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Review

Heart Failure and Diabetes Mellitus: Biomarkers in Risk Stratification and Prognostication

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Abstract: Heart failure (HF) and type 2 diabetes mellitus (T2DM) have a synergistic effect on cardiovascular (CV) morbidity and mortality in patients with established CV disease (CVD). The aim of this review is to summarize the knowledge regarding the discriminative abilities of conventional and novel biomarkers in T2DM patients with established HF or at higher risk of developing HF. While conventional biomarkers, such as natriuretic peptides and high-sensitivity troponins demonstrate high predictive ability in HF with reduced ejection fraction (HFrEF), this is not the case for HF with preserved ejection fraction (HFpEF). HFpEF is a heterogeneous disease with a high variability of CVD and conventional risk factors including T2DM, hypertension, renal disease, older age, and female sex; therefore, the extrapolation of predictive abilities of traditional biomarkers on this population is constrained. New biomarker-based approaches are disputed to be sufficient for improving risk stratification and the prediction of poor clinical outcomes in patients with HFpEF. Novel biomarkers of biomechanical stress, fibrosis, inflammation, oxidative stress, and collagen turnover have shown potential benefits in determining prognosis in T2DM patients with HF regardless of natriuretic peptides, but their role in point-to-care and in routine practice requires elucidation in large clinical trials.

Keywords: heart failure; heart failure with reduced ejection fraction; heart failure with preserved ejection fraction; diabetes mellitus; circulating biomarkers; prognosis

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1. Introduction

Due to the growing prevalence of diabetes worldwide, an increased incidence of premature deaths attributable to both diabetes as well as its complications is consequently to be expected [1]. In 2017, approximately five million deaths in both developed and developing countries were reported which can directly be related to diabetes [1]. The most common cardiovascular (CV) manifestations in individuals with type 2 diabetes mellitus (T2DM) included heart failure (HF), peripheral arterial disease, and coronary heart disease [2]. Prevalence of HF in the patient population with established T2DM is twofold higher than in those without the disease [3,4]. The Reykjavík Study has shown an overall prevalence of T2DM and HF of 0.5% in men and 0.4% in women [5]. Therefore, the odds ratio (OR) for the association between T2DM and HF is 2.8 (95% CI = 2.2–3.6) and between abnormal glucose regulation and HF it is 1.7 (95% CI = 1.4–2.1) [5].

Fatal and non-fatal CV outcomes, a risk of urgent hospitalization, and both short-term and long-term prognoses are sufficiently worse for T2DM patients when compared with those without T2DM [6]. T2DM development coincides with numerous structural and functional changes in the heart, vessels, skeletal muscles, adipose tissue, kidney, and other target organs, which in the presence of traditional CV risk factors contribute to increased HF risk [7,8]. Numerous clinical trials have revealed the synergistic effect of managing both

HF and T2DM on their prognosis and clinical course [9–11]. In this context, biomarkers that reflect various pathophysiological stages of T2DM progression might have promising potential in guiding therapies. In addition, biomarkers offer important diagnostic and predictive information, which cannot be derived from clinical observation or objective data evaluation [12,13]. The aim of the review is to summarize knowledge about the discriminative abilities of conventional and novel biomarkers in T2DM patients at higher risk of or with established HF.

2. Basic Underlying Mechanisms of HF Development in Diabetics

Cardiac dysfunction in T2DM is a result of the development of metabolic abnormalities, attributed to increase fasting glucose, insulin resistance, lipotoxicity, and impaired reparation, sometimes termed diabetic cardiomyopathy, although not widely used [14]. Other causes for the occurrence of HF in diabetics include conventional CV risk factors that include hypertension, dyslipidemia, abdominal obesity, asymptomatic atherosclerosis, CVD, chronic kidney disease (CKD), as well as non-traditional risk factors, such as ectopic calcification and osteoporosis [15–17]. Consequently, cardiac dysfunction in T2DM patients is characterized by primary metabolic disturbances, secondary ischemic injury, cardiac myocyte apoptosis, immunological alterations with subsequent subcellular component abnormalities (mitochondrial stress, endoplasmic reticular formation dysfunction, secretome shaping impairment), oxidative stress with reduced nitric oxide bioavailability, fibrosis, local myocardial and microvascular inflammation, impaired cellular signaling (altered calcium homeostasis, activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS)), endothelial dysfunction, and altered tissue reparation [16,17].

In fact, impaired glucose metabolism, lipotoxicity, altered metabolic memory, and insulin resistance are considered as key factors contributing to mitochondrial stress and myocardial cell injury [17,18]. Indeed, suppressed AMP kinase activity due to mitochondrial dysfunction and consequently lowered phosphorylation of troponin relates to diastolic dysfunction prior to systolic dysfunction beyond the turnover of myosin chain isoforms [19]. In addition, impaired diabetic cardiac function is a result of insulin-dependent activation of phosphatidylinositol 3-kinase (PI3K)/protein kinase B-ACT signaling, which alters titin phosphorylation and consequently leads to titin N2B/N2BA isoform modification and titin-based myocardial stiffness [20,21]. There is a large body of evidence regarding the fact that insulin can directly stimulate the expression of a number of hypertrophic genes in cardiac myocyte including β-myosin heavy chain, insulin-like growth factor 1 receptor, myocyte enhancement factor, and brain-type natriuretic peptide (BNP) [22–24]. Moreover, insulin-like growth factor 1, acting directly as an activator of the insulin receptor and indirectly through extracellular signal-regulated kinase 2 (Erk1/2) and PI3K signaling pathways, mediates cardiac hypertrophy, extracellular remodeling, and suppresses cardiac myocyte apoptosis [25,26].

The development of cardiac dysfunction in T2DM is closely associated with hyperactivity of both the RAAS and sympatico-adrenal nervous system (SNS) [27]. Acting as triggers of gluconeogenesis, lipolysis, and glycolysis, catecholamines, angiotensin-II and aldosterone promote the production of advanced glycation end products (AGE), which directly and along with insulin and glucose activate transforming growth factor beta 1 (TGF-β1)/SMAD signaling pathways through appropriate cell surface receptors (RAGE) [28]. Consequently, increased oxidative stress, inflammatory response, and fibrotic extracellular matrix transformation with collagen cross-linking correspond to adverse cardiac remodeling, acceleration of atherosclerosis, and worsening vascular integrity and endothelial function [29–31]. Of note, impaired GLUT4 and PI3K/Akt/eNOS signaling due to the activation of RAAS and insulin resistance accompany the reduced tyrosine phosphorylation of insulin receptor substrate (IRS)-1/2, which in turn leads to a lowered nitric oxide production. It directly impairs the vasomotor ability of coronary arteries, and substantially

decreases in the recruitment, proliferation, and survival of endothelial progenitor cells that play a pivotal role in endogenous vascular reparation [32].

Metabolic stress-induced pro-inflammatory activation has been cited as a powerful factor contributing to the pathogenesis of T2DM cardiomyopathy and HF [33]. Numerous inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-6, as well as some adipocytokines, act as triggers for insulin resistance via the enhancement of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and fork-head box-containing protein O subfamily (FoxO1) expression, as well as c-Jun N terminal kinase (JNK) activation, that induce the phosphorylation of IRS-1 and hamper the activation of peroxisome proliferator-activated receptors (PPAR)-γ receptors [34,35]. These perturbations mediate insulin resistance of the myocardium and skeletal muscles, adipose tissue inflammation, markedly reduce an interaction of FoxO1 with the promoter region of the β-isoform of myosin heavy chain (β-MHC) as well as negatively regulate β-MHC gene expression [36].

The structure and functional abnormalities result in adverse cardiac remodeling such as diastolic and systolic dysfunction due to cardiac hypertrophy, extracellular matrix accumulation and interstitial fibrosis, resulting in progressive dilated cardiomyopathy and decreased cardiac output, eventually leading to HF [37]. The underlying pathophysiological mechanisms contributing to the development of HF in DM are reported in Figure 1.

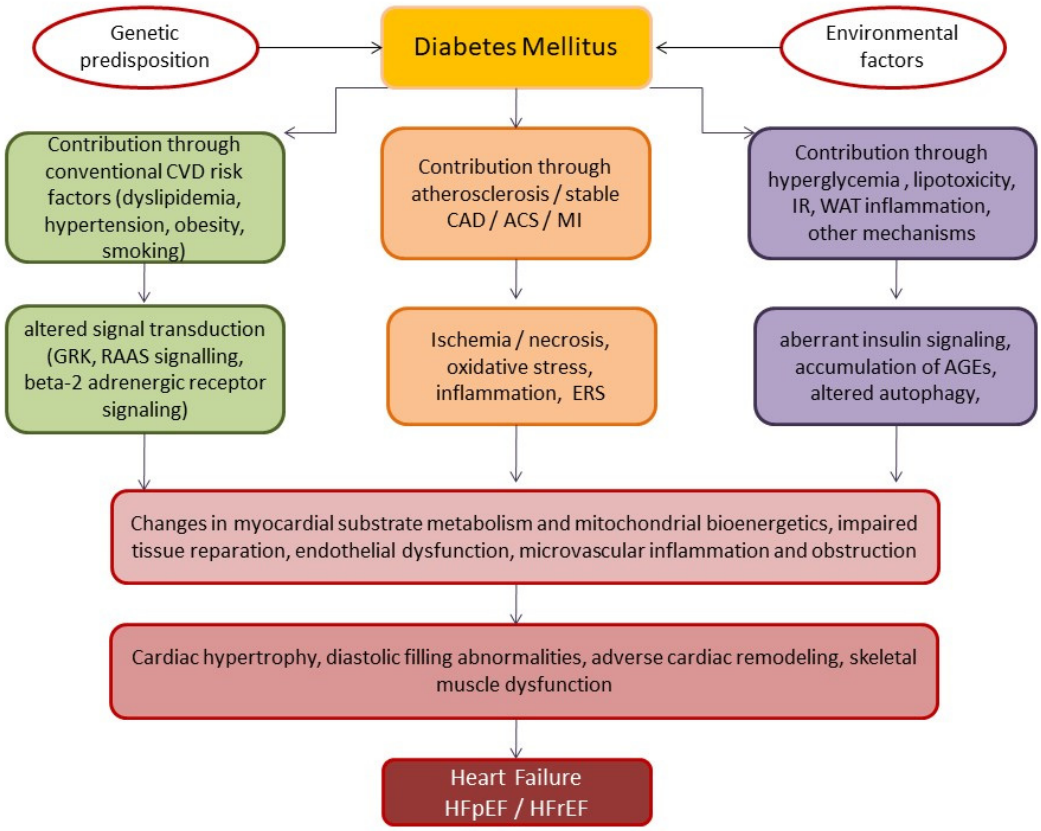

Figure 1. Underlying pathophysiological mechanisms contributing to the development of HF in patients with DM. Abbreviations: ACS, acute coronary syndrome; AGEs, advanced glycated end-products; CAD, coronary artery disease; CVD, cardiovascular disease; GRK, g-protein receptor kinase; ERS, endoplasmic reticulum stress; MI, myocardial infarction; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; IR, insulin resistance; RAAS, renin–angiotensin–aldosterone system; WAT, white adipose tissue.

Of note, there is evidence that approximately one-third of patients with T2DM demonstrate isolated diastolic filling abnormality and subclinical myocardial dysfunction, unrelated to accelerating atherosclerosis or CVD [38]. Therefore, left ventricular (LV) diastolic

dysfunction and LV concentric hypertrophy may be seen as the first signs of cardiac complications in patients with T2DM, independently from metabolic control [39,40]. In addition, uncontrolled T2DM with hyperglycemic status, hyperinsulinemia/insulin resistance, and lipotoxicity may result in cardiotoxicity, acute and chronic LV systolic dysfunction in the absence of CAD, valvular, congenital, or hypertensive heart disease, or alcoholism [41]. In fact, several phenotypes of T2DM-induced cardiac dysfunction may mostly relate to an overlap, but different alterations, which may be observed in failing hearts of T2DM patients. Indeed, substantial abnormalities in contractile (myosin, actin), regulatory (troponin, tropomyosin, and tropomodulin) and structural (predominantly titin, myomesin, and P-actinin) protein expression are responsible for the occurrence of diastolic and systolic dysfunctions as a primary myocardial alteration. For example, a decreased Ca^{2+} sensitivity along with a turnover of cardiac myosin heavy chain from V1 to V3 isoforms contributes to HFrEF [42]. Thus, an imbalance between adaptive and maladaptive molecular mechanisms of cardiac metabolism and reparation secures a link between T2DM and cardiac dysfunction [43–45]. MicroRNA and exosome-shaped transfer of active molecules are therefore also engaged in the pathogenesis of T2DM-induced cardiac dysfunction [46].

3. Biomarkers in Diabetics with Known HF

Biomarkers have been posed as promising surrogate indictors of pathologic changes in target organs (myocardium, kidney, vessels, and skeletal muscles) and metabolic homeostasis, particularly having diagnostic and predictive capabilities for patients with T2DM and HF [47]. 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, to diagnose HF and stratify patients at higher risk of poor prognosis, despite some differences in recommendations for practical use [6,48,49]. Table 1 reports the use of biomarkers in the management of HF according to 2016 ESC and 2017 ACC/AHA clinical guidelines [6,48].

Table 1. 2016 ESC and 2017 ACC/AHA/HFSA recommendations for the use of biomarkers in the management of HF.

Strategy	Biomarkers	ESC, 2016			ACC/AHA/HFSA, 2017		
		COR	LOE	Phenotype of HF	COR	LOE	Phenotype of HF
Diagnosis	BNP/NT-proBNP/MR-proANP *	I	A	AHF, HFpEF, HFmrEF	I	A	AHF, CHF
Risk of in-hospital death	BNP/NT-proBNP	I	C	AHF	I	A	AHF, CHF
	hs-cTr	I	C	AHF	I	A	AHF, CHF
Risk of recurrent hospital admission	BNP/NT-proBNP			-	I	A	AHF, CHF
Risk of post-discharged death	BNP/NT-proBNP	I	A	AHF, CHF	I	A	AHF, CHF
	hs-cTr	I	C	AHF, CHF	I	IIa	AHF, CHF
	Galectin-3			-	IIb	B	AHF, CHF
	sST2			-	IIb	B	AHF, CHF
Prevention of HF onset	BNP/NT-proBNP			-	IIa	B	AHF, CHF
Guided therapy	BNP/NT-proBNP			-	I	A	HFrEF/HFpEF

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; BNP, B-type natriuretic peptide; HF, heart failure; HFSA, Heart Failure Society of America; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST2, soluble ST2; COR, class of recommendation; LOE, level of evidence; MR-proANP, mid-regional pro A-type natriuretic peptide; hs-cTn, high-sensitivity cardiac troponins; HFrEF, heart failure reduced ejection fraction; HFpEF, heart failure preserved ejection fraction; HFmrEF, heart failure mid-range ejection fraction; *, provided for 2016 ESC recommendation only.

Although biomarkers of biomechanical stress (natriuretic peptides) and myocardial injury (high-sensitivity cardiac troponins (hs-cTn)), which are commonly used in HFrEF

and to help to diagnose HFpEF, have high predictive utility in T2DM, they are markers of general pathological processes and consequently are not specific for T2DM-induced HF [50]. Conventional and alternative biomarkers of HF in T2DM patients are reported in Figure 2.

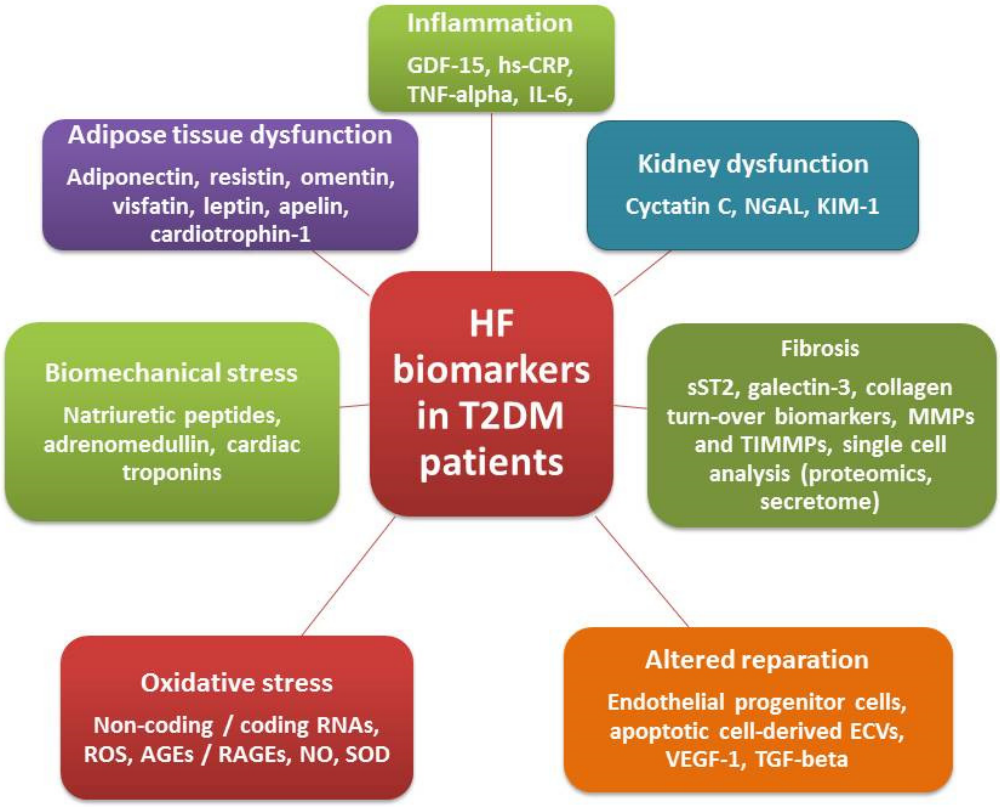

Figure 2. Conventional and alternative biomarkers of HF in T2DM patients. Abbreviations: hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; GDF, growth differential factor; NO, nitric oxide; SOD, superoxide dismutase; RNA, ribonucleic acid; ECVs, extracellular vesicles; VEGF, vascular endothelial growth factor; MMP, matrix metalloproteinase; TNF, tumor necrosis factor; TIMMP, tissue inhibitor of MMP; TGF, transforming growth factor; ROC, reactive oxygen species; AGEs, advanced glycation end products, RAGEs, receptor for AGEs; NGAL, neutrophil gelatinase-associated lipocalin; KIM-1, kidney injury molecule-1.

Novel biomarkers of fibrosis and inflammation (soluble suppression of tumorigenicity-2 (sST2) and galectin-3 (Gal-3)) are included in the ACC/AHA/HFSA HF guidelines as an alternative tool for CVD prediction and HF risk stratification, but their clinical utility in T2DM has not yet been proven and requires thorough elucidation. However, they were surrogate biomarkers for hard endpoints, such as all-cause and CV mortality and hospitalization in several large clinical trials in T2DM [51]. Other alternative HF biomarkers, such as oxidative stress, inflammation, and collagen turn-over biomarkers, have been investigated in the context of offering add-on information for prognoses and personalized risk management among patients with T2DM-induced HF [52–55]. Table 2 reports the advantages and disadvantages of HF biomarkers in patients with T2DM.

Table 2. Advantages and disadvantages of HF biomarkers in T2DM patients.

Biomarkers	Underlying Pathophysiological Mechanisms	Possible Application for HF Phenotype	Advantages	Disadvantages
NPs	Biomechanical stress	HFrEF, HFpEF	Available for diagnosis, risk stratification, prognosis, and point-to-care therapy	High serum level variability, variable cut-off points in patients with AF, CKD, AO, prediction in HFrEF is higher than HFpEF
hs-cTn	Myocardial injury	Manly HFrEF	Available for risk stratification and prognosis	No add-on prediction to NPs
Mid-regional-pro-adrenomedullin	Neurohumoral activation	HFrEF, HFpEF	Better than NPs in predicting short-term mortality in acute HF	No superiority to NPs in predictive ability among chronic HFrEF/HFpEF
hs-CRP, IL-6	Inflammation	HFrEF, HFpEF	Prediction of all-cause mortality, CVD, HF-related events	Not suitable for point-of-care therapy, no ability to increase predictive ability of NPs, not recommended by reputed medical societies
GDF-15	Inflammation	HFrEF, HFpEF	Available for improving predictive ability of NPs, suitable for multiple biomarker strategy and point-of-care therapy	High cost, not recommended by reputed medical societies
sST2, galectin-3	Fibrosis/inflammation	HFpEF	Better than NPs for predicting mortality and HF-related events in non-HF patients, low individual serum level variability	High cost
Collagen turn-over biomarkers	Fibrosis	HFpEF	Available for risk stratification and prognosis	High cost, not recommended by reputed medical societies

Abbreviations: AO, abdominal obesity; AF, atrial fibrillation; CKD, chronic kidney disease; NPs, natriuretic peptides; hs-CRP, high-sensitivity C-reactive protein; sST2, soluble suppressor tumorigenisity-2; GDF-15, growth differential factor-15; IL, interleukin; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.

3.1. Biomechanical Stress Biomarkers

3.1.1. Natriuretic Peptides

Natriuretic peptides (NPs) are released from cardiac myocytes as a result of myocardial stretching, volume overload, inflammation, and ischemia/hypoxic injury [56]. NPs are physiological antagonists of RAAS, and they protect against cardiovascular remodeling through the attenuation of water and sodium homeostasis, suppression of apoptosis, inflammation, and fibrosis, as well as the potentiation of vasodilation and vascular reparation, and attenuation of insulin resistance of the myocardium and skeletal muscles [57,58]. In addition, there is strong evidence regarding the protective capacity of NPs in tissue, which has translated to an improvement of clinical outcomes and decreased risk of HF admission [59].

HF development is associated with a marked increase in NP serum levels, which closely relates to a risk of CV death and HF admission [58]. Nevertheless, the improvements in clinical outcomes and prognoses in patients with HFrEF and HFpEF were strongly associated with lowering NP serum levels [60]. Being conventional biomarkers of biomechanical stress, NPs have been utilized as a diagnostic and predictive tool, predominantly for HF with reduced ejection fraction (HFrEF).

Although the role of NT-proBNP levels in predicting HF and CVD events in persons with prediabetes and T2DM is not yet well established, NPs improved the risk prediction of traditional risk factors for both incident HF and total CVD events in pre-diabetes or T2DM patients from ethnically diverse populations [61]. NPs exhibit optimistic results regarding prognostication of clinical outcomes directly related to HFrHF and HFpEF in diabetics treated with angiotensin receptor neprilysin inhibitor (ARNI), sodium–glucose cotransporter (SGLT)-2 inhibitors, and glucagon-like peptide (GLP)-1 agonists [62–65]. Indeed,

NPs are substrates of neprilysin and thereby B-type of NP (BNP) concentrations rises with neprilysin inhibition, whereas NT-proBNP will continue to decrease with improvement in the functional class of HF [66,67]. At the same time, GLP-1 agonists were able to increase urinary sodium excretion and diuresis independent of NP changes [68]. Moreover, the EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) trial has shown that T2DM patients with persistently high levels of serum NT-proBNP or an increase in NT-proBNP levels over 6 months while taking GLP-1 agonists or dipeptidyl peptidase 4 (DPP-4) inhibitors were at a significantly higher risk of CV mortality and HF occurrence when compared with those who had low levels of NT-proBNP at baseline or during the observation period [69]. SGLT-2 inhibitors have also demonstrated cardiac and renal protective effects in association with improving oxidative stress, LV diastolic filling, endothelial function, and decreasing BNP serum levels [70]. Thus, NPs are a powerful diagnostic and predictive tool for patients with T2DM with established HF and those at higher risk of HF occurrence using different phenotypes [71,72].

3.1.2. Cardiac Troponins

Progression of both T2DM and HF was independently associated with the development of subclinical myocardial damage, characterized by elevated levels of hs-cTn [73]. Metabolic and oxidative stress can damage cardiac myocyte membranes and may induce a leakage of cytoplasmic troponin through it [74]. Additionally, there is evidence of the occurrence of irreversible cardiac troponin modifications by shaping the complex with AGE [73]. These irreversible troponin and AGE complexes occur during myofilament relaxation and may play a key role in the development of contractility dysfunction [74].

Although circulating levels of hs-cTn are largely increased in HFpEF/HFrEF patients with T2DM, when compared to those without T2DM, hs-cTn yields additional prognostic information for HFrEF and HFpEF patients regardless of a presence of T2DM [75]. Moreover, hs-cTn predicts adverse outcomes independently from NT-proBNP and thereby can identify T2DM patients at an extremely high absolute CVD risk [76].

Importantly, TnI is commonly elevated among T2DM patients at higher risk of CVD events, incident HF, and stroke [77]. Circulating levels of hs-cTn in T2DM patients with atherosclerotic CVD were associated with higher hemoglobin A1c levels, severity of hypoglycemia, and markedly predicted subclinical changes in structure and function of the heart, brain, vasculature, and kidney [77,78]. In a meta-analysis of 28 relevant studies by Willeit P. et al. (2017) [79], it was unveiled that those in the general population with high hs-cTn concentrations within the normal range were associated with an increased risk of CVD. The ARIC (Atherosclerosis Risk in Communities) study has shown that elevated hs-TnI ($\geq$3.8 ng/L) in the general population is associated with greater incident CHD (hazard ratio (HR) = 2.20; 95% CI, 1.64–2.95), ischemic stroke (HR = 2.99; 95% CI, 2.01–4.46), atherosclerotic CVD (HR = 2.36; 95% CI, 1.86–3.00), HF hospitalization (HR, 4.20; 95% CI, 3.28–5.37), and all-cause mortality (HR, 1.83; 95% CI, 1.56–2.14) [80]. Overall, T2DM patients having HF with evidence of subclinical myocardial damage are at the highest risk for premature death, CVD, and HF-related events. However, mild elevated hs-cTn did not improve the predictive ability of NPs, and helps to rule out atherothrombotic events rather than HF progression in diabetics. However, hs-cTn did not fit to point-of-care therapy of HF and there is no need in continuous monitoring of the concentration in HF outpatients and ambulatory asymptomatic individuals at high risk of HF.

3.1.3. Adrenomedullin

Mid-regional pro-atrial natriuretic peptide (MR-proADM) is a C-terminal inactive fragment of adrenomedullin, which mediates vasodilatory and natriuretic properties [81]. Being elevated in acute HF and severe chronic HF, mostly in HFrEF, it has been found to have potential diagnostic and prognostic utility, although the findings obtained in clinical trials were controversial [82,83]. The BACH (Biomarkers in Acute Heart Failure) trial has shown that MR-proADM is superior to both BNP and NT-proBNP in predicting short-

term mortality [83]. Serum levels of mid-regional pro-adrenomedullin (MR-proADM) were associated with 1-year CV events and all-cause mortality in patients with overt HF [84]. However, Vazquez-Montes MDLA et al. (2020) [85] reported that MR-proADM was not superior to NT-proBNP in the prediction of chronic HF. In a recently published meta-analysis comparing the diagnostic value of novel biomarkers for HF, Huang Z. et al. (2020) [86] revealed that MR-proADM had a poor discriminative value to confirm or exclude HF. Whether a serial measurement of MR-proADM is able to reclassify a risk of death due to HF individually depending on the presence of other CV risk factors including T2DM is not yet fully understood, because no correlation between T2DM and levels of MR-proADM has been found for mortality or HF hospitalization [87]. Perhaps the evaluation of MR-proADM levels may be important for T2DM patients with abdominal obesity because these individuals exhibit an NP deficiency in early stages of HF, and other biomarkers can be used for the diagnosis and risk stratification of HF [88]. However, uncertainty in the total cost of biomarker implementation does not allow clearly proposing MR-proADM in the strategy of HF care.

3.2. Biomarkers of Inflammation and Fibrosis

Inflammatory biomarkers and biomarkers of fibrosis are not commonly used in routine clinical practice, but their evaluation in diabetics with HFrEF and HFpEF should be considered. The most important biomarkers having a certain predictive value are growth differential factor-15 (GDF-15), high-sensitivity C-reactive protein (hs-CRP), soluble suppressor tumorigenicity-2 (sST2), galectin-3 and interleukin-6 family cytokines.

3.2.1. Growth Differential Factor-15

Growth differential factor-15 (GDF-15) is a stress-induced multifactorial cytokine, which is markedly expressed in cardiac myocytes, endothelial cells, vascular smooth muscle cells, adipocytes, macrophages, and in normal and pathological conditions including HFpEF/HFrEF and T2DM [89]. The main biological function of GDF-15 is to improve glucose metabolism, attenuate energy homoeostasis and weight loss, as well as to protect various tissues, such as the myocardium, the vasculature, and the adipose tissue against injury by the inhibition of JNK, Bcl-2-associated death promoter (Bad), and epidermal growth factor receptor (EGFR) and activating Smad/eNOS, PI3K/AKT signaling pathways [89].

The XENDOS (XENical in the prevention of Diabetes in Obese subjects) trial has shown that the levels of GDF-15 are related to body weight, BMI, waist-to-hip ratio, and insulin resistance in non-T2DM obese individuals [90]. The elevation of circulating levels of GDF-15 strongly predicted the development of T2DM and HF and was associated with an adverse prognosis for both diseases [91]. Using a database derived from 3792 participants from the ARIC (Atherosclerosis Risk in Communities) Study, Echouffo-Tcheugui JB et al. (2021) [92] concluded that higher GDF-15 levels (highest vs. lowest quartile) were positively associated with T2DM (adjusted odds ratio (aOR) = 2.48, 95% CI = 1.89, 3.26), atherosclerotic CVD (aOR = 1.57, 95% CI = 1.16, 2.11), increased hs-cTnT (aOR = 2.27, 95% CI = 1.54, 3.34), increased NT-proBNP (aOR = 1.98, 95% CI = 1.46, 2.70), and HF (aOR = 3.22, 95% CI: 2.13, 4.85). Importantly, GDF-15 added prognostic information to NYHA functional class, LVEF, and serum levels of NT-proBNP in patients with HF, regardless of age, body mass index, HF etiology, concomitant medical therapy, and renal function [93]. Although elevated serum levels of GDF-15 are closely related to mortality rate and the risk of HF occurrence, the exact mechanism of the interrelationship remains uncertain [94]. The prognostic utility of GDF-15 requires further evaluation in large clinical trials in a head-to-head comparison with traditional biomarkers.

3.2.2. High-Sensitivity C-Reactive Protein

Belonging to the superfamily of pentraxins, C-reactive protein (CRP) is a protein of acute systemic inflammation [95]. CRP as a biomarker is useful in identifying CVD risk

when it is measured with highly sensitive assays, even in substantially low concentrations (now known as high-sensitivity CRP (hs-CRP) [96].

Serum levels of hs-CRP have been found to be independently predictive for the development of T2DM and CV disease in the general population [97,98]. T2DM was associated with elevated levels of hs-CRP and other indicators of diabetes-related CV risk, such as homeostatic model assessment, the levels of intact proinsulin and insulin, BMI, and beta-cell dysfunction, but not with fasting glucose [99,100]. However, Aryan Z. et al. (2018) [101], in a population-based study, showed that hs-CRP predicted CV complications including HF and diabetic kidney disease in patients with overt T2DM [101]. Moreover, they found that hs-CRP significantly improved the discriminative capacity of conventional CV risk scores when added to it [101]. In patients with established atherosclerotic CVD, elevated levels of hs-CRP were associated with poor clinical outcomes, especially among non-T2DM patients [102,103]. Additionally, Yang QQ et al. (2020) [104] presented evidence for a positive association between the levels of hs-CRP and the severity of major depression. A reduction in hs-CRP levels during the therapy of dyslipidemia or CAD has been shown to be closely related to an improvement in long-term prognosis [105]. Finally, in HFpEF, high hs-CRP levels were associated with greater comorbidity burden, including T2DM and abdominal obesity, even though almost 40% of HFpEF patients had normal values of hs-CRP [106]. In contrast, the levels of hs-CRP in HFrEF patients were higher when compared to those with HFpEF, and it predicted myocardial dysfunction and HFrEF after acute myocardial infarction [107,108]. Surprisingly, a decrease in hs-CRP levels in acute HF was associated with a significant reduction in the 3-year risk of death in HFpEF patients, but not in HFrHF [109]. In conclusion, although the association of hs-CRP with clinical events has been found to be an independent predictor of CV morbidity and mortality [110], there is sufficient uncertainty in the predictive ability of hs-CRP in patients with different phenotypes of HF and consequently a high heterogeneity in CV risk factors present.

3.2.3. Soluble Suppression of Tumorigenicity-2

Soluble suppression of tumorigenicity-2 (sST2) is an established biomarker of inflammation and fibrosis, having certain predictive potency [111]. ST2 interferes with interleukin-33 and thereby induces the up-regulated expression of the transmembrane isoform ST2 ligand on the surfaces of target cells, resulting in biomechanical myocardial stress, injury, and inflammation. Finally, sST2 exerts protective effects on the myocardium by suppressing fibrosis and attenuating hypertrophy, thus enhancing survival.

Among inflammatory biomarkers, sST2 has been approved by the 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 adds predictive value to NPs and cardiac troponins for HF [112]. In addition, sST2 demonstrates a high discriminative ability for predicting CV morbidity and mortality, HF occurrence and hospitalization independently from common CV, and metabolic comorbidities, such as diabetic kidney disease, renal dysfunction, and hypertension [113–116]. sST2 can also stratify the patients with HFrEF at higher risk of sudden death [113]. Furthermore, elevated levels of sST2 provide additional prognostic information for different phenotypes of HF, exceeding the ability of NT-proBNP [117,118]. Thus, sST2 appears to be a powerful predictor for clinical outcomes in HF patients, regardless of the presence of T2DM, while high economic burden is considered as the main constraint for an implementation of single and serial sST2 measures in routine clinical practice [117].

3.2.4. Galectin-3

Galectin-3 is a β-galactosidase-binding lectin, which belongs to the galectin family [119]. Its biological functions include the modulation of cell growth, proliferation, differentiation, suppression of apoptosis, pre-mRNA splicing, attenuation of angiogenesis, reduction in inflammation, and fibrosis [120–122]. It has been established that a deficiency of galectin-3 mediates tissue injury, whereas the over-expression of galectin-3 was asso-

ciated with tissue protection [123]. In addition, galectin-3 serves as a prognostic cardiac biomarker with promising therapeutic potency [123].

The Dallas Heart Study showed that levels of galectin-3 were associated with T2DM prevalence, incident T2DM, and fat compartments [124]. In addition, galectin-3 levels were 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 [124]. Moreover, serum galectin-3 is independently related to progressive renal disease in T2DM, CVD and increased risk of all-cause mortality [125,126].

Serum levels of galectin-3 have been shown to increase in HF patients, and were associated with myocardial fibrosis, adverse cardiac remodeling, atrial fibrillation, and CAD [127,128]. Furthermore, galectin-3 is considered not only as a powerful predictive biomarker of incident HF, but also as a mediator of T2DM progression [129,130]. Among HFpEF patients, the levels of galectin-3 were significantly positively associated with age, creatinine clearance, arterial stiffness (determined by the measurement of carotid femoral pulse wave velocity), aldosterone and BNP levels, and inversely correlated with LV ejection fraction [131–133]. Among 1386 patients with a $\geq$1 risk factor for HF (e.g., hypertension, T2DM, and atherosclerotic CVD) or previously suspected HF, that were enrolled in the DIAST-CHF study, galectin-3 levels of >313.57 ng/mL (sensitivity = 0.61 and specificity = 0.73) predicted incident HFpEF, adjusted all-cause mortality, and the adjusted composite of CV hospitalization and death [134]. Gocer H. et al. (2019) [135] concluded that galectin-3 concentrations were positively associated with HF severity and negatively correlated with left ventricular ejection fraction.

Elevated levels of galectin-3 substantially predicted mortality in acute HF, as well as in both phenotypes of chronic HF [136]. Although recent investigations found that galectin-3 was not superior to NT-proBNP, sST2, GDF-15, and hs-CRP as a predictor of mortality, the combination of galectin-3 and NPs had better discriminative capacity for predicting mortality when compared with either of the biomarkers alone [137,138]. Overall, galectin-3 has shown the ability to predict HF regardless of T2DM beyond the conventional biomarkers, such as NPs and cardiac troponins, but its role in the point-of-care of HF patients still needs investigation and future studies.

3.2.5. Interleukin-6 Family Cytokines

The interleukin (IL)-6 family is a heterogenic group of cytokines, consisting of IL-6, IL-11, cardiotrophin 1 (CT-1), cardiotrophin-like cytokine (CLC), ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), oncostatin M (OSM), and IL-27 [139]. These cytokines are engaged in metabolic and immune regulation, cardiac repair, and tissue protection [140,141]. The development of both T2DM and HF is associated with high variability in the oxidative stress-dependent activation of eNOS, which is regulated by IL-6 family cytokines. While these findings have hypothetical value, recently, SGLT2 inhibitors have been shown to have a favorable effect on CV outcomes in HFrEF/HFpEF, regardless of T2DM presence in connection with the reduction in inflammatory and oxidative stress and improvement of the NO–sGC–cGMP cascade and protein kinase G type Iα (PKGIα) activity [142–144]. Whether CT-1 and other IL-6- family cytokines can be used as future biomarkers to monitor prospective effects of SGLT2 inhibitors on clinical course of HF and T2DM at higher risk for HF is not fully clear and needs further thorough evaluation in large clinical trials.

3.2.6. Other Biomarkers of Fibrosis

Novel biomarkers (matrix metalloproteinases (MMPs) and tissue inhibitors of MMP (TIMP), collagen degradation products) have been discussed considerably in the context of risk stratification in T2DM with HF but have not yet been tested directly in large clinical trials. Therefore, the clinical perspectives of these biomarkers are not yet known [13]. Despite serious concerns regarding the essential ability of these circulating biomarkers to reflect both quantitative and qualitative morphological changes in the cardiac extracellular matrix,

there is a large body of evidence drawn from preclinical and clinical studies that suggests a promising role of collagen turn-over biomarkers in the development of adverse cardiac remodeling and HF [145]. The potential of T2DM to lead primarily to the development of HFpEF depends on impaired collagen homeostasis and cardiac fibrosis. Indeed, there is a disproportion in the circulating levels of collagen synthesis biomarkers (procollagen type I N-terminal propeptide (PINP), procollagen type III N-terminal propeptide (PIIINP), and biomarkers of collagen degradation (c-terminal telopeptide of collagen type I (CTx)) among HF patients with left ventricular ejection fraction < 50%. In fact, circulating levels of these biomarkers were positively correlated with the severity of HF, which was confirmed by NT-proBNP, E/E', and left atrial volume [146]. Moreover, elevated circulating levels of procollagen I N-terminal peptide (PINP) and procollagen III N-terminal peptide (PIIINP), MMP-1, MMP-3, MMP-9, and TIMP-1 were associated with higher rates of CV mortality and HF hospitalization in patients with overt HFrEF and HFmrEF [147,148]. Surprisingly, long-term prognosis of HF outpatients was comparable, regardless of whether patients had HFpEF or HFrEF [149]. In contrast, the MESA (Multi-Ethnic Study of Atherosclerosis) trial showed that high levels of circulating ICTP and PIIINP were solely associated with incident HFpEF, but not HFrEF [150]. However, Ferreira JP et al. (2019) [151] reported that collagen Lysyl oxidase-like 2 (Loxl2), which is up-regulated in the cardiac interstitium in HF, was found to be a powerful trigger for cardiac fibroblasts via PI3K/AKT to express TGF-β2, promoting the fibroblast-to-myofibroblast transformation. Moreover, LOXL2 concentrations were elevated in the serum of HF patients and positively correlated with BNP and NT-proBNP [151]. Overall, biomarkers of collagen homeostasis transformation could be strongly linked to inflammation, apoptosis, vascular function, extracellular matrix remodeling, blood pressure control, and energy metabolism, and therefore did not have high specificity for HF development or progression [152]. When added to conventional biomarkers, such as BNP, NT-pro-BNP, and sST2, circulating biomarkers reflecting excessive myocardial collagen type-I cross-linking and extracellular matrix remodeling were able to substantially increase the predictive ability of the entire model, especially in HFpEF patients with T2DM, atrial fibrillation, or hypertension [153,154].

4. Multiple Biomarker Strategies

Multiple biomarker predictive models are considered as an effective method to increase the specificity and sensitivity of a single biomarker tool [155]. Data confirm the superiority of multiple models compared with conventional models in risk stratification in HFpEF, whereas the adoption of serial biomarker measurements for risk stratification in HFpEF remains uncertain. However, different combinations of circulating cardiac biomarkers are likely a promising tool to improve prediction, risk stratification, and therapy in T2DM with HF, although there are 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 natriuretic peptide, mid-regional pro-adrenomedullin, and C-terminal pro-endothelin-1) in advanced HF were no better than measurements of the C-terminal fragment of pre-pro-vasopressin [157]. Pandey A. et al. (2021) [158] evaluated the application of a biomarker-based risk score to identify patients with dysglycemia that were at high risk of incident HF. They enrolled individuals from three cohort studies (ARIC (Atherosclerosis Risk In Communities), DHS (Dallas Heart Study), and MESA (Multi-Ethnic Study of Atherosclerosis)). The original biomarker score included hs-cTnT $\geq$ 6 ng/L, NT-proBNP $\geq$ 125 pg/mL, hs-CRP $\geq$ 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; moreover,

the highest risk was noted in patients with total scores of ≥3 (diabetes: 12.0%; pre-diabetes: 7.8%). Thus, it has been established that the biomarker score can stratify the HF risk among patients with T2DM and pre-diabetes. Berezin AE et al. (2019) [159] reported that the combination of NT-proBNP and ST2 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. Consequently, these conflicting results deserve closer investigation in large clinical trials in the future.

5. Point-of-Care Clinical Diagnostics in HF

In the clinical setting, the detection of individual biomarkers or a combined analysis thereof are promising tools to support the manifestation and diagnosis of cardiac diseases, such as HF. The ACC/Aha/HFSA guidelines (2017) [6] have also recommended the measurement of additional biomarkers, such as sST-2 and galectin-3, for the risk assessment in HF. Although multiple assays are available to detect a vast number of biomarkers, they are most often rather expensive and time-consuming. For instance, as far as most enzyme-linked immunosorbent assays (ELISA) are concerned, several hours or one entire day are necessary to obtain the assay results, depending on the kit used. However, in point-of-care clinical diagnostics, it is crucial to obtain reliable results within a short time range. Multiple companies have addressed this challenge and have already successfully rolled out some rapid tests for biomarker analysis.

5.1. Natriuretic Peptides

As mentioned above, NPs are released into sera as a consequence of myocardial stress, such as stretching, overload, inflammation, or ischemia. Therefore, these peptides constitute important biomarkers for risk assessment in HF and are already in clinical application [60]. Originally, there were at least four rapid tests for the quantification of BNP available: (1) The Biosite Triage BNP (Biosite Diagnostics, San Diego, CA, USA) has been widely used in several clinical trials as an approved BNP rapid assay for bedside testing [160,161]. This assay is based on a fluorescence immunoanalysis signal detection which is directly dependent on the amount of BNP in plasma. Quantitative results are gained within 15 min after sampling [161]; (2) The second assay is based on an electrochemiluminescent procedure that detects NT-proBNP which may be obtained within 18 min by a Roche Cobas analyzer (Roche Diagnostics, Indianapolis, IN, USA) [162]; (3) The DVIA Centaur BNP® assay by Bayer Healthcare LLC (Tarrytown, NY, USA) [163]; and the (4) AxSYM® BNP assay by Abbott Diagnostics (Abbott Park, IL, USA) [164] also have found wide application in several studies [165]. Several more rapid kits have been rolled out, mainly manufactured by Alere, Roche, Quidel and pts Diagnostics [166].

5.2. Cardiac Troponins

Besides BNP, cardiac troponin is an important biomarker for cardiovascular events, in particular, cardiac necrosis. The current guidelines for HF recommend the evaluation of cardiac troponin in patients with HFpEF as well as HFrEF. The evaluation of cTn levels is intended to be used for the prognosis prediction in HF. More than 20 years ago, the first rapid tests for the fast detection of cardiac troponin were developed [167]. Since then, several more tests have been established to facilitate their use as bedside tests, such as Spectral Cardiac STATus Troponin I Rapid Test (Spectrum Diagnostics, Cairo, Egypt) [168], Nadal troponin I cassette (Nal Von Minden, Regensburg, Germany), Hexagon Troponin (Human Diagnostics, Wiesbaden, Germany), Troponitest+ (All Diag, Strasbourg, France), and Amicheck-Trop (Zephir Biomedicals, Goa, India) [169]. Nowadays, there are more advanced bedside tests for the detection of cardiac biomarkers available that enable the simultaneous analysis of more than one protein of interest. For instance, H-FABP and cTnI Combo Rapid Test Cassette by BioZEK B.V. (Apeldoorn, the Netherlands) combines the detection of heart-type fatty acid protein (h-FABP), an MI and ischemia marker, with

troponin I in a single test cassette. Although several companies provide cTNI assays, Roche Diagnostics (Indianapolis, IN, USA) has the monopoly for cTNT assays [170].

5.3. Adrenomodullin

Adrenomodullin belongs to the family of peptide hormones and consists of 52 amino acids with a C-terminal fragment and a ring structure [171]. People without health impairments have low ADM levels in their plasma. Several studies have investigated high levels of adrenomodullin in humans with HF and found a correlation with worse long-term prognosis [172,173]. The clinical use of this biomarker is limited due to the potential inconsistency of the laboratory tests. For the achievement of satisfying results, a lot of material, incubation time, and preanalytical sample extraction is necessary. Midregional pro-adrenomodullin was discovered as an alternative option for reliable results [174–176].

A novel sandwich immunoassay has been used (BRAHMS MR-proADM; BRAHMS Aktiengesellschaft, Heningsdorf, Berlin, Germany) since MR-proADM was discovered. Analytical detection with this assay is limited to 0.08 nmol/L. For values > 0.12 nmol/L, the inter-assay coefficient of variance is <20% [176].

5.4. GDF-15

GDF-15 shows clinical relevance because it is released into the circulation in several manifestations, such as CVD and HF [89]. Although GDF-15/MIC-1 Human ELISA from BioVendor Laboratory Medicine (Modrice, Czech Re-public) [177] is approved for clinical diagnostics, automated detection methods have emerged recently, e.g., electrochemiluminescence (Elecsys®) immunoassay by Roche Diagnostics (Basel, Switzerland). It is based on a sandwich immunoassay that enables the detection of GDF-15 in a 35 µL whole blood sample. It is a rapid and straightforward procedure with little personnel effort [178].

5.5. hs-CRP

C-reactive protein (CRP) is a well-researched marker of not only infectious and inflammatory conditions, but also cardiovascular illness [179]. It has been integrated into routine laboratory diagnostics in recent years. Several point-of-care testing devices for CRP are available. Concerning these, several studies were able to demonstrate a benefit in decision-making regarding antibiotic prescriptions in emergency departments [180,181]. For CVDs and risk factors, a benefit of point-of-care CRP diagnostics has been postulated [182,183]. However, evidence supporting routine clinical use is still scarce [184]. Further studies on the decision-making relevance of rapid CRP testing for CVDs are warranted.

5.6. ST-2

sST2 has gained major interest in cardiovascular research, and has emerged as a biomarker for hemodynamic stress, fibrosis, and inflammation [111]. However, it has not yet been established in widespread and routine clinical diagnostics. To date, only two assays have gained certificates for clinical usage: the highly sensitive ELISA kit Presage Assay [185,186], and the ASPECT PLUS ST2 Quantitative Rapid Test Assay [187], both manufactured by Critical Diagnostics (San Diego, CA, USA). Assay results of the latter are obtained within 20 min; therefore, it may provide a promising tool in point-of-care clinical diagnostics [188].

5.7. Galectin-3

It is known that serum levels of galectin-3 increase as a consequence of several cardiovascular events, as mentioned above [127,128]. As far as HF is concerned, several clinical studies have addressed the prognostic properties of Gal-3 [119]. Most studies and clinical trials have used the BGM Galectin-3® Test by BG Medicine Inc. (Foxboro, MA, USA) for the quantification of serum or plasma galectin-3 in HF patients [189,190]. Furthermore, some years later, automated assays such as ARCHITECT assay (Abbott Diagnostics, Abbott Park, IL, USA), based on chemiluminescent microparticle immunodetection, were introduced. It

detects Gal-3 levels in serum or plasma within 29 min for the standard assay; the STATassay can be conducted in 18 min [191,192]. Gal-3 detection by VIDAS® Gal-3 assay (bioMerieux SA, Marcy-I'Etoile, France) uses enzyme-linked fluorescent signal detection [193]. A comparative study has unveiled that the Gal-3 levels measured by VIDAS® Gal-3 assay were comparable to those measured by ELISA. However, in contrast to the ELISA technique, VIDAS® Gal-3 enables the detection of its concentration within 20 min [194]

5.8. IL-6

One of the most important biomarkers indicating inflammation is IL-6, which is also a highly prominent biomarker in HF [195]. Various detection methods have been established so far for the reliable and reproducible measurement of IL-6, such as ELISA, chemiluminescence immunoassays, magnetic colorimetric immunoassays, and a few more which were recently summarized by Huang et al. (2020) [196]. In the last few years, the need of IL-6 bedside tests for point-of-care (POC) medicine has emerged. Therefore, Milenia Biotec (Bad Nauheim, Germany) has developed a lateral flow-based immunoassay POC test, namely, Milenia QuickLine® IL-6. The analysis procedure was briefly described by Chaemsaithong et al. (2015) [197] and enables the semi-quantitative evaluation of IL-6 in serum, plasma, or cell culture supernatant after 20 min of incubation time [198].

5.9. MMPs, TIMP and Collagen Degradation Products

Matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) are responsible for maintenance of the equilibrium between collagen types I and II in the cardiac extracellular matrix. Certain causes of HF are the result of or are accompanied by changes in the cardiac extracellular structure, such as myocardial fibrosis in dilated cardiomyopathy [199,200]. Additionally, MMPs are an integral part of the atherosclerotic plaque extracellular matrix, and MMP plasma levels are elevated after myocardial infarction as a result of plaque rupture [201]. Thus, the MMP/TIMP system can be used as a possible target of HF treatment and possibly may serve as a future indicator of imminent myocardial infarction [202,203].

There are MMP-8-specific immunochromatographic dip-stick tests available, which can be used as a bedside test and deliver rapid information about MMP-8 activity. However, this activity can be a result of various pathologic conditions, such as periodontitis, peri-implantitis, and CVD [204,205]. Therefore, use as an early detection method of atherosclerotic plaque rupture cannot be proven yet. There are an abundance of point-of-care collagen degradation assays, which could be useful in the early detection of cardiac remodeling. However, a relevant clinical use for this application is still to be discovered in the future [206].

6. Conclusions

We found that substantial heterogeneity of CV risk factors, including T2DM, hypertension, and atherosclerotic CVD in patients with HFpEF, hinders accurate risk stratification and prediction. Thus, new biomarker-based approaches would sufficiently improve risk stratification and the prediction of poor clinical outcomes. Although current risk stratification strategies of HFrEF patients are based on the determination of NP levels, their normal concentrations do not exclude a diagnosis of HFpEF besides in diabetics. The combination of multiple biomarkers, such as NPs, sST2, and cardiac troponins, was predominantly observed as a powerful predictor of all-cause mortality and hospitalization in HFrEF, but this combined model may be prognostically important in symptomatic HFpEF. However, their role in T2DM patients with diastolic dysfunction and asymptomatic HFpEF remains uncertain. Novel biomarkers of inflammation (mid-regional pro adrenomedullin), fibrosis (galectin-3), inflammation (GDF-15), and collagen turn-over biomarkers have shown potential benefits in determining the prognosis in T2DM patients with concomitant HFpEF regardless of NPs, although their role in point-of-care and routine clinical practice needs elucidation in large clinical trials. Multiple biomarker models appear to be viable for the

personalized, biomarker-oriented care of T2DM patients at high risk of HF and overt HF. However, the high costs for biomarker-guided administration remain the main constraint for implementation of this approach in routine clinical practice.

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Abbreviations

AGEs	advanced glycation end-products
Bad	Bcl-2-associated death promoter
CV	cardiovascular
EGFR	epidermal growth factor receptor
ECVs	extracellular vesicles
FoxO1	fork-head box-containing protein O subfamily
GDF	growth differential factor
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
hs-CRP	high-sensitivity C-reactive protein
IL	interleukin
JNK	c-Jun N terminal kinase
KIM-1	kidney injury molecule-1
MMP	matrix metalloproteinase
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NGAL	neutrophil gelatinase-associated lipocalin
NO	nitric oxide
PPAR	peroxisome proliferator-activated receptors
PKGIα	protein kinase G type Iα
RAAS	renin–angiotensin–aldosterone system
RAGEs	receptor for advanced glycation end-products
RNA	ribonucleic acid
ROC	reactive oxygen species
SNS	simpatico-adrenal nervous system
SOD	superoxide dismutase
TGF	transforming growth factor
TIMMP	tissue inhibitor of matrix metalloproteinase
TNF	tumor necrosis factor
VEGF	vascular endothelial growth factor
β-MHC	β-isoform of myosin heavy chain

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