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Cardiorenal syndrome in heart failure with preserved ejection fraction—an under-recognized clinical entity

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Abstract
Cardiorenal syndrome (CRS) results from the complex and bidirectional interaction between the failing heart and the kidneys. Limited information exists about the pathophysiology and treatment options for worsening kidney function in the setting of heart failure with preserved ejection fraction (HFpEF). This review summarizes the salient pathophysiological pathways in CRS in patients with HFpEF, with emphasis on type 1 and type 2 phenotypes, and outlines diagnostic and therapeutic strategies that are applicable in this population. Elevated central venous and intra-abdominal pressure, left ventricular hypertrophy, LV strain, RAAS activation, oxidative injury, pulmonary hypertension, and RV dysfunction play key roles in the pathogenesis of CRS in the backdrop of HFpEF. The availability of biomarkers of renal and cardiac injury offer a new dimension in accurately diagnosing and quantifying end organ damage in CRS and will improve the accuracy of goal-directed therapies in this population. Novel targeted therapies such as the development of angiotensin/neprilysin inhibitors and sodium-glucose cotransporter-2 (SGLT-2) inhibitors offer new territory in realizing potential benefits in reduction of cardio-renal adverse outcomes in this population. Future studies focusing exclusively on renal outcomes in patients with HFpEF are crucial in delivering optimal therapies in this subset of patients.

Keywords Heart failure with preserved ejection fraction · Cardiorenal syndrome · Worsening renal function · Kidney

Introduction

Cardiorenal syndrome (CRS) has been defined as "disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other" by the Acute Dialysis Quality Initiative (ADQI) [1]. This complex and bidirectional nature of pathophysiological interactions between failing heart and kidney is a major cause for hospitalizations, health care costs, and poor outcomes [2]. CRS was recognized as a clinical entity in 2004, when the National Heart, Lung, and Blood Institute (NHLBI) working group defined CRS as a state of extreme cardiorenal dysregulation where therapy to relieve heart failure (HF) symptoms is limited by further worsening renal function [3]. Based on the *primum movens* of the disease, CRS was further phenotyped into five types as per the ADQI classification [1]. The different phenotypes of CRS are described in Table 1.

A large body of literature exists with regard to the pathophysiological abnormalities, neurohumoral dysregulation, diagnostic pathways, and therapeutic options in patients with CRS in the context of heart failure with reduced ejection fraction (HFrEF). However, little information exists about the pathophysiology and treatment options for worsening kidney injury in the setting of heart failure with preserved ejection fraction (HFpEF). This review summarizes the salient pathophysiological pathways in CRS in patients with HFpEF, with emphasis on type 1 and type 2 phenotypes, and outlines diagnostic and therapeutic strategies that are applicable in this population.

Epidemiology

Heart failure (HF) is a major clinical and public health problem, affecting over 5.8 million people in the USA and over 23

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Table 1 Types of cardiorenal syndrome with examples

Type 1: Acute cardiorenal syndrome	Acute worsening of heart function leading to acute kidney injury and/or dysfunction	Example: Acute cardiogenic shock or acute decompensated heart failure
Type 2: Chronic cardiorenal syndrome	Chronic abnormalities in heart function leading to progressive kidney injury and/or dysfunction	Example: Left ventricular remodeling and dysfunction leading to CKD
Type 3: Acute reno-cardiac syndrome	Acute worsening of kidney function leading to acute heart injury and/or dysfunction	Example: Acute uremia causing cardiac injury (pericarditis or cardiomyopathy)
Type 4: Chronic reno-cardiac syndrome	Chronic kidney disease leading to heart injury, disease, and/or dysfunction	Example: CKD causing Left ventricular hypertrophy and diastolic heart failure
Type 5: Secondary CRS	Systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney	Example: sepsis, diabetes mellitus, hypertension, amyloidosis

CKD chronic kidney disease, *CRS* cardiorenal syndrome

million worldwide [4]. A recent review of community-based studies showed that 50% of patients with heart failure (HF) have HF with preserved ejection fraction (HFpEF) [5]. Renal dysfunction is one of the most important independent risk factor predicting poor outcomes and all-cause mortality in patients with HF [6]. In patients hospitalized with heart failure, both elevated admitting creatinine and worsening creatinine during hospitalization predict prolonged hospitalization, rehospitalization, and death [7]. As per KDIGO (Kidney Disease Improving Global Outcomes), acute kidney injury (AKI) is defined as any of the following: increase in serum Creatinine (SCr) by ≥ 0.3 mg/dl within 48 h, increase in SCr to ≥ 1.5 times baseline, or urine volume < 0.5 ml/kg/h for 6 h [8]. This definition is not widely used in the context of HF and instead worsening renal function (WRF) is used. WRF is defined as an absolute increase in serum creatinine ≥ 0.3 mg/dl during the treatment of acute decompensated heart failure (ADHF) [9]. As per the ADHERE registry, 30% patients with ADHF had renal insufficiency [10]. Due to the lack of consistency in objective definition, the accurate quantification of CRS especially by phenotype is limited.

Attempts have been made to integrate worsening HF and renal insufficiency to better define CRS. Damman et al. proposed new definitions for CRS in chronic and acute HF. In addition to threshold changes in serum creatinine or eGFR, they recommend including deterioration in HF status not leading to hospitalization (chronic HF) or deterioration in HF status leading to hospitalization, failure to improve, or a need for inotropes, ultrafiltration, or renal replacement therapy (acute HF). Their recommendations are to use the term WRF for chronic HF patients and AKI for acute HF patients [11].

Risk factors and pathophysiology

Multiple factors like older age, hypertension, diabetes, obesity, and coronary artery disease are known to be risk factors for HFpEF [12]. Physiologically, impaired left ventricular (LV) relaxation and increased passive stiffness is the fundamental functional derangement in HFpEF. The increase in LV diastolic pressure causes increased left atrial and pulmonary venous pressure leading to pulmonary venous congestion. Additionally, the systolic ventricular and vascular stiffening with increasing age and hypertension affect the pressure–volume balance and worsen diastolic dysfunction [13]. Longstanding hypertension with its resulting predominant pressure overload leads to cardiac remodeling causing diastolic dysfunction and concentric hypertrophy. With sustained pressure overload, diastolic dysfunction progresses ultimately leading to HFpEF [14].

In patients with HFpEF, renal function can be affected by longstanding hypertension, left ventricular hypertrophy, left ventricular global longitudinal strain, increased central venous pressure, intra-abdominal pressure, right heart failure, pulmonary hypertension, valvular heart diseases, alteration in the RAAS and sympathetic stimulation, and endothelial dysfunction.

Pathophysiological mechanisms operative in cardiorenal syndrome in heart failure with preserved ejection fraction

Central venous pressure (CVP) and intra-abdominal pressure elevation

As per Poiseuille's law, cardiac flow depends on the pressure gradient across the body's capillary networks. As discussed before, HFpEF causes elevation in central venous pressure, which decreases the gradient across the glomerular capillary network, reducing the blood flow through the renal capillaries. The pathophysiology of how increased CVP and intra-abdominal pressure (IAP) affect the kidney function is illustrated in Fig. 1. Animal models have shown that rise in venous pressure by 20 mmHg caused reduction in urine flow by 30% in dogs [15]. Another study in a swine model showed that elevation in renal vein pressure caused significant decrease in renal artery blood flow index and GFR, elevation of plasma aldosterone and renin activity, and urine protein leak [16].

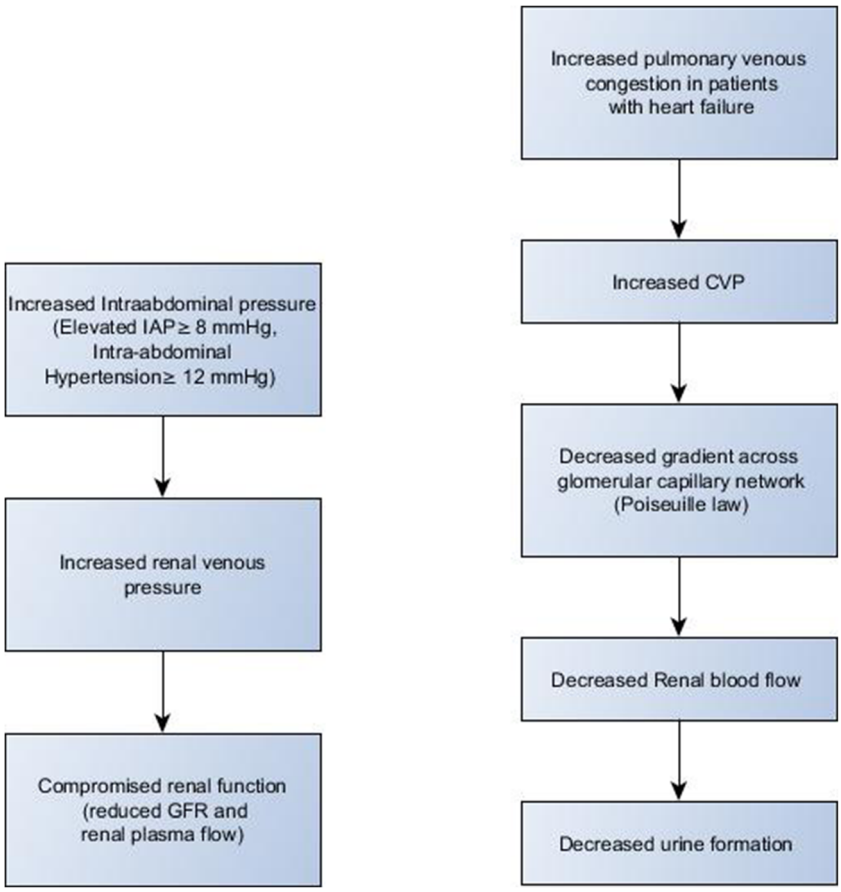

Fig. 1 Pathophysiology of worsening kidney function with increased central venous and intra-abdominal pressure

Besides, higher CVP and renal venous pressure raise intrarenal interstitial pressures, leading to renal interstitial fibrosis and increased tubular pressure, further reducing glomerular filtration rate (GFR) [17].

In a human study, 145 consecutive patients admitted with acute decompensated HF treated with intensive medical therapy guided by pulmonary artery catheter were studied. Patients with greater CVP on admission (18 ± 7 mmHg vs 12 ± 6 mmHg, $p < 0.001$) and after intensive medical therapy (11 ± 8 mmHg vs 8 ± 5 mmHg, $p = 0.04$) developed worsening renal function [18]. A study by Damman et al. ($N = 2557$) also showed that increased CVP was associated with impaired renal function and independently related to all-cause mortality in a broad spectrum of patients with cardiovascular disease [19]. The concept that venous congestion is an important mediator of cardiorenal failure and not arterial blood flow is supported by the findings of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, in which only baseline right atrial pressure correlated with baseline serum creatinine [20].

Recent studies have suggested a strong correlation between renal flow indices and HF outcomes independent of estimated glomerular filtration rate (eGFR) [21]. Nijst et al. [22] recently compared intrarenal hemodynamics in healthy subjects and subjects with HF in response to intravascular volume loading. They estimated resistance index (RI) (a measure of renal arterial flow) and venous impedance index (VII) (reflects alterations in venous compliance, determined by CVP and/or renal interstitial pressure) in 6 healthy subjects and 40 HFrEF and 10 HFpEF patients who were then subjected to volume loading with 1 l of isotonic hydroxyethyl starch. In response to volume expansion, VII increased significantly in HFrEF patients and in HFpEF patients but not in healthy subjects. This outcome was reversed after loop diuretic administration. In contrast, RI did not change significantly after volume expansion. Echocardiographic-estimated filling pressures did not change significantly. Thus, in HF patients, intravascular volume loading might lead to blunted renal venous flow even before cardiac filling pressures rise and affect diuretic efficacy and renal function.

The role of increased intra-abdominal pressure (IAP) in causing renal dysfunction in patients with HF has been recognized in recent years. In HF patients, backward failure and increased arteriolar vasoconstriction cause progressive shift of blood from the effective circulatory volume to splanchnic capacitance veins. Continued congestion can overwhelm this capacitance function and increase IAP, which can be measured through a bladder catheter connected to a pressure transducer. This in turn increases renal venous pressure causing

worsening renal function [23]. In a study of HFrEF patients, 60% of patients with renal dysfunction had IAP > 5–7 mmHg (normal range), mostly without frank ascites [24]. In a small study of 9 patients, following mechanical fluid removal by paracentesis or ultrafiltration, IAP improved immediately with improvement in renal function [25]. Although these studies did not specifically include HFpEF patients, the effects of backward congestion are similar to those in patients with HFrEF.

Role of pulmonary hypertension and right ventricular dysfunction

Pulmonary hypertension is widely prevalent in patients with HFpEF. A population-based study looked into the prevalence and severity of pulmonary hypertension in 244 HFpEF patients and compared with 719 adults with hypertension without HF. They reported the prevalence of PH in HFpEF to be 83% with median pulmonary artery systolic pressure (PASP) of 48 mmHg. PASP also strongly predicted mortality in HFpEF (hazard ratio = 1.3 per 10 mmHg; $p < 0.001$) [26]. Most HFpEF patients have some elevation in PA pressure secondary to elevated left-side filling pressures. However, a subset of these patients develops intrinsic pulmonary vascular disease in addition to elevated LV filling pressure, leading to an increased pulmonary vascular resistance. Compared to patients with HFpEF without pulmonary vascular disease, these patients are more likely to be women and to have right atrial enlargement, right ventricular hypertrophy (reflective of increased RV afterload from PH), and higher right atrial pressure (RAP), according to a study by Thenappan et al. [27].

Right heart failure is one of the most important markers of poor prognosis in patients with pulmonary hypertension [28]. A prospective study by Mielniczuk et al. showed that incidence of worsening renal failure in patients with PH and right HF is approximately 34%, similar to the rate of worsening renal function in patients with left HF [29]. In a recent study of HFpEF patients with worsening renal function (WRF) during acute HF hospitalization, there was a significant decrease in RV function and a significant increase in RV free wall thickness compared with matched patients with no WRF, suggesting that adverse RV remodeling and RV dysfunction occurs in HFpEF patients with WRF [30]. Additionally, the neurohormonal activation and sympathetic activation in patients with right heart failure leads to chronic kidney disease. The combination of PH and CKD causes vascular remodeling of pulmonary and renal circulation mediated by neurohumoral activation [31].

Inflammation and endothelial dysfunction

In recent years, endothelial dysfunction has been identified as the primary pathophysiologic abnormality in HFpEF. Comorbidities in HFpEF (overweight/obesity, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, anemia, etc.) lead to a systemic pro-inflammatory state which causes coronary microvascular endothelial inflammation, which further reduces nitric oxide (NO) bioavailability. Reduced NO signaling then influences adjacent cardiomyocytes and cardiac fibroblasts through the soluble guanylate cyclase (sGC)–cyclic guanosine monophosphate (cGMP)–protein kinase G (PKG) pathway. Low PKG activity leads to hypertrophy because of hypophosphorylation of titin. Stiff cardiomyocytes and interstitial fibrosis contribute to high diastolic LV stiffness eventually leading to HFpEF [32]. It is also interesting to note that CKD itself causes endothelial dysfunction thus contributing to development of HFpEF (CRS types 3 and 4).

Nitric oxide regulates intrarenal hemodynamics and glomerular microcirculation [33]. In addition, it inhibits proximal tubular sodium reabsorption independently and in interaction with angiotensin II [34]. Thus, NO deficiency accompanying endothelial dysfunction may worsen renal function by affecting renal autoregulation and lead to volume overload by affecting sodium reabsorption.

Role of coronary microvascular dysfunction

Coronary microvascular dysfunction (CMD) has been proposed to be a novel mechanism underlying the pathogenesis of HFpEF. In the recently published PROMIS-HFpEF (PRevalence Of MIcrovascular dySfunction in Heart Failure with Preserved Ejection Fraction) trial [35], coronary flow reserve (CFR) was measured in 202 patients with HFpEF without obstructive coronary artery disease and identified CMD in 75% of patients. Worse CFR was associated with higher urinary albumin-to-creatinine ratio (UACR) and NTproBNP and evidence of RV dysfunction on echocardiography. The former is an important diagnostic and prognostic indicator in CKD, while RV dysfunction is associated with elevated CVP, as discussed previously. The association of CMD with CRS would hopefully be clarified in future studies.

Renin–angiotensin–aldosterone axis

Various neurohumoral adaptations including activation of the renin–angiotensin–aldosterone system and adaptive activation of sympathetic nervous system occur in response to hemodynamic changes in patients with heart failure. Traditionally, it was well accepted that due to reduced cardiac output in patients with low ejection fraction, the renal perfusion declines, prompting renin release and RAAS activation, causing afferent glomerular constriction and decline in renal function. However, the ESCAPE trial did not show improvement in renal function with improvement in cardiac index [20]. In patients with atherosclerosis with normal left ventricular

function and in patients with HFrEF, RAAS inhibition has been shown to reduce the occurrence of major vascular events [36]. Three large studies (Heart Outcomes Prevention Evaluation, HOPE trial; the European trial on Reduction of cardiac events with Perindopril among patients with stable coronary Artery disease, EUROPA trial; and the Prevention of Events with ACE inhibition, PEACE trial) demonstrated the positive effects of ACE inhibitors in cardiac and renal disease in patients with cardiovascular disease without having left ventricular failure [37–39]. Though RAAS inhibitors are also commonly prescribed in HFpEF, the evidence of their cardiovascular and renal benefits is less rigorously studied and is discussed in the treatment section.

Role of oxidative injury

Once the RAAS gets activated in a patient with cardiac dysfunction, the angiotensin II causes activation of NADPH oxidase and NADH oxidase. These enzymes lead to generation of reactive oxygen species within vascular smooth muscle cells, cardiac myocytes, and renal tubular epithelial cells causing oxidative injury [6]. Activation of this enzyme cascade can be initiated by both primary cardiac failure and primary renal failure and can potentially cause dysfunction in the secondary organ. The superoxide and other reactive oxygen species cause inactivation of nitric oxide leading to endothelial dysfunction. An animal study done by Tojo et al. showed substantial elevation of AT-II and NADPH oxidase expression and reduced nitric oxide production in kidney tissue of rats with systolic HF [40]. A similar pattern has not been studied in animals or humans with HFpEF, but we might be able to extrapolate these results to patients with HFpEF since the concept of RAAS activation remains similar.

Association of left ventricular hypertrophy, myocardial fibrosis, longitudinal function, and renal dysfunction

In patients with HF, the pressure and volume homeostasis of the left ventricle is altered. Chronic hypertension and vascular stiffness leads to pressure overload, and sodium and water retention results in volume overload. The LV responds to these disturbances by hypertrophy and subsequent dilatation, eventually leading to impaired LV contractility. Patients with HFpEF usually have left ventricular hypertrophy (LVH) without dilation. The association of LVH with impaired renal function was demonstrated in a large scale study of hypertensive patients with CKD where besides estimated glomerular filtration rate (eGFR), LVH was the most significant modifiable predictor of progression to dialysis [41]. In a prospective cohort study of 2418 African-American participants enrolled in the Jackson Heart Study, greater LV mass was significantly associated with eGFR decline > 30% or end-stage renal disease (ESRD) [42]. Thus, one of the targets for prevention and treatment of CRS in patients with HFpEF would be therapies that reduce LV mass. While impaired diastolic function has long been thought to be a key mediator in the pathophysiology of HFpEF, concomitant systolic dysfunction also plays a role. A relatively new measure of myocardial deformability called global longitudinal strain (GLS) has been shown to predict the extent of myocardial fibrosis [43]. Patients with myocardial fibrosis have been shown to have poor prognosis [44]. The ongoing EMPA-HEART trial aimed at comparing the effect of sitagliptan and empagliflozin on global longitudinal strain in diabetic patients with normal LV systolic (2D echo EF > 50%) and renal function (eGFR > 60 ml/min/1.73 mq) [45]. A preliminary report of 10 patients with empagliflozin was associated with 15% reduction in LV mass index and 13% increase in early lateral annular tissue Doppler velocity, a proxy of LV compliance [45]. Though a detailed review of the SGLT-2 inhibitors in context of HFpEF will be discussed in treatment strategies, it is worthwhile mentioning how newer therapeutic strategies targeted at improving myocardial deformation might influence renal function positively.

In the context of discussion on global longitudinal strain, it is worthwhile mentioning that patients labeled with HFpEF may have other pathologies, such as cardiac amyloidosis. While a detailed description of cardiac amyloidosis is beyond the scope of this article, marked LVH on echocardiography along with markedly reduced basal longitudinal strain with relatively preserved strain at the apex may be the first clues to diagnosis of cardiac amyloidosis, which is usually either due to light chain deposition (AL amyloid) or transthyretin deposition (ATTR). In one study, wild-type ATTR (wtATTR) was found in up to 13% of elderly patients presenting with HFpEF [46]. Patients with cardiac amyloid tend to have higher brain natriuretic peptide levels, greater degree of pulmonary hypertension, and RV dysfunction and often present with cardiorenal syndrome. It is important to recognize these entities as treatment may differ. While AL amyloid can be treated with chemotherapy (similar to multiple myeloma), there are several emerging therapies for TTR amyloidosis.

Role of chronotropic incompetence

Patients with HFpEF have chronotropic incompetence (CI) during maximal exercise and abnormal HR recovery after exercise [47]. In a prospective study of 108 HFpEF patients who underwent cardiopulmonary exercise testing, CI was present in 75% cases. Lower estimated glomerular filtration rate (GFR), higher B-type natriuretic peptide, and higher pulmonary artery systolic pressure were each associated with CI. There was an independent association of the decrease in GFR with CI [48]. CI in HFpEF may be due to autonomic dysfunction with

decreased baroreflex sensitivity and increased sympathetic stimulation [47]. Increase in renal sympathetic activity leads to α_1-mediated renal arterial vasoconstriction and β_1-mediated renin secretion (which also increases sympathetic vascular tone), causing reduced renal plasma flow [49]. Alternatively, renal dysfunction may lead to autonomic dysfunction, thus underscoring the bidirectional nature of cardiorenal interactions in these patients.

Biomarkers in cardiorenal syndrome

Biomarkers are circulating substances commonly used in the management of a disease for screening, diagnosis, risk stratification, and as a guide to evaluate the response to treatment. B-type natriuretic peptide (BNP) and its inactive cleavage protein N-terminal pro-B-type natriuretic peptide (pro-BNP) are well-established markers of myocardial stretch commonly used in heart failure management.

Galectin-3 is a new biomarker belonging to the beta-galactosidase-binding lectin family, synthesized by macrophages and interfacing with specific extracellular matrix proteins like laminin, synexin, and integrins. Two studies namely Ludwigshafen Risk and Cardiovascular Health (LURIC) study and German Diabetes Mellitus Dialysis (4D) study demonstrated that galectin-3 concentrations increase with progressive renal impairment. Additionally, the galectin-3 level is independently associated with cardiovascular end points, infections, and all-cause death in patients with impaired renal function [50]. This suggests potential role in diagnosing and prognosticating CRS in patients with acute decompensated HF.

Novel urinary biomarkers like tissue inhibitor of metalloproteinase-2 (TIMP), insulin-like growth factor-binding protein 7 (IGFBP7), neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), and interleukin-18 have been studied as markers of AKI. Among these, NGAL has been extensively studied in cardiorenal syndrome and has diagnostic and prognostic value in patients with acute and chronic HF. It is highly upregulated in the setting of renal inflammation and injury. Urine NGAL has been found to be more sensitive and specific than plasma NGAL [51]. A meta-analysis by Haase et al. ($N = 2000$) demonstrated that serum and urine NGAL measurements were predictors of dialysis and death with pooled AUC of 0.78 and 0.75 respectively [52]. A recent study by Ahmad et al. used this validated biomarker as one of the marker of tubular injury and showed that kidney tubular injury does not have association with worsening renal function in context of aggressive diuresis of acute HF patients, indicating hemodynamic or functional change in glomerular filtration to be the cause for WRF [53].

Treatment strategies

Acute management

The following treatment strategies including diuretics and ultrafiltration are targeted for the acute management of CRS in the setting of HFpEF, mainly by improving cardiac output (Fig. 2).

Diuretics

Diuretics are the mainstay of therapy in acute decompensated HF. However, the response of HFpEF patients to diuretics differs from that of patients with HF with reduced ejection fraction (HFrEF), with the former having a greater likelihood of worsening renal function with diuresis. In a small study including 20 HFpEF patients and 35 HFrEF patients, the total body volume profiles were found to differ between HFpEF and HFrEF patients with acute decompensated heart failure [54]. Quantitated volume analysis demonstrated significant red cell mass (RBCM) and plasma volume excess in HFrEF, whereas a higher RBCM deficit in HFpEF. HFpEF patients had overall less intravascular volume expansion and more interstitial fluid expansion compared to patients with HFrEF. Also, diuresis produced only a modest reduction in intravascular volumes with persistent hypervolemia in both groups, but overall more total body fluid was lost in HFpEF. In a study of acute decompensated HF patients, estimated plasma volume reduction (calculated using body weight, total body volume and hematocrit) was associated with WRF in HFpEF but not in HFrEF patients [55]. Thus, HFpEF patients are more susceptible to develop WRF with diuretics compared to HFrEF patients due to decrease in their preload.

In the recent ROPA-DOP study [56], when a continuous infusion diuretic strategy was compared to an intermittent bolus diuretic strategy in hospitalized patients with HFpEF, continuous infusion was associated with a higher percent increase in creatinine and a higher risk of WRF than intermittent bolus dosing. This may again be explained by the preload dependence of these patients in that a continuous infusion strategy may not allow for adequate re-equilibration of intravascular and extravascular volumes in the setting of congestion. This study also studied low-dose dopamine along with diuresis to prevent renal injury, but dopamine did not modify the percent increase in creatinine.

Diuretic responsiveness in patients with HFpEF also depends on the degree of RV dysfunction and elevated CVP as mentioned above and pre-existing renal dysfunction. One of the major clinical decisions to be made in patients with HFpEF and worsening renal function is accurate determination of their volume status, which may require right heart catheterization if clinicians are not confident in their clinical assessment of volume status and

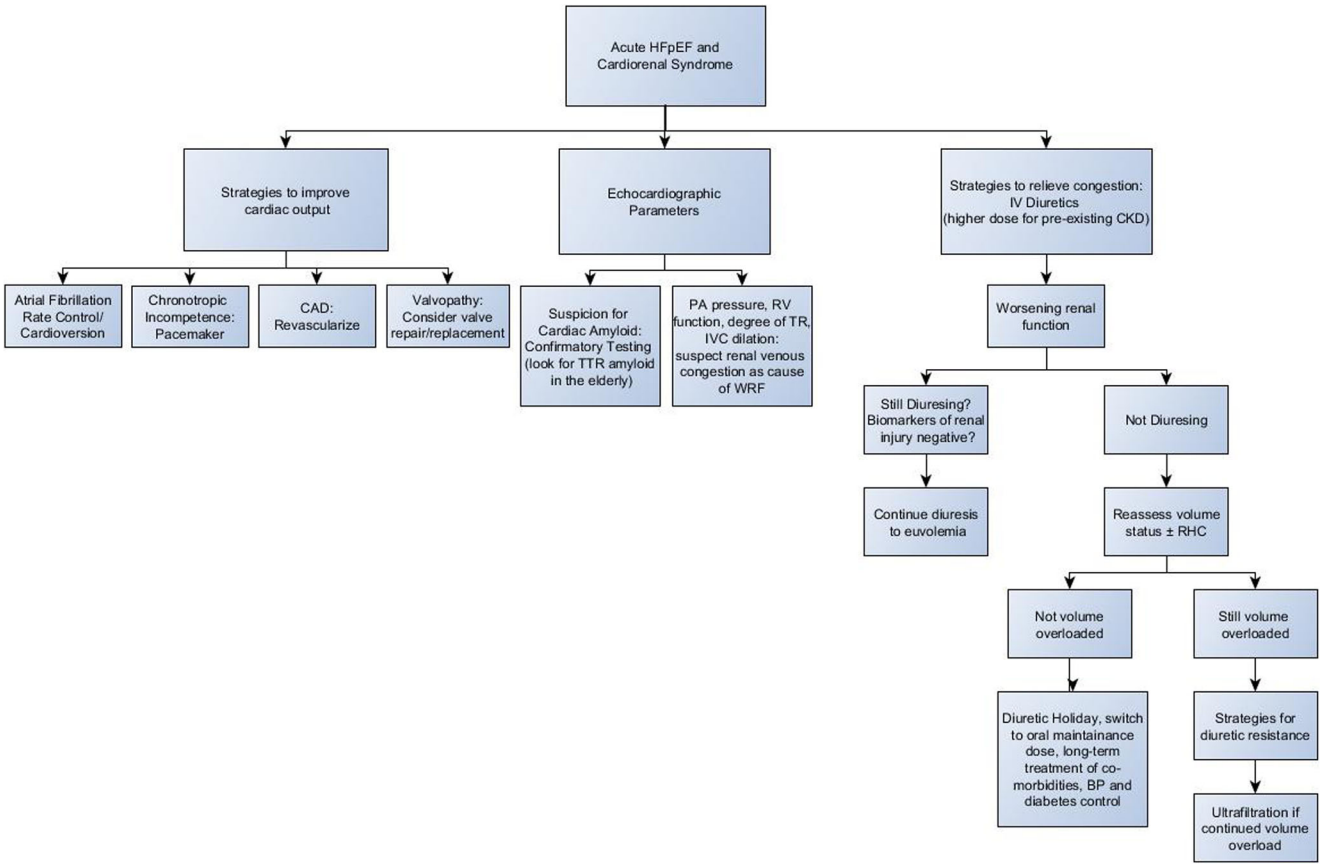

Fig. 2 Approach to acute HFpEF with cardiorenal syndrome

renal function continues to worsen with diuresis (listed as a class IIa recommendation in the 2013 ACC/AHA guidelines for management of HF) [57]. If the patient is indeed volume overloaded and not responding to diuretics, several strategies can be attempted to overcome diuretic resistance. The possible causes of diuretic resistance and strategies to overcome them are summarized in Table 2. One of the most commonly employed strategies is that of sequential nephron blockade with addition of metolazone to loop diuretics, inhibiting compensatory distal tubular sodium reabsorption and enhancing natriuresis. While this strategy promotes diuresis in the short term, in a recent analysis of ~ 14,000 acute decompensated HF admissions, metolazone was independently associated with hypokalemia, hyponatremia, WRF, and increased mortality after controlling for the propensity to receive metolazone and baseline characteristics, while high-dose loop diuretics were not, thus calling into question this practice [58].

Table 2 Diuretic resistance—causes and management strategies

Causes of diuretic resistance	Potential solutions
1. Wrong diagnosis: patient may not be volume overloaded	Consider diuretic holiday or right heart catheterization
2. Drug not reaching the kidney	
-Non-compliance with drug or sodium restriction	Attention to sodium restriction
-Dose too low or too infrequent	Increase dose, increase frequency of dosing
-Poor oral absorption due to gut edema -Poor renal blood flow	Change to diuretic with better oral bioavailability (bumetanide/torsemide) or an intravenous diuretic
3. Impaired diuretic secretion into tubular lumen	
-CKD	Use higher diuretic dose
-Nonsteroidal anti-inflammatory drugs	Stop offending drugs
4. Renal adaptation	
-Distal tubule hypertrophy with sodium retention	Addition of thiazide diuretics-metolazone for sequential nephron blockade

Another issue to consider in the treatment of these patients is the actual impact of worsening renal function with diuresis. An analysis of data from the ESCAPE trial revealed that patients who had more aggressive decongestion during hospitalization as evidenced by hemoconcentration had greater odds of worsening renal function but lower mortality at 180 days [59]. Similarly, in the DOSE trial, high-dose diuretics caused more renal function worsening without adversely impacting the 60-day outcomes [60]. While the former included patients with HFrEF only, about a quarter of the patients in the latter had HFpEF. In the ROPA-DOP trial [56], there was a significant increase in creatinine, but not in cystatin-C levels with the continuous infusion strategy. *These data suggest that transient worsening of renal function with diuresis should not prompt clinicians to hold or decrease diuretics in a congested patient*. Biomarkers as mentioned above can help in advocating the diuretic therapy in such scenarios. In the absence of significant urine biomarker evidence of AKI, WRF seen with diuresis could represent impaired plasma refill (assuming cardiac output is normal) and is not a contraindication for decongestion. It is also important to note that positive urine AKI biomarkers had paradoxically improved survival outcomes [53]. Thus, the significance of mild biomarker-related AKI is less clear when euvolemia clearly drives outcomes.

Ultrafiltration

Ultrafiltration (UF) for decompensated heart failure is usually reserved for patients with renal failure or those unresponsive to pharmacologic therapy. The Relief for Acutely Fluid Overloaded Patients with Decompensated Congestive Heart Failure (RAPID-CHF) was the first trial ($N = 40$) demonstrating that early application of UF for patients with CHF was feasible and well-tolerated but did not result in a significant weight loss after 24 h (2.5 kg vs 1.86 kg, $p = 0.24$) [61]. This was followed by Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial comparing ultrafiltration and intravenous diuresis in patients hospitalized for HF with ≥ 2 signs of hypervolemia ($N = 200$). The results supported the use of ultrafiltration as an alternative therapy, safely producing greater weight and fluid loss [62]. The following CARESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) trial was benchmark in studying the use of ultrafiltration in patients with ADHF complicated by persistent congestion and worsened renal function ($N = 188$) [63]. They concluded that stepped pharmacological therapy algorithm was superior to ultrafiltration for the preservation of renal function at 96 h, with a similar amount of weight loss with the two approaches. It is of high importance that all these trials did not mention the EF of patients being enrolled in these studies. The patients were included based on their symptoms of decompensated heart failure and no differentiation between HFrEF or HFpEF was undertaken. Currently, there is no evidence to suggest ultrafiltration is the first-line therapy for patients with HF and CRS.

Chronic management

Multiple classes of medications including ACE inhibitors, angiotensin receptor blockers, mineralocorticoid antagonists, SGLT2 inhibitors, and incretin-based therapies have been discussed below for their role in chronic management of CRS in HFpEF.

Role of ACE inhibitors/ARBs/mineralocorticoid antagonists

In comparison to HFrEF, there is less rigorous evidence to support the use of RAAS inhibitors in patients with HFpEF. The I-PRESERVE trial enrolled 4128 patients with heart failure with EF ≥ 45%, assigning them to irbesartan or placebo [64]. They demonstrated that irbesartan did not improve the outcomes of patients with HFpEF. The primary outcome was death from any cause or hospitalization for a cardiovascular cause (heart failure, myocardial infarction, unstable angina, arrhythmia, or stroke). Damman et al. used the data from patients included in the I-PRESERVE trial and examined the change in eGFR and development of worsening renal function (WRF) after initiation of irbesartan in patients with HFpEF. They found that WRF developed in 6.4% of patients, and occurred more frequently with irbesartan treatment (8% vs 4%) [65].

The TOPCAT trial studied 3445 patients with symptomatic heart failure and LVEF of ≥ 45% receiving either spironolactone or placebo [66]. In this trial, treatment with spironolactone did not significantly reduce the incidence of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization in patients with HFpEF. A meta-analysis was performed investigating the relationship between RAAS inhibitor therapy, worsening renal function (WRF) in both HFpEF and HFrEF, and mortality. Only two studies were included in the group of HFpEF [67]. They concluded that RAAS inhibitors cause renal dysfunction in both HFrEF and HFpEF. Additionally, in patients with HFpEF, RAAS inhibitor induced worsening renal function has an increased mortality risk.

The deleterious effects of RAAS blockade on renal function can be explained based on the pathophysiology of HFpEF. HFpEF patients have a steep diastolic pressure–volume relationship and a steep, almost vertical end-systolic pressure–volume relationship, leading to a fixed stroke volume, with inadequate increase during periods of high oxygen demand such as exercise. Thus, these patients have a greater dependence on preload, and preload reduction by vasodilators such as ACEI and ARBs can cause a greater drop in stroke volume and blood pressure despite high filling pressures.

Such fluctuations in preload may dramatically decrease renal flow resulting in renal dysfunction [68]. Table 3 summarizes the current evidence on RAAS inhibitors and mineralocorticoid antagonist in patients with HFpEF [69–75].

Sacubitril–valsartan—a new paradigm

The PARADIGM-HF trial was revolutionizing in introducing an innovative new formulation LCZ-696, composed of neprilysin inhibitor sacubitril (AHU377) and valsartan. LCX-696 was superior to enalapril in reducing risks of death and hospitalization for HF in patients with HFrEF [76]. Additionally, it showed beneficial effects on renal function, thereby proving as a new evidence in cardiorenal protection through RAAS inhibition. In the PARAMOUNT trial, over 36 weeks, the eGFR declined less in the LCZ696 group compared to the valsartan group and the incidence of worsening renal function (defined as increase in serum creatinine of > 0.3 mg/dl at any time point) trended lower in the LCZ696 group [75]. This study thus suggests that sacubitril–valsartan may attenuate the decline in renal function in HFpEF patients. The ongoing PARAGON-HF trial will assess the effects of the same drug in patients with HFpEF, hopefully opening doors towards the use of this relatively new drug in patients with HFpEF [77].

Role of SGLT-2 inhibitors

Sodium-glucose cotransporter 2 (SGLT 2) inhibitors or the glifozin drugs are a class of medication approved for treatment of DM type 2. They inhibit the reabsorption of glucose in the kidney by inhibiting SGLT 2, thereby lowering blood sugar. The SGLT2i-mediated natriuresis and glycosuria reduce plasma volume and lower cardiac preload, whereas afterload reductions may occur through lowering of arterial pressure and stiffness (see Fig. 3). Thus, these drugs have cadioprotective effects in HF [78].

SGLT-2is also have renoprotective effects [78]. Increased rates of glomerular filtration and microalbuminuria are prognostic markers of early renal dysregulation mediated by hyperglycemia and hypertension. SGLT2i lower sodium reabsorption in the proximal nephron leading to an increased supply of sodium to the distal juxtaglomerular apparatus which activates tubuloglomerular feedback, afferent vasoconstriction, and reduces glomerular pressure. Up to 30% to 40% reduction in albuminuria has been observed with SGLT2 inhibitor agents, including empagliflozin, dapagliflozin, and canagliflozin. The effect on renal hemodynamics persists even in patients with CKD.

In 2015, EMPA-REG trial reported a 35% reduction in hospitalization for HF and 38% reduction in cardiovascular death in patients being treated with empagliflozin vs placebo [79]. Another large study called the CANVAS trial showed the benefit of canagliflozin in patients with type 2 diabetes mellitus ($N = 10,142$) with respect to the progression of albuminuria (hazard ratio, 0.73; 95% CI, 0.67 to 0.79) and composite outcome of sustained 40% reduction in estimated glomerular filtration rate, the need for renal replacement therapy or death from renal causes (hazard ratio, 0.60; 95% CI, 0.47 to 0.77) [80]. The ongoing EMPA-HEART trial aimed at comparing the effect of sitagliptan and empagliflozin on the global longitudinal strain in diabetic patients with normal LV systolic (2D echo EF > 50%) and renal function (eGFR > 60 ml/min/1.73 mq) [45]. A preliminary report in 10 patients with empagliflozin was associated with 15% reduction in LV mass index and 13% increase in early lateral annular tissue Doppler velocity, a proxy of LV compliance [45]. These studies are limited in not being specifically for HFpEF and being for HF altogether. However, there are large ongoing trials called EMPEROR HF-Preserved and EMPEROR HF-Reduced investigating the safety and efficacy of empaglifozin in patients with chronic heart failure with preserved and reduced heart function respectively with renal end points as well (EMPEROR-EMPagliflozin outcome tRial in Patients with chronic heart Failure) (https://clinicaltrials.gov/ct2/show/NCT03057977, https://clinicaltrials.gov/ct2/show/NCT03057951). It is still unclear if the positive cardiovascular effects of SGLT 2 inhibitors like empagliflozin are due to its metabolic effects (decrease in HbA1c, body weight, blood pressure, and increased HDL cholesterol) or hemodynamic effects (reduced blood pressure and decreased extracellular volume). Nevertheless, its use in diabetic patients seems to have a positive myocardial effect and might improve global longitudinal strain improving the myocardial contractility proving a potential agent to improve ventricular dysfunction in patients with diabetes. A recent analysis of the EMPA-REG database showed that in vulnerable patients with type 2 diabetes mellitus, established cardiovascular disease, and chronic kidney disease, empagiflozin reduced the risk of cardiovascular death by 29% compared to placebo, the risk of all-cause mortality by 24%, and risk of hospitalization for heart failure by 39% [81]. With more research on their use in patients with HFpEF and its renal outcomes, SGLT 2 inhibitors might have a potential role in the treatment of patients with cardiorenal syndrome.

Incretin-based therapies

Two relatively newer classes of therapeutic agents for treatment of type 2 diabetes, glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 inhibitors (DPP-4i) exert their actions through potentiation of incretin receptor signaling. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes (LEADER) trial was a landmark study comparing liraglutide (GLP-1 agonist) with placebo in patients with type 2 DM and high cardiovascular risk [82]. The primary outcome

Table 3 Summarized current evidences on RAAS inhibitor and mineralocorticoid antagonist in patients with HFpEF

Study name	Number	Study design	Medication	Population	Baseline kidney function	Follow up	Concomitant therapy	Outcome	Renal outcome
ACEI/ARB									
Philbin et al. [69]	302	Prospective	ACEI	HF registry mean age 75 years, 30% male, HFpEF defined as EF > 50%	Mean GFR 57 ml/min	6 months	Diuretics 82% β-blocker 19% CCB 35%	Death or readmission: 0.88 (0.54–1.44)	N/A
Yusuf et al. [70] "CHARM-PRESERVE"	3023	RCT: candesartan vs placebo	ARB (candesartan)	Mean age 67 years, 60% male, HFpEF defined as EF > 40%	N/A	3 years	ACEI 19% Diuretics 75% β-blocker 56% Spironolactone 11%	CV death or readmission: 0·86 (0·74–1·00)	N/A
Massie et al. [64] "I-PRESERVE"	4133	RCT: irbesartan vs placebo	ARB (irbesartan)	Mean age 72 years, 40% male, HFpEF defined as EF > 45%	Mean GFR 72 mL/min 30% has GFR < 60 ml/-min	5 years	ACEI 25% Diuretics 83% β-blocker 58% Spironolactone 15%	Death or admission due to CV causes: 0.95 (0.86–1.05)	N/A
Tribouilloy et al. [71]	358	Prospective	ACEI	Mean age 76 years, 50% male, HFpEF defined as EF > 50%	N/A	5 years	Diuretics 85% β-blocker 25% Spironolactone 20%	All-cause mortality: 0.58 (0.40–0.82)	N/A
Lund et al. [72]	6658	Prospective propensity matched	ACEI, ARB	Swedish heart registry Mean age 79 years, 47% male, HFpEF defined as EF > 40%	Mean GFR 53 ml/min	5 years	Diuretics 85% β-blocker 75% Spironolactone 30%	All-cause mortality: 0.90 (0.85–0.96)	N/A
Patel et al. [73]	10,570	Prospective propensity matched	ARB	Inpatient Medicare data Mean age 80 years, 30% male, HFpEF defined as EF > 40%	CKD: 70%	6 years	Diuretics 57% β-blocker 46% Spironolactone 5%	All-cause mortality or HF hospitalization: 0.88 (0.74–1.06)	N/A
Damman et al. [65] Sub-analysis of I-PRESERVE trial	3595	Subgroup analysis of RCT	ARB (irbesartan)	Patients from I-PRESERVE with available baseline and 8-week Cr Mean age 72 years, 40% male, HFpEF defined as EF > 45%	Mean GFR 72 ml/min 30% has GFR < 60 ml/-min	46 months	ACEI 25% Diuretics 83% β-blocker 58% Spironolactone 15%	N/A	WRF: 1.97 (1.50–2.58)
Damman et al. [74] Sub-analysis of CHARM	836	Subgroup analysis of RCT	ARB (candesartan)	Mean age 67 years, 56% male, HFpEF defined as EF > 40%	Mean GFR 75 ml/min	26 months	ACEI 25% Diuretics 85% β-blocker 56% Spironolactone 11%	N/A	≥26.5 μmol/L and ≥ 25% increase in creatinine at 6 weeks OR for WRF with Candesartan: 1.98 (1.28–3.07)
Voors et al. [75] "Paramount"	301	RCT	Neprilypsin inhibitor vs valsartan	Mean age 70 years, 45% male, HFpEF defined as EF > 45%	Mean GFR 66 mL/min	9 months	Diuretics 100% β-blocker 80% Spironolactone 20%	N/A	WRF: LCZ696(12%) vs valsartan (18%) $p = 0.28$

Table 3 (continued)

Study name	Number	Study design	Medication	Population	Baseline kidney function	Follow up	Concomitant therapy	Outcome	Renal outcome
					40% has GFR < 60 ml/-min				
Mineralocorticoid antagonist									
Pitt et al. [66] "TOPCAT"	3445	RCT	Spironolactone vs placebo	Median age 69 years, 50% male, HFpEF defined as EF > 45%	Median GFR 65 ml/min	6 years	N/A	CV death or hospitalization: 0.89 (0.77–1.04)	N/A

RCT randomized controlled trial, *HFpEF* heart failure with preserved ejection fraction, *CV* cardiovascular, *WRF* worsening renal function, *ACEI* angiotensin converting enzyme inhibitor, *ARB* aldosterone receptor blocker, *GFR* glomerular filtration rate, *CKD* chronic kidney disease

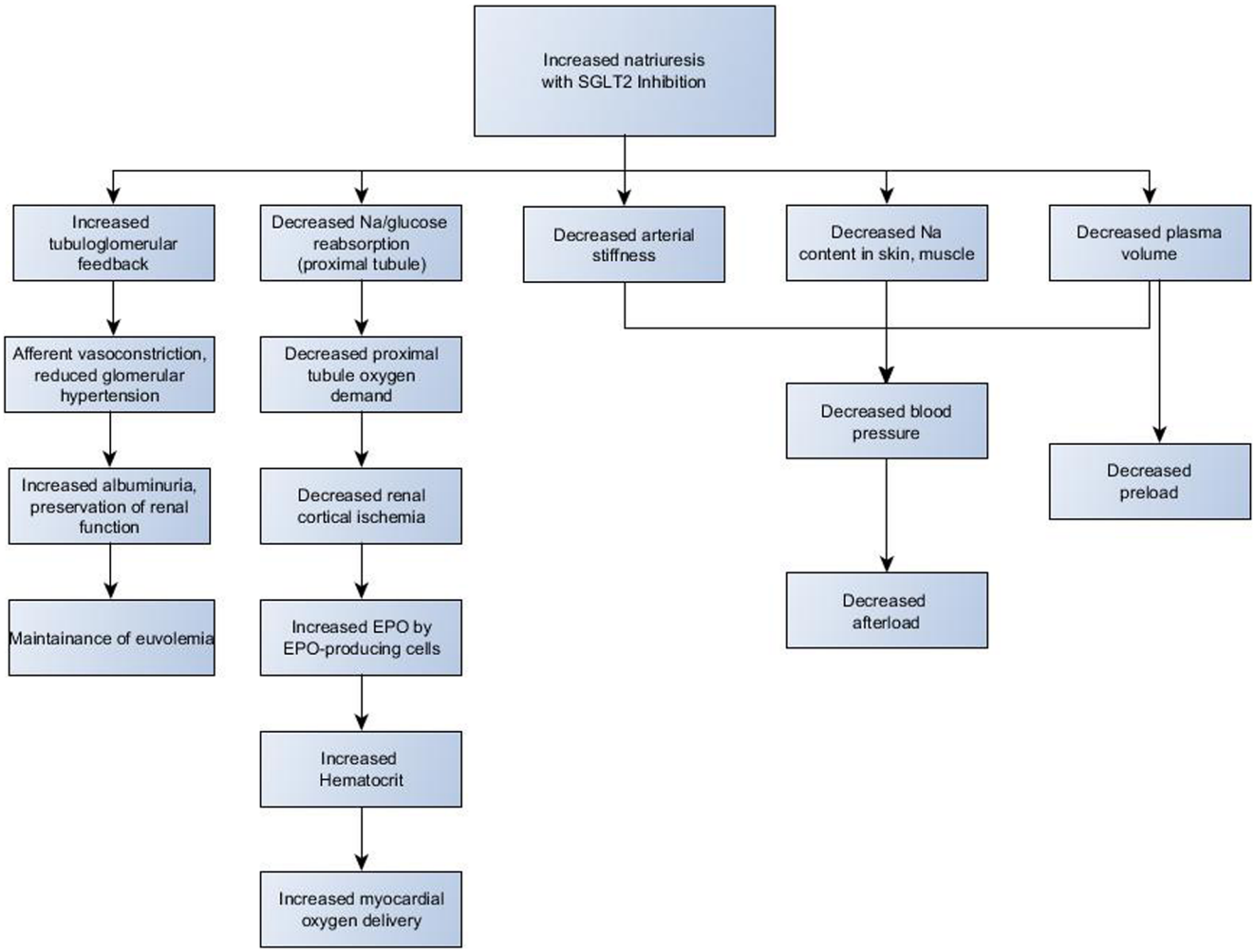

Fig. 3 Cardiorenal effects of SGLT-2 inhibition

(first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) occurred in significantly fewer patients in liraglutide group (13%) than in placebo group (14.9%), (hazard ratio, 0.87; CI 0.78–0.97, $p = 0.01$ for superiority, $p < 0.001$ for non-inferiority) [82]. The secondary outcomes included lower all-cause mortality (8.2% vs 9.6% for placebo, $p = 0.02$), lower chronic heart failure hospitalization (4.7% vs 5.3%, $p = 0.14$), and lower incidence of nephropathy (5.7% vs 7.2%, $p = 0.003$) [83]. Similar studies namely SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) and ESXCEL (Effects of Once-Weekly Exenatide on Cardiovascular Outcome on Type 2 Diabetes) trial studied semaglutide and exenatide showing lower primary outcome in the therapy arm [84, 85]. A study on rat model of HFpEF demonstrated that treatment with sitagliptin (DPP 4 inhibitor) attenuated the diastolic dysfunction, reduced mortality, and reduced cardiac DPP 4 activity [86]. Like SGLT-2 inhibitors, this class of drugs also needs more research and real-world data to find their role in treatment of HFpEF patients with cardiorenal syndrome.

Role of implantable hemodynamic monitoring

As discussed earlier, congestion plays an important role in worsening renal function in patients with HF. Thus, hemodynamic monitoring is valuable in tailoring diuretics in these patients. One of the newer devices to assess pulmonary pressures is CardioMEMS HF System, which is a pressure sensor that is percutaneously placed in the pulmonary artery branch and interrogated via a wireless detection system which can be remotely reviewed by clinicians. It permits outpatient measurement of right-sided pressures which usually rise before overt signs of volume overload develop in a patient. Thus, this data can be used to guide treatment similar to that derived from a right heart catheterization. In the landmark CHAMPION trial, significant reduction in hospitalization was seen in patients with New York Heart Association class III HF patients managed with this system [87]. The trial included both HFrEF and HFpEF patients, but those with significant baseline renal insufficiency were excluded. Nevertheless, by permitting better volume management of HFpEF patients, implantable hemodynamic monitoring has the potential to prevent worsening of renal function.

Newer emerging therapies

Few investigational therapies like serelaxin and inorganic nitrites are opening new avenues into our understanding of their effects in heart failure. Serelaxin is a recombinant human relaxin-2 hormone that acts primarily via nitric oxide causing vasodilatory effects and increase in renal plasma flow. It has been shown to cause reduction in pulmonary artery pressure, pulmonary capillary wedge pressure, and NT-pro-BNP [88]. The RELAX-AHF trial demonstrated that in patients with HFpEF, serelaxin was well tolerated and effective in relieving dyspnea with positive secondary end points. The secondary end points included cardiovascular death or rehospitalization for heart or renal failure and days alive and out of hospital through day 60 [89]. Inorganic nitrites are another class of drugs that may have potential in patients with HFpEF. Inorganic nitrites are targeted at restoring NO-cGMP signaling and potentially attenuate left ventricular systolic and diastolic dysfunction, pulmonary vascular disease and endothelial dysfunction [90]. A small randomized study in 17 patients reported increased exercise capacity in patients with HFpEF on taking inorganic nitrate-rich beetroot juice (converted to nitrite in the mouth). It increased exercise vasodilatory and cardiac output reserve and reduced arterial wave reflections, which are linked to left ventricular dysfunction and remodeling [91]. However, in the randomized INDIE-HFpEF trial, inhaled nebulized inorganic did not improve quality of life parameters compared to placebo [92], suggesting that more research is needed in this area. More recently, a novel class of drugs called soluble guanylate cyclase (sGC) stimulators and sGC activators is being studied. They enhance cGMP production independent of nitric oxide (NO). Riociguat and vericiguat are direct sGC stimulators that are being currently studied for the treatment of HFpEF [93]. In the SOCRATES-PRESERVED study, vericiguat as compared with placebo, improved patient-reported outcomes in quality of life, and appeared to improve early diastolic relaxation in patients with HFpEF [94]. The effects of riociguat on right heart parameters are being studied in patients with HFpEF and pulmonary hypertension [95]. By addressing the underlying pathophysiologic mechanisms behind HFpEF, these studies may improve cardiorenal outcomes.

Novel catheter-based approaches are also under investigation in patients with HFpEF. In patients with HFpEF, LV diastolic dysfunction leads to elevated left atrial (LA) pressure with subsequent elevation in pulmonary venous pressure, especially during exertion. An interatrial septal communication can potentially unload the LA transferring the excess LA blood volume to the larger capacitance right atrium and systemic veins. Based on this concept, a novel interatrial shunt device (IASD) was developed and tested in a randomized sham controlled trial (the REDUCE LAP-HF 1 trial) in patients with symptomatic HF with EF $\geq$40%. In this study, IASD treatment was shown to significantly reduce pulmonary capillary wedge pressure during exercise at 1 month compared to controls. Regarding renal function, no patient in the IASD group developed worsening renal function. While this study was not designed to look at renal function as an end point, it would be interesting to see in future trials if reducing LAP by creating an IASD (potentially overloading the right side of the heart) has a positive effect on preserving or improving renal function [96].

Summary and future prospects

We are currently experiencing an epidemic of heart failure which is responsible for significant morbidity, mortality, and health care expenditure, especially in the context of coexistent kidney disease. With almost 50% of patients with heart failure having preserved ejection fraction, it is important to understand the renal consequences of HFpEF. In patients with heart failure, both AKI and advanced CKD have been shown to be independent predictors of in-hospital mortality. Elevated central venous and intra-abdominal pressure, left ventricular hypertrophy, LV strain, RAAS activation, valvular disease, oxidative injury, and role of pulmonary hypertension and RV dysfunction play key roles in the pathogenesis of cardiorenal syndrome in the backdrop of HFpEF. A sound understanding of hemodynamic factors involved in this interface of HF and renal impairment is critical in delivering optimal decongestive therapies as well as goal-directed medical therapy for cardiorenal syndrome. Finally, novel targeted therapies such as the development of angiotensin/neprilysin inhibitors and SGLT-2 inhibitors offer new territory in realizing potential benefits in reduction of cardiorenal adverse outcomes in this population. Future studies focusing exclusively on renal outcomes in patients with HFpEF are crucial in delivering optimal therapies in this subset of patients. To this end, the availability of biomarkers of renal and cardiac injury offer a new dimension in accurately diagnosing and quantifying end organ damage in cardiorenal syndrome and will improve the accuracy of goal-directed therapies in this population.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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