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# Evidence based review of management of cardiorenal syndrome type 1

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## Abstract

Cardiorenal syndrome (CRS) type 1 is the development of acute kidney injury in patients with acute decompensated heart failure. CRS often results in prolonged hospitalization, a higher rate of rehospitalization, high morbidity, and high mortality. The pathophysiology of CRS is complex and involves hemodynamic changes, neurohormonal activation, hypothalamic-pituitary stress reaction, inflammation, and infection. However, there is limited evidence or guideline in managing CRS type 1, and the established therapeutic strategies mainly target the symptomatic relief of heart failure. This review will discuss the strategies in the management of CRS type 1. Six clinical studies have been included in this review that include different treatment strategies such as nesiritide, dopamine, levosimendan, tolvaptan, dobutamine, and ultrafiltration. Treatment strategies for CRS type 1 are derived based on the current literature. Early recognition and treatment of CRS can improve the outcomes of the patients significantly.

**Key Words:** Cardiorenal syndrome; Heart failure; Acute kidney injury; Renal insufficiency; Management

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**Core Tip:** Cardiorenal syndrome (CRS) type 1 is defined as the development of acute kidney injury or worsening renal function in patients with acute decompensated heart failure. Impaired renal function in acute decompensated heart failure is often associated with prolonged hospitalization, a higher rate of rehospitalization, high morbidity, and high mortality. The aim of this paper is to discuss the different treatment strategies and provide a guideline for the management of CRS type 1. Early recognition and treatment of CRS can improve the outcomes of the patients significantly.

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## INTRODUCTION

Cardiorenal syndrome (CRS) type 1 is defined as the development of acute kidney injury or worsening renal function in patients with acute decompensated heart failure (HF)[1]. Acute CRS occurs in approximately 25% to 33% of patients admitted with acute decompensated HF[1]. CRS has been associated with adverse outcomes, increased risk of hospitalization, and death[2]. Impaired renal function is a stronger predictor of mortality compared to left ventricular ejection fraction or New York Heart Association class[3]. Besides that, the development of renal dysfunction in HF patients may worsen the preexisting HF[4].

The causes of CRS in hospitalized patients include venous renal congestion due to hemodynamic changes, neurohormonal activation, hypothalamic-pituitary stress reaction, inflammation, and infection[1]. Moreover, administration of intravenous diuretics in patients with acute decompensated failure may lead to worsening renal function[5]. The common underlying risk factors of developing CRS in the setting of acute decompensated HF include severe atherosclerotic disease, hypertension, diabetes mellitus, elderly age, and a history of renal insufficiency or HF[6]. Furthermore, the presence of renal dysfunction is one of the major risk factors that contribute to refractory congestive HF[7]. There is a lack of high-quality evidence or guidelines on the management of CRS, and the management of CRS remains empirical and deduced from the treatment of HF, acute kidney injury, or chronic kidney diseases (CKDs)[8,9]. Therefore, the aim of this paper is to review randomized controlled trials and observational studies to describe the clinical efficacy of different therapeutic options in managing patients with CRS type 1.

## METHODOLOGY

A systematic search was conducted using the two major electronic medical literature databases, PubMed and ScienceDirect. Search terms included the following keywords and word combinations: "cardiorenal syndrome type 1", "heart failure", "kidney injury", and "renal failure". Relevant articles published in English from 2005 to 2010 were identified. Additional articles of interest were retrieved from the reference list of selected papers. Review articles and case reports were excluded from this review. PRISMA guidelines were used as a basis for reporting the results of this systematic review.

The inclusion criteria for this review were randomized control trials and observational studies that investigated the efficacy of different therapeutic options for CRS and reported at least one biochemical datum. The exclusion criteria include studies on biochemical markers of CRS, prognosis studies, and prevalence studies. Review articles and case reports were also excluded. The outcomes used in this study were changes in renal function tests such as creatinine levels, glomerular filtration rate (GFR), blood urea nitrogen, cystatin C, urine output, and weight. The flow diagram of the study selection process is shown in [Figure 1](#).

## CHARACTERISTICS OF INCLUDED STUDIES

The main characteristics of the studies included in this review are shown in [Table 1](#).

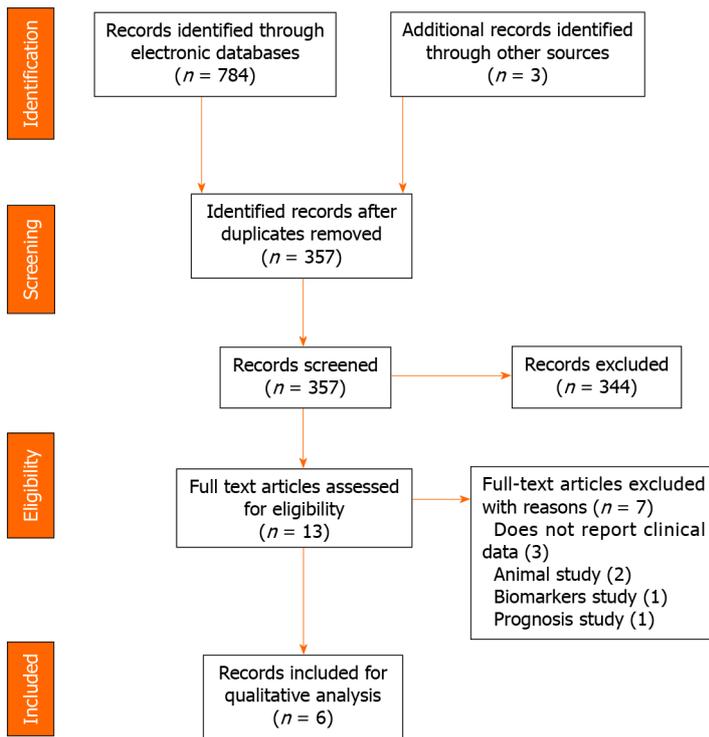
The study by Owan *et al*[10] enrolled 35 patients to standard therapy arm and 37 patients to standard therapy plus nesiritide arm. All the patients received standard therapy for HF as determined by the attending cardiologist and standardized diuretic therapy based on renal function. The patient in the nesiritide was administered intravenous nesiritide of a bolus of 0.2 mcg/kg followed by 0.01 mcg/kg per min[10].

The study by Bart *et al*[11] enrolled 94 patients in each pharmacologic therapy and ultrafiltration arm. Loop diuretics were discontinued in the ultrafiltration arm, and intravenous diuretics were used in pharmacologic therapy. The median duration of

**Table 1 Characteristics and main findings of included studies**

Ref.	Population	Sample size	Intervention	Duration of follow-up	Main findings
Owan <i>et al</i> [10], 2008	ADHF with renal dysfunction	72	Standard therapy <i>vs</i> standard therapy plus nesiritide (bolus of 0.2 mcg/kg followed by 0.01 mcg/kg per min)	72 h	Nesiritide produced greater reduction in blood pressure and preserved renal function
Bart <i>et al</i> [11], 2012	ADHF with worsened renal function	188	Ultrafiltration therapy <i>vs</i> stepped pharmacologic therapy (intravenous diuretics)	96 h	Stepped pharmacologic-therapy with intravenous diuretics was superior to ultrafiltration
Fedele <i>et al</i> [12], 2014	ADHF and renal impairment	21	Levosimendan (loading dose 6 µg/kg + 0.1 µg/kg per min) for 24 h <i>vs</i> placebo	72 h	Levosimendan improves the laboratory markers of renal function and renal hemodynamic parameters
Chen <i>et al</i> [13], 2013	AHF and renal dysfunction	360	Low dose dopamine (2 µg/kg per min for 72 h) <i>vs</i> low dose nesiritide (0.005 µg/kg per min for 72 h) <i>vs</i> placebo	72 h	Neither low dose dopamine nor low dose nesiritide improved renal function when added to diuretic therapy
Inomata <i>et al</i> [14], 2017	HF with diuretic resistance and renal impairment	81	Additive tolvaptan (≤ 15 mg/d) <i>vs</i> increased furosemide (≤ 40 mg/d)	7 d	Additive tolvaptan increased urine volume compared with patients receiving an increased dose of furosemide
Lannemyr <i>et al</i> [15], 2018	Chronic HF and impaired renal function	32	Levosimendan (loading dose 12 µg/kg + 0.1 µg/kg per min) <i>vs</i> dobutamine (7.5 µg/kg per min) for 75 min	60 mo and 75 mo after treatment	Levosimendan is the preferred inotropic agent compared to dobutamine

ADHF: Acute decompensated heart failure; HF: Heart failure.



**Figure 1 Flow diagram of the study selection process.**

the pharmacologic therapy was 92 h (interquartile range, 56 to 138), while the median duration of ultrafiltration was 40 h (interquartile range, 28 to 67)[11].

The study by Fedele *et al*[12] enrolled 14 patients in levosimendan arm and 7 patients in the placebo arm. The patients in the levosimendan arm received 10 min intravenous loading dose of levosimendan (6 µg/kg) followed by an infusion (0.1 µg/kg per min) for 24 h. All the patients were on other drugs, which included angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), aldosterone blocking agents (spironolactone), and beta-blockers (bisoprolol or carvedilol). Placebo group patients also received loop diuretics in addition[12].

The study by Chen *et al*[13] randomized 360 patients to nesiritide strategy and dopamine strategy in a 1:1 allocation ratio. In nesiritide strategy, 119 patients were allocated to low dose nesiritide, while 58 patients were allocated to placebo. In dopamine strategy, 122 patients were allocated to low dose dopamine while 61 patients were allocated to placebo. Patients in the nesiritide strategy were administered with either 0.005 µg/kg per min for 72 h infused or placebo. Patients in the dopamine strategy were administered 2 µg/kg per min for 72 h infused or placebo[13].

The study by Inomata *et al*[14] enrolled 40 patients in additive tolvaptan arms and 41 patients in the increased furosemide arm. The mean dose of furosemide received by the patients before the study was 51 ± 25 mg/d, and the patients were also treated with pharmacotherapy such as ACE inhibitors, angiotensin II receptor blockers, β-blockers, and mineral corticoid receptor blockers. The patients were either administered additive tolvaptan arms of ≤ 15 mg/d or increased furosemide dose of ≤ 40 mg/d. The treating physician determined the dose of added tolvaptan or increased furosemide[14].

The study by Lannemyr *et al*[15] enrolled 16 patients in each levosimendan and dobutamine arm. The patients in the levosimendan arm were given a loading dose of 12 µg/kg given over 10 min, followed by a continuous infusion of 0.1 µg/kg per min for 65 min. The patients in the dobutamine arm were given as a continuous infusion started at 5.0 µg/kg per min for 10 min and thereafter increased to 7.5 µg/kg per min for 65 min[15].

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## CHANGES IN CLINICAL PARAMETER

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The changes in the clinical parameters of the studies included in this review are shown in Tables 2-7.

The study by Owan *et al*[10] showed that nesiritide patients had less increase in creatinine and blood urea nitrogen compared to patients on standard therapy. The cumulative weight loss was greater in patients on standard therapy than in nesiritide patients, however, the difference was not significant[10].

In the study by Bart *et al*[11], the mean change in the serum creatinine level from the baseline was a decrease of 0.04 ± 0.53 mg/dL and an increase of 0.23 ± 0.70 mg/dL in the pharmacologic-therapy group and ultrafiltration, respectively. There was no significant difference in weight loss in both intervention groups[11].

The study by Fedele *et al*[12] showed that levosimendan was beneficial, which was confirmed by the decrease in blood urea nitrogen, serum creatinine, and cystatin C. Besides that, levosimendan increased the GFR and urine output significantly compared to placebo[12].

The study by Chen *et al*[13] showed that low dose dopamine had no significant effect on cumulative urine volume in 72-h, change in creatinine, and change in cystatin-C compared to placebo. Similarly, low dose nesiritide also had no significant effect on cumulative urine volume in 72-h, change in creatinine, and change in cystatin-C compared to placebo[13].

In the study by Inomata *et al*[14], the changes in urine volume between baseline in the tolvaptan group were significantly higher compared to the furosemide group. Besides that, the tolvaptan group had a smaller increase in serum creatinine on day 7 from baseline compared to the furosemide group. However, there were no significant changes in body weight in both groups[14].

The study by Lannemyr *et al*[15] showed that levosimendan and dobutamine had similar increases in renal blood flow. However, the levosimendan group showed an increase in GFR by 22% but remained the same in the dobutamine group. Filtration fraction remained unchanged in levosimendan group but decreased by 17% in the dobutamine group[15].

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## DISCUSSION

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The treatment strategy for CRS type 1 is shown in [Figure 2](#).

### **Diuretics and diuretic resistance**

Loop diuretics are the primary class of diuretics in the management of acute HF with or without CRS[16]. Loop diuretics lead to natriuresis and volume loss in HF due to the inhibition of Na<sup>+</sup>K<sup>+</sup>2Cl<sup>-</sup> cotransporter in the thick ascending limb of the loop of

Table 2 Changes in clinical parameters of the included studies

Intervention		Clinical parameters evaluated							
Ref.		Creatinine (mg/dL)		Change in BUN (mg/dL)		Cystatin C (mg/L)		Weight loss (kg)	Cumulative urine volume (mL)
		Baseline	Mean changes	Baseline	Mean changes	Baseline	Mean changes	Mean changes	
		Nesiritide	Owan <i>et al</i> [10], 2008	1.85 ± 0.71	0.04 ± 0.44	44.8 ± 23.3	-1.3 ± 12.8	NA	
	Owan <i>et al</i> [10], 2008 (placebo)	1.65 ± 0.42	0.09 ± 0.25	38.3 ± 16.6	2.4 ± 6.8	NA	NA	-4.25 ± 3.42	NA
	Chen <i>et al</i> [13], 2013	1.65	0.02	NA	NA	1.66	0.07	NA	8574
	Chen <i>et al</i> [13], 2013 (placebo)	1.70	0.02	NA	NA	1.86	0.11	NA	8296

BUN: Blood urea nitrogen; NA: Not available.

Table 3 Changes in clinical parameters of the included studies

Intervention		Clinical parameters evaluated									
Ref.		Creatinine (mg/dL)		Change in BUN (mg/dL)		Cystatin C (mg/L)		Weight loss (kg)		Urine output (mL/d)	
		Baseline	Mean changes	Baseline	Mean changes	Baseline	Mean changes	Baseline	Mean changes	Baseline	Mean changes
		Furosemide	Inomata <i>et al</i> [14], 2017	1.6	0.20 ± 0.27	NA	NA	NA	NA	61	-2.1 ± 2.6

BUN: Blood urea nitrogen; NA: Not available.

Table 4 Changes in clinical parameters of the included studies

Intervention		Clinical parameters evaluated									
Ref.		Creatinine (mg/dL)		Change in BUN (mg/dL)		Cystatin C (mg/L)		GFR (mL/min)		Urine output (mL/d)	
		Baseline	72 h	Baseline	72 h	Baseline	72 h	Baseline	72 h	Baseline	72 h
		Levosimendan	Fedele <i>et al</i> [12], 2014	1.76 ± 0.37	1.51 ± 0.5	45.08 ± 22.19	33.14 ± 16.63	2577.5 ± 700.6	2083 ± 731.4	38.71 ± 7.94	53.34 ± 14.93
	Fedele <i>et al</i> [12], 2014 (placebo)	1.6 ± 0.2	1.7 ± 0.2	44.4 ± 13.1	47 ± 12.8	2498.5 ± 262	2470 ± 409.9	43.33 ± 7.99	40.24 ± 6.58	1571.4 ± 125.3	1778.51 ± 798.1
	Ref.	Creatinine (mg/dL)		Change in BUN (mg/dL)		RBF (mL/min)		GFR (mL/min)		FF	
		Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment
	Inomata <i>et al</i> [14], 2017	NA	NA	NA	NA	426 ± 197	518 ± 276	36.5 ± 18.3	44.5 ± 19.0	0.146 ± 0.080	0.143 ± 0.069

BUN: Blood urea nitrogen; FF: filtration fraction; GFR: glomerular filtration rate; NA: Not available; RBF: renal blood flow.

Henle[16]. Studies suggested that torsemide is a more effective decongestive therapy compared with furosemide in patients with HF because torsemide has more predictable oral bioavailability and a longer half-life[16].

The study by Felker and Mentz[5] suggested that there were no significant differences in observed symptoms or change in renal function in acute HF patients when

**Table 5 Changes in clinical parameters of the included studies**

Intervention	Clinical parameters evaluated										
	Ref.	Creatinine (mg/dL)		Change in BUN (mg/dL)		Cystatin C (mg/L)		Weight loss (kg)		Cumulative urine volume (mL)	
		Baseline	Mean changes	Baseline	Mean changes	Baseline	Mean changes	Baseline	Mean changes	Baseline	Mean changes
Dopamine/dobutamine	Chen <i>et al</i> [13], 2013 (dopamine)	1.59	0.00	NA	NA	1.71	0.12	NA	NA	8524	
	Chen <i>et al</i> [13], 2013 (placebo)	1.63	0.02	NA	NA	1.66	0.11	NA	NA	8296	
	Ref.	Creatinine (mg/dL)		Change in BUN (mg/dL)		RBF (mL/min)		GFR (mL/min)		FF	
		Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment
	Lannemyr <i>et al</i> [15], 2018 (dobutamine)	NA	NA	NA	NA	397 ± 121	499 ± 154	47.1 ± 14.5	47.3 ± 16.9	0.193 ± 0.070	0.161 ± 0.075

BUN: Blood urea nitrogen; FF: filtration fraction; GFR: glomerular filtration rate; NA: Not available; RBF: renal blood flow.

**Table 6 Changes in clinical parameters of the included studies**

Intervention	Clinical parameters evaluated										
	Study	Creatinine (mg/dL)		Change in BUN (mg/dL)		Cystatin C (mg/L)		Weight loss (kg)		Urine output (mL/d)	
		Baseline	Mean changes	Baseline	Mean changes	Baseline	Mean changes	Baseline	Mean changes	Baseline	Mean changes
Tolvaptan	Inomata <i>et al</i> [14], 2017	1.5	0.06 ± 0.32	NA	NA	NA	NA	62	-2.1 ± 1.8	1306 ± 494	459 ± 514

BUN: Blood urea nitrogen; NA: Not available.

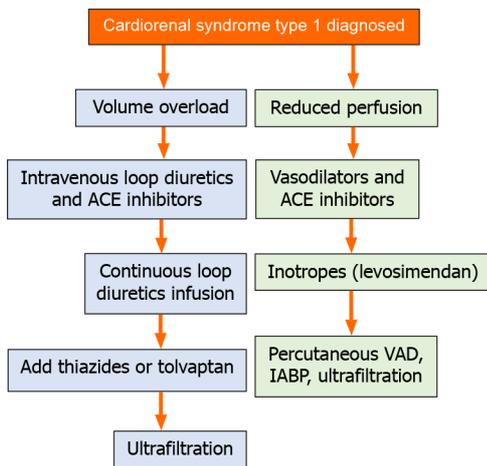
**Table 7 Changes in clinical parameters of the included studies**

Intervention	Clinical parameters evaluated									
	Study	Creatinine (mg/dL)		Change in BUN (mg/dL)		GFR (mL/min per 1.73 m <sup>2</sup> )	Weight loss (lb)		Urine output (mL/d)	
		Baseline	Mean changes	Baseline	Mean changes	Mean changes	Baseline	Mean changes	Baseline	Mean changes
Ultrafiltration	Bart <i>et al</i> [11], 2012	2.09	-0.04 ± 0.53	50.5	5.68 ± 18.29	1.67 ± 10.94	234	12.1 ± 11.3	NA	NA
	Bart <i>et al</i> [11], 2012 (pharmacologic therapy)	1.90	+0.23 ± 0.70	48.7	12.54 ± 24.81	0.93 ± 14.60	207	12.6 ± 8.5	NA	NA

BUN: Blood urea nitrogen; GFR: Glomerular filtration rate; NA: Not available.

the furosemide therapy was administered as a bolus compared with continuous infusions or at a low-dose compared to high-dose regimen. Nevertheless, the study by Palazzuoli *et al*[17] showed that continuous infusion of loop diuretics was associated with worsened renal filtration function even though the treatment resulted in greater reductions in brain natriuretic peptide from admission to discharge.

Diuretics use can increase systemic vascular resistance, plasma renin, aldosterone activity, norepinephrine, and arginine vasopressin and indirectly lead to deterioration



**Figure 2 Management strategy for cardiorenal syndrome type 1.** The management strategy in left arm is for patients presented with volume overload (decompensated heart failure, venous congestion, venous hypertension, edema, ascites, weight gain). The management strategy in right arm is for patients presented with reduced perfusion (decreased cardiac output, effective circulating volume, renal blood flow and renal plasma flow, arterial hypotension). ACE: Angiotensin-converting enzyme; IABP: Intra-aortic balloon pump; VAD: Ventricular assist device.

of left ventricular function[18]. Diuretics use can result in renal dysfunction through the above mechanisms[18]. However, the study by Ahmad *et al*[18] showed that kidney tubular injury detected by biomarkers in aggressive diuresis of patients with acute HF was not associated with worsening renal function. Furthermore, the study by Mentz *et al*[19] showed that high-dose loop diuretic therapy did not result in renin-angiotensin-aldosterone system (RAAS) activation greater than that with low-dose diuretic therapy. Ultrafiltration resulted in a greater increase in plasma renin activity compared with stepwise pharmacological care[19].

Loop diuretic resistance in HF can occur due to a decrease in renal perfusion, likely from low cardiac output[20]. Besides that, CKD reduces the excretion of diuretic into the tubular lumen thereby reducing and diminishing the filtered load of sodium[16]. HF can also increase proximal reabsorption of sodium through RAAS activation and increased expression of  $\text{Na}^+\text{K}^+\text{Cl}^-$ , which then limits the peak effect of drug delivered to the lumen[21]. However, increased furosemide dose in loop diuretic resistance can cause aggressive fluid removal, which leads to depletion of intravascular volume without refilling from the extravascular space[22]. Moreover, hyperdiuresis can lead to prerenal renal dysfunction due to the potential risk of hypotension[23].

Diuretic resistance can be managed by continuous infusion of furosemide starting at 5 mg/dL to 10 mg/dL followed by an intravenous thiazide diuretic[6]. This combination therapy can result in a sequential nephron blockade of sodium reabsorption, but it may cause excessive sodium and potassium loss[6]. The systematic review by Salvador *et al*[24] showed that continuous infusion of loop diuretic showed greater urine output, shorter duration of hospitalization, and better safety profile compared with bolus injections in patients with congestive HF. The study by Bart *et al*[11] also showed that stepwise pharmacological care including thiazide diuretics, inotropes, and vasodilator therapy was more effective compared to ultrafiltration for preserving renal function and relieving congestion. In addition, the study by Inomata *et al*[14] suggested that additive tolvaptan increased urine volume and prevented renal dysfunction in HF patients with diuretic resistance and renal impairment.

### ACE inhibitors and ARBs

Clinical data have shown that RAAS inhibitors can slow CKD progression and are one of the components in managing patients with left ventricular systolic dysfunction in HF[6,16]. However, the use of RAAS inhibitors in acute CRS with underlying renal disease may lead to an increase in serum creatinine levels[16]. The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) enrolled patients with severe HF with renal dysfunction with serum creatinine concentrations less than 3.4 mg/dL [25]. The study showed that patients who were in the enalapril arm had a reduction in symptom burden and HF-associated mortality compared to placebo but were associated with doubling the serum creatinine by 11%[25]. Besides that, the subgroup of HF patients with creatinine levels higher than 2 mg/dL showed improvement in symptoms and outcomes when treated with an ACE inhibitor[25].

A *post hoc* analysis of Study of Left Ventricular Dysfunction (SOLVD) study showed that patients with HF and CKD in the enalapril group had higher mortality benefits even with more advanced stages of CKD[26]. A study by Ahmed *et al*[27] followed 1165 patients age  $\geq 65$  years, with systolic HF (ejection fraction  $< 45\%$ ) and CKD (eGFR  $< 60$  mL/min per  $1.73$  m<sup>2</sup>) where 1046 received ACE-inhibitors or ARBs for 8 years. The results showed that patients receiving ACE-inhibitors or ARBs had a significant reduction in all-cause mortality and HF hospitalization[27]. Therefore, patients with CRS should be started on the lowest dose of an ACE inhibitor, and the dosage titrated up carefully. Concomitant use of NSAIDs should be avoided to prevent further deterioration of kidney function[6]. ACE-inhibitors or ARB therapy should be continued in patients with CRS unless there is the development of severe renal dysfunction and hyperkalemia[6].

### **Vasodilators and inotropes**

Nesiritide can reduce afterload and increase cardiac output *via* the coronary, arterial, and venous vasodilatory properties without inotropic effects[16]. The study by O'Connor *et al*[28] randomized 7141 patients with acute HF to receive either intravenous nesiritide or placebo for 1 d to 7 d in addition to standard care. The result showed that nesiritide had a small and non-significant effect on dyspnea improvement [28]. However, nesiritide therapy was associated with increased rates of hypotension and no differences in renal function, rate of death, and hospitalization compared to the placebo group[28]. The study by Owan *et al*[10] showed that the recommended dose of nesiritide can lower blood pressure more compared to the standard therapy but had no adverse effect on changes in creatinine or cystatin C levels. Furthermore, the study by Wang *et al*[29] also suggested that nesiritide did not improve renal function in patients who had decompensated HF with renal insufficiency. Therefore, nesiritide does not improve clinical outcomes, decongestion, or renal function in recommended dose[29].

The study by Chen *et al*[13] showed that patients treated low dose nesiritide did not enhance decongestion or improve renal function. Besides that, the study also showed that low dose dopamine neither improved decongestion nor preserved renal function [13]. However, the findings of the study are contrary to the guidelines for the management of acute HF that suggest the use of low dose dopamine can be considered to improve diuresis and preserve renal function[30]. Observational studies also indicate that the use of nesiritide and dopamine in acute HF is associated with longer length-of-stay, higher mortality, and higher costs[31]. Therefore, use of low dose dopamine or low dose nesiritide as renal adjuvant therapies is not recommended in patients with CRS as it does not provide benefits on renal function, decongestion, and clinical outcome[13].

Levosimendan is a positive inotrope with Ca<sup>2+</sup> sensitization that improves the calcium sensitivity of cardiac muscle cells and therefore provides hemodynamic and symptomatic improvement[32]. Besides that, levosimendan has a vasodilatory effect on vasculature *via* activation of ATP-sensitive K<sup>+</sup>, voltage-dependent K<sup>+</sup>, and Ca<sup>2+</sup>-activated K<sup>+</sup> channels[33]. Levosimendan can achieve maximal improvement in hemodynamic parameters at 1 to 3 d after starting the infusion and the effects can be sustained for at least a week[34,35]. Levosimendan can also improve renal function through the increased cardiac output[12]. Moreover, levosimendan can reduce the right-sided pressures, pulmonary artery wedge pressure, and central venous pressure, thereby improving the function of the right ventricles[36,37].

The study by Bragadottir *et al*[38] showed that levosimendan also increases both renal blood flow and GFR by inducing pre-glomerular vasodilation. The study by Lannemyr *et al*[15] showed that the renal filtration fraction remained unchanged in levosimendan group but decreased in dobutamine. This is due to levosimendan preferentially vasodilating the afferent arterioles, while dobutamine has balanced vasodilation of both afferent and efferent arterioles[15]. Furthermore, levosimendan increases glomerular capillary surface area by inhibiting angiotensin II-mediated mesangial cell contraction[39].

The study by Yilmaz *et al*[40] also suggested that levosimendan offered more beneficial effects in terms of ejection fraction, systolic pulmonary artery pressure, 24-h urine output, and creatinine compared to dobutamine in patients with biventricular HF. The study by Packer *et al*[41] showed that levosimendan provided rapid and durable symptomatic relief in the first 5 d but was associated with an increased risk of adverse cardiovascular events such as hypotension, cardiac arrhythmias, and a numerically higher risk of death at 90 d[41]. However, inotropic therapy should be reserved for patients with severe low cardiac output where vasodilatory agents cannot be used to avoid a further decrease in systemic pressure or systemic vascular resis-

tance[42,43].

### Ultrafiltration

Ultrafiltration can be an effective decongestion strategy because of the ability to remove the isotonic plasma and therefore more sodium for the same amount of water [44]. The study by Costanzo *et al*[45] showed that weight loss and net fluid loss were greater in the ultrafiltration group compared to intravenous diuretics. Moreover, the rate of re-hospitalized for HF at 90 d was significantly lower in the ultrafiltration group[45]. However, there were no differences in episodes of hypotension within the first 48 h and serum creatinine at 90 d between the two groups[45]. On the contrary, the study by Bart *et al*[11] showed that there was a significant increase in serum creatinine level 96 h after enrollment in the ultrafiltration group compared with the pharmacologic therapy group, but there were no significant differences in weight loss. Patients who had ultrafiltration experienced an early rise in the creatinine level due to a transient decrease in intravascular volume[11]. GFR in patients with pharmacological therapy improved significantly after 60 d[11]. Besides that, a higher percentage of patients in the ultrafiltration group experienced a serious adverse event compared to the pharmacologic-therapy group over the 60-d period of follow-up[11]. The most common adverse events associated with ultrafiltration treatment included kidney failure, complications, and catheter-related complications[11]. Therefore, ultrafiltration treatment is not justified for patients with CRS due to the complexity and high cost of treatment[11]. Pharmacological therapy is recommended as the first-line therapy, and ultrafiltration should only be reserved in cases of refractory congestion[8].

## CONCLUSION

CRS in patients with decompensated HF is associated with several cardiovascular and renal adverse events such as myocardial infarction, stroke, need for hemodialysis, high rates of hospitalization, and mortality[16,46,47]. However, management of CRS type 1 is often challenging due to the various underlying mechanisms of renal impairment and the lack of novel therapeutic options targeting renal impairment in HF patients[6, 8]. Therefore, early recognition of the condition by using different novel biomarkers and imaging techniques is important to initiate optimal treatment and care of the patients[16]. Moreover, patients with underlying HF should be educated to manage their condition well to prevent decompensation. A multidisciplinary team approach with cooperation between internists, cardiologists, and nephrologists is important to establish an effective treatment plan for patients with CRS to improve their quality of life[6]. Further research on drugs targeting the pathophysiological mechanism CRS, which includes both cardiac and renal dysfunction, can be conducted to improve the survival of the patients.

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