min Li[1,2,3] · Lan Li[1,2,3] · Enoch Acheampong[2] · Zhou Zhengcan[1,2] · Qin Xiaoyan[1,2] · Xu Yunsheng[1,2] · Mao Jingyuan[1] · Gao Xiumei[2] · Fan Guanwei[1,2]

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Abstract
Despite the enhanced knowledge of the pathophysiology of heart failure (HF), it still remains a serious syndrome with substantial morbidity, mortality, and frequent hospitalizations. These are due to the current improvements in other cardiovascular diseases (like myocardial infarction), the aging population, and growing prevalence of comorbidities. Biomarker-guided management has brought a new dimension in prognostication, diagnosis, and therapy options. Following the recommendation of natriuretic peptides (B-type natriuretic peptide and N-terminal-proBNP), many other biomarkers have been thoroughly studied to reflect different pathophysiological processes (such as fibrosis, inflammation, myocardial injury, and remodeling) in HF and some of them (like cardiac troponins, soluble suppression of tumorigenesis-2, and galectin 3) have subsequently been recommended to aid in the diagnosis and prognostication in HF. Consequently, multi-marker approach has also been approved owing to the varied nature of HF syndrome. In this review, we discussed the guidelines available for HF biomarkers, procedures for evaluating novel markers, and the utilities of both emerging and established biomarkers for risk stratification, diagnosis, and management of HF in the clinics. We later looked at how the rapidly emerging field—OMICs, can help transform HF biomarkers discoveries and establishment.

Keywords Heart failure · Biomarkers · Natriuretic peptides · Myocardial fibrosis · Myocardial injury · Omics

Introduction

Heart failure (HF) is a serious condition that occurs when the heart is unable to pump enough blood and oxygen to support other organs in the body. Generally in an adult population, the estimated prevalence rate is around 2% (1–3%) but sharply upsurges to about 5–9% in people aged 65 years and above [1, 2]. In the USA, the number of adults living with heart failure is on the rise, increasing from about 5.7 million (2009–2012) to about 6.5 million (2011–2014) [1]. Grounded on this data, it was projected that the number of people living with heart failure will increase by 46% from 2012 to 2030, accounting for more than 8 million American adults. Currently, the existing data on HF is estimated to be 26 million adults worldwide, and it is expected to increase continually due to three main factors: aging population, increasing prevalence of comorbidities or risk factors, and improved survival of post-myocardial infarction [3, 4]. HF can be broadly classified based on ejection fraction. Patients with ejection fraction ≤ 40% are termed as HF with reduced ejection fraction (HFrEF), and those with ejection fraction ≥ 50% are termed HF with preserved ejection fraction (HFpEF). Patients whose ejection fraction is in between the two are considered as borderline ejection fraction [5] or midrange ejection fraction (HFmrEF) [6]. The signs and symptoms of HF are often deceptive with a wide differential diagnosis, making clinical presentation thought-provoking, due to the fact that the "old way" of ascertaining suspected patients with HF—medical history, physical examination, chest radiography, electrocardiography, and standard laboratory investigations—have been noted to be partially reliable [7]. Due to the extensive burden of the disease coupled with the complexity of the syndrome of HF, mechanisms to supplement the information established from clinical history and physical examination are currently necessary.

Biomarkers have been known since its inception in 1989 and was initially recognized as a "measurable and quantifiable biological parameter used to assess health and physiology in

✉ Fan Guanwei
fgw1005@163.com

[1] First teaching hospital of Tianjin University of Traditional Chinese Medicine, Number 314 Anshanxi Road, Nankai District, Tianjin, China

[2] State Key Laboratory of Modern Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin, China

[3] Tianjin Laboratory of Translational Research of TCM Prescription and Syndrome, Tianjin 300193, China

patients in terms of disease risk and diagnosis" [8]. This definition was later altered to suit a National Institute of Health working group and hence defined biomarker as "an objectively measured parameter that is an indicator of normal biological processes, pathogenic process or as a response to pharmacological therapy" [9]. Biomarker-guided management, diagnosis, and treatment have increasingly gained popularity most importantly in the acute settings—where majority of patients with HF are mostly found initially [10]. This is purposely due to the accruing number of evidences that have evolved suggesting that molecular biomarkers can help unravel the pathophysiology of HF, which will aid in predicting the disease' adverse consequence, provide innovative drug target, and judge therapeutic efficacy.

In this review therefore, we discuss the available guidelines regarding HF biomarkers, emphasized the general procedures for evaluating novel biomarkers, as well as the clinical utility of both established and emerging biomarkers in HF diagnosis, risk stratification, management, and probable prevention approaches. Lastly, we will discuss the future approach and the advent of Omics in the discovery of HF biomarkers.

Available guidelines on heart failure biomarkers

Major practical guidelines have recognized the utility of recommended biomarkers in diagnosis and management of HF, as summarized in Table 1. The American College of Cardiology Foundation/American Heart Association (ACC/AHA), Heart Failure Society of America (HFSA), and the European Society of Cardiology (ESC) have all established the usefulness of the natriuretic peptides (NPs) to provide assistance in the diagnosis of HF in suspected patients [5, 6, 11, 12]. The HFSA and ESC have however alerted on the use of the NPs in certain instances. For instance, using the NPs in screening patients without the existence of symptoms of HF is not recommended by the HFSA guidelines. The ESC on the other hand has noted a high negative predictive value of NPs at certain precise threshold, and hence recommended their use to rule out HF but not to ascertain diagnosis. The ACC/AHA guideline has given the NPs a Class I recommendation for prognosis or disease severity of HF once there is established HF diagnosis, and a Class IIa and IIb recommendations to guide therapy in chronic HF and acutely decompensated HF, respectively. Consequently, the ACC/AHA 2017 update has given a Class IIa recommendation for NPs to aid in the prevention of development of LV dysfunction or new-onset HF.

In clinical settings, the utilities of novel biomarkers are less established. Whereas the ACC/AHA guidelines recommended the use of biomarkers of myocardial injury (cardiac troponins I and T) and myocardial fibrosis (sST2 and galectin 3) in HF, the ESC has not realized any strong evidence to recommend the use of sST2 and galectin 3, but gave a class Ic recommendation for use of cardiac troponins in patients with suspected acute HF. The HFSA refused to acknowledge no other biomarker apart from the NPs. Upon the analysis of these differences in recommendations of novel biomarkers by the various guidelines, we sought to delineate the criteria used to evaluate such biomarkers in order to be of clinical importance.

Criteria for evaluating novel biomarkers

Though there are different kinds of biomarkers in living organisms (such as physiological parameters, clinical images, and tissue-specimen biopsies), ideal biomarkers are in constant circulation other than those routinely determined as part of clinical care such as electrolytes or hemoglobin [13]. Many objective criteria have been proposed to evaluate the possible

Table 1 Summary of recommended biomarkers in heart failure from ACC/AHA 2013 and 2017, ESC 2016, and HFSA 2010 documents

Biomarker	Guideline	COR	Setting
Natriuretic peptides	ACC/AHA	I	Support diagnosis or exclusion of HF
		I	Prognosis: ambulatory and acute settings
		I	Prognosis: admission levels for ADHF
		IIa	Ambulatory HF: achieve GDMT
		IIa	Prevention: incident of LVD or new-onset HF
		IIb	Acute HF: guide for ADHF medical therapy
	ESC		Diagnosis: rule out HF
		IIa	Initial assessment in newly diagnosed HF
	HFSA	REC	Diagnosis: in case of suspected HF
		N/REC	Routine screening in asymptomatic patients
Myocardial injury	ACC/AHA	I	Additive risk stratification: ambulatory, acute
	ESC	Ic	Diagnosis: suspected acute HF
Myocardial fibrosis	ACC/AHA	IIb	Additive risk stratification: ambulatory, acute

ADHF acute decompensated heart failure, *COR* class of recommendation, *GDMT* guideline-directed medical therapy, *HF* heart failure, *LVD* left ventricular dysfunction, *N/REC* not/recommends

relevance of these biomarkers in clinical settings. For a novel biomarker to be selected and used clinically in diagnosis and management of cardiovascular diseases, six phases of evaluation have been proposed by AHA, which include the proof of concept, incremental value, clinical utility, prospective validation, clinical outcome, and cost effectiveness [14]. In addition to these, Morrow and de Lemos [15] devised the benchmarks that a biomarker should fulfill to be clinically useful.

They stated more categorically that a useful biomarker should be cost effective and allow repetitive and precise measurements with a rapid processing time. It should provide information that is above the one provided by clinical assessment with a superior performance compared with other available tests, and above all, it should assist decision making and enhance clinical care [15]. In a succeeding review, van Kimmenade and Januzzi [16] also proposed four main criteria specifically for HF biomarkers: (1) thorough evaluation has been carried on to assess those markers in a wide range of patients characteristics of the diagnosis with rigorous statistical methods; (2) they can be easily, quickly, and accurately measured with defined biological variability and low analytical imprecision of the assay; (3) they demonstrate an important component of HF pathophysiology; and (4) they provide clinically useful information for caregivers and patients to assist in diagnosis, risk stratification, and management by providing additional information to the standard clinical laboratory data [16]. Lastly and more specific to the field of heart failure, the National Academy of Clinical Biochemistry has expounded comparable objectives for novel biomarkers to be used in clinical settings. In that definition, biomarkers must be able to recognize fundamental causes of HF, authorize presence of HF syndrome, assess its severity, and foresee the risk of the disease progression [17]. Thus far, only the NPs fulfill all the above criteria; however, other multiple novel biomarkers are gaining relevance and hence needed to be well studied.

Established and emerging biomarkers in heart failure

Various cardiac remodeling, altered renal function, and neurohormonal activation pathways depicted by the pathophysiology of the progression of HF due to cardiac insult, cardiac injury, and ventricular dysfunction have shown their actions influenced for biological investigations. In actual fact, from the inception of HF risk factors to progression of the syndrome, there are numerous proteins whose measurements depict significant information about HF [18]. These protein markers can mostly reveal pathophysiological characteristics of HF, including biochemical wall stress, inflammation, myocyte injury, neurohormonal upregulation, myocardial remodeling, and extracellular matrix turnover [5]. Table 2 gives the classification of the established and some emerging HF biomarkers.

Biomarkers of myocyte stretch

Biomarkers for myocyte stretch, especially the natriuretic peptides (brain natriuretic peptide (BNP) and NT-proBNP), are the most referenced biomarkers and against which other markers are constantly compared. Since HF is characterized by progressive fatigue and dyspnea leading to reduced tolerance to exercise, increasing wall stress and neurohormonal activation stimulates BNP and NT-proBNP discharge which are adversely associated with left ventricular (LV) systolic function.

Natriuretic peptides

The NPs are peptide hormones synthesized by the brain, heart, and other organs. In the heart, these hormones are provoked by atrial and ventricular distention and neurohormonal stimulations in response to HF. BNP is a natriuretic hormone that is usually recognized originally in the brain but is discharged predominantly from the ventricles of the heart in reaction to volume expansion and overload. Cleavage of the prohormone (proBNP) produces biologically active amino acid BNP in addition to the inert amino acid N-terminal proBNP (NT-proBNP). The atrial natriuretic peptide (ANP), on the other hand, is released by the myocardial cells in the atria or sometimes the ventricles in response to intravascular volume expansion and/or increasing wall stress [19]. BNP and its precursor NT-proBNP are particularly useful in ascertaining whether acute dyspnea is caused by HF. Again, the concentrations of these biomarkers in patients who have been diagnosed with chronic HF suggest valuable indication about prognosis which has led to their exploration as focus for HF therapy [16]. In normal patients, concentrations of circulating BNP and NT-proBNP are found to increase with age and appear to be higher in women than in men [20]. When these two factors are ruled out, healthy adults have BNP levels of 25 pg/mL or less and NT-proBNP levels of less than 70 pg/mL [21]. However, in the presence of acute dyspnea, these levels or concentrations increase drastically to about BNP ≤ 100 pg/mL or NT-proBNP ≤ 300 pg/mL which are clear indications to rule out HF as the cause of dyspnea [22, 23]. Above these risk brinks is an indication of higher risk of adverse outcome, whereas below this verge is a considerably lower risk [24]. In view of these, the authors of the ESC guidelines for HF have set a lower BNP cutoff value (35 pg/mL) and NT-proBNP (125 pg/mL) to refute HF allegations in patients with slow onset of HF signs and symptoms which reflect lower NP levels as compared to those at the emergency department [6].

Currently, researchers have tailored their work in the field of focusing on the role of monitoring NP concentrations for both hospitalized patients and the larger populace in order to modify their therapy for HF for each individual patient's need. This is chiefly because NP values strongly correlate with the

Table 2 Established and emerging biomarkers in HF

Main group	Subgroup	Biomarker
Myocardial insult	Myocyte stretch	ANP, BNP,[a] NT-proBNP,[a] MR-proANP, GDF-15, neuregulin
	Myocardial injury	Troponin T,[a] Troponin I,[a] hsTN, heart type fatty acid protein, myosin light-chain kinase 1, creatinine kinase MB fraction
	Oxidative stress	Myeloperoxidase, MR-proADM, oxidized low-density lipoprotein, urinary biopyrrins, plasma malondialdehyde
Neurohormonal-Activation	Renin-angiotensin system	Renin, angiotensin II, aldosterone
	Sympathetic nervous system	Norepinephrine, chromogranin A
	Arginine vasopressin system	Arginine vasopressin, Copeptin
	Endothelin	Endothelin-1, big proET-1
	——	Chromogranin A and B
Myocardial-Remodeling	Inflammation	C-reactive protein, TNF-α, Fas (APO-1), interleukins 1, 6, and 18, cytokines, procalcitonin, adipokines, adiponectin
	Hypertrophy/fibrosis	Soluble ST2,[a] Galectin-3,[a] matrix metalloproteinases, collagen peptide

ANP atrial natriuretic peptide, *BNP* B-type natriuretic peptide, *GDF-15* growth differentiation factor 15, *NT-proBNP* N-terminal pro B-type natriuretic peptide, *MR-proANP* mid-regional pro atrial natriuretic peptide, *MR-proADM* mid-regional pro-adrenomedullin, *TNF-α* tumor necrosis factor

[a] Established biomarkers

hemodynamic parameters such as pulmonary capillary wedge pressure and LV edge-diastolic pressure, thereby signify the actual hemodynamic status of the patient [25]. Another reason is due to the availability of authorized computerized and point-of-care tests rendering the assessment of the NPs very suitable, cost effective, and rapid for the physician and patient as a whole. During admission and prior to discharge of patients from the hospital, a universal agreement has been debated on the measurement of BNP concentrations in cases of severe HF intensification that demand hospitalization [26]. This consensus is in conformity with the fact that many findings have demonstrated the decrease in BNP concentrations during admissions to foretell better results, whereas patients with comparatively constant or augmented BNP values are more likely to experience readmission or increased mortality rates [24, 27, 28].

Results from different studies have concluded that approximately 20 to 30% mortality reduction are recorded for biomarker-guided HF care above traditional clinical care [29], and potential studies have confirmed that progressive patient evaluation of NPs are indications of increased concentration of HF medications and decrease in concentrations of NPs [30, 31]. In an echocardiography evidence, Weiner and colleagues [32] concluded that there is an improved LV volume and cardiac function when concentration of NT-proBNP was decreased, regardless of the treatment allocation within the study.

The best diagnostic approach for BNP and NT-proBNP is to augment clinical findings, but not to totally replace it with traditional criteria. This is chiefly because BNP and NT-proBNP concentrations are also found to upsurge in myocarditis, valvular heart diseases, acute coronary syndrome, cardiotoxic drugs, atrial fibrillation, and among other comorbidities of HF [24]. On this issue, Richards and co-researchers [33] studied the impact of atrial fibrillation on the diagnostic ability of the NPs and concluded that atrial fibrillation can significantly lessen the diagnostic accuracy of BNP and NT-proBNP in a large cohort research. Again, the GUIDE-IT trial which was instituted to offer central support for biomarker directive in HFrEF management was discontinued in the early stage due to ineffectiveness [34]. In that trial, the researchers noticed that about 37% of subjects in the guided-based group and approximately the same percentage in the usual care group experienced primary endpoint of cardiovascular death and HF readmission [34].

Possibly, the most vital modification in the subject of HF biomarkers is its recommendation to aid in the prevention of developing LV dysfunction (systolic or diastolic) or new-onset HF [12]. In a large-scale unblinded single-center study—STOP-HF, BNP-based screening and cooperative care decreased rate of development of HF among risk patients, and LV systolic and diastolic dysfunction. Patients at high risk of developing HF, depending on the presence of hypertension, diabetes mellitus, or known vascular diseases, without recognized LV dysfunction or baseline symptomatic HF, were assigned and subjected to BNP screening or normal primary care [35]. Similarly, in a small single-center randomized control trial, accelerated up-titration of renin-angiotensin-aldosterone system antagonists and beta blockers decreased cardiovascular outcomes in patients with diabetes and increased NT-proBNP levels but in the absence of cardiovascular disease at baseline [36]. These two major studies provided evidence that the NPs can aid in preventing new-onset HF using biomarker screening, thereby the new Class IIa recommendation in the ACC/AHA 2017 update [12].

So far, the ACC/AHA has given a Class I recommendation to the NPs to support diagnosis or to refute HF in ambulatory

patients with dyspnea, specifically when there are uncertainties surrounding the diagnosis. Another Class I was recommended to be used in establishing the prognosis or disease severity in ambulatory, acute as well as acute decompensated HF patients. Further, a Class IIa has been offered in ambulatory HF patients to achieve guideline-directed medical therapy and also for prevention of left ventricular dysfunction or new-onset HF. The other guidelines have also recommended the NPs to be used to either rule out cases of HF, for initial assessment in newly diagnosed HF and also to be used in case of suspected HF. What is left to be established in the near future is to fully provide guidance in medical therapy of which many researchers have begun pushing towards vivid evidence in this direction, especially after the ACC/AHA gave a somewhat green light in cases of acute decompensated HF patients. Lastly, though a Class IIa recommendation has been offered for the NPs to aid in preventing new-onset HF, more researches are warranted to ascertain the cost effectiveness and the perils involved in such screening, and also its influence on life quality and mortality rate.

Growth differentiation factor-15

Growth differentiation factor-15 (GDF-15) also known as macrophage inhibitory cytokine-1 (MIC-1) is part of the transforming growth factor beta (TGF-β) cytokine superfamily [37]. It is known to regulate mitochondrial function of wide range of cells that are concerned with inflammation, oxidative stress, apoptosis, immune reaction, fibrosis, reparation, and malignancies [38, 39]. In response to severe injury to the heart, kidney, liver, and the lung, the concentrations of GDF-15 are upregulated [40, 41]. In CVD models, GDF-15 has been noted for its anti-apoptotic, anti-inflammatory, and antihypertrophic actions [37]. However, elevated values of GDF-15 have been found to correlate with a number of CVDs including LV hypertrophy, stable coronary artery disease, MI, acute and chronic HF, and asymptomatic atherosclerosis [42, 43].

Among healthy women in a community-based population, Brown and fellow researchers concluded that upsurge serum concentrations of GDF-15 is associated with higher risk of future cardiovascular events [44]. Following this, Kempf and co-researchers measured the circulating levels of GDF-15 in chronic HF patients and discovered that about 342 patients out of the 445 participants had high levels of GDF-15 and were highly associated with increasing severity of HF and subsequently multiplied risk of death after 2 years follow-up [45]. The investigations by many researchers that have been confirmed by Wang and colleagues have substantiated the fact that concentrations of GDF-15 are strongly correlated with high risk of HF and its mortality [20]. Similar findings was reached in the HF-ACTION study and found that plasma GDF-15 was positively associated with HF severity, highest values of NT-proBNP, all-cause mortality rate [46].

Despite these findings, comprehensive statin treatment in the PROVE-IT study did not have any action on GDF-15 concentrations in patients with acute coronary syndrome [47]. This suggests that increased levels of GDF-15 are linked with other diseases such as pulmonary arterial hypertension [48], pulmonary embolism [49], pneumonia, renal disease, and sepsis [50].

Conclusively, it is evident from a well-conducted research [20] and many other important studies that GDF-15 is a strong predictor of adverse outcome as well as new-onset HF. Owing to its relation to other diseases, enough clinical evidence must be established in the future to elucidate how the prognostic strength of GDF-15 can be combined in a multi-marker studies for examining patients and devising therapeutic options. Also, studies are warranted to elucidate the molecular pathways involving GDF-15 and to determine how knowledge about this marker be used to make therapeutic decisions.

Biomarkers of hypertrophy/fibrosis

Biomarkers for ventricular remodeling and fibrosis such as soluble ST2 and galectin 3 have been reportedly approved by the US Food and Drug Administration [5] to depict myocardial fibrosis and cardiac remodeling, which are key in the pathophysiology of HF.

Soluble ST2

sST2, a member of the IL-1 receptor category, is known to be a marker of inflammation, hemodynamic stress as well as cardiomyocyte strain. There are two major isoforms of ST2: the transmembrane receptor (ST2L) and the circulating soluble form (sST2). The ST2L exerts its action through an ST2 ligand which has antifibrotic and antihypertrophic effect, IL-33. The sST2 can however bind to the IL-33 to function as a bait receptor to inhibit the antihypertrophic and antifibrotic actions of IL-33.

As a predictive for future risk of developing HF, a data from the PRIDE study indicated that patients who had higher sST2 concentrations will die within 1 year, and higher concentrations predicted substantial risk [51]. Also, Mueller and researchers found that the average baseline sST2 plasma values were notably higher in patients who died as compared to those who survived [52].

Soluble ST2 concentrations have also been implicated in the disease severity and risk stratification in HF patients. For example, in the CORONA study, Broch and researchers found that baseline sST2 was a significant predictor of cardiac death, non-fatal MI or stroke, death, and worsening in HF and rehospitalization in HF patients after initial adjustment for established clinical and biochemical variables [53]. Also

Binas et al. [54] and O'Meara et al. [55] concluded that sST2 could predict all-cause mortality and cardiovascular death in patients with non-ischemic HF.

Thus far, sST2 in the ACC/AHA 2017 recommendation has been categorized as a marker for myocardial fibrosis for additive risk stratification to the NPs. However, a study by Mueller and Jaffe [56] concluded that sST2 is non-specific to be included in a clinical setting for distinct medical condition but is rather a general marker of disease and mortality. Hence, the supply of the circulating ST2 apart from the heart must be thoroughly studied, given the prognostic role of ST2 to foretell inception of diseases across a wide array of risk profiles, it is realistic to predict that vascular endothelium performs a substantial role and this requires more examination.

Galectin-3

Galectins are characterized by specific binding of soluble β-galactosides that are known to play controlling roles in inflammation, immunity, and cancer. Increased levels of galectin-3 in the Framingham Cohort Survey was found to be highly significant with increased risk for new-onset of HF and associated with all-cause mortality even after adjustment of several clinical factors including BNP [57, 58]. A study by Leone and researchers among healthy individuals concluded that galectin-3 can be used as a great predictive biomarker for the new-onset of HF [59], and as an additional marker for depicting worse prognosis, mortality, and rehospitalization [60]. Also, the COACH and TRIUMPH study conducted by Meijers and colleagues [61] discovered from a huge panel of 29 biomarkers that galectin-3, erythropoietin alpha (EPO), TNFαR1a, and TGF-β emerged as predictors for low risk stratification in HF patients.

Though galectin-3 has been discovered to be upregulated in the infarcted size [62], its prospective function as a marker to predict post-myocardial infarction remodeling and HF is inadequately supported by research. For instance, when Weir and researchers conducted a research on patients who had acute myocardial infarction and LV dysfunction, galectin-3 levels were highly associated with other markers of matrix turnover and inflammation but was however insignificantly related to remodeling related factors [63]. In addition to these, the study by Srivatsan and associates [64] disproved the evident that galectin-3 can predict all-cause mortality, especially when factors of renal function, NT-proBNP, and LVEF were considered. They however reiterated that galectin-3 may be a powerful tool for prognostication if included in a multi-marker panel. On the basis of these shortcomings and lack of definite evidence regarding the use of galectin-3 in clinical conditions, Ponikowski and colleagues [6] refused to recommend it for clinical practice.

In conclusion, though the ACC/AHA has given galectin-3 a Class IIb to be considered for additive risk stratification, it is not a marker that is specifically expressed in the heart, and there is not yet clarity as to which organs or tissues adds to its increase, and to what extent in HF. Due to this, future studies assessing the function of galectin-3 in cardiac remodeling may offer additional understandings into its role in the pathophysiology of HF. Again, ascertaining the value of galectin-3 in guiding therapy decision must be researched because repeated measurements might prove supportive to identify individuals who are more likely to respond to treatments. Moreover, it remains to be tackled whether galectin-3 may be targeted by specific anti-galectin-3 therapy, and the number or amount of galectin-3 measurements needed for optimal prognostication and therapy monitoring.

Biomarkers of inflammation

The function of inflammation in the pathophysiology and progression of HF is known to exert important therapeutic and diagnostic consequences. Treatment options that target the immune response of patients with inflammation being the cause of HF will be of much advantage; however if inflammation is just a marker of a disease, then there is doubt in treatment targeting immune response. Notwithstanding, levels of inflammatory biomarkers have been found to correlate with both the development and severity of HF in asymptomatic patients [65]. Additionally, a more recent work by Mantel et al. [66] has reiterated that inflammation is directly linked to the cause of HF. Inflammation became a subject of interest in HF when C-reactive protein were found in about 75% of patients with chronic heart failure, and higher levels were detected in those patients with more severe HF [67]. In this section, we look at some important inflammatory markers (like C-reactive protein) and pro-inflammatory cytokines such as interleukin 1 and 6, as well as tumor necrosis factor-α in HF.

C-reactive protein

C-reactive protein (CRP), a non-specific marker of inflammation, mainly synthesized in the liver and is stimulated by interleukin-6 (IL-6). An acute phase reactant, CRP functions as blueprint detection molecule in the innate immune system. CRP has been known to facilitate low-density lipoprotein (LDL) uptake by macrophages and stimulate the discharge of monocyte of pro-inflammatory cytokines like IL-1b, IL-6, and TNF-α [68]. In a more recent research by Van Tassel and assistants [69], it was deduced that reducing serum CRP levels with anakinra in acute decompensated HF patients enhanced survival by decreasing hospital readmission after 2 weeks of continual treatment. There was however upsurge in readmission rate 6 weeks after termination of treatment indicating that

elevated CRP levels increases readmission in HF patients. A small cohort study has concluded that about 70% of patients with hs-CRP values > 4.25 mg/L were dead as compared to only 6.5% of those with hs-CRP < 4.25 within the 90-day hospitalization [70]. Another research on a great number of patients with DCM also concluded that higher concentrations of circulating hs-CRP was an independent marker of all-cause mortality [71].

The utility of CRP concentrations gleaned from most studies thus far indicates its ability to foretell worse outcome in HF patients as well as other established risk predictors in several CV populations. Also, there is an undisputable fact that CRP levels can be reduced in many researches by the use of statin and other anti-CRP therapies, unfortunately the reduction in HF patients did not result in enhanced consequence [72, 73]. The difficulty surrounding its recommendation stems from the several inflammatory pathways involved in a complicated syndrome like HF, in which CRP alone cannot handle. Due to these shortcomings, further studies are required in the future to combine CRP in a multi-marker setting and should be complimented by other markers.

Cytokines

These are protein molecules released by effector cells in response to a variety of stimuli. Pro-inflammatory cytokines in living cells are responsible for activating the cellular and molecular mechanisms that activate tissue repair in the heart [74]. These cytokines (TNF-α, IL-1, and IL-6) are reported by Anker and von Haehling [75] to be produced by nucleated cells in the heart and are the most successful inflammatory cytokines that have been demonstrated to be useful biomarkers in HF [76]. Several reports have confirmed the upregulated expression and release of these cytokines in patients with HF, and their higher concentrations appear to be directly proportional to NYHA functional class as well as LVEF [65, 66, 77, 78]. In recent studies, Van Tassel and colleagues [79] reiterated the fact that blocking IL-1 with anakinra in patients with diastolic HF yielded a positive result after 12 weeks.

Targeting pro-inflammatory biomarkers such as TNF-α whose activities are depicted in hemostatic or repairing activities can lead to lethal results. This is because TNF-α generates production of free radicals which basically further causes myocardial destruction [80]. A small-scaled trial using etanercept (a soluble receptor infusion) proved to be effective clinically when TNF-α expression was obstructed leading to enhanced LV function [81].

In patients with heart attack or acute myocardial infarction, increased concentrations of IL-6 are found to provide beneficial consequences to the myocardium by stimulating anti-apoptotic effects, thereby decreasing the infarct size [77]. Nevertheless, its lasting signaling is linked to alteration of Ca^{2+} handling, reduced cardiomyocyte functioning, decreased contractility as well as myocardial hypertrophy. Hence, the functions of IL-6 in cardiac inflammation and remodeling leading to HF are found to be vague. This is purposely because despite the fact that most researchers have found increased IL-6 expression correlating with the inflammatory response and worsening detrimental effects following myocardial infarction [82, 83], inhibition of IL-6 however did not contribute any defensive effect in mice experiment [84].

In conclusion, several studies have shown increased concentrations of inflammatory cytokines in serum and circulating leukocytes and are noticed to be mediators of processes contributing to hypertrophy, fibrosis, and apoptosis. However, no single cytokine has offered satisfactory conclusion to move the transition to day-to-day clinical utility as prognosticator in HF due possibly to their adaptive and maladaptive effects. Future research must therefore focus on critical mediators and their processes of actions in the immune pathogenesis of HF, and principally elucidate the balance between adaptive and maladaptive effects of these molecules. Lastly, the usefulness of cytokines in clinical settings is still counterpoised by the arduous cost and restricted accessibility of assays, which also necessitates future search for low cost and readily accessible assays.

Fas (APO-1)

As a member of the TNF gene superfamily, Fas (APO-1) has been recognized to be expressed in variety of cells, including the myocytes. Li et al. [85] discovered that overexpression of Fas/FasL in granulation tissue portrayed a critical role in LV remodeling after acute myocardial infarction, and its restraint lessened post-infarction ventricular remodeling and enhanced survival. Moreover, increased serum levels of solvable Fas have been identified in HF patients and the levels correlated with the disease severity [86–88].

Though Fas levels have been found to correlate with NYHA functional class of HF patients, to date, the mechanism of circulating Fas in these patients remains undefined, and due to this, research on the efforts to reduce serum/plasma Fas levels are still in their early stage. However, if more work is done in these arenas, it might represent a new direction in HF prevention and treatment.

Procalcitonin

Procalcitonin (PCT) is another novel biomarker of inflammation whose expression in the parenchymal tissue is stimulated following bacterial infection by either endotoxin or cytokine (IL-6). Since its discovery, PCT has been used as a marker for ascertaining the seriousness of bacterial infection and accordingly for managing antibiotic treatment, and has as well been recently detected in some non-infective inflammatory conditions [89]. Among these non-infective inflammatory

conditions is HF, of which most researchers have found that increasing concentrations of serum PCT correlate with the severity of the disease [39, 90, 91]. Additionally, serum PCT concentration has been a useful marker in patients with HF by excluding pneumonia and guiding therapy [92, 93]. In patients with acute dyspnea admitted to the emergency section, PCT has been fully established as a precise diagnostic indicator for pneumonia and assists as an independent prognostic tool for 1-year mortality [94].

The usefulness of PCT is established to rest on its ability to distinguish non-cardiac dyspnea from cardiac dyspnea. It is an exceptional substitute of ongoing bacterial infection and may be of use in clinical setting in the presence of diagnostic uncertainty in patients with HF with underlying pneumonia. However, its role in guiding antibiotic usage is still in its conceptional stage, and large clinical trials can further delineate its function in controlling treatment. Also, its utility as a biochemical marker in HF among patients without infection must be established in a large study.

Biomarkers of myocyte injury

There are reports of higher occurrence of myocyte necrosis/injury in HF, which might originate from tissue ischemia relating to both coronary and non-coronary artery diseases and cell death in the failing heart due to neurohormonal activation, inflammation, or apoptosis [16]. Meanwhile, irrespective of the major reason of cell dysfunction, myocardial injury markers have been found to reflect a wide array of pathophysiological processes including instability of lipid layers of membranes due to lipid peroxidation and destroying of the cells due to necrosis or apoptosis [95]. The abnormal concentrations of markers of myocyte injury or necrosis are closely associated with anthracycline-induced myocyte death and cardiotoxicity as well as loss of myocyte contractility [96]. Though the interruption of usual cardiac myocyte membrane causes the discharge of several cellular and structural proteins such as cardiac fatty acid binding protein, creatine kinase, myoglobin, and troponins, only the latter has emerged as the yardstick of care marker for establishing the presence of myocardial infarction [97].

Cardiac troponins (I and T)

The use of high sensitive troponin (hsTn) assay which allow for determination of trivial amount of myocardial injury or necrosis may be particularly useful to identify cardiotoxicity, which in-turn predicts risk for HF and other cardiovascular occurrences [98]. In fact, the advent of hscTn in HF has been of great tool in the hands of researchers and clinicians for early and strong prediction and prognostication. For instance, in the study of Latini and co-researchers, when standard assay was employed in the determination of cardiac troponins, only 10% of the patients with chronic HF had detectable TnT and it was associated with increased risk of death and readmissions. However, when high sensitivity cardiac troponin assay was used on that same cohort, almost 92% of the patients had detectable TnT [99].

Slightest increase of circulating cTn concentrations has mostly been realized in patients with HF exclusive of ischemia or coronary artery disease, signifying continuing myocyte injury or necrosis in affected individuals [100, 101]. Many reports have indicated that increase of cTn is accompanied with weakened hemodynamics, gradual LV dysfunction, and upsurge rate of mortality in patients with HF [100–102]. Convincingly in the ADHERE-HF registry, approximately 6.2% of patients with acute decompensated HF who had elevated levels of cTn were later found to be linked with adverse in-hospital mortality [103]. These earlier observations have been thoroughly confirmed especially after the discovery of highly sensitive assays of cTn (hscTn) in recent times [99, 104]. Following this approach, significantly greater number of patients with acute decompensated HF were found to have high concentrations of hsTnT, and these levels were further noted to be independent predictors of all-cause mortality in a multivariable model which included NT-proBNP and sST2 [105].

Owing to the aforementioned findings that increased concentrations of serum troponins have direct association with disease severity, worse clinical outcome, and subsequent mortality, two main researches that targeted the reduction of troponin levels over time found better prognosis than persistent elevation of troponins in both acute and chronic HF patients [106, 107]. Subsequently, the writing committee for ESC has also recommended assessment of troponin levels in all patients presenting with suspected acute HF [6].

It is already established that elevations in concentrations of cardiac troponins in acute HF and ADHF patients are of prognostic significance and needs to be interpreted cautiously in clinical settings. Also, since the most vital addition a biomarker can provide in clinical context is to affect management and ultimately improve clinical outcome, recent and future research on hscTn must be focused on tailoring medical therapy according to the rise in the levels of hscTn. Additionally, the diagnostic and prognostic value of a single time point and serial assessment of hscTn in routine practice and their role as a surrogate efficacy endpoint in clinical trials must be well delineated. Lastly, the challenge still abounds to ascertain the clinical usefulness of cTn values in primary prevention approaches and to establish if cTn could be used to scrutinize the advantageous consequences of cardioprotective remedies.

Heart-type fatty acid binding protein (hFABP)

hFABP is a protein that facilitates long-chain fatty acid reuptake, lessens calcium transport in cardiomyocytes, and

regulates inflammatory response in reply to some lipid signals [108]. Due to its tissue-specificity, it is much abundant in the myocardium and is known to be released into the circulation after myocyte injury, making it an ideal marker for myocardial infarction even in the early stage of the disease progress [95]. This is made possible due to its smaller size (15 kDa) thereby being detected at the early stage in the serum immediately after myocardial infarction when compared to other markers like creatinine kinase (CK) and troponins [109]. Again, it has proven to be of value as an independent prognostic biomarker in patients with acute coronary syndrome and elevated levels correlate higher risk of mortality and major cardiac events [110, 111]. Additionally, hFABP has been found by Setsuta and colleagues to be correlated with future cardiovascular consequences in patients with chronic HF following myocardial infarction, dilated cardiomyopathy, valvular and congenital heart diseases [112].

Though there are many other reports that indicate the prognostic success of hFABP in myocardial infarction, coronary artery disease, and HF, there are yet confusions surrounding the total improved precision of entire predictive model after combining it with NPs and/or galectin-3 [113–115]. Hence, as a new marker to be recommended by the major HF guidelines, more researches in the clinical settings are needed now and the future.

Neurohormonal activation biomarkers

The activation of systemic neurohormones is a basic procedure involved in the progression of HF, and it occurs due to imbalance in cardiac homeostasis [76]. Though neurohormonal activation markers from the renin-angiotensin system and the sympathetic nervous system have been very familiar, the utility of these neurohormones as diagnostic or prognostic markers in HF is diverse predominantly because of the positive impact of various blocking agents as beta blockers, ACE inhibitors, and aldosterone receptor blockers on HF [116]. Generally, circulating levels of the neurohormones indicate severity of HF, and due to this they have been implicated in HF management.

Norepinephrine

One of the early markers in this arena is the norepinephrine, which was reported back in the 1960s that HF patients had remarkably elevated plasma concentrations of norepinephrine at rest and further increase occurred during physical activities [117]. Following this discovery, Cohen and colleagues [118] also realized that elevated amounts of plasma and urinary excretion of norepinephrine were independently associated with mortality due to HF. These earlier findings led to the thoughtful research concerning the lethal effects of neurohormonal activations in HF [119]. In the Val-HeFT study where activities of renin, BNP, norepinephrine, aldosterone, and endothelin were investigated for their prognostic ability among patients with HF, multivariate analysis depicted that apart from BNP, only norepinephrine was significantly correlated with adverse consequence after the 23 months follow-up [120].

There is a strong correlation between neurohormone concentrations in the blood and the clinical cause of HF; nevertheless, Givertz and Braunwald have observed that the utility of norepinephrine as a routine clinical marker is unrealistic given the need for complex assays and handling procedures like high-performance liquid chromatography [121]. Also, several lines of substantiations have supported the role of neurohormones in the development of LV dysfunction, and subsequent HF, they are not markers that must be relied on for point-of-care services due to these complicated analyses and management measures. Lastly, variations in plasma norepinephrine may not constantly suggest the changes in the disease prediction. Hence, newer and readily available assays are needed for future research to define the prognostic utility of norepinephrine for clinical usage.

Endothelin-1

This is an effective vasoconstrictor peptide with a lasting effect of cell growth and produced in the endothelial cells of blood vessels and also acts as a marker for sympathetic activation [13]. Elevated levels have been identified by other researchers to be correlated with parameters of diastolic dysfunction as well as poor prognosis in HF due to LV systolic dysfunction [122]. More recently, Ara-Somohano and colleagues found that endothelin was independently associated with predicting acute and chronic HF irrespective of LV ejection fraction [123].

Given these and many other relevant studies, it is worth noting that the prognostic utility of endothelin-1 is a great future tool in the hands of caregivers. These notwithstanding, clinical trials engaging numerous endothelin-1 receptor blockers as potent therapy did not yield any substantial clinical conclusion or preventive effects [124]. Also, cutoff points for endothelin are varied and determined by the assay type; hence, future studies are warranted to confirm relevant cutoff points for endothelin levels by examining and adopting a single endothelin assay that could aid clinicians to arrive at a standard conclusion for prognostication.

Adrenomedullin

It is a potent vasodilator which was originally discovered in pheochromocytoma cells arising from the adrenal medulla [125]. Afterward, adrenomedullin (ADM) has been detected in many tissues including lung, brain, kidney, heart cardiomyocytes, adipose tissues, and fibroblasts, and its

mRNA are greatly expressed in endothelial cells [126]. Patients with chronic HF, diastolic LV dysfunction, and restrictive filling are known to have elevated levels of ADM and its concentrations are found to correlate with increasing HF severity [74]. However, because ADM is biologically unstable and complex to measure regularly, determining the mid-regional pro-adrenomedullin (MR-proADM) was lately developed, and it frankly reveals the levels of the actively degraded peptide ADM [74, 127]. MR-proADM is noted to be elevated in patients with infection, acute dyspnea, acute or chronic HF, myocardial infarction, and during the early stage of stroke [128]. In the BACH study, MR-proADM was a powerful prognosticator for 90-day mortality and its prognostic value was found to add value beyond that of the natriuretic peptides [129], and was subsequently approved in the PRIDE study where it was noted as a strong predictor of 1-year mortality [28]. Recently, there is confirmation that MR-proADM could foretell early in-hospital death caused by respiratory diseases, medical procedures, and circulatory diseases [130, 131]. A notable research among chronic HF patients from the Australia-New Zealand study also found that MR-proADM was a powerful and independent predictor of 18-month all-cause mortality, and treatment with carvedilol considerably lessened the risk of death and HF readmission [132].

Whereas many researchers noted positive correlation between MR-proADM levels and HF severity, others have observed that it was unable to improve risk stratification in patients with chronic HF and mild anemia [133]. Thus, from the above data, it is clear that the utility of MR-proADM in determining short-term outcomes in critically ill patients with severe dyspnea, respiratory diseases, and acute HF appears more promising. Larger, multicenter-trials are needed to warrant its acceptance as a prognostic tool. Also, its function in precise patient populations is less established, and the interpretation levels of MR-proADM vary across multitude of chronic diseases, the elderly, and immunosuppressed groups including cancer patients. Future directions must also be steered towards prediction and triage of patients exhibiting other acute conditions as fevers, myocardial infarction, sepsis and shocks, and acute chest pains. Lastly, it would be an added advantage if further research could determine specific cutoff values that may arrange patients into stages of risks, such as low-, intermediate-, and high-risk patients.

Arginine vasopressin

Arginine vaopressin (AVP) or antidiuretic hormone (ADH) is a peptide hormone produced in the hypothalamus, stored in the posterior pituitary gland, and released owing to sympathetic stimulation [126]. AVP is known to have both antidiuretic and vasoconstrictive properties and its elevated concentrations strengthen HF related to dilutional hyponatremia, liquid build-up, and systemic vasoconstriction [13]. Though increased plasma concentration of AVP has been found to correlate with both acute and chronic HF [134], its direct measurement has been burdened with complexities. Due to this, its C-terminal derivative of pre-provasopressin, copeptin, has been used as an exceptional substitute marker which predicts adverse outcome in patients with acute decompensated HF [135], and chronic stable coronary artery disease [136]. Elevated levels of copeptin in the general populace are very strong in predicting increased rate cardiovascular diseases, cardiovascular mortality, as well as all-cause mortality in crucial situations [137]. Further, its serial assessment offered vital information for discrimination of risk of all-cause mortality and HF-related consequences [138, 139].

Though increased levels of copeptin in HF patients were independent prognosticator of unfavorable clinical consequences, its role in HF risk stratification as well as the mechanism are yet to be elucidated. This is because some researchers have concluded that the increased levels of copeptin can also be due to some metabolic activities like hyperglycemia [115, 140]. Further, the prognostic use of copeptin assessment for predicting adverse events and more importantly risk of mortality warrants prospective cohort studies with large sample size.

Oxidative stress biomarkers

Due to an imbalance between production of reactive oxygen species and anti-oxidant defense mechanism, there is an increased oxidative stress which is noted to be one of the common characteristics in the progression and development of HF. Due to the difficulties associated in assessing the level of oxidative stress in clinical settings, surrogate markers such as malondialdehyde, myeloperoxidase, plasma-oxidized low-density lipoproteins, and urinary biopyrrins have been commonly used [13, 141]. There are numerous small cohort studies substantiating the fact that these oxidative stress markers can reflect HF severity. For instance, McMurray et al. [142] and Mak et al. [143] discovered that regardless of the disease etiology, CHF correlates with biomarkers of oxidative stress when compared with age-match control groups (Table 3).

Malondialdehyde

Malondialdehyde is only one of many aldehyde compounds produced by lipid peroxidation and it arises as the results of the final product of oxidation of polyunsaturated fatty acid undergoing an attack by reactive oxygen species (ROS) [167]. Studies have shown chronic HF patients have increased plasma concentrations of malondialdehyde as compared to those without HF [168]. Another study, confirming the presence of malondialdehyde in HF patients, also concluded that the level of malondialdehyde highly correlated with HF

Table 3 Summary of existing data on different biomarkers

Category	Biomarker	Study type	Sample size	Findings	Limitation	Ref
Myocyte stretch	BNP and NT-proBNP[a]	Cohort	1586	For establishing or excluding of CHF diagnosis in patients with acute dyspnea	1. Limited to patients more than 18 years presenting with acute dyspnea 2. Patients with acute myocardial infarction or renal failure were excluded	[22]
		Cross-sectional	558	In the ambulatory care setting, both symptomatic and asymptomatic chronic stable systolic HF may present with wide range of BNP levels. In a subset of symptomatic patients, plasma BNP levels are below the diagnostic criteria	1. Limited by retrospective and cross-sectional nature 2. Echocardiography was not performed simultaneously with BNP testing	[144]
		Cohort	2429	Both BNP and NT-proBNP accurately discriminated subjects with LVH or LVSD in young and healthy population In young men, NT-proBNP performed slightly than BNP for screening	Echocardiography was not performed for these subjects to evaluate LV diastolic abnormalities, subclinical valve disease and pulmonary hypertension on false positives	[145]
		Randomized control trial	300	Accelerated increments of renin-angiotensin-aldosterone system antagonists and beta blockers decreased cardiovascular outcomes in patients with diabetes using NT-proBNP	1. Absence of patient randomization for treatment 2. Study was conducted in predominantly Caucasians	[36]
		Randomized control trial	1374	Among patients at high risk of HF, screening with BNP decreased the combined rates of LV systolic and diastolic dysfunction and subsequent HF	1. This trial was confined to a single region 2. Non blinding of patients and practices	[35]
		Cohort	297	NT-proBNP is an independent predictor of mortality and HF	1. Did not include conclusions about whether or not NT-proBNP could predict benefits from beta blockers without previous introduction of ACE inhibitor treatments 2. Limited to only patients with ischemic left ventricular dysfunction receiving standard therapy with ACE inhibitors and loop diuretics	[146]
		Cohort	1869	In normal patients, gender and age are the major factors that influence NT-proBNP concentrations and should be considered when interpreting values	Limited number of patients with reduced EF	[147]
		Cohort	3497	Diagnostic ability of NT-proBNP equals that of the reported BNP in screening for LVH and LVDS Gender and age influences NT-proBNP concentrations	Fewer number of patients had LVEF less than 50% which highly reduced the possibility for subdividing	[148]
		Cohort	2042	NT-proBNP is a more robust cardiac biomarker compared with NT-proANP and is an independent predictor of CV morbidity	1. The study did not include patients with stage C or D HF and those with renal insufficiency 2. Confined to one area	[149]

Table 3 (continued)

Category	Biomarker	Study type	Sample size	Findings	Limitation	Ref
				NT-proBNP is an independent marker for mortality but not HF, MI, or CVA and ANP lacks independent predictive value in a large cohort		
		Cohort	1256	NT-proBNP is effective for diagnostic evaluation and short-term prognosis estimation in dyspneic subjects with suspected or confirmed acute HF	1. The study lacks predefined endpoints 2. The cut-points proposed for identifying or excluding acute HF lacked the addition of 1800 pg/mL for patients > 75 years	[150]
		Cohort	1445	AF is associated with increased levels of MR-proANP, BNP, and NT-proBNP in patients without HF	1. Number of missing values for the multivariate analysis has potential risk because of possible biased populace 2. Single cutoff was used for evaluation of serial measurement 3. The number of observed deaths within 90 days was limited for any subgroup analysis	[33]
		Cohort	1301	In patients hospitalized for ADHF, integrating NT-proBNP levels at discharge as well as the dynamic change in NT-proBNP during hospitalization allows professionals to predict the risk at discharge to prevent the outcome rate of death and a composite end-stage of death and readmission within 180 days	1. Limited by individual patient data meta-analysis 2. Missing data is considered as another limitation 3. NT-proBNP values were missing for the external validation cohort 4. Compensation for one relatively small study cohort by extending the follow-up to 12 months	[151]
		Randomized controlled trial	897	Among high risk patients with HFrEF, an approach of NT-proBNP-guided therapy was not more valuable than usual care strategy in enhancing outcome	1. The unblinded nature of this study could lead to bias 2. Patients NT-proBNP levels assessed at non-study sites or clinicians might have caused diminish in the difference between study group 3. Patients in both groups had more frequent clinical encounters than should occur in clinical practice	[34]
		Cohort	1853	NT-proBNP offered greatest prognostic utility for adverse outcome in chronic HFrEF patients with moderate anemia Additional neurohormonal, renal and inflammatory biomarkers did not predict adverse outcome as strongly and did not add to basic clinical prediction model which included NT-proBNP, though incremental information was provided by hsTnT	1. Clinical trial cohort was used, hence the data may not be generalized to other CHF cohorts 2. Presence of regional differences in patients' characteristics 3. Majority of patients had relatively advanced HFrEF	[133]
	MR-proANP	Cohort	525	Independent predictor of mortality in CHF Adds prognostic information to BNP	1. Did not include female patients 2. Small number of patients in NYHA functional class 1	[152]
		Cohort	1641	Significant diagnostic utility in patients with acute dyspnea	1. Not included high risk patients 2. Blinded the gold standard physicians from biomarker levels taken at the site	[129]

Table 3 (continued)

Category	Biomarker	Study type	Sample size	Findings	Limitation	Ref
					3. Excluded patients with known clinical values of BNP 4. Number of deaths was limited by 90-day follow-up duration	
		Cohort	137	Assist in prediction of clinical course in patients with severe HF undergoing CRT	1. Limited by small number of patients 2. Limited multivariable adjustments	[153]
		Cohort	200	A serial monitoring strategy of MR-proANP, and of lesser impact copeptin, in addition to cTnT may be beneficial in noticing and managing the highest risk HF outpatients	1. Complete 2-year follow-up was not accomplished for 18 patients for reasons other than the primary endpoint 2. Death of 8 patients after enrollment but before the first 3-month follow-up	[154]
	GDF-15	Cohort	455	GDF-15 is a new biomarker of the risk of death in patients with established CHF and provides prognostic information beyond established markers	Limited by small number of subjects	[45]
		Cohort	3428	GDF-15, sST2 and hsTn predicts future risk of death, HF and CV events. Addition of these biomarkers improves discrimination and leads to potentially relevant changes in risk classification	–	[20]
		Cohort	984	Increased levels of GDF-15 are associated with major CV events in patients with HF, ACS and stable coronary disease	1. Study could not exclude confounding from unmeasured variables 2. Predominated by male patients 3. Higher range of measured GDF-15 values	[73]
		Randomized controlled trial	910	GDF-15 is associated with long-term CV outcome Doubling the concentration of GDF-15 was significantly associated with all-cause mortality	1. Post-hoc analysis limitation (analysis not specified before the data was seen) 2. Patient population were predominantly from USA 3. Subjects demonstrated increased use of evidence-based therapies compared to other studies	[43]
		Cohort	810	Age-dependent of GDF-15 centile values from healthy adults are independent predictors of HF and all-cause mortality	1. Numerous important diagnosis for choosing the apparently healthy groups were only available as self-reported data 2. Quite small number of all-cause mortalities detected during follow-up potentially reduces the power of survival analysis 3. Confined to entirely Caucasian older adults	[155]
Myocyte injury	Troponin T and I[a]	Cohort	238	Detection of serum cTnI was associated with impaired hemodynamics, elevated BNP, and progressive LV dysfunction cTnI was a significant predictor of increased mortality rates in patients with ischemic and non-ischemic HF	1. Study collected information on patients with advanced HF referred for transplant evaluation 2. cTnI levels were assessed at a single point in time 3. Neither neurohormone nor cytokines were assessed, and BNP was measured in only a subset	[100]

Table 3 (continued)

Category	Biomarker	Study type	Sample size	Findings	Limitation	Ref
				Patients with detectable cTnI and elevated BNP were at higher risk of death	4. Limited multivariate analysis was performed	
		Cohort	4053	Noticeable cTnT predicts adverse outcome in CHF By the highly sensitive assay, cTnT retains a prognostic value at previously undetectable concentrations	1. Background neurohormonal therapy appeared to influence outcome 2. Several other causes exist for increasing troponin concentrations	[99]
		Cohort	84,872	In acute decompensated hospital patients with HF, a positive troponin test is associated with more frequent adverse events including in-hospital mortality, independently of treatments and other prognostic variables HF patients with positive troponin required longer stay in the hospital and intensive care unit	1. Cause and effect was not established due to its retrospective nature 2. Data are not confounded due to the prespecified subgroup of patients receiving predefined treatment 3. because troponin was measured only at the time of admission to the hospital, number of patients with acute myocardial infarction cannot be ascertained	[103]
		Cohort	172	Combined use of hsTnT and copeptin determined by single measurement might predict clinical outcome of patients with chronic stable HF	1. Low number of patients included 2. Repeated measurements of copeptin and hs-cTnT were not preformed	[104]
		Cohort	1016	Using high sensitivity, cTnI could be determined in nearly all elderly study subjects Increased cTnI over time was significantly correlated with CV risk, and emerged as a powerful and independent predictor of both all-cause mortality and CV mortality	1. Limited to white subjects aged 70 years and above 2. Participants in the 5-year follow-up examinations represent a somewhat healthier subsets of the total population 3. Changes in cTnI levels were evaluated on a continuous scale 4. Low modeling approach gave somewhat a low event rates for some outcomes	[156]
		Cohort	196	In HF patients without ACS, the persistence of TnI elevation, even at low levels is associated with a worse survival and increased all-cause mortality than sporadic TnI elevations of higher magnitude or any single elevation in TnI	1. Retrospective in nature and was limited by size 2. TnI measurements were obtained according to clinical description, not by trial design 3. Frequency and periods at which additional TnI measurements were obtained were not controlled	[106]
		Cohort	351	In an ambulatory and hospitalized HFpEF patients, hsTnI was increased in a large majority of hospitalized patients and more than half of outpatients with HFpEF, creating the hypothesis of myocyte injury	1. A post-hoc analysis of a pooled cohort three studies which were not powered to detect clinical endpoints according to baseline, peak or change in hsTnI levels 2. Results may not be generalized to ambulatory HFpEF patients because trials were skewed towards white partakers	[157]
		Cohort	525	Elevated levels of hsTnI in a stabilized phase after an ACS event are associated with higher all-cause cardiovascular mortality independent from comorbidities, renal function and LVEF	1. This is a single-center study and hence outcomes in both groups could have been influenced by local practices 2. Since coronary interventions were not performed onsite, data	[158]

Table 3 (continued)

Category	Biomarker	Study type	Sample size	Findings	Limitation	Ref
					regarding type of revascularization were not accessible for most patients 3. Data on some patients presenting with STEMI who received reperfusion therapy was not known 4. Adherence to guideline recommended for ACS was sub-optimal	
	Heart type fatty acid protein	Cohort	179	Elevated H-FABP is an indication of latent and ongoing cardiomyocyte damage and identifies patients at high risk future cardiac events in CHF	1. Limited by small number of participants	[159]
		Cohort	2287	Elevated levels of H-FABP are associated with an increased risk of death and adverse CV events when measured during the first days after hospitalization for ACS	1. The value of H-FABP testing in the setting of chest pain but a lower probability of ACS remains unknown 2. The experiment was conducted in a single treatment arm of the OPUS-TIMI 16 trial 3. Inability to ascertain the relative prognostic utility of H-FABP in patients with severe renal insufficiency	[111]
		Cohort	1080	The prognostic value of increased levels of H-FABP is additive to troponin in low- and intermediate-risk patients with suspected risk ACS patients	1. 53% of the eligible patients admitted during the recruitment were enrolled into the main study 2. Limitations inherent to statistical modeling and multivariate adjustment	[110]
		Cohort	3503	H-FABP was increased in association with greater numbers of CV risk factors and was an independent risk factor for all-cause and CV death H-FABP could be an independent risk factor for the early identification of high risk subjects the general population	1. collected baseline information at a single time point hence serum H-FABP might affect subsequent medical intervention 2. Non-fatal diseases were not assessed 3. Echocardiogram was not performed to assess structural heart disease	[160]
		Cohort	278	The combined measurement of H-FABP with NT-proBNP provides a highly reliable means of short-term mortality prediction for patients hospitalized for ACS, non-ACS cardiac disease or infectious disease	Blood samples were not obtained serially from time of symptom onset. The relationship between the three marker levels and disease status	[161]
		Cohort	1072	H-FABP was an independent predictor for total CV events in patients with stable coronary heart disease, mainly in CV death and acute HF-related hospitalization	1. Possibility of clinical bias arising from clinical profiles, investigator participation, and treatment adherence by the patients 2. Limited by geographical variations because it was a hospital-based 3. Patient medications may have been adjusted by special cardiologist during follow-up 4. Insufficient statistical power of predictive value of H-FABP	[162]

Table 3 (continued)

Category	Biomarker	Study type	Sample size	Findings	Limitation	Ref
					could be derived from the multivariate analysis	
Oxidative stress	Myeloperoxidase	Cohort	3733	There is an independent association between MPO and development of HF in apparently healthy elderly subjects, particularly beyond MI and traditional risk factors	1. MPO was measured at a single time, hence its variability over time was not available 2. There was lack of other biomarkers for HF to be compared to 3. Lack of careful characterization of other comorbid conditions	[163]
		Cohort	667	MPO levels at presentation were similar in patients with acute HF and those with non-cardiac cause of dyspnea. MPO is an independent predictor of 1-year mortality in acute HF, is additive to BNP, and could be helpful to identify patients with a favorable prognosis despite increased BNP concentrations	1. Data was derived from a single-center study 2. Classification of death in clinical practice can be sometimes difficult and unreliable, hence all-cause mortality was assessed 3. Subsequent MPO concentrations were not available	[164]
		Cohort	604	Single assessment of MPO in the plasma independently projected early risk of MI, as well as the risk of adverse major adverse events in the ensuing 30-day and 6-month period MPO levels, in contrast to cTnT, CK-MB and CRP levels, identified patients at risk for cardiac events in absence of myocardial necrosis, highlighting its potential usefulness for risk stratification among patients who present with chest pain	Physicians had access to the CK-MB results, though they were blinded to the other markers	[165]
		Cohort	1331	MPO and CRP had incremental roles in LVSD detection together with NT-proBNP, improving the specificity and sufficiently making screening possible	1. Screening was performed on only white people 2. Analysis using MPO and CRP was post-hoc 3. Interobserver variability in echocardiography analysis is also potential limitation 4. The costings for echocardiography, NT-proBNP, CRP and MPO assays may differ depending on locally negotiated contracts	[166]
	MR-proADM	Cohort	1641	MR-proADM is an important prognostic utility in patients with high mortality risk It also adds incremental prognostic value to BNP	1. Not included high risk patients 2. Blinded the gold standard physicians from biomarker levels taken at the site 3. Excluded patients with known clinical values of BNP 4. Number of deaths was limited by 90-days follow-up duration	[129]
		Cohort	1225	There is a firm evidence of diagnostic utility for MR-proANP and prognostic value for both MR-proANP and MR-proADM in acute dyspneic patients	1. Hazard modeling for 30- and 90-days was hypothesis generating 2. No serial biomarker measurements	[28]

Table 3 (continued)

Category	Biomarker	Study type	Sample size	Findings	Limitation	Ref
					3. Study did not examine relationships between cardiac structure and function	
		Cohort	134	Significant association between elevated proADM levels and 10-year all-cause mortality in a primary care cohort with respiratory tract infection	1. incomplete baseline risk assessment as with the availability of proADM levels in the cohort 2. Recall bias is possible to occur 3. No information was available on the cause of death 4. Small sample hence only few events for the analysis of the relationship between proADM levels and adverse outcome	[130]
		Cohort	277	In COPD patients admitted to emergency for exacerbations, MR-proADM was significantly associated with the risk of poor outcome at 7 and 30 days, even after adjustment for the clinical risk category MR-proADM alone or combined with clinical risk score was a moderate strong predictor of short-term outcome	1. Short-term follow-up (only 30-days) 2. Prevalence of the primary outcome was slightly lower than expected 3. Severity of COPD was not easily comparable to other studies since lung function measurement were inconsistently available	[131]
	Malondialdehyde	Cohort	15	Clinical improvement after intensive medical treatment in patients with decompensated CHF is associated with a decrease in patients oxidative stress status without changes in antioxidant enzyme actions	1. Limited by small number of participants from a single unit 2. Data did not show the tissue origins of MDA 3. The study did not address the mechanism of increased lipid peroxidation	[167]
		Cohort	53	Plasma MDA levels are abnormally elevated in chronic HF patients and are strongly associated with the chronicity of the HF state	1. Limited by small number of patients 2. Patients with renal or liver insufficiency were excluded	[168]
	Serum uric acid	Cohort	4912	Hyperuricemia is a novel, independently associated with greater incidence of HF in a group of young general community dwellers	1. Observational data on SUA are essentially left-truncated 2. Long interval between follow-up visits may be too long to capture HF that resulted in death in shorter time 3. Distribution of SUA concentration was higher in men than women	[169]
		Cohort	281	In hospitalized patients with acute HF, increased SUA levels were associated with both CKD and pulmonary congestion After controlling for potential confounders, hyperuricemia was associated with readmission and death at 6 months	1. Limited by small sample size and retrospective in nature 2. No considerable background information with respect to diet, gout, or kidney stones to make inference on the origin or duration of hyperuricemia 3. No serial measurement of SUA over time to fully understand the role of hemoconcentration	[170]
		Cohort	3440	SUA is associated with increased risk of HF in older men on antihypertensive treatment which is independent of known risk factors	1. It was based on older, predominantly white male population of European origin 2. Based on doctor diagnosed HF, likely to underestimate true incident of HF	[171]

Table 3 (continued)

Category	Biomarker	Study type	Sample size	Findings	Limitation	Ref
				Measurement of SUA in old hypertensive patients in primary care may help identify high risk patients who may benefit from further evaluation of subclinical cardiac dysfunction and pharmacological intervention	3. Echocardiogram was not available 4. SUA was only measured at single point in time	
		Cohort	140	Due to the predictive role of baseline UA and Na for early post-discharge outcome and the absence of significant changes in their levels during initial hospitalization, measurements of Na and UA on admission can be considered as prognosticators in ADHF	1. Limited by small respondents 2. Conducted in a single referral center including relatively advanced HF patients	[172]
		Meta-analysis	12,854	Heightened SUA level independently predicts all-cause mortality and the combined endpoint of death or readmission in AHF patients Measurement of SUA level may improve risk stratification of adverse outcome in these patients	1. The study analyzed the retrospective study-level data but not individual patient data 2. Number of analyzed study in individual outcome was small 3. Majority of patients analyzed were elderly population 4. Optimal cutoff value of hyperuricemia was not determined	[173]
		Cohort	394	Although atherosclerotic risk factors were not independently associated with a poor prognosis, elevated SUA and BUN levels were independently correlated with poor prognosis in patients with hyperuricemia acute HF	1. Performed at single center 2. The study population was mainly patients with severe acute HF and admitted to ICU 3. SUA concentrations for all the study participants could not be measured 4. Factors at the compensated phase were excluded from the multivariate analysis	[174]
Inflammation	C-reactive protein	Cohort	76	Higher CRP levels correlates with higher NYHA functional class patients signaling a poor therapeutic response Higher CRP levels were also linked to increased rates of readmission and mortality and could also be an independent marker of improvement and readmission	Limited by the small number of subjects	[175]
		Randomized controlled trial	12	IL-1 blockade with anakinra for 14 days significantly reduced systemic inflammatory response and improves aerobic exercise capacity in patients with HFpEF and elevated plasma CRP levels The decrease in CRP levels was correlated with an improvement in peak oxygen consumption	1. Small number of subjects and short duration of treatment and observation 2. Sample was predominantly women, only 1 man out of the 12 patients	[69]
		Cohort	3075	There is a significant association between inflammatory markers and risk of incident HF Multiple biomarker elevations at baseline were associated with pronounced risk for HF	1. Diagnosis of HF was based on hospitalization. 2. Echocardiography was not performed at baseline and thus participants with asymptomatic HF might have been included	[78]

Table 3 (continued)

Category	Biomarker	Study type	Sample size	Findings	Limitation	Ref
					3. Left ventricular function was not prospectively assessed during hospitalization	
		Cohort	622	Higher hs-CRP and NT-proBNP values are associated with all-cause mortality in DCM and were independent predictors of all-cause mortality after adjusting for the classic risk factors of HF in DCM patients	1. There may be variations in length of preclinical phase that influenced the relations between the markers and mortality 2. Study was limited to patients with DCM who required hospitalization 3. All the biomarkers were measured just at admission without the discharge values	[71]
		Cohort	1608	Increased levels of both hs-CRP and NT-proBNP had worse clinical outcomes in AHF patients	1. Confounding factors might have influenced the relationship between hs-CRP and NT-proBNP and clinical outcomes 2. Only patients with available hs-CRP and NT-proBNP results were included in this study	[176]
		Randomized controlled trial	5010	There is a direct correlation between elevated plasma CRP and the progression of HF CRP is a predictor of adverse clinical outcome independent of ischemic/non-ischemic etiology and other predictors of outcome, such as BNP	1. This was a post-hoc analysis which was not designed to address the present findings 2. The effect of improvement versus worsening of HF on CRP, independent of any drug effect is difficult to assess 3. Model misspecification and overfitting might limit generalization of the results	[177]
	Cytokines (IL-1 and 6, TNF-α)	Cohort	1169	Cytokines represent an important therapeutic target in patients with HF Circulating levels of TNF-α and IL-6 are independent predictors of increased mortality in patients with AHF Circulating levels of cytokines are modified by age, sex, and cause of HF	Data on Hispanics were regarded to be provisional due to smaller number of subjects	[178]
		Cohort	180	Enhanced inflammatory response is associated with greater burden of symptoms and worse outcome Treatment with anakinra (IL-1 receptor antagonist) showed improvement in exercise tolerance after 12 weeks but did not show any recovery after 2 weeks	Limited by small number of subjects and short-term treatment	[79]
		Randomized controlled trial	90	Concentrations of IL-1, IL-6, and TNF-α were negatively correlated with cardiac function	Limited by small number of study participants from a single center	[179]
		Cohort	732	In an elderly population, a single determination of inflammatory markers, particularly IL-6 was associated with increased risk of CHF patients without prior myocardial infraction	1. Echocardiography was not performed at baseline examination 2. Study sample was predominantly whites and elderly	[180]
	Fas (APO-1)	Cohort	61	Serum levels of Fas increased with severity of HF and was related to	Small number of participants were enrolled	[86]

Table 3 (continued)

Category	Biomarker	Study type	Sample size	Findings	Limitation	Ref
				soluble forms of the similar receptor family, TNF receptors		
		Cohort	88	Circulating levels of soluble Fas was found to increase in patients with advanced CHF The failing heart may contribute to the increased concentration of soluble Fas ligand	The number of cohorts was small and they were drawn from a single center	[87]
		Cohort	15	Marked increase of myocardial Fas expression is present in end-stage HF and correlates with TNF expression IL-6 was significantly reduced by LVAD support	1. Protein levels were not assayed, only transcripts were 2. Transcriptional analysis used RNase protection assay rather than quantitative PCR	[88]
	Procalcitonin	Cohort	1641	PCT may aid in the diagnosis of pneumonia, particularly in cases of high diagnostic uncertainty It may also aid in the decision to administer antibiotics to patients presenting with AHF where clinical ambiguity exist	1. Antibiotics treatment was neither randomized nor standardized in types and dosage 2. CRP measurements were not included in the analysis 3. Confirmation of diagnosis was performed by two independent cardiologists	[93]
		Case-control	59	Serum PCT is a potential biochemical marker that may aid in the early diagnosis of HF and for assessing disease severity	1. This is limited by the retrospective design and small sample size 2. Limited numbers of patients in each NYHA class	[181]
		Cohort	501	In patients admitted, measurement of PCT and MR-proADM improves risk stratification and management Combined use of the biomarkers predicted both rehospitalization and mortality at 30 and 90 days	1. Lack of further value of the biomarkers at the exact discharge time from the hospital 2. Data about the causes of rehospitalization or mortality is unknown	[90]
		Cohort	4698	PCT levels increases significantly with increasing severity of HF in non-infected patients PCT has certain diagnostic values for simple infections and infections intricate by HF, however, positive predictive value of PCT decreases with the severity of HF Close attention must be paid to cardiac function and PCT expression in aged patients with infections complicated by HF	1. It is a short-term prognostic analysis 2. The three commonly used infection markers were ignored	[91]
		Randomized controlled trial	1781	Patients with AHF and significantly elevated PCT levels indicating probable undiagnosed/untreated bacterial infection, had poorer in-hospital and post-discharge outcome	1. The study is retrospective in nature and patients were not followed with the primary goal of determining bacterial infection 2. Several cutoff values of PCT were of varying performances were recorded for diagnosing bacterial infection 3. The presence and source of bacterial infection were not confirmed with the gold standard diagnostic tools, like culture 4. LVEF data was not available for more than half of the subjects	[92]

Table 3 (continued)

Category	Biomarker	Study type	Sample size	Findings	Limitation	Ref
		Cohort	453	In emergency department patients with acute dyspnea, PCT is an accurate diagnostic marker for pneumonia and adds independent prognostic indication for 1-year mortality	1. Modest size limited the statistical power 2. Number of patients diagnosed with pneumonia was low as compared to that of HF 3. Lack of serial measurement of PCT and other markers 4. Few patients with elevated PCT went untreated with antibiotics	[94]
Hypertrophy/fibrosis	Soluble ST2[a]	Cohort	599	In dyspneic patients with and without AHF, sST2 concentrations are strong predictors of mortality at 1 year and might be useful for prognosis when used singly or combined with NT-proBNP	1. Biological role of sST2 in the heart are poorly understood 2. Limited by single-center study 3. Numerous significant differences between decedents and survivors are identified and this might lead to the risk of spectrum bias	[51]
		Randomized controlled trial	815	Clinical predictors along with NT-proBNP were strongly associated with increased risk of death from pump failure and sudden cardiac death, with insignificant incremental contributions of ST2 and galectin 3 Predicting sudden death risk was less strong and improved by evidence stipulated by novel markers	1. Analysis was limited to a subset of HF-ACTION patients in whom plasma levels of NT-proBNP, galectin 3 and ST2 were available 2. Baseline characteristics of patients with and without available NT-proBNP levels are statistically similar 3. Adopted the study population from HF-ACTION trial and as such, susceptible to the limitations central to the clinical trial population 4. Majority of our subjects had impaired ejection fraction (≤ 35%)	[182]
		Consecutive case series study	891	Head-to-head comparison of ST2 and galectin 3 in CHF exposed the superiority of ST2 over galectin 3. The additive value of galectin 3 was insignificant	1. Whether serial measurements both markers at predefined time points would have improved risk stratification was not incorporated into the design 2. Ultrasound was primarily used to characterize ventricular remodeling and cardiac magnetic resonance imaging was not routinely performed on all patients 3. It was a general HF population treated at a specific and multidisciplinary HF unit	[183]
		Randomized controlled trial	151	Among CHF patients, baseline measurements of novel biomarkers added independent prognostic information to clinical variables and NT-proBNP Except serial measurement of ST2 appeared to add prognostic information to baseline concentration and predicted change in LVEF	1. Post-hoc analysis of small single study 2. Non-uniform follow-up time interval 3. Starting levels of biomarkers as well as the degree of change should be considered when interpreting a change in concentration	[184]
		Cohort	262	ST2 as a continuous variable was a predictor of all-cause mortality and cardiovascular mortality in non-ischemic HF patients	1. Small number population 2. Women were under-represented	[54]

Table 3 (continued)

Category	Biomarker	Study type	Sample size	Findings	Limitation	Ref
				Intermediate levels of galectin 3 allows for better prognosis	3. Multivariate analysis was performed in the subgroups with limited event rate	
		Randomized double-blind controlled trial	8442	Treatment with sacubitril/valsartan when compared with that of enalapril was linked to greater reductions and less increase in ST2 over time Baseline ST2 levels were independently associated with a significant change in the risk of subsequent outcome	Centers in Asia/South Pacific and in South America did not participate in the PARADIGM-HF trial	[55]
	Galectin-3[a]	Cohort	599	Among dyspneic patients with and without ADHF, galectin 3 levels are related with echocardiographic markers of ventricular function In patients with ADHF, a single admission galectin 3 levels predict mortality to 4 years, independent of echocardiography markers	1. Echocardiography was obtained during the index admission which may cause delays between collection of biomarkers and echocardiograms 2. Relationships between galectin-3 and echocardiography variables are not necessarily definitive 3. Small patient cohort limited the study of galectin 3 in patients with HF and preserved versus depressed LV dysfunction	[185]
		Cohort	592	Galectin 3 is a strong and independent marker for HF outcome and is particularly useful in HFpEF Inflammatory markers are positively correlated with galectin 3 levels	1. Galectin 3 levels could only be measured in subsets of patients for whom baseline plasma levels are available 2. Follow-up samples were available from a minority of patients which could have caused bias and reduce power in repeated galectin 3 sampling 3. Echocardiography evaluation was not standardized to a protocol	[186]
		Cohort	3353	Higher concentrations are associated with increased risk of incident HF and mortality	1. While addition of galectin 3 to clinical factors resulted in improved classification, changes in the c-statistics were negligible 2. Number of HF events was modest and likely limited the power to conduct quartile analysis to check the role of kidney function in the link between galectin 3 and HF	[58]
		Cohort	877	Out of the 29 biomarkers studied, galectin 3 emerged as predicted HF patients at low risk for 30-day and 180-day mortality and HF rehospitalization	1. This is a sub-study and hence conclusions are limited to that of generating hypothesis 2. Many of the assays evaluated 3. Most biomarkers were measured on a multiple platform 4. All patients studied were hospitalized and sample collection took place before discharge	[61]
		Cohort	496	Repeated measurement of galectin 3 seemed to be strong predictor of outcome in AHF patients, independent of NT-proBNP	1. The study population is not a complete representative of the average HF population 2. Women were under-represented 3. Only 18% of the included HF	[187]
Neurohormonal activation	Norepinephrine		5010		1. Subgroups defined by demographic characteristics were	[188]

Table 3 (continued)

Category	Biomarker	Study type	Sample size	Findings	Limitation	Ref
		Randomized controlled trial		Baseline NE and BNP are independent prognostic markers in HF patients	similar to the study population as a whole 2. Background neurohormonal therapy appeared to influence the outcome	
		Cohort	106	Single resting venous blood sample showing the plasma norepinephrine concentration provides a better guide to prognosis than any other commonly measured indexes of cardiac performance	1. Limited number of deaths does not provide accurate statistical power 2. The distinction between pump failure and sudden death is difficult 3. The study did not include comprehensive evaluation of indexes of cardiac dysfunction that are measured by non-invasive procedures	[118]
		Randomized controlled trial	4300	All the neurohormones were found to be significant predictors of HF morbidity and mortality Numerous of these markers have been associated as contributors to the progression of HF, but BNP was the most powerful indicator for poor outcome	Background neurohormonal therapy appeared to influence the outcome	[120]
	Endothelin-1	Cohort	3223	Increased concentrations of plasma endothelin-1 is specifically associated with elevated pulmonary artery systolic pressure on echocardiogram, and may identify at-risk population that could be evaluated for targeted reduction and management strategies for future studies	1. The analysis of endothelin and PASP levels was cross-sectional, therefore it cannot be determined whether elevations in endothelin caused development of pulmonary hypertension or vice-versa 2. Data on the use of endothelin receptor antagonists were not available; these medications can elevate plasma endothelin levels 3. Cutoff values for endothelin was lower than that observed in other studies	[122]
		Cohort	384	In patients presenting with acute onset of severe dyspnea on admission, endothelin, as well as MR-proADM, MR-proANP, copeptin, troponin, procalcitonin and CRP were independent predictors of day-28 outcome	1. The study was performed in a single center 2. Patients with severe acute dyspnea were hospitalized in two different units (emergency unit and intensive care unit), with very different day-28 mortality 3. No external validation analysis was conducted	[123]
	Arginine vasopressin (Copeptin)	Cohort	557	Pointedly increased 90-day mortality, readmissions, and emergency department visits in patients with higher copeptin, specifically those with hyponatremia Copeptin was highly prognostic for 90-day adverse events in acute HF subjects, adding prognostic values to clinical predictors, serum sodium and NPs	1. Limited by modest size of acute HF cohort and short follow-up period	[135]
		Cohort	3717	In seemingly low-risk patients with stable coronary artery disease and preserved LVEF, elevated levels	1. The study was predominantly white, male population of over 50 years	[136]

Table 3 (continued)

Category	Biomarker	Study type	Sample size	Findings	Limitation	Ref
				of novel biomarkers reflecting CV stress may be useful both for identifying patients who are at higher risk of CV death and HF and to select patients who receive a significant from ACE inhibitors	2. Blood samples were obtained from a only a subgroup of the participants 3. The formation of multi-marker score should be considered exploratory	
		Cohort	251	hs-CRP levels but not copeptin were increased in primary aldosteronism patients at baseline compared with matched controls Copeptin and hs-CRP concentrations reduced after specific primary aldosteronism treatment suggesting effective CV risk and mortality reduction	1. Complete data sets of baseline and follow-up after 1-year were only available for less than half of the total patients 2. Control cohort of one of the study groups is not strictly hypertensive and hence cannot conclude that blood pressure had an influence in the results	[137]
		Meta-analysis	18,455	Elevated levels of plasma copeptin is highly associated with an increased risk of HF and all-cause mortality in patients with HF Copeptin might serve as a practical guide for the prevention and treatment of HF	1. Only English published articles were selected 2. Number of included studies is relatively small 3. Uncontrolled confounders cannot be resolved as the potential explanation for the observed association	[139]
		Cohort	60	Copeptin levels are increased in patients presenting with obstructive and non-obstructive hypertrophic cardiomyopathy Patients with heightened levels of copeptin may have higher risk for future adverse CV effects	1. Relatively small study population 2. Only one measurement was obtained for copeptin and NT-proBNP 3. The findings do not imply causal relationship between copeptin levels and hypertrophic cardiomyopathy	[140]
Renal injury	Cystatin C	Cohort	990	High cystatin C levels predict significant enhanced risks of all-cause mortality, CV events, and incident HF among ambulatory persons with CHD Higher cystatin C concentrations predicted increased risk of these adverse clinical outcomes even in persons without microalbuminuria or low estimated GFR	1. The diagnosis of CV events and incident HF may be subject to misclassification bias 2. Number of outcome events within each quartile was quite small 3. Elderly and predominantly male participants were used	[189]
		Cohort	587	Cystatin C correlated well with the UA level and showed the cardiac risk stratification early and easily The combined index of SUA and cystatin C levels at admission appears to be more useful predictor of clinical events than other renal measures in HF patients presenting with dyspnea	1. Follow-up of the cause of renal dysfunction in the hospital was not achieved due to unavailable data 2. Patients showed relatively low incidence of clinical outcome 3. The design did not permit to assess non pharmacological treatment like implantable-defibrillator	[190]
		Cohort	232	Cystatin C was an independent risk factor for cardio-renal prognosis and its hazard ratio was persistently sturdy throughout the 2-year follow-up Cystatin C could provide more useful information for risk stratification than UA and	1. Limited by its retrospective nature 2. Total number of enrolled respondents was small	[190]

Table 3 (continued)

Category	Biomarker	Study type	Sample size	Findings	Limitation	Ref
				NT-proBNP specifically in acute HF		
		Cohort	3155	Increased cystatin C concentrations is probably associated with an increased risk of all-cause mortality and rehospitalization among HF patients The increased risk is independent of creatinine or estimated GFR	1. Inflammatory, hyperthyroidism, glucocorticoids use, and current smoking status could have influenced cystatin C levels 2. Cystatin C level was determined only at baseline 3. Different cutoff values were utilized in each study 4. Generalizability to younger HF patients should be with caution due to predominantly elderly populace	[191]
	NGAL	Cohort	2130	Tubular damage as indicated by increased urinary levels of NGAL, NAG, and KIM-1 is independently associated with impaired outcome in CHF patients, even at normal eGFR	1. Markers of tubular damage were measured in only morning spot urine samples and corrected them for creatinine concentrations 2. Creatinine generation is decreased in HF, which may result in higher urinary creatinine adjusted values of measured markers 3. Urine was collected at variable time intervals after randomization	[192]
		Cohort	562	Plasma NGAL predicts mortality in HF patients with or without CKD It is a stronger predictor for mortality than the eGFR and cystatin C	1. Primary renal disease at baseline was not excluded 2. Insufficient data on albuminuria in some cohorts 3. Plasma NGAL was used rather than urine, which might affect results	[193]
		Cohort	61	Urine NGAL concentrations early after MI is associated with NT-proBNP levels and even lower levels below the usual cutoff points had high specificity for HF	1. Only urine concentration was used, which may follow a different timeline than serum concentration 2. The cutoff value for urine NGAL with high specificity for HF was derived from the analyzed sample itself 3. Discharged patients from the ICU within 24 h were excluded	[194]
		Cohort	132	In patients with AHF, an increase in tubular damage markers, especially urine NGAL predicts development of true WRF Increased concentrations of urine NGAL and cystatin C in the first 2 days of hospital stay could be used to identify patients with high risk of post-discharge mortality	1. Limited by small number of subjects with true WRF 2. Only white subjects were enrolled	[195]
		Cohort	927	Plasma NGAL was not superior to creatinine for the prediction of WRF or adverse in-hospital outcomes The use of NGAL to diagnose acute kidney injury in AHF cannot be recommended at this time	1. Samples were collected after diuretic therapy which might have influenced NGAL levels 2. The first measured creatinine value was used as baseline for assessment of WRF 3. Creatinine levels were not tested at core laboratory and are subject to between laboratory variability	[196]

Table 3 (continued)

Category	Biomarker	Study type	Sample size	Findings	Limitation	Ref
		Cohort	1447	Plasma NGAL was not independent predictor of poor outcome, though serial measurements provide some additional information for the prediction of clinically significant WRF in AHF patients	1. Study is retrospective in nature 2. Frozen samples were used to assessed NGAL 2. Performance of urinary NGAL could not be compared to that of plasma due to unavailable urine sample	[197]

ADHF acute decompensated heart failure, *AHF* acute heart failure, *AF* atrial fibrillation, *ANP* atrial natriuretic peptide, *BNP* B-type natriuretic peptide, *BUN* blood urea nitrogen, *CHD* coronary heart disease, *CRP* C-reactive protein, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *cTn* cardiac troponin, *CVD* cardiovascular disease, *eGFR* estimated glomerular filtration rate, *GDF-15* growth differentiation factor 15, *HFrEF* heart failure reduced ejection fraction, *HFpEF* heart failure preserved ejection fraction, *IL* interleukin, *KIM-1* kidney injury molecule-1, *LVEF* left ventricular ejection fraction, *LVH* left ventricular hypertrophy, *LVSD* left ventricular systolic dysfunction, *MDA* malondialdehyde, *MR-proANP* mid-regional pro atrial natriuretic peptide, *MR-proADM* mid-regional pro-adrenomedullin, *NT-proBNP* N-terminal pro B-type natriuretic peptide, *TNF-α* tumor necrosis factor-α, *NGAL* neutrophil gelatinase-associated lipocalin, *NAG* N-acetyl-D-glycosaminidase, *PCT* procalcitonin, *STEMI* ST-elevation myocardial infarction, *SUA* serum uric acid, *WRF* worsening renal function

[a] Established biomarkers

severity as well as increased oxidative stress as compared to the control group [167].

There are so far established correlations of malondialdehyde in HF patients. As to whether the increased malondialdehyde predicted HF incidence or HF and comorbidities led to the increased malondialdehyde concentrations is not well established. Besides, studies that have been conducted thus far are all limited by small number of participants and single study centers. Larger clinical trials are currently needed to define its predictive role in the management of HF patients.

Myeloperoxidase

Myeloperoxidase (MPO) is an enzyme derived from excited neutrophils and leukocytes and catalyzed formation of several reactive oxidant molecules and contributes to endothelial dysfunction by reducing nitric oxide levels [163, 164]. It has been found to predict cases of acute coronary syndrome and chest pain [165, 198], and has lately been identified in cases of HF demonstrating positive relationship with both NYHA stages and diastolic dysfunction [199]. Another study has demonstrated that MPO can predict development of HF in old adults without history of traditional risk factors [163], and likewise its chlorinated activity has been found to increase in elderly chronic HF patients [200]. In screening for LV systolic dysfunction among community individuals, combining MPO to CRP provided an additive value to BNP. Besides, the researchers also noted that MPO independently discovered 27 of the 28 patients with undiagnosed systolic dysfunction [166].

While there are many other results that indicate a promising use of MPO in HF management, the lack of therapeutic consequences and the pre-analytical concerns connected with its assessment challenges its potential value [201]. Also, MPO concentration increases in patients presenting with dyspnea who had acute decompensated HF and those with other cause of dyspnea, an indication that many causes of dyspnea other than HF can elevate MPO values [201, 202]. Though the MPO inhibitor AZD4831 was safe, tolerable, and decreased serum uric acid in the first human trial, however, that trial was limited by number of participants, its exploratory nature, and only White participants [203]. Further larger trials may lead to decreasing MPO levels and aid clinicians to assess if it can aid in clinical decision making. Also, studies evaluating free and leucocytes-associated MPO levels as prognosticators of short- and long-term risk of CV events are needed.

Serum uric acid

Another prognostic marker that hints causal oxidative stress is serum uric acid (SUA), which has been reported to depict the degree of xanthine oxidase activation in HF patients; and in addition, proven to be a marker of cell death when other purines are degraded [202]. Elevation of serum uric acid was noted to predict HF onset in the Framingham Offspring Study. In this study, the researchers found that among the 4912 healthy individuals, HF incidence was six times higher in patients with highest values of serum uric acid as compared with those with lowest concentrations [169]; and this finding was later confirmed by Palazzuoli and colleagues [170]. Beyond its relation to HF incidence, there are numerous clinical substantiations that have accentuated the predictive role of serum uric acid for early post-discharge for HF outcomes, HF severity as well as 1-year mortality [172, 174]. Though inhibition of xanthine oxidase with allopurinol decreased serum uric acid concentrations and enhanced endothelial function in HF, a uricosuric agent (probenecid) failed to improve endothelial utility in HF [204]. There is a report that this action of xanthine oxidoreductase may be a precise prognosticator of HFpEF severity and HF medical

consequences than serum uric acid [205]. This is because, in the OPT-CHF study, oxypurinol which is a known xanthine oxidase inhibitor decreased the concentrations of serum uric acid levels, but the reduction failed to yield any improvement in the combined primary endpoint that included readmission and CVD mortality [206].

The above data and many other studies have confirmed the highly specific prognostic role of SUA in HF patients. To be fully accepted and used in clinical context, various current and future studies with adequate power to detect small improvement in clinical outcomes would be needed to determine whether HF can be prevented. Also, larger randomized controlled trials must be conducted to assess the use of xanthine oxidase inhibitor to enhance the SUA prognosis.

Reactive oxygen metabolites

Reactive oxygen metabolites (d-ROMs) test has recently been investigated as a novel marker of oxidative stress used in clinical setting. For instance, a current study has indicated that d-ROMS can assess prognosis and predict risk of further cardiovascular outcomes [207]. It can also foretell initial HF admission in old patients and its strength in prediction increases when combined with BNP in a multi-marker strategy [208]. Several of such substantiations are needed to warrant its recommendation as a clinical tool for HF management.

Makers of renal injury

Several early markers of renal injury have been unveiled that appear to reflect close interaction between the heart and kidneys in cardio-renal dysfunction, whether from advanced HF and poor renal perfusion or due to excess diuretic use and subsequent kidney dysfunction. Notable among them are cystatin C and neutrophil gelatinase-associated lipocalin (NGAL).

Cystatin C

Cystatin C is a 23-kDa cysteine protease inhibitor synthesized at a continual rate by all nucleated cells that is filtered and then catabolized by tubular cells [209]. Many characteristics of cystatin C make it exceptional to creatinine as an assessment of glomerular filtration rate (GFR), and hence there has been extensive interest in the potential use of cystatin C as a marker of both acute injury as well as chronic renal failure [7]. The realization of a strong correlation between renal failure and HF prompted the research into targeting cystatin C as a marker for cardio-renal dysfunction. In this regard, Kim and colleagues [210] as well as researchers in the Heart and Soul study have discovered that increased concentrations of cystatin C were highly associated with upsurge risk of all-cause mortality, cardiovascular outcomes as well as HF incident in patients with known coronary heart diseases [189]. Latest report indicates that cystatin C seems to be related to LV diastolic dysfunction and variations in collagen metabolism irrespective of predictable GFR [211]. Again, increased cystatin C levels in acute HF patients offered an incremental prognostic utility more than that provided by NT-proBNP and uric acid [190].

It is an irrefutable fact that cystatin C predicts CV and especially acute HF outcomes; additional investigations are thereby required to clarify its role as an independent predictor in patients with chronic HF, and to evaluate the impact of therapy on sequential assessment of cystatin C. Also, research to evaluate the beneficial potential by suppression of cystatin C concentrations are warranted currently.

Neutrophil gelatinase-associated lipocalin

NGAL is a small glycoprotein (25 kDa) released by neutrophils and several epithelial cells during acute kidney injury or during inflammation [212]. NGAL has been used as a marker for early kidney injury and a prognosticator of worse consequences in HF due to its early detection in the urine or serum [7, 213]. Since concentrations of NGAL are associated strongly with neurohormonal and clinical measures of the severity of the disease in patients with chronic HF, its assessment may be appropriate for guessing the onset of failing renal function in HF patients when combined with values of NPs especially [135]. Initial data from the research conducted by Damman and colleagues indicated that levels of NGAL do not significantly change in adjustment of diuretic therapy [192]. Further, the researchers of AKINESIS and the PROTECT studies have cautioned the use of serum NGAL in diagnosing acute kidney injury in acute HF, and they further stated that plasma NGAL was not superior to creatinine in predicting worsening renal function or adverse in-hospital outcomes [196, 197].

Categorizing people at risk of developing kidney dysfunction and poor outcomes remains a huge task due to the mixed results provided by newer biomarkers such as NGAL. Due to this, NGAL must be thoroughly investigated (including the type of sample that provide the ideal results, given the mixed results concerning either serum or urine samples) to elucidate its role in administering therapy for HF and also to unearth candidate therapeutic potentials available for this molecule. Furthermore, other candidate markers for predicting worsening renal function in HF patients must be researched on and targeted to reduce the incident of renal function in HF patients.

Multi-marker testing

Given that HF syndrome involves different kinds of interplay ranging from cardiac remodeling to altered renal function and neurohormonal activation pathways, significant results in risk stratification as well as HF management may be obtained from a multi-marker approach in the context of several other

biomarkers that tackle different pathophysiological pathways. This is because such a multiple biomarker strategy possesses the capability to strongly specify the care of patients with HF. As a proof, Ky et al. [214] examined seven markers that included hs-CRP, BNP, myeloperoxidase, troponin I, sST2, creatinine, soluble fms-like tyrosine kinase receptor-1, and uric acid which represent different pathophysiological pathways. The researchers hypothesized that when those markers are assessed together could predict the risk of adverse consequence, define mortality, cardiac transplantation, or implantation of ventricular assist device. Surprisingly, the combined multi-marker score provided excellent measurement of risk, with the hazard ratios of the intermediate risk and high risk tertiles significantly elevated to 3.5 and 6.8 respectively compared with the most commonly used clinical risk scores in HF, the Seattle HF model (SHFM) [214].

Many other investigators have confirmed the strong predictive role of multi-marker strategy than any single marker could predict in the panel. For instance, a recent work from the RELAX-AHF trial also using seven circulating biomarkers concluded that serially evaluation of those markers (NT-proBNP, hs-cTnT, sST2, GDF-15, hs-CRP, galectin-3, and cystine-C) provided the strongest prognostic improvement incomparable to a single time point-based single marker strategy [215].

Currently, since the NPs remain the gold standard and have really demonstrated its utility in prognosis, diagnosis, management, and development of novel therapy, this approach is largely based on involving the NPs with markers of myocardial injury and fibrosis (mainly sST2 and galectin-3). This new score has been authenticated by the 2017 ACC/AHA/HFSA Updated Guidelines [12] for HF and is reported to be apposite for individuals at risk for HF, those with ascertained chronic HF, patients with suspected and/or documented acute HF, as well as HF patients discharged from the hospital. Newly unraveled biomarkers of HF like the mid-proANP, MR-proADM, pro-endothelin, as well as copeptin were investigated in 28-day predictive value in patients with dyspnea and suspected acute HF. It was noted that MR-proADM improved discriminative value of NPs when combined with copeptin and cTnT [123]. Hence future studies to combine MR-proADM with the NPs, copeptin, and cardiac troponin will be of added advantage.

Though there are reports of lack of clarity and consistent evidence in this multi-marker approach in improvements in cardiovascular mortality and outcomes [95], cardiac troponins, sST2, and galectin-3 could enhance the prognostic utility of the NPs in HF-associated readmission and cardiovascular mortality. This strategy has recently been confirmed by specialists of several medical organizations and it is the only authorized multi-marker strategy at the moment [76].

In conclusion, since most of these upcoming biomarkers are non-specific and have been noted to be associated with other tissues and organs, their prognostic utilities cannot be fully guaranteed and therefore their recommendation is in limbo. On the contrary, subjecting these biomarkers to intense scrutiny and rigorous comparison to the "gold standard" markers like NPs and cTns leading to their discrimination statistically may seem sensible from the clinical point of view, but may pose serious threat to the broadening of mechanistic insights into the pathological processes of HF syndrome. Hence, as proposed by Piek and colleagues [216], incorporating preclinical investigations in animal models could enlighten the relationship that co-exist between plasma marker concentrations and the procedures of cardiac remodeling, and further clarify the possible influences of other pretentious organs and tissues. This consequently leads to a formation of the multi-marker system, which has been of interest in current and future research. As several processes are involved in the development and progression of HF through different mechanisms, combination of newer markers to recommended ones could possibly offer excellent predictive value in HF.

Future approach: advent of omics in HF

Almost all the above recognized biomarkers were speckled through classical, hypothetical-driven research approach. With the advent of omics, innovative research fields that are targeted to outline complex biochemical interactions have presented researchers with new ways of monitoring health and disease, including the identification of biomarkers. A crucial area in HF is the requisite to move the role of these biomarkers beyond use exclusively for diagnosis and prediction towards better incorporation for the selection and titration of specific medication and treatment strategies. This therefore requires larger fields of research blended with concurrent rapid surge in the capacity to recognize novel biomarkers through improvements in the omics approach.

This approach incorporates several biological disciplines from genome to transcriptome, proteome, metabolome, epigenome as well as microbiome to focus on the assessment of varied range of biomolecules [217]. These approaches arose from the inception of the Human Genome Project in the 1980s, and since then, there have been exceptional developments in the technologies to examine nucleic acids, proteins, and metabolic analytes at scale [218]. In general, there are two major implications that can be gleaned from the omics study: firstly, molecules that are nonchalantly involved in the pathogenesis of HF can be targeted by therapeutic intervention; and secondly, protein molecules which are modified in an expected approach in reaction to the disease condition can be used as stage-specific markers of the disease [219].

Genomics Genomics, the most advanced form of the omics approach, has been utilized in many successful genome-wide association studies (GWAS) towards genes-related participation in HF have been conducted by integrating single

nucleotide polymorphisms (SNPs) of numerous genes in predictive scores among HF patients [95]. In this context, some researchers have identified some distinctive loci (CLCNKA, BAG3, HSPB7) associated with HF caused by dilated cardiomyopathy [220–222], SNPs of genes encoding enzymes related to oxidative stress [222], LVEF [223, 224], as well as genotypes of GNB3 in HF onset and progression using GWAS analysis. Many other GWAS analyses have recognized momentous relations of abundant mutual DNA differences with HF and other cardiovascular diseases [225, 226]. New risk scores reflecting variabilities in genetics and epigenetics characteristics in HF development and progression appear encouraging [227], and have further been used to foretell risk of coronary heart disease and encrypt diverse routes of lifetime risk that are not portrayed by conventional risk scores [228].

Epigenomics Some researchers have verified that epigenomics regulation may perform an imperative part in the pathogenesis of HF by playing a crucial role in the phenotypic reaction in the failing heart [229]. The mechanisms of epigenetics can be acquired and constitute a path by which interactions between genes and the environment can occur. Consequently, modifications of the epigenome could assist in clarifying genes by environmental interactions that are assumed as one of the major promoters to pathogenesis of the disease. Epigenetic regulation occurs by some key mechanisms including DNA methylation, histone modifications (acetylation, methylation, phosphorylation), chromatin remodeling, and non-coding RNAs (microRNAs, long non-coding RNAs, small interfering RNAs). One of the groundbreaking researches which endorsed epigenome analysis as a contributor to HF development was when Movassagh and co-researchers [230] revealed differential histone methylation profiles associated with HF using ChIP-seq. Afterwards, a group of researchers also established and simulated genome-wide inscriptions of lower resolution DNA methylation changes in patients with dilated cardiomyopathy leading to HF [231]. More recently, Meder and colleagues have offered a complete mapping of DNA methylation in human heart and recognized novel loci associated with HF using a comprehensive analysis technique [232].

Transcriptomics Unlike genome, transcriptome portrays additional fascinating clues to the function of genetic variants due to its highly dynamism in reacting to acute and developing exposers. Research on transcriptomics can help unravel significant transcripts and genes that influence the pathogenesis of HF [233]. This is because transcriptome analysis has the capability of detecting variations in gene expression levels between different cohorts, thus identifying potential genes that may be highly or lowly regulated in HF settings. Using high-throughput RNA-seq analysis has disclosed modifications in cytoskeletal and nucleocytoplasmic transport-related genes and other key pathways in the failing heart [234–236]. It has also recently discovered particular variations transpiring in the transcriptome of HF patients and further identified novel genes which are associated with human heart tissues and HF development [237]. Lastly, transcriptome biomarker panel which has the potential to discriminate HFrEF from HFpEF has been identified using gene expression microarray [238]. Transcriptomic analysis of human dilated cardiomyopathy suggests that a consistent and distinct pattern of gene expression is found in HF and a gene expression signature can predict HF disease progression. Moreover, deregulated expression of coding and non-coding genes directly affects HF development and progression.

Proteomics This comprises of the study of the full set (or a large subset) of proteins present in a cell or tissue. Proteomes are constantly changing with changes in physiological conditions such as different phases of cell cycle, aging cell and functions, as well as environmental factors like stress. The pathophysiology of HF is characterized by differences in proteome expressions and configurations, making it the basic concept underlying the application of proteome in this syndrome. Thus, the study of the proteomes' active flexibility permits the molecular phenotyping of HF and offer acumens into its associated pathogenic processes. Most of the proteomics studies in HF research have been performed using patients' plasma which is most often debatable because of its complication and forcefulness [239]. Irrespective of these difficulties in plasma proteomics, a novel candidate biomarker—quiescin Q6 sulfhydryl oxidase 1 (QSOX-1), has been identified as a most prominent protein marker to recognize patients with acute decompensated HF [240]. After its discovery, QSOX-1 was noted to have been induced in the hearts of rats with HF after aortic thoracic constriction. Changes related to proteins of extracellular matrix, cardiomyocyte cytoskeleton and protection, contractile apparatus, and energy productions that are either enhanced or downregulated have been as well revealed by proteomics analysis [241, 242]. Among elderly individuals, proteomics-originated markers that are capable of predicting incident HF independent of established risk factors have been identified in a recent study [243]. These nine protein peptides identified from the study were found to be implicated in processes such as apoptosis, inflammation, and remodeling. Earlier research has indicated that though proteomics has the likelihood to provide fingerprints of circulating proteins in a variety of cardiovascular diseases including HF [244], but the challenge was to focus on its analytical techniques and significance in the clinical setting.

Metabolomics It acts as an indication of gene and protein functional activity by bagging indication that is nearer to a given disease phenotype while covering the spectrum from genetic sequence to cellular physiology [245]. Since metabolomics profiling technologies such as nuclear magnetic

resonance (NMR) spectroscopy and mass spectrometry (MS) can produce hundreds and thousands of biological markers from single bio-sample, they have the capability to elicit innovative accuracy to HF research and medical treatments. Some major features that make metabolomics profiling more important are its ability to offer the possibility of supplementing other cellular procedures such as the massive genetic information derived from DNA sequencing in humans and even their integrative effects of environmental exposures such as nutritional intake, corporal health, microbiota variation, and toxicant exposures (Fig. 1).

Though metabolomics studies in HF are limited at the moment, researchers like Hunter et al. [246] found that long-chain acylcarnitine is highly linked with HF and further discriminated between patients with HFrEF and HFpEF. Lastly, researchers of the HF-ACTION study confirmed elevations in circulating C16 and C18:1 acylcarnitines in end-stage HF patients versus those with chronic systolic HF, and this obvious increase was associated with increased risk for readmission and mortality in those patients [247]. Fascinatingly, metabolomic profiling after LV assist device implantation in those end-stage HF patients triggered a decrease in these circulating L-C acylcarnitines, indicating that focusing on the metabolomics profiling could help manage HF patients.

Multi-omics approach

Due to the extensive nature of HF, combination of multiple omics technologies will offer a more comprehensive trait of the elements and functions of the diseases and further provide far deeper information for predictive modeling of the phenotypes. Additionally, it will offer the opportunity to enlighten the flow of information that triggers most cardiovascular diseases better than studying at the single omics level.

Though several challenges abound in implementing this approach, a group of researchers have recently developed an adaptable and expedient computational network, Mergeomics, to execute the incorporation workflow to ascertain disease networks, pathways, and key regulators that are informed by multi-omics data sets [248]. Also, huge statistical tests that would be performed at each omics level could lead to false positive results. Due to this, statistical approaches such as Bonferroni correction, Benjamin-Hochberg false discovery, q value, and permutation tests have been developed to curtail these impending problems [233]. The future of integrating the Omics approach in HF biomarkers looks prominent with more research in this field.

Conclusion

The interest in the use of biomarkers in HF has expanded exponentially in recent times. The NPs remain the gold standard biomarker in this arena, with cardiac troponins, galectin 3, and sST2 also advancing rapidly hence their recommendation by ACC/AHA guideline. The clinical usefulness of myriads of other cardiovascular biomarkers has been linked to HF but most of them have not satisfy the criteria to be recommended. This may be purposely due to their lack of cardiac and HF specificity, and hence recent research need to link

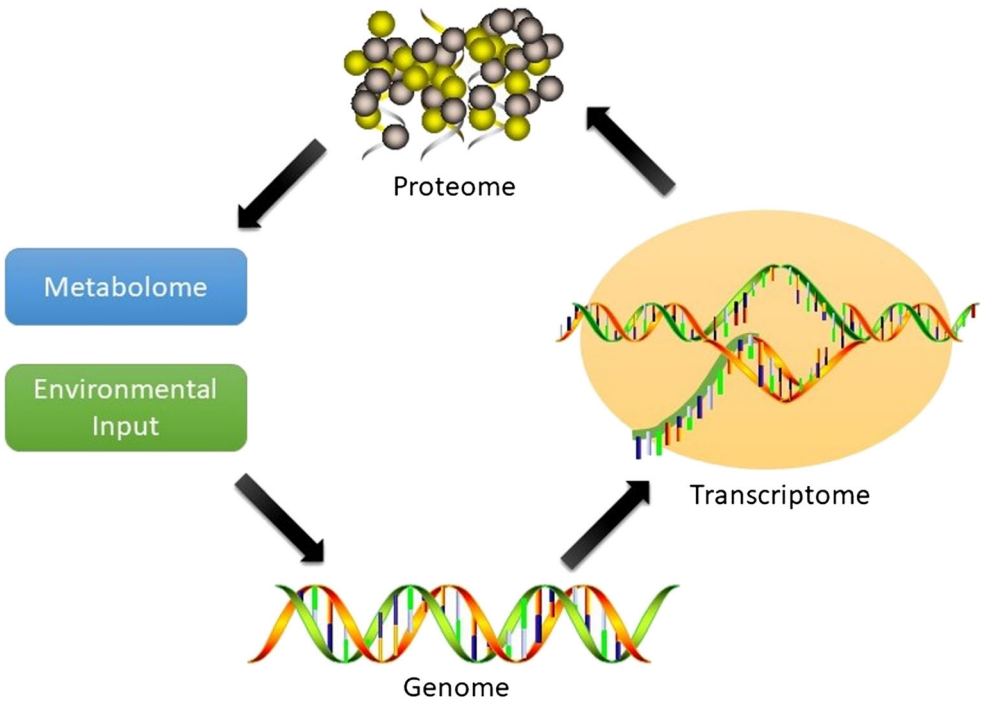

Fig. 1 Integration of the various omics approaches for patient phenotype. Metabolome denotes one of the lower-part end product of the environs' relation with the genome-transcriptome-proteome

these markers to their specific cardiac roles. By this, we suggest incorporating more comprehensive non-clinical studies in animal models to gain thorough acumens into the correlation between plasma biomarkers and the progressions of cardiac remodeling, and into the probable contribution of other organs and tissues whose roles can possibly affect such new markers. This subsequently leads to an outcome in multi-marker approach. Hence, current and future research should be focused on adopting this multi-marker approach to improve risk prediction models, diagnosis, and management of this widespread syndrome. Lastly, the subject of HF biomarkers has encountered a dramatic change with the advent of comprehensive OMICs platforms allowing for abrupt assessment of novel and existing circulating biomarkers. Hence researchers need to focus much attention on this platform.

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Compliance with ethical standards

Disclosure statement The writers declare no conflict of interest.

Ethical standard The manuscript does not contain clinical studies or patient data.

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