Review Article

Heart failure among patients with prediabetes and type 2 diabetes mellitus: diagnostic and predictive biomarkers: a narrative review

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Objective: This narrative review is to provide an updated view of circulating biomarkers to improve diagnosis and prognosis in heart failure (HF) patients with diabetes mellitus (DM) and pre-diabetes (pre-DM).

Background: HF is a leading cause of premature death among patients with overt cardiovascular (CV) disease worldwide. Natriuretic peptides (NPs) and high sensitive cardiac troponins remain powerful tools to stratify, diagnose, and manage patients at risk of HF and with established HF.

Methods: The bibliographic databases of MEDLINE, EMBASE, Medline (PubMed), Web of Science, and Cochrane Central were searched for English publications using the following key words [heart failure]; [diabetes mellitus], [type 2 diabetes mellitus], [pre-diabetes]; [pre-T2DM]; [cardiovascular risk], [cardiovascular risk factors], [cardiac biomarkers]; [circulating biomarkers]; and [prognosis].

Conclusions: NPs demonstrated their optimal ability to diagnose and predict HF with reduced (HFrEF), mildly reduced (HFmrEF), and preserved (HFpEF) ejection fraction regardless of presentation of different metabolic comorbidities, such as DM and pre-DM. The role of soluble suppressor of tumorigenesis-2 (sST2), growth differential factor-15 (GDF15), and galectin-3 are critically discussed in terms of the improvement of incremental value of conventional biomarker strategies to predict CV and HF-related outcomes. We found alternative biomarkers reflecting several pathological stages of HF progression (inflammation, endothelial dysfunction, oxidative stress, altered vascular and myocardial reparation, adipose tissue dysfunction, and skeletal muscle metabolism) continue to be deeply investigated as new powerful tools to improve the discriminative potency of traditional predictive scores in patients with HFrEF, HFmrEF, and HFpEF.

Keywords: Heart failure (HF); diabetes; pre-diabetes (pre-DM); biomarkers; prediction; outcomes

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Introduction

Heart failure (HF) remains a serious public health and social-economic problem affecting more than 23 million patients worldwide (1). Acute HF and chronic HF with reduced (HFrEF) and mildly reduced (HFmrEF) left ventricular ejection fraction (HFrEF) remain a leading

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cause of cardiovascular (CV) mortality among in-patients including those who have clinically significant comorbidities including diabetes mellitus (DM) and chronic kidney disease (2). Dramatic increases in the number of new cases of DM worldwide have seen HF as a steadily growing life-threatening complication of that disease (3,4).

Several biomarkers are reported to be associated with HF, such as natriuretic peptides (NPs), high sensitive cardiac troponins, soluble suppressor of tumorigenesis-2 (sST2), and galectin-3 (5,6), and their diagnostic and predictive abilities substantially distinguish each other in HFrEF/HFmrEF and HFpEF patients, even those having co-morbidities. However, there is limited evidence to show their discriminative potency for DM progression and risk of HF development (7,8). Additionally, the economic burden of this strategy appears to be challenging and requires more attention before an optimal choice of biomarkers in routine clinical practice can be made.

The recently reported New Universal Definition and Classification of HF proports to use a biomarker strategy based on the measure of circulating and genetic indicators to identify patients at higher risk of HF (stage A) and pre-HF (stage B). This assists in determining the risk of moving these patients from early stages to the end stage of the disease, and to choose an optimal strategy to diagnose and treat it (9). Nevertheless, there is a large amount of conflicting data from research designed to distinguish the value of a biomarker strategy in HFpEF and HFrEF/HFmrEF (10-12). Although biomarkers can assist clinicians with timely diagnosis, risk stratification, and prognosis determination of HFrEF/HFmrEF and HFpEF patients to provide individualized treatment (13), there is no biomarker-guided strategy for DM patients at higher risk of HF and for HF patients with at risk or overt DM (14). This review provides an updated analysis of circulating biomarkers which can be used with an aim of improving diagnosis and prognosis among HF with DM. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jlpm.amegroups.com/article/view/10.21037/jlpm-21-37/rc).

Methods and methodology

The MEDLINE, EMBASE, Medline (PubMed), Web of Science, and Cochrane Central databases were searched for English publications satisfying the following key words [heart failure]; [HFrEF]; [HFmrEF]; [HFpEF]; [diabetes mellitus], [type 2 diabetes mellitus], [pre-diabetes]; [pre-T2DM]; [cardiovascular risk], [cardiovascular risk factors], [cardiac biomarkers]; [circulating biomarkers]; [diagnosis]; and [prognosis]. All authors independently selected articles, evaluated the quality of the data, its presentation, and its interpretation correspondence to the main idea of the study, and constructed the final list of references.

Contemporary biomarker strategy to predict and diagnose HF

Biomarkers are promising surrogate indicators of pathologic changes in target organs (myocardium, lungs, kidney, vessels, adipose tissue, and skeletal muscles) and maladaptive homeostasis for patients with T2DM and different phenotypes of HF (15). Although biomarkers of biomechanical stress (NPs), myocardial injury (high sensitive cardiac troponins), fibrosis (sST2), and inflammation (galectin-3) have revealed variable results in their potency to predict HF onset at an early stage, diagnose HF, decrease the risk of admissions due to HF progression, and manage the condition, they undoubtedly remain a proof supporting personified therapy of HFrEF and HFpEF (16). Current clinical guidelines of the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA), and European Cardiology Society (ESC) have proposed the use of biomarkers in personalized medical care of HF patients regardless of T2DM, and to diagnose HF and stratify patients at higher risk of poor prognosis, despite some differences in recommendations for practical use (9,17). *Table 1* reports the utilization of biomarkers in the diagnosis, prediction, and management of HF according to 2021 ESC and 2017 ACC/AHA clinical guidelines (9,17).

NPs

NPs are well known and deeply investigated indicators of biomechanical stress (18), which are gold standard biomarkers for HF with different phenotypes, as well as for acute/acutely decompensated HF (19). According to current clinical guidelines (9,17) B-type natriuretic peptide (BNP), N-terminal proBNP (NT-proBNP), and mid-regional-atrial NP (MR-proANP) are used for diagnosis and prognosis of HF (19), while their performance appears to be better for HFrEF and HFmrEF than for HFpEF (19,20). However, their role in risk stratification in high risk of HF development

Table 1 2021 ESC and 2017 ACC/AHA/HFSA recommendations for the use of biomarkers in the management of HF

Recommendations	Biomarkers	COR	LOE	Phenotype of HF	Stage of HF
Prediction of HF					
ESC, 2021	BNP/NT-proBNP	IIa	B	AHF, CHF	C, D
ACC/AHA/HFSA, 2017					
Diagnosis of HF					
ESC, 2021	BNP/NT-proBNP/MR-proANP	I	A	AHF, HFpEF, HFmrEF	A–C
ACC/AHA/HFSA, 2017		I	A	AHF, CHF	
Risk of in-hospital death					
ESC, 2021	BNP/NT-proBNP	I	C	AHF	C, D
ACC/AHA/HFSA, 2017	hs-cTn	I	C	AHF	
Risk of recurrent hospital admission					
ESC, 2021	BNP/NT-proBNP	I	A	AHF, CHF	C, D
ACC/AHA/HFSA, 2017		I	A	AHF, CHF	
ESC, 2021	hs-cTn	I	C	AHF, CHF	
ACC/AHA/HFSA, 2017		I	IIa	AHF, CHF	
ACC/AHA/HFSA, 2017	Galectin-3	IIb	B	AHF, CHF	
ACC/AHA/HFSA, 2017	sST2	IIb	B	AHF, CHF	C, D
Biomarker-guided therapy of HF					
ACC/AHA/HFSA, 2017	BNP/NT-proBNP	I	A	HFrEF/HFmrEF/HFpEF	C

ESC, European Cardiology Society; ACC, American College of Cardiology; AHA, American Heart Association; HFSA, Heart Failure Society of America; HF, heart failure; COR, class of recommendation; LOE, level of evidence; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; AHF, acute heart failure; CHF, chronic heart failure; MR-proANP, mid-regional pro A-type natriuretic peptide; HFpEF, heart failure preserved ejection fraction; HFrEF, heart failure reduced ejection fraction; hs-cTn, high sensitive cardiac troponins; sST2, soluble ST2; HFmrEF, heart failure with mildly reduced ejection fraction.

patients, including those who have DM (A stage of HF) and asymptomatic pre-HF individuals (B stage of HF), have further expanded beyond HF to several CV conditions, such as abdominal obesity, atrial fibrillation/flutter, T2DM, and systemic hypertension (21,22). While NPs are considered predictors for atrial fibrillation/flutter and HF manifestation in patients with DM and obesity, the serum levels of these biomarkers are remarkably variable for these patients and those who have chronic kidney disease (23,24). Adipose tissue accumulation was found to be associated with near normal plasma NP levels, but chronic kidney disease was, on the contrary, a frequent cause of a dramatic rise of NP levels due to lowered kidney clearance (25). In fact, patients with T2DM at risk of HF, CV events, and impaired renal function demonstrate different cut-off points to the diagnostic and predictive levels of MR-proANP, BNP, and NT-proBNP for acute and chronic HF (26). In this context, the optimum threshold values require adjustment to the estimated glomerular filtration ratio categories and body mass index in T2DM patients with a higher risk of HF and established HF. Indeed, the levels of NT-proBNP >400 pg/mL in patients with HFrEF who were included in the PARADIGM-HF trial (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) and the ATMOSPHERE trial (Aliskiren Trial to Minimize Outcomes in Patients With Heart Failure) have demonstrated high predictive value for adverse CV outcomes, regardless of comorbidities such as atrial fibrillation (27). There is no point to argue that extremely high levels of NT-proBNP (>3,000 pg/mL) have optimal accuracy to diagnose acute/acutely decompensated HFrEF, while their ability in risk stratification and diagnostic utility among asymptomatic patients with HFpEF needs

to be reappraised. Nevertheless, adding NT-proBNP to the traditional risk factor score significantly increased the predictive value of the whole model for major adverse CV events (MACEs) in pre-T2DM and T2DM patients (28).

In addition, among high CV risk patients (n=5,509) with T2DM who were enrolled in the ALTITUDE (Aliskiren in Type 2 Diabetes Using Cardiorenal Endpoints) trial, elevated levels of NT-proBNP predicted both CV mortality and composite CV events (CV death, resuscitated cardiac arrest, nonfatal myocardial infarction, stroke, or HF hospitalization) (29). Idzerda *et al.* (30) hypothesized that measure of the levels of NT-proBNP could predict the effects of additional therapy with aliskiren on cardio-renal endpoints among patients included in the ALTITUDE (Aliskiren in Type 2 Diabetes Using Cardiorenal Endpoints) trial. They reported the total number of cardio-renal endpoint events were reduced by 20% and 2% in the two lowest NT-proBNP tertiles respectively, among patients with T2DM treated with aliskiren. Similarly, CV and end-stage renal disease endpoints were substantially reduced in these individuals having lowers tertiles of NT-proBNP concentrations (30). The EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) trial, in which 5,380 patients with T2DM were included, has shown that dynamic NT-proBNP levels allowed re-stratifying risks for CV death and HF hospitalization (31).

The implementation of BNP biosensing platforms based on optical and electrochemical immunosensor methodology allowed sufficiently reducing total expenditures on BNP level monitoring in follow-up and demonstrated unsurpassed sensitivity, selectivity, and reproducibility (32). Prausmüller *et al.* (33) reported preliminary results of an investigation of the prognostic ability of the ESC/European Association for the Study of Diabetes (EASD) risk model compared to the Systematic COronary Risk Evaluation (SCORE) risk model and NT-proBNP among T2DM patients. The primary finding of the study was that the levels of NT-proBNP (0.80 versus 0.53, P<0.001) and SCORE (0.64 versus 0.53, P=0.001) had remarkably higher discriminative values than the ESC/EASD risk model for CV death and all-cause death (0.73, 0.66 versus 0.52, P<0.001 for both). Thus, single NT-proBNP plasma level measure would improve predicting 10-year CV disease and all-cause mortality in T2DM individuals.

The above results show NPs are the most accurate test for HF diagnosis and progression of the disease as well as for predicting adverse outcomes and guiding therapy.

Highly sensitive cardiac troponin (hs-cTn)

hs-cTn are biomarkers of myocardial injury and necrosis which are released from damaged cardiac myocytes into the circulation. hs-cTn are structural proteins of cardiac myocytes troponins commonly elevated in not only acute coronary syndrome/myocardial infarction, but also in clinical conditions that are strongly associated with subclinical myocardial damage due to biomechanical and oxidative stresses, inflammation, and volume overload (34). Nowadays hs-cTn T/I have been regarded as the gold-standard marker for cardiomyocyte necrosis having unprecedented predictive value for CV outcomes including all-cause and CV mortality, HF onset, hospitalization, and coronary revascularization (35).

In the last two decades, attempts have been made to identify minor asymptomatic myocardial injury and interpret its clinical relevance in patients beyond acute myocardial infarction and acute coronary syndromes. These attempts have been enabled by the development and use of new analytical approaches to detect cardiac troponins with higher accuracy and reproducibility. Indeed, the measurement of cardiac troponin levels using commercially available second generation high-sensitive tests has caused previous opinion of them as only indicators of myocardial injury to that of biomarkers of biochemical stress (36,37). Moreover, the increased risk for mortality, CV events, and HF-related complications correlated with high-sensitivity cardiac troponins even when their levels were mildly above the normal level (38). Yet, hs-cTnT/I elevation was found to be strongly linked to poor CV outcomes in several clinical conditions, even though the elevation was stable over time (39).

Mildly elevated levels of hs-cTnT/I have been shown in T2DM patients and individuals at risk of HF/established HF and independently predicted all-cause and CV mortality, hospitalization, and CV intervention (40-42). Interestingly, the ARIC (Atherosclerosis Risk in Communities) study showed that circulating levels of hs-cTnT among 3,056 adult patients with higher atherosclerotic risk were independently associated with diabetes status, while among participants without T2DM, there were also significant associations of NT-proBNP levels and the urine albumin-to-creatinine ratio (43). In addition, elevated levels of both hs-cTnI (≥9.4 ng/L) and hs-cTnT (≥25 ng/L) were remarkably associated with prevalent coronary heart disease, HF, chronic kidney disease, pulmonary disease,

hypoglycemia, hypertension, dementia, and frailty (44). Yet, the CRIC Study showed that hsTnT levels in patients with established kidney impairment, including diabetes-induced chronic kidney disease, were associated with a greater risk for progression of the disease (45). A meta-analysis of 45 clinical studies showed that hs-cTnT had the highest sensitivity [0.86 (95% CI: 0.84–0.88)], specificity [0.82 (95% CI: 0.79–0.84)], positive predictive value [0.80 (95% CI: 0.77–0.83)], and negative predictive value [0.87 (95% CI: 0.85–0.89)] to diagnose HF compared with other biomarkers, such as copeptin, galectin-3, MR-proANP, MR-proadrenomedullin, and sST2 (46). In summary, hs-cTnT/I appears to be a general surrogate biomarker of myocardial damage and higher mortality risk in patients with T2DM and HF regardless of its phenotypes, while the powerful predictive value of hs-cTnT was found irrespective of comorbidity burden.

sST2

The novel biomarker of fibrosis and inflammation sST2, was included in the 2017 ACC/AHA/HFSA HF guideline, but not in the 2016 and 2021 ESC guidelines for HF as an alternative tool for HF prediction and risk stratification, although its diagnostic and discriminative utilities in T2DM require further elucidation (17). In addition, the 2021 ESC guidelines for HF recommend that more clinical evidence is needed before sST2 and other biomarkers as additional diagnostic tests should be included in the guidelines (17). However, unlike other inflammatory biomarkers, sST2 has been approved by experts from the ACC/AHA/HFSA for risk stratification of patients with HF, because it has demonstrated high accuracy and reproducibility in serial measures at a reasonable cost and improved predictive value of NPs and hs-cTnT/I for HF (14).

Being a member of the interleukin-1 receptor family, sST2 acts as an endogenous suppressor of beneficial impact of interleukin-33 on myocardium and vessels leading to cardiac hypertrophy, fibrosis, and dysfunction (47). Previous clinical studies have shown that elevated levels of sST2 demonstrated a high discriminative ability for predicting all-cause and CV mortality, sudden death, HF occurrence, HF-related events, and HF hospitalization regardless of common CV risk factors including T2DM, chronic kidney disease, and hypertension (48-51). Interestingly, in the comparative HF study, by Najjar *et al.* (52) patients with HFpEF had lower sST2 levels when compared to HFrEF individuals but were potentially more strongly related to poor outcomes.

There is evidence that the improved clinical status and hemodynamics in acutely decompensated HF patients were associated with a significantly greater decline in circulating sST2 levels (10), suggesting serial measures of sST2 levels could also stratify patients with HF at a higher risk of death (53,54). Furthermore, elevated levels of sST2 provide additional prognostic information for acute HF and different phenotypes of chronic HF, exceeding the ability of NT-proBNP (55). Thus, sST2 demonstrates powerful predictive value for clinical outcomes in HF patients regardless of T2DM presence, but high economic burden is considered as the main constraint for an implementation of single and serial sST2 measures in routine clinical practice (56).

Galectin-3

Galectin-3 is a multiphase protein belonging to the β-galactoside-binding lectin family (57) that is overexpressed in different types of cells due to tissue injury or stress (58). There has been a continuously rising interest in galectin-3 due to extensive studies involving the molecule in adverse cardiac remodeling, atherosclerosis, and T2DM. Indeed, over-expression of galectin-3 in the myocardium increased collagen I protein production and fibronection accumulation via the protein kinase C-α pathway leading to myocardial fibrosis and hypertrophy (59). In addition, experimental data raised a hypothesis that the detrimental proliferative effect of aldosterone might be at least particularly mediated by galectin-3 (60,61), suggesting that in this context, galectin-3 is both a biomarker and causal factor for HFpEF and HFrEF/HFmrEF (61).

In clinical settings galectin-3 was found to be a better predictor for HFpEF than HFrEF/HFmrEF (62). The observational Diast-CHF study that enrolled 1,386 patients at high risk of HF or with suspected HF showed that galectin-3 being added to NT-proBNP significantly improved predictive value for the combined model to diagnose HFpEF (63). Although the admission levels of galectin-3 among in-patients with HFrEF were strongly correlated with higher interleukin-6 and C-reactive protein levels and independently associated with all-cause mortality and HF hospitalization, serial measures of galectin-3 levels over 6 months did not improve prognostic value compared with baseline concentrations (64). de Boer *et al.* (65) investigated the associations of 12 CV biomarkers (hs-cTnT or I, C-reactive protein, urinary albumin to

creatinine ratio, renin to aldosterone ratio, D-dimer, fibrinogen, sST2, galectin-3, cystatin C, plasminogen activator inhibitor 1, and interleukin-6) with incident HFpEF versus HFrEF among adults from the general population after an adjustment for CV risk factors, and did not find a direct relation between galectin-3 and certain phenotypes of chronic HF. In contrast, Kanukurti *et al.* (66) reported that elevated levels of galectin-3 were the most optimal predictive biomarker for HFpEF manifestation.

Considering T2DM patients and metabolic syndrome individuals are at a higher risk of HFpEF than HFrEF, galectin-3 might ideally lead to a reclassification of cardiometabolic risk. The Dallas Heart Study showed that levels of galectin-3 correlated well with incident T2DM, metabolic syndrome, and body fat compartments (67) and positively correlated with levels of hs-CRP, IL-18, monocyte chemoattractant protein 1, soluble TNF receptor 1A, myeloperoxidase, C-peptide, and homeostatic model assessment for insulin resistance (68). Overall, cross-sectional analyses of 2,946 Framingham Heart Study participants unveiled that circulating levels of galectin-3 were associated with higher body mass index, waist circumference, hypertension, and triglycerides levels (68). Despite investigators emphasizing that galectin-3 levels being adjusted to cardiometabolic risk factors were not able to predict incident cardiometabolic disease, it remained a powerful predictor for T2DM and metabolic syndrome in the general population.

Alternative biomarkers

Although a conventional biomarker strategy based mainly on NPs and cardiac troponins is recommended to diagnose any phenotype of HF, its predictive ability appears to be higher for HFrEF, whereas a risk stratification of patients with suspected or overt HFpEF needs improvement (69). In this context, previous investigations have revealed that biomarkers of biomechanical stress, cardiac injury and necrosis, and inflammation markedly better predict HFrEF than HFpEF (14,21). Consequently, biomarkers of fibrosis, oxidative stress, adipose tissue dysfunction, and altered endogenous reparation are increasingly being used to assess HFpEF and probably HFmrEF (42,56). *Figure 1* illustrates a network of conventional and alternative biomarkers in HF patients having pre-diabetes (pre-DM) or T2DM, and the most informative of these are discussed in the section below.

Biomarkers of oxidative stress

The role of biomarkers reflecting oxidative stress is controversial (70). In fact, T2DM modulates the expression of the NFE2L2 gene that essentially encodes the key transcription factor Nrf2 and regulates the expression of antioxidant and detoxification genes (71,72). In addition, Nrf2 is activated in various CV diseases including HF, and supports cardiac protection through regulation of genes that are involved in cell signaling, differentiation, transcription, proliferation, energy metabolism, and autophagy (73). Therefore, oxidative stress enhances mitochondrial damage and contributes to cell injury, extracellular matrix remodeling, and altered tissue reparation (74). Although subclinical oxidative stress and inflammatory conditions are the result of HF comorbidities including T2DM with abdominal obesity, there is no strong evidence that conventional circulating biomarkers of oxidative stress, such as superoxide dismutase (SOD), reactive oxygen species (ROS), peroxide species of lipids, and AGE/RAGEs provide additional prognostic information for HF patients with T2DM (75,76). Future investigations may evaluate non-coding RNAs analysis and proteomics/secretom of extracellular vesicles (ECVs) (77). Non-coding RNAs, including small non-coding RNAs (microRNAs, circular RNAs, and long non-coding RNAs), as regulators of insulin resistance, cardiomyocytes apoptosis, microvascular inflammation, and myocardial hypertrophy, are of interest, especially due to their protective effect on cardiac function in HF patients (78,79). The testing of oxidative stress biomarkers needs to be investigated in future clinical interventions to evaluate their potential role in stratification of T2DM patients at high risk of CVD and HF occurrence.

Biomarkers of adipose tissue dysfunction

The development of HF in T2DM patients closely relates to comorbidities such as abdominal obesity, diabetes-induced kidney disease, and myocardial infarction (79). Ectopic perivascular and pericardial adipose tissue, along with other white adipose tissue (WAT), are the source of synthesis and release of active molecules called adipokines that exhibit pro-inflammatory as well as anti-inflammatory properties with the capacity to directly affect the energy metabolism of myocardium and skeletal muscles, vascular integrity, endothelial function, and insulin resistance (80). There

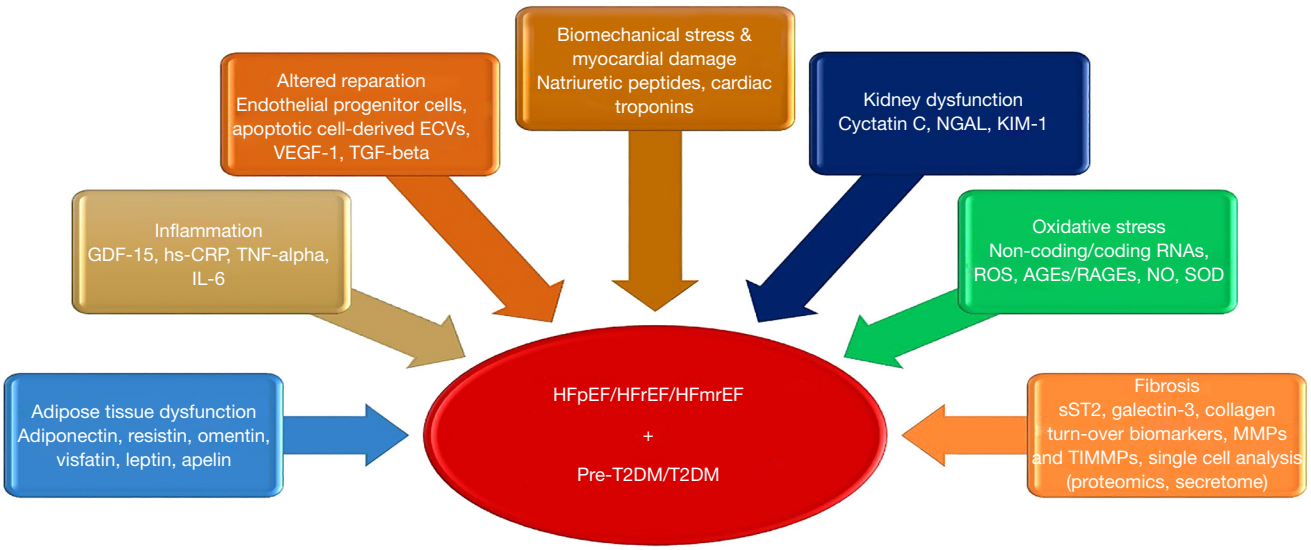

Figure 1 Network of conventional and alternative biomarkers in HF patients with pre-DM or T2DM. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; GDF, growth differential factor; hs-CRP, high sensitive C-reactive protein; TNF, tumor necrosis factor; IL, interleukin; ECVs, extracellular vesicles; VEGF, vascular endothelial growth factor; TGF, transforming growth factor; NGAL, neutrophil gelatinase-associated lipocalin; KIM-1, kidney injury molecule-1; RNA, ribonucleic acid; ROS, reactive oxygen species; AGEs, advanced glycation end products; RAGEs, receptor for advanced glycation end products; NO, nitric oxide; SOD, superoxide dismutase; MMP, matrix metalloproteinase; TIMMP, tissue inhibitor of matrix metalloproteinase; HF, heart failure; pre-DM, pre-diabetes.

is a large body of evidence regarding the association of exacerbated WAT inflammation with the altered circulating profile of adipokines (81,82). Indeed, HF patients have lowered levels of omentin, zinc-α2-glycoprotein, glypican-4, apelin, and chemerin, and increased levels of adiponectin, resistin, and leptin (83-85).

The results of the Framingham Offspring Study have shown that an incident HF might accompany increased circulating levels of several adipokines, such as resistin, and that this relationship was changed after adjustment for prevalent CAD, abdominal obesity, insulin resistance, and inflammation (86). In contrast, adiponectin did not show a significant association with the risk of HF (84). Therefore, adverse cardiac remodeling in T2DM patients is associated with altered adiponectin/leptin ratio (86-88). Among the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam cohort the levels of chemerin-1 and omentin were found to be powerful predictors for atherosclerotic CVD, whereas chemerin-1, but not omentin, yielded discriminative potency for incident HF (89). Overall, the relationships between serum levels of the majority of pro-inflammatory adipokines and CV risk and a risk of HF development were not linear but J-shaped (adiponectin) or U-shaped (chemerin-1, omentin) associations, which were diminished for adiponectin after adjustment for additional potential confounders (88,89). However, decreased levels of apelin, chemerin-1, omentin-1, visfatin, and increased levels of adiponectin and leptin were found to have predictive value for CV mortality and HF progression in both T2DN and non-T2DM patients with overt HF (90-95). Thus, an altered profile of adipokines can be a novel circulating biomarker for predicting poor CV and HF-related events in patients with HF regardless of the presence of T2DM.

Biomarkers of calcium and phosphate metabolism

Altered calcium and phosphate metabolism plays an important role in the development of T2DM-dependent angiopathy, ectopic vascular calcification, and adverse cardiac remodeling. Blood level changes in several circulating biomarkers, including osteonectin, osteoprotegerin, osteopontin, and RANK ligand correspond well to risk progression of T2DM and HFpEF and CV

mortality. One of the most promising of these is fetuin-A.

Fetuin-A

Fetuin-A (also known as alpha2-Heremans-Schmid glycoprotein), is a protein secreted from hepatocytes (so-called hepatokine) and is known to exert multiple physiological and pathophysiological functions including the inhibition of calcification processes and protein transport for calcium and phosphate. Previous studies have shown that low fetuin-A levels were associated with increased CV mortality (96). Moreover, it can interact with insulin receptors and is associated with the development of metabolic syndrome and progressive atherosclerotic disease. High levels of fetuin-A are thought to have protective effects in inflammatory conditions (e.g., in adipose tissue inflammation), while associations of low fetuin-A concentrations have been described with coronary artery disease and valvular calcification. Lower levels of fetuin-A have also been found in ischemic cardiomyopathy in comparison to dilative cardiomyopathy. This led to the assumption that fetuin-A might serve as a potential discriminator or biomarker for differentiation between those two disease entities (97).

Of special interest is the role of fetuin-A in the development of diabetes, as it is an inhibitor of the insulin receptor tyrosine kinase in diverse tissues (98,99), and both animal and clinical studies have shown that fetuin-A effects insulin resistance. Whereas high levels have been associated with lower rates of vascular calcification, in the context of diabetes accompanied with insulin resistance and obesity, more negative effects of high fetuin-A concentrations have been found (100,101). For example, patients with T2DM evidenced elevated fetuin-A levels in comparison to those without diabetes (102-104). This phenomenon has been verified by three meta-analyses (105-107).

These different regulatory mechanisms in patients with diabetes compared to cardio-vascular patients without diabetes remain poorly understood. The answer to this conundrum might be the fact that fetuin-A exerts an inhibitory signal to the insulin receptor tyrosine kinase which leads to a reduction in phosphorylation of the insulin receptor (108,109). A secondary effect might also be of interest as fetuin-A can aggravate insulin resistance via toll-like receptor 4, subsequently affecting adipose tissue inflammation and finally increasing resistance to insulin signaling (108). This pathway might also be influenced by an altered expression of adiponectin with its anti-inflammatory effects and functions on insulin-sensitization (110). Still, the pathophysiological connection between fetuin-A and T2DM-indiced HF is not fully elucidated.

Bone-related proteins

Bone-related proteins (osteopontin, osteoprotegerin, osteonectin, tenascin C, and thrombospondins 1 and 2) are matricellular proteins involved in the modulators of bone development, cardiac and vascular remodeling, and tissue regeneration (111). Previous studies showed that several members of the bone-related proteins family, such as tenascin-C, osteopontin, and osteonectin were up-regulated after ischemic myocardial injury and inflammation (112). However, a growing body of evidence strongly demonstrates that both inflammatory and reparative processes are under close regulation of bone-related proteins, which are released in response to several stimuli, such as ischemia/hypoxia, inflammation, and biomechanical stress, and provide tissue protective capacity (113).

An increased expression of osteopontin, an extracellular matrix protein, is known to lead to hypertrophy of the myocardium and the development of HF (114). In the diabetic heart, osteopontin shows higher expression in response to high glucose levels by signaling via angiotensin II and protein kinase C, and both cardiomyocytes and cardiac fibroblasts respond to higher glucose concentrations with osteopontin expression. Elevated levels of osteopontin were associated with an increased CV risk in T2DM patients, whereas other bone related proteins were not (115,116). Its expression increased greatly after myocardial ischemia, and data obtained in transgenic mouse studies suggests that osteopontin has some protective effects in myocardial remodeling after infarction via a modulation of collagen production and fibrosis (114). In the setting of HF, levels of osteopontin increase in concordance with the severity of HF, and its regulation of myocardial remodeling has been shown a potentiation of galectin-3 up-regulation and secretion (115). In addition, osteopontin improved HF diagnosis when combined with NT-proBNP. From a diagnostic point of view, osteopontin can provide help for assessing acute HF (115,116), and in in patients suffering from HFpEF, it has been shown to be of prognostic potential in a multi-marker analysis (115). Moreover, elevated levels of osteopontin predicted high 1- and 5-year CV mortality and re-hospitalization due to HF (117,118). Reports have confirmed the predictive role of other bone-

related proteins for CV events and HF outcomes in studies with higher proportions of patients with chronic kidney disease or large coronary artery occlusive disease (116-120). Cumulatively, bone-related proteins as markers of CV risk on diabetics with HF seem to be promising biomarkers, but more clinical trials are required to elucidate their role.

Growth differential factor-15 (GDF15)

GDF15 is a stress-induced multifactorial cytokine which belongs to the transforming growth factor (TGF) beta superfamily and is markedly expressed in a wide range of cells in both normal and pathological conditions (119). Acting as a suppressor of JNK, Bcl-2-associated death promoter (Bad), and epidermal growth factor receptor (EGFR) and activator of Smad/eNOS, PI3K/AKT signaling pathways GDF-15 improves glucose and energy homoeostasis, regulates appetite, potentiates weight loss, and induces tissue protection from ischemia/oxidative stress damage (120,121). Importantly, GDF15 was found to be a crucial mediator of anorexia-cachexia syndrome in advanced stages of severe HF, T2DM, nonalcoholic fatty liver disease, chronic renal disease, and cancer (122).

The clinical relevance of GDF-15 in energy homeostasis was thoroughly established in the XENDOS (XENical in the prevention of Diabetes in Obese subjects) trial that included 496 obese, nondiabetic individuals (123). Investigators found that GDF15 levels were strongly associated with BMI, waist-to-hip ratio, and insulin resistance (123). Echouffo-Tcheugui *et al.* (124) also established that higher circulating levels of GDF15 were positively associated with (highest versus lowest quartile) occurrence of T2DM [adjusted odds ratio (aOR) =2.48; 95% CI: 1.89–3.26], HF (aOR =3.22; 95% CI: 2.13–4.85), atherosclerotic CV events (aOR =1.57; 95% CI: 1.16–2.11), elevated levels of hs-cTnT (aOR =2.27; 95% CI: 1.54–3.34), and NT-proBNP (aOR =1.98; 95% CI: 1.46–2.70) in the general population.

Among HFpEF patients included in the multicenter PROMIS-HFpEF (Prevalence of Microvascular Dysfunction in Heart Failure With Preserved Ejection Fraction) study, elevated levels of GDF15 mediated the relationship between metabolic comorbidity and echocardiographic parameters, such as mitral E velocity, E/e' ratio, and tricuspid regurgitation velocity (125). A pooled analysis of both cohorts of patients who were enrolled in the PIVUS (Prospective Investigation of the Vasculature in Uppsala Seniors) study (n=901) and the ULSAM (Uppsala Longitudinal Study of Adult Men) study (n=685) unveiled that elevated levels of GDF15 were better associated with worsened left ventricular systolic function, but not diastolic dysfunction (50). Kanagala *et al.* (126) reported that both focal and diffuse fibrosis of the myocardium corresponded to increased GFD15 levels, while GDF15 and composite event (all-cause mortality and/or HF hospitalization) rates did not distinguish HFrEF and HFpEF patients. However, there is a large body of evidence regarding the possibility that GDF15 may improve prognostic information in terms of predominantly HFrEF being added to the NYHA functional class, LVEF, and serum levels of NT-proBNP (127,128). A recent systematic review by Rabkin and Tang (129) has shown that to distinguish HFpEF from HFrEF, GDF15, along with other inflammatory biomarkers, might be incorporated into a conventional biomarker strategy. Yet, Bouabdallaoui *et al.* (130) reported that GDF-15 was not significantly modified by ARNI sacubitril/valsartan among out-patients with HFrEF, while the baseline levels of this biomarker were strongly associated with all-cause mortality and CV outcomes (130). In summary, GDF-15 is considered a promising indicator of poor clinical outcomes in HFrEF/HFpEF and a predictor of the occurrence of HFpEF rather than HFrEF.

Biomarkers of kidney injury and dysfunction

Circulating biomarkers of acute kidney injury (AKI) and renal dysfunction, such as cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), and kidney injury molecule-1 (KIM-1), were associated with CV events and were significantly higher in decedents with HF than in survivors with HF. However, research evaluating relationships between serum concentrations of these biomarkers and AKI, CV risk factors, BNP, NT-proBNP, circulating biomarkers of collagen homeostasis, HFpEF occurrence, HF progression, HF NYHA functional class, and mortality shows disparate results (131-134). For instance, increased cystatin C levels in serial measurements were not accurate for predicting AKI in HF but remained independently associated with mortality (132). A meta-analysis of 10 randomized clinical trials by Chen *et al.* (132) showed an elevated cystatin C level was positively associated with an increased risk of all-cause mortality and re-admission due to HF progression regardless of creatinine and estimated glomerular filtration rate (eGFR). However, cystatin C was not able to predict CV events and CV disease in patients

with CV risk factors and T2DM (133,134).

In contrast to cystatin C, elevated levels of NGAL accurately predicted acute renal dysfunction in patients with chronic HF regardless of eGFR (135). In addition, NGAL correlated positively with galectin-3 in HF patients (136), as well as with cardiac hypertrophy and diastolic dysfunction in T2DM individuals (137). Data received from the Farmacology and NeuroHumoraL activation (FAR NHL) multicenter prospective registry have shown that serum levels of NGAL (>80 ng/mL) were a stronger predictor of 1-year all-cause mortality, acute HF hospitalization, left ventricle assist device implantation, and orthotopic heart transplantation (126). The multicenter, prospective GALLANT (NGAL EvaLuation Along with B-type NaTriuretic Peptide in acutely Decompensated Heart Failure) study revealed that elevated levels of NGAL along with a high BNP value at the time of discharge were strong predictors for 30-day out-comes in patients admitted for acute HF (137). Therefore, NGAL has been identified as a prospective biomarker for the management of acute HF, but not chronic HF (138). When included in multiple biomarker models, NGAL gave additive predictive value for incident HF, but it was no longer associated with mortality (139-142).

Serum levels of KIM-1 were found to be elevated in patients with T2DM-induced kidney disease and HF and correlated with eGFR and NGAL, but not with CV risk factors or the albumin-to-creatinine ratio (142,143). Previous studies showed no association of elevated serum levels of KIM-1 with clinical outcome in either acute or chronic HF after adjustment for NT-proBNP but predicted re-hospitalization in patients with acute HF (144-146). In fact, KIM-1 can improve the discriminative potency of CV risk factors for prediction of HF occurrence, whereas its ability to add prognostic information to conventional scores in patients with overt HF remains uncertain.

Biomarkers of altered cardiac and vascular reparation

Endothelial (EPC) and mesenchymal (MPC) progenitor cells are a core element of the endogenous reparation system, which plays a pivotal role in restoring architecture of the myocardium and extracellular matrix, vascular integrity, and endothelial and cardiac function after injury (147). Progenitor cells are involved in neovascularization, angiogenesis, reendothelization, and tissue reparation through the enhancement of cell proliferation, differentiation, and survival (148). There is a large amount of evidence that low numbers and weak function of EPCs/MPCs are independent predictors of adverse cardiac remodeling and poor clinical outcomes including death and hospitalization in patients with overt CV disease, T2DM, and HF (149-152). Therefore, circulating EPCs/MPCs could not only be powerful predictive biomarkers for the occurrence of HFpEF and progression of HFrEF, but also markers to assess multiple therapeutic strategies directed to the attenuation of adverse cardiac remodeling, muscle myopathy, and vascular function in HF (153-155). Although the number and function of both EPCs and MPCs appear to be powerful predictors for HF and T2DM-related complications, it is not clear whether these new biomarkers add additional predictive information to conventional models based on CV risk factors, phenotypes of HF, and traditional biomarkers.

Multiple biomarker strategies

Multiple biomarker predictive models are considered an effective method to increase specificity and sensitivity of a single biomarker tool (5). Data confirm the superiority of multiple models compared with conventional models in risk stratification in HFpEF, whereas the adoption of biomarker serial measurements for risk stratification in HFpEF remains uncertain. Different combinations of circulating cardiac biomarkers are likely a promising tool to improve prediction, risk stratification, and therapy in T2DM with HF, although there is limited data on the optimal number of biomarkers that can be allocated to improve point-of-care therapy among both HFrEF and HFpEF patients (156). There is no strong evidence that single biomarker use is superior to a multiple biomarker strategy for every clinical condition in HF patients. For instance, the MOLITOR (Impact of Therapy Optimisation on the Level of Biomarkers in Patients with Acute and Decompensated Chronic Heart Failure) study has shown that serial measurements of multiple biomarkers (C-terminal fragment of pre-pro-vasopressin, NT-proBNP, mid-regional pro-atrial NP, mid-regional pro-adrenomedullin, and C-terminal pro-endothelin-1) in advanced HF were no better than measurement of C-terminal fragment of pre-pro-vasopressin (157). Pandey *et al.* (158) evaluated the application of a biomarker-based risk score to identify patients with dysglycemia who were at high risk for incident HF. By enrolling individuals from three cohort studies; [ARIC, DHS, and Multi-Ethnic Study of Atherosclerosis (MESA)], the original

biomarker score included hs-cTnT ≥6 ng/L, NT-proBNP ≥125 pg/mL, hs-C-reactive protein (hs-CRP) ≥3 mg/L, and left ventricular hypertrophy identified by electrocardiography with one point for each abnormal parameter. The authors found that the 5-year risk for HF was associated with an increase in biomarker score, and the highest risk was seen in patients with total scores of ≥3 (diabetes: 12.0%; pre-DM: 7.8%), showing biomarker scores could stratify HF risk among patients with T2DM and pre-DM. Berezin *et al.* (159) reported that the combination of NT-proBNP and sST2 had higher prognostic ability when compared with each biomarker alone in patients with acute HF, except for galectin-3 and hs-CRP, which did not increase in discriminative potency when compared to a multiple biomarker model in ischemia-induced HF. However, a number of circulating $CD31^+$/annexin V^+ ECVs and EPCs improved the predictive ability for conventional HF biomarkers (NPs, sST2, galectin-3) (160,161). Therefore, while several novel biomarkers such as sST2 and GDF-15, and fetuin A, correlated to each other and conventional biomarkers (NT-proBNP and high sensitive cardiac troponins), these correlations were not found in connection with an increased risk of HF development (161). In addition, biomarkers reflecting myocardial fibrosis and inflammation, such as galectin-3, N-terminal pro-peptide of procollagen type III, and sST2, marginally improved the predictive ability of conventional models for adverse cardiac remodeling and dysfunction (162). Consequently, these conflicting results deserve closer investigation in large clinical trials in the future.

Limitations

The are several limitations to this review which include the small number of face-to-face comparative investigations of circulating biomarkers in specifically designed large clinical trials, especially studies depicting NPs and cardiac troponins. In addition, the results of cohort studies dedicated to alternative biomarkers, are mainly based on small sample size, although their quality is quite high. However, although not desirable, we believe these limitations do not compromise the accuracy of the reported findings or lead to their misinterpretation.

Conclusions

Patients with pre-DM/T2DM frequently have HFpEF, rather than HFrEF/HFmrEF, and need an improved biomarker strategy for risk stratification and prognosis of the disease. Conventional biomarkers, such as NPs and cardiac troponins have an optimal ability to diagnose and predict HFrEF and HFpEF, and are recommended by current guidelines on HF. However, their utility to stratify individuals at risk and manage patients with HFpEF is limited due to their high variability in the presence of CV disease and metabolic comorbidities. Alternative biomarkers reflecting several pathological stages of HF progression (inflammation, endothelial dysfunction, oxidative stress, altered vascular and myocardial reparation, adipose tissue dysfunction, and skeletal muscle metabolism) continue to be investigated as new powerful tools to improve the discriminative power of traditional predictive scores. Large clinical studies are required to better elucidate whether a multiple biomarker approach including both conventional and alternative biomarkers will be clinically useful and cost effective.

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Footnote

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