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REVIEW ARTICLE

Cardiorenal syndrome

Pearl Pai [a,b,*]

[a] *Department of Medicine, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China*
[b] *Department of Medicine, The University of Hong Kong-Queen Mary Hospital, Hong Kong, China*
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Abstract Patients with cardiorenal syndrome (CRS) suffer from extremely high levels of morbidity and mortality. The pathophysiology of the CRS involves inter-related hemodynamic and neurohormonal mechanisms including the renin–angiotensin–aldosterone system (RAAS), endothelin, and arginine–vasopressin system activation. The management of CRS remains a challenge despite extensive research into the pathophysiology, discovery of new biomarkers, and ongoing drug trials. This article reviews some of the most important trials for patients with acute decompensated heart failure and CRS using diuretics, vasodilator, levosimendan (a calcium sensitizer), vasoactive and neurohormonal therapies, and finally ultrafiltration for refractory cases. In addition, the trials of a new agent that combines angiotensin-receptor blockade with neprilysin inhibition (enhancing endogenous natriuretic peptide action), and of a new recombinant human relaxin-2 called serelaxin are discussed. For chronic CRS, the blockade of the RAAS and levosimendan given in repetitive dosing is discussed. Finally, some data on how the newer generation devices such as left ventricular assist device may improve outcome of CRS are presented; additionally, some new ideas about prevention and treatment of calcification-induced congestive cardiac failure in renal patients are presented.

心腎綜合症(CRS, cardiorenal syndrome)是嚴重的疾病，死亡率極高，其致病過程涉及一系列血行動力-神經內分泌機轉的變化，包括腎素-血管緊縮素-醛固酮系統(RAAS, renin–angiotensin–aldosterone system)、內皮素(endothelin)及抗利尿素(arginine–vasopressin)系統的活化。至今，即使已有大量關於病理生理學、生物標識物、及藥物治療的研究問世，然而CRS仍然是臨床上的一大挑戰。本文將針對合併有CRS的急性失代償性心衰竭 (ADHF)患者，回顧利尿劑、血管擴張劑、levosimendan (鈣增敏劑)、血管活性及神經內分泌療法的相關重要研究，更會回顧超過濾(UF, ultrafiltration)在頑抗性個案間的治療表現。此外，我們亦會探討利鈉肽(NPs, natriuretic peptides)或神經荷爾蒙藥物的潛在效用，包括一種兼具血管緊縮素受體阻斷(ARB)與neprilysin抑制作用(促進內源性NP活動)的新藥物、及一種新的重組人類relaxin-2 (稱為serelaxin)。至於慢性CRS，我們主要著眼於RAAS阻斷劑與levosimendan的重複給藥、及腹膜透析(PD)療法。最後，我們將回顧新世代裝置例如左心室輔助裝置(LVAD)對CRS的潛在效用，更會對腎病患者間，鈣化誘發鬱血性心衰竭(CCF)的預防與治療作出探討。

* Department of Medicine, The University of Hong Kong-Queen Mary Hospital, Pokfulam Road, Hong Kong, China.
E-mail address: ppai1@hku.hk.

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Introduction

Chronic kidney disease (CKD) is very common in patients with heart failure (HF). In the Acute Decompensated Heart Failure National Registry (ADHERE),[1] >60% of 118,465 patients admitted to U.S. hospitals with acute decompensated HF (ADHF) had Stage 3 [estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2] or worse CKD. Furthermore, during the treatment of ADHF, a significant proportion of patients develop varying degrees of worsening renal function (WRF). In a study of approximately 1000 patients admitted with ADHF, the serum creatinine level increased by > 0.1 mg/dL (8.8 μmol/L) in >70% of patients and by > 0.5 mg/dL (44 μmol/L) in up to 20% of patients within 3 days of hospitalization.[2] In 2008, a consensus conference under the auspices of the Acute Dialysis Quality Initiative[3] agreed to classify the syndrome into five distinct types depending on whether heart or kidney was the initial organ of injury. In cardiorenal syndrome (CRS) Types 1 and 2, worsening of HF in acute (Type 1) or chronic HF (Type 2) leads to worsening of kidney function. In Types 3 and 4 (termed acute and chronic renocardiac syndromes, respectively), acute kidney injury (AKI) or CKD leads to worsening HF. In Type 5 CRS, systemic conditions cause simultaneous dysfunction of the heart and kidney. In most studies, a rise in serum creatinine level of ≥0.3 mg/dL (26 μmol/L) or a ≥25% increase from baseline is used to define acute or Type 1 CRS. Using this definition, the prevalence of Type 1 CRS has been reported in the 27–45% range.[4,5] The prevalence of Type 2 CRS is around 32–50% in large chronic HF trials.[6–8] This review is predominantly based on a discussion of Types 1 and 2 CRS. The five subtypes of CRS are presented in Table 1.

In CRS, the impaired forward flow and decreased effective circulating volume in case of severe systolic HF or cardiogenic shock lead to arterial underfilling and activation of neurohormonal and inflammatory pathways, resulting in fluid retention and increase in venous pressure (VP) and important repercussions on renal perfusion. Autoregulation of the GFR fails and kidney function declines, subsequently leading to worsening fluid retention, preload, and afterload. A series of maladaptive responses including the activation of the renin–angiotensin–aldosterone system (RAAS), tubuloglomerular feedback, and activation of sympathetic nervous system occur in HF.[9] Furthermore, venous congestion and high right-sided pressure, such as in the case of HF with preserved ejection fraction (EF) or isolated right HF, may lead to decreased arteriovenous perfusion gradient, increased kidney interstitial edema, and worsening of fluid retention.[9,10] A higher central VP (CVP) was found to be inversely related to GFR and independently associated with all-cause mortality.[11] Moreover, an incremental risk of developing WRF with increasing CVP was observed in patients with ADHF independent of the cardiac output (CO). Thus, further understanding of the role of increased VP in CRS may provide future novel drug targets and gauge therapeutic efficacy.

CRS is a systemic illness that results from the interplay among myocardial factors, systemic inflammation, renal dysfunction, and neurohormonal activation including adenosine, endothelin, and decreased response to atrial natriuretic peptide (ANP). Insights into the pathophysiology of HF have allowed the identification of several biomarkers that represent key disease pathways. Among others, promising biomarkers identified for this purpose include cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), *N*-acetyl-β-D-glucosaminidase, and kidney injury molecule-1.[12–14] The application of these biomarkers may provide future therapeutic modifications aiming at an earlier stage, thereby attenuating further damage to the kidneys.

Table 1 Classification of the five subtypes of cardiorenal syndrome.

Type 1	A rapid worsening of cardiac function leading to acute kidney injury
Type 2	Chronic abnormality in cardiac function (e.g., congestive cardiac failure) leading to progressive chronic kidney disease (CKD)
Type 3	An abrupt and primary worsening of kidney function (e.g., ischemia) leading to acute cardiac dysfunction (e.g., heart failure)
Type 4	CKD (e.g., chronic glomerulonephritis) as the cause of decreased cardiac function (e.g., left ventricular hypertrophy, diastolic dysfunction, chronic heart failure)
Type 5	Presence of combined cardiac and renal dysfunction due to acute or chronic systemic disorders

CKD = chronic kidney disease.

Worsening renal function

Several studies have demonstrated that WRF during the treatment of ADHF leads to increased mortality.[15,16] Renal dysfunction is a major independent risk factor for mortality in patients with postinfarction left ventricular dysfunction and HF, as shown in the Survival And Ventricular Enlargement (SAVE) trial.[17] These data were subsequently confirmed by the results of other trials, including the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity trial,[7] which showed that the relationship between kidney dysfunction and poor outcome was present regardless of EF. Data from the ADHERE study[1] showed that blood urea nitrogen (BUN), serum creatinine, and systolic blood pressure (BP) were strong predictors of in-hospital mortality in acute HF patients. However, the use of serum creatinine rise as a marker of WRF is not ideal. For example, the early rise of serum creatinine level following the introduction of an angiotensin-converting enzyme inhibitor (ACEI) reflects changes in glomerular hemodynamics and does not translate to a worse outcome. This was illustrated by the limited data set analysis of the Studies of Left Ventricular Dysfunction (SOLVD), which was undertaken to examine the interactions between early WRF (decrease in eGFR ≥ 20% at 14 days), randomization to enalapril, and mortality end point in 6377 patients.[18] In total, 606 patients (9.5%) experienced early WRF between baseline and 14 days after randomization with a mean decrease in eGFR of

29.2 ± 9.8% in the enalapril group and 28.9 ± 9.3% in the placebo group. In the overall population, early WRF was associated with increased mortality [hazard ratio (HR) 1.2, 95% confidence interval (CI) 1.0–1.4; $p = 0.037$], however, it had no adverse prognostic significance in the enalapril group (HR 1.0, 95% CI 0.8–1.3; $p > 0.99$, p interaction $= 0.09$), which showed a survival advantage over placebo (HR 0.66, 95% CI 0.5–0.9; $p = 0.018$).[18]

In the Placebo-Controlled Randomized Study of the Selective Adenosine A1 Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) trial,[19] it was shown in a subset of 1969 patients with acute HF, mild to moderate renal dysfunction, and serial hemoglobin (Hb) measurements that hemoconcentration was associated with higher serum albumin, greater weight loss, and less residual congestion on Day 7 (41.1% vs. 53.2%, $p < 0.01$) but a higher serum creatinine.[20] Despite the increase in serum creatinine, patients with hemoconcentration experienced lower rates of all-cause mortality at 180 days, which indicates better decongestion than those without hemoconcentration. In a multivariable analysis adjusted for age and renal function, the absolute change in Hb (i.e., hemoconcentration), and not baseline Hb, was associated with the risk of death (HR 0.66, 95% CI 0.51–0.86; $p < 0.002$).

Diuretic treatment

Diuretics remains the mainstay of acute HF therapy, however they contribute to the development of WRF, especially when administered in high doses. The *post hoc* analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) demonstrated a robust relationship between diuretic dose and mortality.[21] However, on further analysis of the available data of 336 patients with a baseline/discharge pair of hematocrit, albumin, or total protein values, it was apparent that aggressive decongestion substantially improved survival at 180 days (HR for mortality, 0.31; $p = 0.013$).[22] In relatively less severe cases with a higher probability of survival, however, WRF might generate a vicious cycle leading to further aggravation of kidney injury and to adverse clinical outcomes in the medium to long term.

The Diuretic Optimization Strategies Evaluation (DOSE) trial is one of the few recently published large prospective studies in this field.[23] DOSE was a prospective, double-blind, randomized controlled trial (RCT) that randomized 308 patients with ADHF into four different regimens of intravenous (IV) furosemide, either in bolus every 12 hours or by continuous infusion, and at either low (pre-existing oral dose) or high doses (2.5-fold oral dose). Coprimary end points were symptoms score and change of renal function (i.e., serum creatinine levels) at 72 hours. The trial did not show significantly different outcomes for bolus versus continuous infusion or between high- and low-dose groups. A near-significant trend ($p = 0.06$) was observed for symptomatic improvement in the high- versus low-dose groups, alongside a greater diuresis and transient WRF. Overall, there were no differences with respect to the application route or the dosage of the diuretic on the coprimary end points. High-dose therapy led to a faster relief of dyspnea and a greater loss of fluid and weight at the cost of a more pronounced, transient WRF. The DOSE trial thus challenges the widely held belief that high-dose diuretic therapy worsens renal function and thus worsens outcomes. Therefore, a short-term diuretic treatment intensification, aimed at relieving congestion in ADHF patients, may provide long-term cardiovascular (CV) benefits.

Efforts have been focused on finding alternative therapies that allow freedom from congestion without precipitating WRF. Some researchers were searching for biomarkers other than serum creatinine to define WRF that distinguishes CRS and renal injury from WRF due to hemoconcentration/hemodynamic effect. According to a single-centered study of 119 patients with acute HF, a single plasma NGAL measurement above a cutoff value of 170 ng/L (from the 1st day onward) could identify all patients developing Type 1 CRS within 48–72 hours with a 50% false-positive rate.[14] An NGAL value less than the cutoff value of 170 ng/L has a negative predictive value of 100%. However, at present, the role of novel biomarkers in clinical trials remains unproven and further studies are required to elucidate their characteristics and validity as related to established HF end points.

The persistence of renal vasoconstriction, tubuloglomerular feedback, actions of vasoactive peptides (e.g., adenosine and endothelin), and diminished response to endogenous NP are important pathophysiological components of diminished GFR in HF.[9] Some of the earlier trials of these agents including nesiritide, vasopressin V2-receptor antagonist, and adenosine 1 (A1)-receptor antagonist were showing early promise.[24] Other treatment strategies for chronic CRS including β-blocker and anemia correction using erythropoietin have also been reviewed.[24] In this review, an update on the pharmacological and mechanical approaches for treatment of Types 1 and 2 CRS is provided.

Vasopressin V2-receptor antagonist

Tolvaptan is a selective vasopressin V2-receptor antagonist that acts on the distal nephron, causing loss of electrolyte-free water. In the randomized, placebo-controlled study of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST), patients with ADHF were given tolvaptan or placebo in addition to standard treatment.[25] Patients with serum creatinine levels >3.5 mg/dL (308 μmol/L) were excluded. Although tolvaptan reduced many signs and symptoms of HF and improved hyponatremia without significant adverse effects on BP or renal function, there was no significant benefit with respect to mortality or hospitalization rate. Currently, according to the American guideline[26] (Class IIb, level of evidence B), tolvaptan may be used for short-term treatment of severe hyponatremia associated with ADHF and volume overload.

Natriuretic peptides

Nesiritide, a recombinant human brain natriuretic peptide (BNP), is a venous and arterial vasodilator with modest

diuretic and natriuretic effects. Nesiritide has been used for a long time in the ADHERE.[1] In the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial, 489 patients with acute congestive cardiac failure (CCF) were randomized to receive nesiritide versus nitroglycerin versus placebo. Nesiritide showed an improvement of dyspnea and a reduction in pulmonary capillary wedge pressure (PCWP) at 3 hours compared with placebo.[27] The placebo-controlled Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) randomized 7141 acute HF patients to receive nesiritide or placebo. Treatment with nesiritide showed a small but nonsignificant benefit on dyspnea at 6 hours and 24 hours, respectively, without any effect on the composite end point of rehospitalization for HF or death within 30 days.[28] There was also a significant increase in hypotension. In the Renal Optimization Strategies Evaluation study in Acute Heart Failure (ROSE-AHF),[29] a lower dose (0.005 μg/kg/min) of nesiritide (one half of the dose tested in ASCEND-HF) was tested in patients with CCF and kidney dysfunction (eGFR 15–60 mL/min/1.73 m^2) and compared with low-dose dopamine (2 μg/kg/min) and placebo for 72 hours, in addition to standard diuretic therapy. There were a total of 360 patients. Even then, hypotension was common in the nesiritide-treated patients. The coprimary end points were 72-hour cumulative urine volume (decongestion end point) and change in serum cystatin C from enrollment to 72 hours (renal function end point). Neither dopamine nor low-dose nesiritide appeared to enhance decongestion or preserve renal function. In the absence of hypotension, nesiritide may be considered as an adjuvant to relieve acute dyspnea in ADHF cases (Class IIb, level of evidence A).[26]

A1-receptor antagonist (rolofylline)

Adenosine was thought to be an important mediator of WRF and diuretic resistance in HF. It stimulates renin release through stimulation of its A1 receptor and reduces GFR. It is believed that in patients with HF, A1-receptor antagonists may preserve GFR, enhance sodium excretion, and improve diuretic responsiveness. The Placebo-Controlled Randomized Study of Selective Adenosine (A1)-Receptor Antagonist Rolofylline for Patients Hospitalized with ADHF and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) enrolled 2033 patients receiving IV infusion of rolofylline or placebo.[19] The mean creatinine clearance was 50 mL/min/1.73 m^2 (range 20–80 mL/min/1.73 m^2). Despite the favorable outcome of the pilot study, the PROTECT study failed to reduce the primary end point (mortality or rehospitalization due to renal or CV causes) or secondary end point (persistent increase in serum creatinine on Day 7). Moreover, there was a concern about safety, because 1% of the patients developed seizure, a known adverse effect of A1-receptor antagonists owing to inhibition of the central A1 receptors.

Levosimendan use in Type 1 CRS

Levosimendan is an inotrope with a vasodilatory effect. It has been in clinical use for decompensated HF for >10 years. Levosimendan exerts positive inotropic effect by binding to cardiac troponin C, thereby increasing the susceptibility of myofilaments to calcium. Its vasodilatory effects are brought about by adenosine triphosphate-dependent opening of potassium channels and phosphodiesterase inhibition. In contrast to other inotropes, levosimendan acts independently of β-adrenergic receptors. It has been shown to reduce proinflammatory cytokines and BNP[30] and preserve renal function.[31]

The renal effect of levosimendan was studied in 21 patients with ADHF and moderate renal impairment with a PCWP >20 mmHg.[32] An intravascular renal artery Doppler examination was performed at baseline, after levosimendan bolus, and 1 hour thereafter. The results were significantly different from placebo in terms of renal blood flow ($p = 0.037$) with ensuing improvements in serum levels of BUN ($p = 0.014$), creatinine ($p = 0.042$), and cystatin C ($p = 0.05$). Concomitantly, levosimendan provided a significant increase in urine output up to 72 hours ($p = 0.02$) as well as favorable changes in cardiac index ($p = 0.029$) and PCWP ($p < 0.001$). However, the results of several major clinical studies of levosimendan have been inconsistent.[33,34] In the Levosimendan Infusion versus Dobutamine (LIDO) trial, levosimendan led to an increased hemodynamic improvement that was associated with a lower risk of mortality compared with dobutamine administered according to a protocol-based regime.[33] However, in the larger, randomized Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support trial including 1327 patients hospitalized with ADHF requiring inotropic support, levosimendan treatment did not improve the 180-day mortality or any other secondary clinical outcome compared with dobutamine administered according to the clinical need.[34] It was imaginable that the differences in mortality in the LIDO study were not due to a decrease in mortality with levosimendan, but rather due to an increase in mortality with the use of dobutamine. A further randomized study of 60 patients with ADHF on β-blocker treatment showed that levosimendan was comparable to dobutamine with respect to hemodynamic and neurohormonal improvements, although there was a higher rate of hypotension in the levosimendan group (10% vs. 2%).[35] The European guideline[36] has recommended the use of levosimendan (Class IIb, level of evidence C) in patients with acute HF on pre-existing β blockers.

Levosimendan use in chronic advanced HF and CRS

The use of repetitive levosimendan infusion as an outpatient therapy in stable chronic advanced HF patients has caused much interest.[37] After a 24-hour infusion of levosimendan, its pharmacodynamic effects (i.e., CO and PCWP) were shown to persist for at least 1 week.[38] In the Randomized EValuation of Intravenous LeVosimendan Efficacy (REVIVE II) trial,[39] which compared levosimendan (bolus of 6–12 μg/kg over 10 minutes followed by 0.1–0.2 μg/kg/min for 24 hours) with placebo, on top of standard care, in patients with ADHF, the percentage of patients free of dyspnea favored levosimendan over placebo for up to 5 days after the completion of treatment. The LevoRep study[40] was a large, prospective, multicentered, randomized, placebo-

controlled, double-blind, two-armed, parallel-group study carried out to examine the effect of repetitive, ambulatory administration of levosimendan in advanced stable HF patients [New York Heart Association (NYHA) III/IV, left ventricular ejection fraction $\leq$ 35%]. Patients were randomized to receive placebo or levosimendan (0.2 μg/kg/min) for 6 hours at 2-week intervals for a total of four infusions in addition to other HF therapy. At the end of 24 weeks, the treatment group failed to reach the combined primary end point for improvement in functional capacity of $\geq$20% according to the 6-minute walk test, and improvement in patient quality of life of $\geq$15% as assessed by the Kansas City Cardiomyopathy Questionnaire score. However, there was an improved survival as part of the secondary end point after 24 weeks (17.4% vs. 35.1%, $p = 0.037$).

Most reports on the effect of levosimendan indicated an improvement of renal function in HF, however, the study designs differed considerably.[31] Importantly, in the largest HF study (REVIVE I and II),[39] no significant changes in renal function were detected. In 2014, an expert consensus was reached in that for stable chronic advanced HF patients, levosimendan may be given as an infusion at a rate of 0.2 μg/kg/min, for 6–24 hours every 2–4 weeks, with a view to improve symptoms while accepting that more studies are required to determine any survival benefit.[37]

Serelaxin and acute CRS

Serelaxin is a recombinant form of human relaxin-2. This is a naturally occurring peptide hormone that increases during pregnancy and mediates the maternal physiological CV and renal adaptations and has potential protective effects against organ damage.[41] These biological effects suggest that relaxin might be an ideal therapeutic agent in acute HF where the opposite pathophysiological changes are observed. Among other potential mechanisms, relaxin acts by increasing the expression of endothelin-type B receptors, which have a clearance function for endothelin-1, a potent vasoconstrictor. Therefore, relaxin is a functional endothelin-1 antagonist.

In the randomized, placebo-controlled pre-RELAXin in Acute Heart Failure (pre-RELAX-AHF) trial, treatment with serelaxin significantly reduced dyspnea and the combined end point of CV death or admission due to heart and renal failure on Day 60.[42] The phase III RELAX-AHF trial is another RCT designed to compare serelaxin ($n = 581$) with placebo ($n = 580$) in patients with acute HF.[43] The median time from presentation was 6 hours and patients were required to have a systolic BP $>$ 125 mmHg and elevated levels of NP at the time of screening. The primary end point was evaluating dyspnea improvement using the visual analog scale (VAS) from baseline to Day 5 and the proportion of patients with moderate or marked dyspnea improvement using the Likert scale during the first 24 hours. Secondary end points were days survived out of the hospital up to 60 days and CV death or rehospitalization due to heart or renal failure within 60 days. Approximately 70% of patients in either group had an eGFR $<$ 60 mL/min/1.73 m^2, and approximately 47% had an eGFR $<$ 50 mL/min/1.73 m^2. Within the first 5 days, using VAS, treatment with serelaxin improved the primary dyspnea end point compared with placebo. However, serelaxin did not reduce the rate of CV death or HF readmissions up to Day 60 or affect the days alive out of the hospital up to Day 60 (secondary end points). In a *post hoc* analysis undertaken by Metra et al,[44] serelaxin administration was associated with significant reduction of markers of end-organ damage (cardiac, renal, and hepatic) at Day 2 from randomization. There was also a 37% reduction in CV mortality after a follow-up period of 180 days in the serelaxin group versus placebo with a larger reduction in CV mortality and all-cause mortality being observed in patients aged $\geq$ 75 years, and those with an eGFR $<$ 50 mL/min/1.73 m^2. The result of an ongoing phase 3 study of 6300 patients is expected in 2016.

Neprilysin

Neprilysin is a neutral endopeptidase that catalyzes the degradation of a number of vasodilator peptides, including ANP, BNP, bradykinin, substance P, and adrenomedullin, and contributes to the breakdown of angiotensin II.[45] Therefore, inhibiting this enzyme will augment the naturally occurring NP. Neprilysin plays no role in the breakdown of N-terminal prohormone of BNP (NT-proBNP). Because neprilysin inhibitors may potentially increase circulating angiotensin II levels, it provides a rationale for developing a compound that dually blocks this enzyme and the RAAS.

Angiotensin receptor neprilysin inhibitor trial in chronic HF and CRS

The investigational drug LCZ696 is an angiotensin receptor neprilysin inhibitor (ARNI) composed of two distinct pharmacological moieties, namely, a neprilysin inhibitor prodrug and the angiotensin-receptor blockade (ARB), valsartan.

The efficacy of LCZ696 as a treatment for HF with preserved EF was assessed in Prospective comparison of ARNI with ARB on Management Of Heart Failure with Preserved Ejection Fraction (PARAMOUNT), a phase II clinical trial comparing the effect of LCZ696 versus valsartan.[46] This trial enrolled patients with EF of $\geq$45% who were classified as NYHA Class II–III with NT-proBNP level $>$400 pg/mL. The primary end point was change in NT-proBNP levels and a measure of ventricular wall stress at baseline and at 12 weeks. LCZ696 was superior to valsartan in reducing NT-proBNP at 12 weeks ($p = 0.005$). After 36 weeks, NT-proBNP levels remained reduced in the LCZ696 arm, however, reduction was also observed in the valsartan arm, so that between-group treatment differences were no longer significant [496 (401–613) pg/mL vs. 607 (484–760) pg/mL]. However, patients receiving LCZ696 had significant improvement of NYHA class and left atrial size compared with those receiving valsartan at 36 weeks.

The Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor with Angiotensin-Converting-Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF) was a phase III, double-blind RCT that compared the effect of LCZ696 versus enalapril in Class II–IV chronic HF patients.[47] Patients with an EF of $\leq$40% and an average serum creatinine level of 1.13 $\pm$ 0.3 mg/dL (100 $\pm$ 26 μmol/L) were

randomized to receive either LCZ696 (at a dose of 200 mg 2 times daily) or enalapril (at a dose of 10 mg 2 times daily) in addition to recommended therapy. Patients with BP $<$ 100 mmHg or eGFR $<$30 mL/min/1.73 m^2 at screening were excluded. The trial was terminated early after a median follow up of 27 months because the benefit of LCZ696 exceeded the prespecified rules. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril group (HR for the LCZ696 group was 0.80; 95% CI 0.73–0.87; $p < 0.001$). A total of 711 patients (17.0%) receiving LCZ696 and 835 patients (19.8%) receiving enalapril died (HR for death from any cause was 0.84; 95% CI 0.76–0.93; $p < 0.001$). Of these patients, 558 (13.3%) and 693 (16.5%), respectively, died from CV causes (HR 0.80; 95% CI 0.71–0.89; $p < 0.001$). Compared with enalapril, LCZ696 also reduced the risk of hospitalization for HF by 21% ($p < 0.001$) and decreased the symptoms and physical limitations of HF ($p = 0.001$).

Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction (PARAGON-HF) is an ongoing double-blind RCT that began in late 2013 to compare prospectively ARNI with ARB global outcomes in HF cases with preserved EF. It was designed to enroll 4300 patients with signs and symptoms of chronic HF, NYHA Class II–IV, EF of $>$45%, a history of HF hospitalization within 9 months or an elevated NT-proBNP level at entry, or evidence of structural heart disease to either the LCZ696 or valsartan group. Patients with eGFR $<$ 30 mL/min/1.73 m^2 were excluded. The primary outcome measures include CV death and total HF hospitalizations.

Renin inhibitor and mineralocorticoid receptor antagonist

The use of aliskiren, a direct renin inhibitor, represents another pharmacologically distinct method for RAAS blockade with the theoretical benefit of upstream RAAS inhibition at the point of pathway activation. In the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) trial,[48] 1639 stabilized HF patients (EF $\leq$ 40%) with elevated NP level admitted to the hospital with symptoms and signs of fluid overload were randomized to receive either aliskiren or placebo in addition to standard treatment including an ACEI (84.2%), β blocker (82.5%), and mineralocorticoid receptor antagonist (MRA; 57.0%). Patients with an eGFR $<$ 40 mL/min/1.73 m^2 or a serum potassium level $>$5 mmol/L were excluded. Aliskiren did not reduce the combined primary end point of CV death or hospitalization for HF at 6 months or 12 months after discharge, although the NT-proBNP levels were significantly and sustainably reduced. Comparing aliskiren with placebo, there were more adverse effects including hyperkalemia (20.9% vs. 17.5%), hypotension (17.1% vs. 12.65%), and renal dysfunction (16.6% vs. 12.1%).

On this note, it will be worth revisiting the data of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial, which showed a benefit of adding low-dose eplerenone, an MRA, to standard therapy in acute myocardial infarction and HF patients with left ventricular systolic dysfunction.[49] Eplerenone increased the survival by 15%. Further analysis of the study undertaken by Rossignol and colleagues[50,51] showed a WRF in 16.9% of patients in the eplerenone group versus 14.7% of patients in the placebo group after 1 month, however, the eGFR change in the eplerenone group correlated positively with the estimated plasma volume change indicative of a hemodynamic process. Although eplerenone induced a more frequent early decline in eGFR, it did not affect its clinical benefit on CV outcomes.

Patients with diuretic refractoriness may benefit from mechanical removal of fluid (ultrafiltration, UF). Two modalities of renal replacement therapy can be used in these patients, namely, isolated UF and peritoneal dialysis (PD).

Peritoneal dialysis

The clinical usefulness of PD as a maintenance therapy for intractable chronic HF patients has been accumulating since 1990s. Nakayama[52] has recently undertaken a review on the usefulness of PD as a chronic supportive therapy for CRS Types 2 and 4. In the nonuremic predialysis setting of chronic HF, PD was shown to improve cardiac function and preserve residual renal function. In theory, the removal of proinflammatory factors (e.g., tumor necrosis factor-α and cardiac depressant factor) from the PD fluid might improve cardiac function. It is likely that PD preserves residual kidney function by slowing fluid removal, thus leading to less stimulation of the renin–angiotensin system or the sympathetic nervous system, or both. Furthermore, Courivaud et al[53] presented the largest cohort of patients with chronic refractory HF (CRHF) in whom PD was initiated to manage volume overload and diuretic refractoriness. The retrospective analysis included 126 CRHF patients who were treated with PD between 1995 and 2010 at two centers in France (Besançon and Dunkerque). The mean age was 72 $\pm$ 11 years; the mean eGFR was 33.5 $\pm$ 15.1 mL/min/1.73 m^2. Patients with eGFR $<$ 15 mL/min/1.73 m^2 were excluded. As much as 55% had an eGFR $>$ 30 mL/min/1.73 m^2 (mean 45.5 $\pm$ 12.7 mL/min/1.73 m^2), 28% had an eGFR of 20–30 mL/min/1.73 m^2, and 17% had severe renal dysfunction and an eGFR of 15–20 mL/min/1.73 m^2 (mean 17.2 $\pm$ 1.4 mL/min/1.73 m^2). The causes of HF were ischemic cardiomyopathy (62%), dilated cardiomyopathy (52%), valvular cardiomyopathy (29%), and diastolic dysfunction (10%). As much as 46% of the patients suffered from atrial fibrillation. PD was associated with a dramatic reduction in the number of days of HF-related hospitalization after initiation of PD therapy—from 3.3 $\pm$ 2.6 d/mo to 0.3 $\pm$ 0.5 d/mo ($p < 0.0001$). The 1-year mortality rate was 42%. The mean survival duration was 16 $\pm$ 16 months (range 14 days–8.4 years) with a trend toward lesser survival in patients with an LVEF $<$30%. Overall, the LVEF improved significantly during the 1st year of PD therapy (38 $\pm$ 19% at baseline vs. 42 $\pm$ 17% at 1 year, $p = 0.001$), and more so in those with an LVEF of $<$30% (20% $\pm$ 6% at baseline vs. 30% $\pm$ 10% at 1 year, $p < 0.0001$). The peritonitis rate was one episode in 26.2 patient-months. Thus, PD therapy would appear to be an appropriate and feasible option for CRHF patients in whom conventional therapies have not resulted in the desired therapeutic response, although prospective analyses to elucidate the clinical significance and possible risk of PD in patients with chronic HF are warranted.

Ultrafiltration

The earlier trials of UF have demonstrated its usefulness in HF cases resistant to diuretics, however, these trials had small patient groups and short follow ups. The Relief for Acutely Fluid Overloaded Patients with Decompensated Congestive Heart Failure Trial[54] was a small, multicenter RCT that compared the effects of a single, early, 8-hour UF treatment strategy with diuretic therapy in patients hospitalized for ADHF of any etiology. All patients experienced an improvement in symptoms in 48 hours including global congestive HF and dyspnea assessments, and more so in the UF group; however, there was no significant difference between weight losses in the two groups after 24 hours, a primary end point.

The UF versus IV Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure Trial (UNLOAD) randomized 200 patients to UF versus diuretics either given in bolus or continuously.[55] Approximately 75% of patients from each group had an EF of <40% on admission. The average serum creatinine level was 1.5 ± 0.5 mg/dL (132 ± 44 μmol/L). The primary end points of the UNLOAD study were weight loss and patients' dyspnea assessment after 48 hours. Weight loss was more pronounced in the UF arm compared with the standard-care arm although the change in dyspnea score was similar. There were significantly fewer secondary end points in the UF group at 90 days, including rehospitalizations and unscheduled visits. There were no differences in serum creatinine among the groups up to 90 days. The UNLOAD trial has been criticized in terms of the suboptimal dose of diuretics used, because according to the treatment protocol, the minimum dose of IV diuretics was planned to be at least two times the before-hospitalization daily furosemide (oral) dose of 119 ± 116 mg, however, there was only a 50% increase (i.e., 181 ± 121 mg).[56]

After the UNLOAD trial, the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) was designed to compare the effects of UF at a fixed rate (200 mL/h) with those of stepped pharmacologic therapy on renal function and weight loss in HF patients with persistent congestion.[57] In this study, 188 patients with median EF of 30−35% were randomized to receive UF or diuretics. The median eGFR was 1.9−2.09 mg/dL (range 167−184 μmol/L). The primary end point was bivariate change from baseline in the serum creatinine level and body weight, as assessed 96 hours after randomization. In contrast to UNLOAD, which favored UF, the use of stepped pharmacological therapy was more superior to UF in CARRESS-HF with respect to the bivariate end point ($p = 0.003$) owing primarily to an increase in the serum creatinine level in the UF group. There was also a nonsignificant increase in all-cause readmission rate in the UF group. Because of a significantly higher rate of serious adverse events including kidney failure, bleeding complications, and catheter-related complications associated with the UF arm, the trial was terminated early. In the case of CARRESS-HF, it was commented that the use of an individually tailored UF rate as determined by refilling pressure would have been more appropriate instead of the fixed UF rate of 200 mL/h.[58] The current guidelines recommend the use of UF in cases of refractory HF and volume overload to alleviate congestive symptoms (Class IIb, level of evidence B) or in patients resistant to diuretics (Class IIb, level of evidence C).[26,36,59]

It has been observed that the amount of fluid subtraction estimated on the basis of weight loss during hospitalization for ADHF appeared to bear no relationship with clinical improvement as defined on the basis of the degree of fatigue and dyspnea.[60] Furthermore, tolvaptan produced an important weight reduction in HF but the reduced fluid volume did not translate into a sustained improvement in symptoms.[61] These observations support fluid redistribution as a cause of pulmonary congestion rather than net fluid gain as the critical event precipitating symptom in ADHF, a phenomenon depending on arterial and venous constriction induced by neural and endocrine mechanisms, inflammation, and kidney dysfunction.[58] In ADHF and CRS, the monitoring of lung water by ultrasound scan and/or bioimpedance may provide a better opportunity in establishing whether and when UF may be advantageous when compared with diuretic treatment.[58]

Left ventricular assist device

Left ventricular assist device (LVAD) has been increasingly used as a bridge to heart transplant or as a "designation treatment" for those unsuitable for receiving a transplant (Class IIa, level of evidence B).[26] In the United States, approximately 2000 devices are being inserted annually. The device is divided into pulsatile and continuous flow; the latter is smaller, less noisy, and more durable and is being used in 95% of the cases. Many patients receiving these devices have underlying renal dysfunction varying from mild, moderate, to severe; 4917 patients belonging to the Interagency Registry for Mechanically Assisted Circulatory Support were studied in retrospect.[62] As much as 30% of the patients had moderate to severe renal dysfunction and 6% had severe renal dysfunction following LVAD implantation. Compared with patients with mild or moderate renal dysfunction, patients with severe renal dysfunction were more likely to develop respiratory failure, cardiogenic shock, right ventricular failure, hepatic dysfunction, and to die within the first 3 months of receiving an implant. However, in survivors, there was usually a significant improvement of eGFR and reduction in various neuroendocrine components such as ANP, renin, and aldosterone.[62]

In a single-center analysis undertaken in retrospect by Hasin et al,[63] 83 LVAD patients were assessed for their renal function before and after implantation. For the majority of the patients, there was an increase in eGFR after LVAD, indicating an hemodynamic response. The mean eGFR increased significantly 1 month post-LVAD implantation (87.4 ± 27.9 mL/min/1.73 m^2) compared with baseline (53.2 ± 21.4 mL/min/1.73 m^2; $p < 0.0001$). Interestingly, at 3 months and 6 months, there was a partial decline of eGFR compared with the 1-month post-LVAD period, however, the mean eGFR remained significantly above the pre-LVAD values ($p < 0.0001$). Of the 51 patients with eGFRs < 60 mL/min/1.73 m^2 before LVAD implantation surviving at 1 month, the eGFRs improved to >60 mL/min/1.73 m^2 in 34 (67%) patients. The predictors for reversibility of renal

dysfunction in a multivariate model were atrial fibrillation and the use of intra-aortic balloon pump. Eight patients developed AKI requiring dialysis support. Only two of these eight patients had their renal function recovered, two died, and four required long-term dialysis therapy. It was not known whether LVAD had directly contributed to the kidney injury after the implantation. Mild hemolysis is common due to mechanical cause after LVAD, with a case of severe hemolytic uremic syndrome being reported.[64]

Calcification

Finally, the association between CKD and calcification and CV disease has been established. It is believed that phosphate plays a direct role in promoting vascular calcification, however, there is now some evidence that the increased level of FGF23 that occurs in CKD may lead to left ventricular hypertrophy and CCF, independent of klotho.[65,66] These findings indicate that phosphate and FGF23 play distinct roles in the pathogenesis of CV disease in CKD patients and future therapeutic strategies should target both factors. In a rat model, the fibroblast growth factor-receptor blockade has been shown to protect the animal from FGF23-induced cardiac toxicity.[66]

Summary and conclusion

CRS is a growing health problem and is associated with high morbidity and mortality. WRF during the treatment of ADHF has been correlated with poor outcome. In HF, there are different pathophysiological processes resulting in WRF, each carrying different prognostic implications. This has led to the specific examination of this outcome in the context of clinical trials. The use of serum creatinine as a primary end point was notoriously inadequate as a biomarker for monitoring very short-term changes in GFR associated with an hemodynamic effect. For example, a decline in kidney function due to worsening HF is associated with poor prognosis. By contrast, if the decline in kidney function reflects adequate diuresis or decongestion, it has been shown to improve outcomes.[20,22] Similarly, in both SOLVD and EPHESUS trials, early decline in renal function that occurred during treatment with RAAS blockade or ACEI or aldosterone blockers was associated with better outcome compared with placebo.[18,50,51]

Although diuretics have been the main stay of treatment for HF, the preferred mode of administration and dosing remains unclear. Extrapolating the results from the DOSE trial,[23] high-dose loop diuretics given either in boluses or as an infusion resulted in faster relief of dyspnea with greater fluid and weight loss; however, it did not cause renal adverse effect. Putting the results of the DOSE[23] and CARRESS-HF[57] trials into perspective, a strategy for care of patients with ADHF might comprise using accelerating loop diuretic dose, possibly high-dose infusion over bolus administration, with addition of oral metolazone, if necessary, while reserving vasodilators, inotropes, and salvage UF for more refractory cases, to improve symptoms and decongest patients without necessarily compromising the kidney function further.[67] The benefit of ACEI/ARB/aldosterone antagonists in HF is affirmed. However, there are potential detrimental effects on serum potassium and creatinine levels if more than two RAAS blockades are used, making the addition of a renin inhibitor to dual ACEI/ARB and aldosterone blocker difficult.[48] In addition, many vasoactive agents have been studied in the hope of augmenting cardiac function, improving symptoms and patients' outcome while preserving renal function. Because an important pathophysiological component in relation to HF involves action of RAAS, adenosine, endothelin, and a diminished response to NPs, there has been great interest in targeting these maladaptive responses. The vasopressin V2-receptor antagonist and nesiritide are being used as adjuvant therapies to relieve acute dyspnea associated with ADHF although larger-scale RCTs have failed to show any medium- to long-term benefit.[25,28,29] The novel agents, ARNI, combining a neprilysin and an ARB, and serelaxin are showing promising results. Levosimendan is a promising treatment, which is an inotrope independent of the β-adrenergic receptors; however, this has been showing inconsistent results in the treatment of acute CRS. Further studies are thus required to determine whether repetitive dosing of levosimendan will benefit the survival of patients with stable advanced CRS.

Many of the larger HF trials have demonstrated inconsistent results from earlier, smaller studies. This is partly due to the heterogeneity of the underlying cardiac diseases and EF, BP, and the different end points. The use of biomarkers for early detection of renal injury in acute CRS is still at an early stage and more research is required.[12,13]

Both UF and PD have been reserved for CRS patients resistant to diuretics, however, their renal effect and long-term outcomes are not clear. Future studies will need to define the role of UF and PD in the management of CRS, and shed light on aspects such as indications, patient selection, dosing, and timing of start. Finally, in selected patients with CRS, LVAD implant may improve renal function and outcome. In the future, tackling of calcification in CKD patients may provide new means to prevent CCF.

Conflicts of interest

The author declares no conflicts of interest.

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