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The Assessment of Cardiovascular Risk in Patients with Acute Decompensated Heart Failure Accompanied by Chronic Kidney Disease

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Abstract

Heart Failure (HF) with its high prevalence and high death rates, is a complex chronic condition. It has distinct phenotypes classified depending on the ejection fraction. Comorbidities play a crucial role in HF. Kidney disease, which frequently accompanies HF worsens its prognosis. Heart failure and chronic kidney disease aggravates their courses in a complicated network of mutual relationships known as Cardio-Renal Syndrome (CRS). It is essential to establish the multimarker strategy in order to better evaluate the patients' condition and to assess cardiovascular risk, which could lower the rehospitalization rates, reduce mortality and improve prognosis. Using multimarker panels composed of numerous protein biomarkers and miRNAs can provide a non-invasive method for diagnosis and disease progression prediction.

Introduction

Heart Failure (HF) is a chronic, highly prevalent condition characterized by high death rates and is associated by the consumption of large healthcare resources [1,2]. According to estimations, in developed countries, HF affects approximately 1-2% of adults [3]. HF population in Poland is estimated to be about 600 000 - 700 000 people [4,5]. Recent data have indicated that morbidity rises remarkably with age [6]. It has been assessed that one fifth adults will have developed heart failure at some point in their lives [7].

Despite advances in medicine and the development of new therapy options, the HF death rate is high – 11% of patients die within the first year after acute decompensation. It is estimated that about 30% of HF patients need readmission within 60-90 days [8,9]. In most European studies, rehospitalization rates for HF, range from 24% at 12 weeks to 44% at 1 year post initial hospitalization [10,11].

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Acute Decompensated Heart Failure (ADHF) accounts for 80% of hospitalizations caused by HF. Solomon has proved that the death rate in HF increases by more than 30% after second rehospitalization [12]. Approximately 10% of patients hospitalized due to ADHF die within 60-90 days after the discharge [13,14].

The prognosis is even worse in the presence of multi-organ failure, especially – kidney failure, which is considered as the independent prognostic factor in HF patients [15]. Kidney dysfunction plays a crucial role in ADHF and Chronic Heart Failure (CHF), as it is associated with poor survival [16]. The functioning of both heart and kidney is closely related in terms of hemodynamic and neurohormonal mechanisms as well as the activity of sympathetic nervous system [17]. Swedish Heart Failure Registry demonstrated that Chronic Kidney Disease (CKD) is a stronger predictor of death in subgroup of patients with heart failure with reduced ejection fraction (HFrEF) and heart failure with mid-range ejection fraction (HFmrEF) than in those with heart failure with preserved ejection fraction (HFpEF) patients [15]. Numerous studies have confirmed that Chronic Kidney Disease (CKD), as well as the Worsening of Renal Function (WRF) are independent risk factors of death, both in short-term and long-term observation. Therefore, the assessment of renal function, in the context of determining prognosis, has become an important element in the care of patients with HF. There is a constant search for new methods of identifying patients at high risk of rehospitalization and other adverse cardiovascular events that would reduce the frequency of hospitalization due to HF and improve the prognosis of this group of patients by intensifying treatment and outpatient care after discharge from the hospital.

Heart failure

The latest HF Guidelines published by European Society of Cardiology (ESC) in 2016 offer new HF classification depending on the ejection fraction (EF), as presented in Table 1.

Table 1: Heart failure subgroups – adapted from ESC Guidelines 2016 [1].

	Category		
Ejection fraction	HFpEF	HFmrEF	HFrEF
	>50%	40% - 50%	<40%

HFpEF – heart failure with preserved ejection fraction; HFmrEF – heart failure with mid-range ejection fraction; HFrEF – heart failure with reduced ejection fraction.

The development of HF is associated with the presence of various underlying pathologies, including cardiovascular and systematic causes [18]. Typically HFpEF is observed in elderly hypertensive women. In patients with reduced ejection fraction the number of cardiovascular risk factors is frequently higher as this type of HF is predominantly related to underlying ischemic etiology. Recent studies concerning HFpEF have demonstrated three potential molecular mechanism leading to HF development [19]. These include: systemic microvascular inflammation, cardiometabolic functional abnormalities and cellular/extracellular structural abnormalities, as presented on Figure 1.

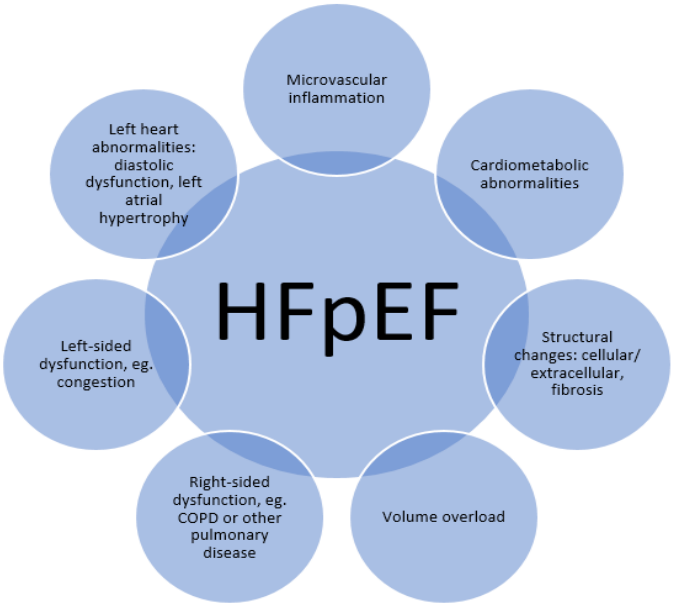

Figure 1: Mechanisms of the development of heart failure with preserved ejection fraction–adapted from [19].

Left ventricular diastolic dysfunction, defined as increased cell stiffness and disturbances in ventricular relaxation, is the basic phenomenon underlying the development of HFpEF [1]. Immune-inflammatory activation in chronic HF is closely related to the release of inflammatory mediators which initiates processes in the left ventricle, including its remodeling and profibrotic processes that lead to HFpEF development [19]. The evidences of inflammatory processes in HFpEF patients are visible not only in myocardial tissues, but also in lungs, kidneys and muscles [20].

The pathophysiology of HFmrEF is yet not clear. However it seems that it is associated with mild systolic and diastolic dysfunction [18]. Patients with HFmrEF present many comorbidities, including atrial fibrillation, chronic obstructive pulmonary disease (COPD), anemia, diabetes mellitus and kidney failure. The risk of all-cause and HF-related re-hospitalizations in case of patients with HFmrEF is similar to that observed in individuals with HFpEF and HFrEF [21]. However, the mortality rates differ between the aforementioned subgroups. The results of OPTIMAZE-HF trial indicated that mortality rate was: 3.9% for HFrEF, 3.0% for HFmrEF and 2.9% for HFpEF [14].

Kidney disease in heart failure

Heart failure and chronic kidney disease aggravates their courses in a complicated network of mutual relationships, which is known as Cardio-Renal Syndrome (CRS). HF exert negative impact on kidney function however, at the same time, CKD can impairs cardiac function due to hemodynamic changes, parenchymal damage, increased neuroendocrine activity, inflammatory and endothelial activation, and other factors affecting both heart and kidneys [22]. There are 5 types of CRS:

Type 1: In cardiogenic shock or in acute decompensated heart failure, sudden deterioration of cardiac function causes acute renal failure.

Type 2: Chronic heart failure causes the progression of chronic kidney failure.

Type 3: Acute kidney injury in the course of acute glomerulonephritis causes acute cardiac decompensation – arrhythmia, acute coronary syndrome, ADHF.

Type 4: Chronic kidney failure caused by irreparable renal injury, contributes to cardiac hypertrophy and to the enhancement of cardiovascular risk.

Type 5: CRS secondary to systemic diseases, such as diabetes, sepsis.

As demonstrated above, kidney disease is an important risk factor of heart failure development. The presence of renal failure leads to multiple changes, mainly in vascular system. It contributes to the worsening of cardiovascular system functioning via salt retention, pulmonary congestion and edema, the hyperactivation of renin-angiotensin and sympathetic system. Other mechanisms that worsen the cardiac outcome involve: endothelial dysfunction, inflammatory reaction, abnormal fibrinolytic system activity, insulin resistance and vascular calcification due to calcium phosphorus production.

High prevalence of kidney impairment in patients with HF has been confirmed in numerous studies. In a large systematic review and meta-analysis, 29% of patients with HF had moderate to severe impairment, while 63% of patients had any renal impairment [23]. The presence of moderate to severe renal impairment was associated with more than 100% higher relative mortality risk and absolute mortality rate of 51% during five years of follow-up, while in patients with any degree of renal impairment relative mortality risk was increased by approximately 50% in comparison to patients of normal renal function. In the SwedeHF study, Löfman [15] has demonstrated that 51% of HF patients had kidney dysfunction at moderate stage (with eGFR <60 mL/min/1.73m^2), including 11% of patients with severe dysfunction (eGFR <30 mL/min/1.73m^2). Hypertension, diabetes mellitus type 2, atrial fibrillation and valvular heart disease were among the other most common comorbidities. In SwedeHF study, almost one-third of hospitalized patients with severe kidney dysfunction died during hospitalization, while 50% of patients with eGFR<15 mL/min/1.73m^2 died within 6 months to 1 year from discharge. The increasing mortality along with decreasing kidney function seems to be independent on age and NYHA (New York Heart Failure Association) class. The aggravation of renal function in the course of HF was also confirmed in a large GISSI-HF trial [24]. In this study, overall, eGFR decreased by 2.57 mL/min/1.73 m^2/year, while in case of 25% of patients the progression of CKD by ≥1 KDOQI stage was observed. The decrease in CKD stage was strongly associated with cardiovascular event rates. Retrospective analysis of GISSI-HF also demonstrated that every 10 mL/min/1.73 m^2/year reduction in eGFR was related to a 10% higher prevalence of the combined end point, while the improvement in renal function resulted in considerable better outcomes in comparison with patients with relatively stable renal function [24]. In turn, Lala et al. [25] proved the existence of correlation be-tween Acute Kidney Injury (AKI) and HF. In their study, patients with HF and AKI had higher in-hospital mortality rates. The rate was strongly associated with ejection fraction. AKI have the strongest prognostic impact in HFmrEF patients. The impact of kidney impairment on the functioning of cardiovascular system was also demonstrated by Baskin et al. who found statistically significant improvement (p<0.01) in all cardiac parameters in ESRD patients with severe cardiac risk who underwent renal transplantation [26]. In transplant patients, they observed within six months the in-crease in mean Ejection Fraction (EF) (from 34.4 ± 9.1% to 68.4±7 .6%, p<0.01), reduction in mean left ventricular diastolic diameter (LVDD) and mean Systolic Diameter (SD) (from 53.8 ± 8.8 to 40.6 ± 8.5 and from 44.7 ± 8.6 to 25.5 ± 7.4, respectively, p<0.01).

The relative risks of all-cause mortality, cardiovascular mortality and CKD progression, vary depending on Albumin-to-creatinine ratio (ACR) and GFR, as presented in Tables 2, 3 and 4 [27].

Table 2: All-cause mortality (adjusted relative risk (RR)) for general population – adapted from [27].

	ACR <10	ACR 10-29	ACR 30-299	ACR ≥300
eGFR>105	1.1	1.5	2.2	5.0
eGFR 90-105	Ref	1.4	1.5	3.1
eGFR 75-90	1.0	1.3	1.7	2.3
eGFR 60-75	1.0	1.4	1.8	2.7
eGFR 45-60	1.3	1.7	2.2	3.6
eGFR 30-45	1.9	2.3	3.3	4.9
eGFR 15-30	5.3	3.6	4.7	6.6

Table 3: Cardiovascular mortality (adjusted relative risk (RR)) for general population – adapted from [27].

	ACR<10	ACR 10-29	ACR 30-299	ACR≥300
eGFR>105	0.9	1.3	2.3	2.1
eGFR 90-105	Ref	1.5	1.7	3.7
eGFR 75-90	1.0	1.3	1.6	3.7
eGFR 60-75	1.1	1.4	2.0	4.1
eGFR 45-60	1.5	2.2	2.8	4.3
eGFR 30-45	2.2	2.7	3.4	5.2
eGFR 15-30	14	7.9	4.8	8.1

Table 4: Progressive chronic kidney disease (adjusted relative risk (RR)) for general population – adapted from [27].

	ACR<10	ACR 10-29	ACR 30-299	ACR≥300
eGFR>105	Ref	Ref	0.4	3.0
eGFR 90-105	Ref	Ref	0.9	3.3
eGFR 75-90	Ref	Ref	1.9	5.0
eGFR 60-75	Ref	Ref	3.2	8.1
eGFR 45-60	3.1	4.0	9.4	57
eGFR 30-45	3.0	19	15	22
eGFR 15-30	4.0	12	21	7.7

Data presented above suggest that both albuminuria and eGFR are important parameters enabling the estimation of cardiovascular risk and death rates. Most of the risk factors that are characteristic for Cardiovascular Diseases (CVD), such as: older age, hypertension, cardiac hypertrophy, diabetes mellitus, or low HDL levels, are also useful in the estimation of risk of CKD development or its progression [28].

Biomarkers

In the diagnosis of HF there are many diagnostic test as at the beginning this disease is recognized on the basis of suggestive symptoms and signs followed by the results of imaging examination, such as echocardiogram in order to confirm accompanying left ventricular structural and functional abnormality [29,30]. Moreover, patients with the suspicion of HF undergo Electrocardiogram (ECG) and chest X-ray, and in some cases also Magnetic Resonance Imaging (MRI), cardiac Computerized Tomography (CT) or coronary angiography to evaluate heart functional and structural abnormalities as well as to examine coronary artery functional integrity to reveal the underlying etiology [29]. The growing knowledge of HF-related mechanisms has resulted in the development of diagnostic and prognostic biomarkers for HF. Biomarker is a term defined generally as an indicator of health or disease. Establishing multimarker strategy which enables better evaluation of patients' condition and assessment of cardiovascular risk as well as the risk of CKD progression to dialysis is of key importance. Numerous studies aimed at finding the "ideal" biomarker characterized by high sensitivity and specificity which would improve the estimation disease stage and reliable monitoring of its progression [31]. Cardiac biomarkers may enable the identification of patients at high-risk for HF and the early introduction of appropriate therapy [32]. Numerous studies suggested that levels of neurohormones, such as angiotensin, aldosterone, renin, norepinephrine, arginine-vasopressin and endothelin may be utilized as prognostic biomarkers, the concentration of ANP, MR-proANP, BNP and NT-proBNP may mirror ventricular function while cardiac specific structural proteins, including troponin T and troponin I as well as crucial component of cell membrane, lectin-like oxidized low-density lipoproteins receptor-1 (LOX-1) may reflect the severity of cardiac injury and/or dysfunction [29,33-36]. In turn, cardiac remodeling process can be assessed on the basis of the level of Interleukin 6 (IL-6), Tumor Necrosis Factor alpha (TNFα) (inflammatory factors) as well as soluble ST2 (interleukin 1 receptor), C-reactive protein (CRP), galectin-3, matrix metalloproteinases (MMP) (factors involved in fibrosis and hypertrophy) [37].

Commonly determined cardiac markers include troponins and NT-proBNP. According to studies, high sensitivity troponin T (hsTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) predict HF in the general population. [32,38,39]. However, NT-proBNP cannot be used as an independent risk factor in HFpEF and HFmrEF patients, because of its limited clinical usefulness due to its unspecific character [31]. Bansal et al. [32] confirmed that the associations for traditional cardiac biomarkers, such as NT-proBNP and hsTnT were stronger for HFrEF, while relation observed in case of newer cardiac biomarkers including sST2 and GDF-15 were stronger for HFpEF.

Cardiac troponin T (cTnT) and I (cTnI) are sensitive markers of cardiac injury [40,41]. The rise of hsTnT levels is associated with myocardial injury, myocardial remodeling or left ventricular hypertrophy [42,43]. However, the interpretation of cTns values in CKD patients remains controversial, however, this effect cannot be ascribed to diminished clearance. Observational cohort study of non-dialysis patients with CKD at-tending an outpatient clinic revealed that plasma cTnI-Ultra exceeded the upper limit of normal in 33% of patients compared with 18% with the cTnI-standard assay and 43% with the cTnT assay [44]. Also, in a prospective multicenter diagnostic study assessing diagnostic performance of using highly sensitive (hs)-cTnT and hs-cTnI at zero and 1 h after presentation to the emergency department demonstrated that these markers were sensitive in ruling out NSTEMI in CKD patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, however, the specificity to rule-in disease turned out to be lower compared to patients with normal kidney function (88.7 vs. 96.5% for hs-cTnT, 84.4 *vs.* 91.7% for hs-cTnI) [45]. The analysis of diagnostic accuracy of base-line and serial high-sensitivity cTnI (hs-cTnI) measurements for myocardial infarction and 30- and 180-day mortality according to renal function indicated that impaired kidney function did not considerably affect sensitivity or negative predictive value of hs-cTnI, however, its specificity was reduced in patients with lower eGFR stages, from 93–95% in persons with normal kidney function (eGFR ≥90 mL/min/1.73 m^2) to 57–61 % in eGFR <30 mL/min/1.73 m^2) to 40–41% in end-stage kidney disease (ESKD) patients on dialysis [46].

NT-proBNP is secreted from cardiac myocytes in response to myocardial stretch associated with pressure or volume overload [32,47]. According to studies, its levels in-crease with growing left ventricular mass [48,49]. The level of circulating BNP and NT-proBNP decreases significantly in the course of heart failure. The introduction of BNP/NT-proBNP plasma levels testing for the diagnosis and risk prediction of recur-rent cardiac decompensation and mortality has considerably improved HF management and treatment [29]. However, some confounding factors, including age, obesity, renal function and atrial fibrillation limit diagnostic and prognostic accuracy of NT-proBNP and BNP, therefore, the identification of additional biomarkers which could enhance the accuracy of HF diagnosis and treatment is a goal of numerous studies [29,50]. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008 suggested the rule-out and rule-in diagnostic thresholds for acute heart failure in patients with normal kidney function (BNP of < 100 and >500 ng/L respectively) as well as in those with kidney dysfunction with eGFR <60 mL/min/1.73 m^2, a higher rule-out cutoff of <200–225 ng/L [51]. In case of those with eGFR < 60 mL/min/1.73 m^2, NT-proBNP value >1,200 ng/L seems to best for exclusion of heart failure. The accuracy of the exclusion of heart failure by NT-proBNP testing diminishes in patients with eGFR <30 mL/min/1.73 m^2 [52].

The Breathing Not Properly Study Multinational Study of patients admitted to the emergency department with acute dyspnea demonstrated that the rise in BNP concentration was associated with increasing severity of HF (P<0.001) [53]. Multivariable logistic regression analysis revealed that compared with physical examination, chest x-ray, or laboratory other tests, BNP >100 pg/mL was the most accurate predictor of the diagnosis of acute dyspnea HF with overall sensitivity of 90%, specificity of 76%, and accuracy of 85%. In turn, the PRIDE (ProBNP Investigation of Dyspnea in the Emergency Department) Study found that patients with ADHF had considerably higher NT-proBNP level compared with patients without HF (median, 4054 pg/mL [interquartile range, 1675–10 028 pg/mL] versus 131 pg/mL [interquartile range, 46–433 pg/mL]; P<0.001) and it was the strongest predictor of ADHF diagnosis [54]. Moreover, the increase in NT-proBNP correlated with aggravating severity of HF (P=0.001). NT-proBNP cutoff value of 900 pg/mL has been shown to have identical performance to that described for a BNP of 100 pg/mL in aforementioned study (Breathing Not Properly Multinational Study) [55]. In a prospective, multicenter study of adults with chronic kidney disease, patients in the highest quartile of NT-proBNP and hsTnT had a 7-fold and 2-fold higher risk of incident HF, respectively [32]. The observed associations were independent of the presence

of cardiovascular risk factors, left ventricular mass index and left ventricular ejection fraction. As it has been mentioned above, patients suffering from renal diseases frequently have elevated levels of NT-proBNP and hsTnT even in the absence of clinical heart disease. Several possible mechanisms that may explain higher NT-proBNP and hsTnT levels in patients with CKD have been suggested. Previous myocardial infarction/unrecognized coronary ischemia, left ventricular hypertrophy, ventricular fibrosis, cardiac stress resulting from increased filling pressures, left ventricular dilation, endothelial dysfunction, inflammation as well as cardiac injury are among the most frequently suggested causes [56-58]. Bansal et al. [32] suggested that the increase in the aforementioned cardiac biomarkers may signal early HF pathophysiology in patients with CKD.

Apart from B-type peptides, also circulating levels of Atrial Natriuretic Peptide (ANP) quickly rise with cardiac stretch; however, due to its short half-life, it is difficult to measure and therefore its immediate precursor protein, proANP, which is stable and has a longer half-life, could be used for testing. Midregional propeptide assay for ANP (MR-proANP) assay could prove useful in HF patients [55]. For the first time, MR-proANP utility was examined in the Biomarkers in the Acute Heart Failure (BACH) trial [59]. It turned out to be non-inferior to BNP or NT-proBNP in the diagnosis of ADHF; MR-proANP cutoff point of ≥120 pmol/L had a sensitivity of 97%, specificity of 60% with accuracy of 74% [55,59]. The PRIDE study [60] demonstrated that NT-proBNP performed marginally better than MR-proANP in the diagnosis of ADHF (AUC=0.94 for NT-proBNP versus 0.90 for MR-proBNP, P=0.001 for difference), how-ever, it was the measurement of MR-proANP which enabled the correct reclassification of patients who had false negatives and false positive results in NT-proBNP tests alone. The analysis of the predictive power of MR-proANP in stable chronic HF patients in GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca–Heart Failure) study [61] revealed that MR-proANP ≥278 pmol/L had good prognostic accuracy for 4-year mortality compared with several novel and established biomarkers (AUC=0.74; 95% CI, 0.70–0.76).

Nowadays, new markers attract attention of scientists. Serum levels of cathepsin D (CatD), which is a marker of healthy endogenous phagocytosis and remodeling, have been suggested to be increased in patients with Acute Myocardial Infarction (AMI). Yamac et al. [62] observed considerably higher serum CatD activity in patients with AMI after PCI and during follow-up (FU) in comparison to age-matched controls (16.2 ± 7.5 and 29.8 ± 8.9 vs. 8.5 ± 4.2 RFU; p<0.001). After 6-month follow-up, serum CatD activity inversely correlated with new-onset cardiac dysfunction in these patients. According to authors, serum activity of CatD was impaired in patients with new-onset cardiac dysfunction, and moreover, its diminished serum concentrations were observed in those who experienced MACE at the 6-month post-MI follow-up [62]. However, the utility of this biomarker has to be confirmed in a large trials.

Apart from, inflammation, also cardiac remodeling and fibrosis are potentially essential pathways involved in the pathogenesis of HF [32]. Numerous studies have indicated that levels of galectin-3, Growth Differentiation Factor-15 (GDF-15), and soluble ST2 (sST2) may reflect alterations in these biological pathways. Moreover, US Food and Drug Administration approved galectin-3 and sST2 for clinical use in risk-stratifying patients with established HF (myocardial injury and cardiac fibrosis in case of Gal-3) [63].

First of them, galectin-3 is a member of β-galactoside–binding protein family. It exerts proinflammatory and profibrotic in cardiomyocytes [32,64]. Galectin-3 crosslinks with glycoproteins in order to promote cell-cell and cell-matrix interactions, leading in con-sequence to fibrosis and extracellular matrix stiffening [65]. It is highly expressed in neutrophils, endothelial cells, epithelial cells as well as cardiac macrophages. It is involved in myofibroblast proliferation, fibrogenesis, tissue repair, and myocardial re-modeling and in heart it promotes cardiac fibrosis [63]. In turn in the kidney, it stimulates tubulointerstitial fibrosis and is associated with increased risk of incident CKD [65-68]. The levels of galectin-3 increases with advancing CKD and therefore it may not be a useful diagnostic biomarker of cardiac injury in this setting [69]. Elevated levels of galectin-3 strongly predict all-cause mortality in patients with normal kidney function and HF, however, only few studies analyzed its utility in the assessment of clinical outcomes in patients with CKD [70,71]. Tuegel et al [72] demonstrated a relationship between galectin-3 level and mortality of CKD patients. Also LURIC (Ludwigshafen Risk and Cardiovascular Health study) and 4D (Die Deutsche Diabetes Dialyse Studie) studies found that in CKD and end-stage renal disease patients elevated galectin-3 levels statistically correlated with the increased occurrence of combined cardiovascular end points (myocardial infarction, sudden cardiac death, stroke, and death attributable to HF in hospitalized patients) [69]. Moreover, Zamora et al. [73] reported that prognostic value of galectin-3 for cardiovascular disease was reduced after adjusting for eGFR. Bansal et al. [32] found that the increase in galectin-3 con-centration better mirrored short-term risk of HF. They also indicated that its levels were not considerably associated with either HFpEF or HFrEF and only a borderline relationship was found between galectin-3 and incident HF overall. Furthermore, several cohort studies have found that eGFR but not heart failure was a major determinant of galectin-3 levels which can be high independently of heart failure or left ventricular ejection fraction [41,74]. The widespread tissue expression of galectin-3 together with its reduced renal clearance resulting in systemic accumulation complicates the usefulness of galectin-3 as a cardiac biomarker in CKD patients [41]. However, Savoj et al. [41] suggested that this protein may provide incremental prognostic value for mortality as a biomarker in the dialysis population.

Growth Differentiation Factor-15 (GDF-15), which belongs to the transforming growth factor-β cytokine family, is involved in cardiomyocyte repair [75-77]. Its expression is not constitutive in adult cardiac tissue, but it is upregulated when cardiomyocytes are under stress such as during tissue ischemic injury, however, it remains unknown whether this mechanism is a compensatory or putative response to injury [32,77]. The results of studies on animal models indicate that GDF-15 hinders chemokine-triggered integrin activation, preventing inflammatory cell extravasation at sites of cardiac in-jury and succeeding inflammatory damage [78,79]. Moreover, endogenous GDF-15 has been suggested to limit *in vivo* myocardial damage [77].

Bansal et al. [32] found that higher GDF-15 was associated with risk of incident HF. Numerous clinical studies confirmed the relationship between elevated levels of GDF-15 and HF and HF severity (assessed on the basis of New York Heart Association class), recurrent hospitalizations and mortality risk in patients without CKD, in some cases independently of established clinical and biochemical risk markers, such as troponin T or BNP, however in those with renal disease the amount of evidences is sparse [80-82]. Tuegel et al [72] observed similar relationship

between increased concentrations of GDF-15 and HF also in 2 CKD cohorts. They suggested that the rise in GDF-15 level may indicate early HF physiology and that its measurement may enable the identification of CKD patients at highest risk for HF, particularly for HFpEF. However, elevated levels of GDF-15 can be also independently associated with CKD and acute kidney in-jury [82,83]. The precise mechanisms of the rise of GDF-15 levels in patients with kidney injury are not known. This upregulation could be induced by kidney injury or associated with decreased urinary clearance or both [41]. However, GDF-15 was shown to provide added prognostic value, regardless of the established kidney disease. Breit et al. [84] demonstrated that GDF-15 is an independent serum marker of mortality in CKD capable of considerably improving the mortality prediction of other established markers.

ST2, which is a member of the interleukin-1 receptor family, has two forms - soluble ST2 (sST2) and the membrane bound (transmembrane) ST2 receptor (ST2L) [32,41]. ST2 is a marker of cardiac stress which upregulation is associated with myocyte stretch, similar to BNP. It interacts with IL-33 participating in a complex network of signaling pathways in inflammation and cardiovascular disease [41]. ST2L binds ligand inter-leukin-33 and exerts cardioprotective effects *in vivo*, due to the fact that such interaction diminishes the apoptosis of cardiomyocytes and prevents the occurrence of ad-verse cardiac remodeling after cardiac ischemia [85,86]. In turn, the soluble form disrupts the binding of ST2L and interleukin-33, thus canceling its cardioprotective effects [87].

The studies of general population and patients with established heart disease, demonstrated that higher concentrations of GDF-15 were strongly associated with all-cause death and cardiovascular events, independent of traditional biomarkers and risk factors [80,81,85,88]. Due to the presence of CKD-specific risk factors and decreased clearance the pathophysiology of HF is unique in patients with CKD and also the utility of GDF-15 may differ in this group of people [89,90]. It has been demonstrated that elevated sST2 levels in CKD patients correlate inversely with eGFR and creatinine clearance [91,92]. Again, similarly to the aforementioned biomarkers, the cause of in-creased sST2 in CKD remains unclear [41]. However, Kim et al. [93] observed that sST2, unlike BNP, was not affected by the degree of kidney insufficiency in non-dialysis CKD patients with acute heart failure as its level did not change with the degree of renal function. Moreover, they suggested that the measurement of predischarge sST2 could be useful in predicting short-term outcomes in acute decompensated HF patients with renal insufficiency. Also Bansal et al. [32] reported a modest statistically significant relationship between sST2 and the risk of incident HF. Following the stratification by HF subtype, they found that sST2 (and also NT-proBNP, GDF-15) were associated with HFpEF [32].

Nowadays also collagen markers are gaining interest. Matrix Metalloproteinases (MMPs) and their endogenous tissue inhibitors (TIMPs, tissue inhibitors of metalloproteinases) due to their role in cardiac Extracellular Matrix (ECM) remodeling have been suggested to play an important role in pathological cardiac remodeling [94,95]. Numerous studies confirmed the importance of metalloproteinases MMP2 and MMP9 in the pathogenesis of left ventricular hypertrophy, aneurysm, heart failure, myocardial infarction [96-98],[99]. ECM preserves accurate cardiac geometry and myocardium structural integrity, however, its pathological, irreversible remodeling related to disequilibrium between the deposition and degradation of matrix proteins leads to compensatory hypertrophy and congestive decompensated heart failure [96]. In many pathological conditions, increased MMP serum level accompanied by decreased level of TIMPs are observed, thus leading to excessive substrate turnover and disease progression [100]. Higher activity of metalloproteinases has been reported in HFrEF, while in patients with HFpEF, the opposite situation is observed - collagen synthesis, not its degradation, is predominant. Studies results revealed that excessive cardiac collagen deposition underlines the deterioration of diastolic function [96]. MMP-2 levels were indicated to be important predictor of HF-PEF and diastolic dysfunction [101]. The sensitivity (91%) and specificity (76%) of such determination for predicting HF-PEF was greater in comparison to the best-known marker - BNP [101]. In turn, George et al [102] demonstrated that MMP-2 serum level was an independent predictor of mortality in patients with chronic heart failure. They observed higher circulating levels of MMP-2, -9, and TIMP-1 in individuals with CHF in comparison to age-matched controls, however, only MMP-2 levels correlated significantly with New York Heart Association (NYHA) class [101]. The metalloproteinases are also involved in the progression or kidney impairment. Patients with CKD were shown to have higher levels of MMP-2 and TIMP-2 [101]. Hsu et al. [103] observed that circulating MMP-2, -3 and -9 are independently associated with kidney disease progression in non-diabetic CAD patients. In turn, Nagano et al. [104] found correlation between MMP-2 levels and kidney function parameters. According to these authors, MMP-2 can be used as an indicator of atherosclerosis severity in CKD patients. MMP2 has also been shown to be important marker used in the assessment of CKD stage and patients' prognosis [105]. The increase in the activity of this marker correlates with the concentration of creatinine and the intensity of albuminuria. Circulating MMP-2 levels also strongly correlated with intima thickness in ESRD patients on hemodialysis [106]. In turn, MMP-9 concentration has been demonstrated to be strongly associated with carotid atherosclerotic burden, irrespectively of other contributing factors in the early, moderate, and advanced stages of CKD [107,108]. Also, MMP-8 levels were increased in patients with Coronary Artery Disease (CAD) compared to those without it [109]. The role of circulating collagenases in patients with atherosclerosis and hypertensive heart disease seems to have been confirmed, however, their utility in patients with renal diseases remains vague. Therefore, future studies are required to define the importance of collagenases in kidney disease and also to reveal possible links between renal disease and increased cardiovascular risk in these patients.

Another molecules that have gained great interest as biomarkers for various conditions are microRNAs (miRNAs). The main role of miRNA, which are small non-coding RNAs of 21–25 nucleotides, is the modulation of gene expression by regulating transcription in the human body, initiation of mRNA degradation, suppression of mRNA expression, mRNA deadenylation and mRNA sequestration [29,110-112]. miRNA-related regulation is accomplished via its incomplete or complete complementary binding to target sequences within the 3′ Untranslated Region (UTR) of mRNA [112,113]. miRNAs have been demonstrated to be useful as biomarkers; they can not only indicate the presence of a pathology but also enable the assessment of the stage, progression, or genetic link of pathogenesis [100]. Moreover, miRNA could be used in the treatment of some diseases, and also the adjustment of specific miRNAs expression can alter the drug sensitivity thus increasing drug efficiency;

furthermore they allow for the evaluation of response to treatment [114]. miRNA can be found in body fluids, such as blood, urine, saliva, seminal fluid or breast milk [115] and other fluids produced in the process of tissue damage, apoptosis and necrosis. Distinct miRNA profiles observed in diseased tissues and in the circulation may mirror the underlying molecular pathology of the disease [116]. Numerous studies have observed that some circulatory miRs are associated with HF and are involved in the pathogenesis of cardiovascular disease [112,117]. Muscle-specific miR-1 can be found in cardiac and skeletal muscles. It has been demonstrated that the higher the miR-1 levels, the greater is the CVD risk. It is the biomarker of myocardial damage and reperfusion injury [118]. miR-1 plasma levels were demonstrated to be up-regulated in patients with AMI-HF [119,120]. Plasma levels of miR-126 were found to negatively correlate with NT-proBNP levels in patients with Chronic Heart Failure (CHF) and also to be up-regulated with the improvement of the NYHA class [117]. Serum levels of specific microRNAs: miR-423-5p, miR-320a, miR-22, and miR-92b were up-regulated in HF, enabled the identification of systolic heart failure patients and correlated with important clinical prognostic parameters [121]. Also, Zhao et al. [122] observed high di-agnostic accuracy of miR-210, miR-30a and correlations with blood N-terminal pro-hormone of brain natriuretic peptide. The authors suggested that miR-210 seemed to be more closely related to the pathological mechanisms of HF, including vascular smooth muscle contraction, calcium signaling, transforming growth factor-β signaling, and aldosterone-regulated sodium reabsorption pathways. miR-155 is an important regulator of the inflammatory response [123]. It can be used as a CVD predictor, according to the inflammatory mechanism of HFpEF development and CKD progression. miR-195 levels were demonstrated to be increased in both diabetic cardiomyopathy-HF left ventricle tissues and HF myocardial biopsy [124,125]. Ellis et al. [126] found that in HF, levels of some miRNA, such as of miR—18a-5p, miR-26b-5p, and miR-30b were decreased while concentration of other miRNA (miR-499) was increased were observed.

Discrepancies in the expression of miR-126 relative to control was observed in three samples: plasma, serum and in circulating endothelial progenitor cells [29]. Moreover, miR-1 and miR-21, were reported to be differentially expressed in the circulation as well as in cardiac tissues from HF patients, which may suggest the existence of a possible correlation between the miRNAs observed in circulation and events in cardiac tis-sue. Apart from the aforementioned also miR-124-3p, -126, -150, -195, -21, -210, -30a, -342-3p, -499-5p and -622 were demonstrated to be differentially expressed in HF cohorts [29]. Some of the aforementioned miRNAs target important genes that participate in cardiac remodeling. miR-1 and miR-30a were found to be involved in cardiac hypertrophy and apoptosis, while miR-21 targets crucial molecules in the signaling pathways related to cardiac fibrosis, hypertrophy and apoptosis [127-130]. Genes involved in apoptosis signaling are the target of miR-92a, miR-195 and miR-499-5p [131-133].

Eskildsen et al. [134] found that miR-132/212 regulated several genes associated with angiotensin II signaling in cardiac fibroblasts. In turn, Kotlo et al. [135] examined miRs in signaling by ANP and NO in Human Vascular Smooth Muscle Cells (HVSMC). They found that the transfection with pre-miR-21 contracted cells and ANP and SNAP blocked miR-21-induced HVSMC contraction, while the transfection with anti-miR-21 inhibitor reduced contractility of HVSMC ($p<0.05$). These results may imply the role of miRs in NO and ANP signaling in general and miR-21 in particular in cGMP signaling and vascular smooth muscle cell relaxation [134]. Some miRNA have been shown to negatively regulate neurohormonal activity. For example, miR-155 interacts with the 3'UTR of the Angiotensin II Type I Receptor (AGTR1) transcript, while miR-425 with the 3'UTR of ANP which may result in the down-regulation of ANP production [136,137]. The results of study performed by Maharjan et al. [138] suggest that miR-766 may downregulate the expression of human aldosterone synthase gene by binding to the 735G-allele of the 3'UTR of CYP11B2 transcripts and decrease blood pressure in human subjects containing -344T allele. Numerous studies have shown that miRNA targets frequently comprise Angiotensin II Receptors (AGTRs), Natriuretic Peptide Receptors (NPRs) endothelin receptors (EDNRs), mineralocorticoid receptor/Nuclear receptor subfamily 3 group C member 2 (NR3C2) and Corticotrophin-Releasing Factor Receptors (CRHR2) which may imply that miRNA-related modulation of neurohormonal signaling cascades in HF involves the diminishing of the expression of the cognate receptors.

However, the review of numerous studies of miRNAs possibly involved in the pathomechanisms related to HF in various populations clearly show that their results are sometimes conflicting. The lack of agreement between studies may be associated with differences in gender ratio, ethnicity, the acuity or severity of HF, underlying co-morbidities, clinical criteria for patient recruitment, inter-cohort variation in miRNA profiles differences in the genomic profiling technologies used and small sizes of studied groups. Moreover, background pathophysiology of heart failure is complex as may be associated with the presence of from cardiac, vascular, renal, endocrine, ad-renal, pulmonary, hematological and biochemical perturbations [29].

The analysis of levels of selected biomarkers together with the assessment of cardio-vascular and renal function risk factors should allow to determine patient's profile and predict the risk of progression of heart failure, renal failure and death. Moreover, multimarker strategy should enable the development of a multi-brand strategy which will hamper the progression of cardiorenal syndrome in patients with heart failure and coexisting chronic kidney disease. In the future, the discriminative miRNA(s) signatures or miRNA clusters will be available for HF diagnosis and risk stratification.

Summary

Cardiorenal syndrome is a complex and very common condition. Cardiovascular mortality in HF patients is 10 to 30 times higher in patients with CKD stage 5 or treated with hemodialysis. The role of biomarkers is well determined in HFrEF and HFpEF patients. However, the role of biomarkers in HFmrEF individuals still remains unclear. There is a constant search for new methods of identifying patients at high risk of re-hospitalization and other adverse cardiovascular events that would reduce the frequency of hospitalization due to HF and improve the prognosis of this group of patients by intensifying treatment and outpatient care after discharge from the hospital. The results of studies indicate that, among patients with CKD, increased levels of NT-proBNP, hsTnT, GDF-15, sST2, and galectin-3 strongly correlate with incident HF. These biomarkers may show early, subclinical changes occurring in cardiac structure and function which in consequence contribute to clinical HF. Many of these relation-ships remained strong after the adjustment for the other biomarkers, which implies that they are complementary, but they may represent distinct biological pathways involved in HF development. Therefore, further studies are required to con-

firm the potential role of these biomarkers in a comprehensive HF risk prediction and prevention strategy. Also the validation of miRNA targets is necessary in order to identify HF-related miRNA signatures enabling the early diagnosis, the understanding of underlying pathomechanisms and facilitate the treatment.

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