**Name of Journal:** *World Journal of Methodology*

**Manuscript NO:** 62011

**Manuscript Type:** MINIREVIEWS

**Evidence based review of management of cardiorenal syndrome type 1**

Ong LT. Management of cardiorenal syndrome type 1

Leong Tung Ong

**Leong Tung Ong,** Faculty of Medicine, University of Malaya, Kuala Lumpur 50603, Wilayah Persekutuan Kuala Lumpur, Malaysia

**Author contributions:** Ong LT designed and performed the literature search, analyzed the data, wrote the paper, and approved the final manuscript.

**Corresponding author: Leong Tung Ong,** Faculty of Medicine, University of Malaya, Jalan Profesor Diraja Ungku Aziz, Kuala Lumpur 50603, Wilayah Persekutuan Kuala Lumpur, Malaysia. leotungong@gmail.com

**Received:** December 25, 2020

**Revised:** May 9, 2021

**Accepted:** May 20, 2021

**Published online:** July 20, 2021

**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

**©The** **Author(s) 2021.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Ong LT. Evidence based review of management of cardiorenal syndrome type 1. *World J Methodol* 2021; 11(4): 187-198

**URL:** https://www.wjgnet.com/2222-0682/full/v11/i4/187.htm

**DOI:** https://dx.doi.org/10.5662/wjm.v11.i4.187

**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.

**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.

**Methodlogy**

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 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].

**CHANGES IN CLINICAL PARAMETER**

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].

**DISCUSSION**

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+K+2Cl- cotransporter in the thick ascending limb of the loop of 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 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 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 Na+K+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 ≥ 65 years, with systolic HF (ejection fraction < 45%) and CKD (eGFR < 60 mL/min per 1.73 m2) 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 Ca2+ 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+, voltage-dependent K+, and Ca2+-activated K+ 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 resistance[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.

**REFERENCES**

1 **Ronco C**, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. *J Am Coll Cardiol* 2012; **60**: 1031-1042 [PMID: 22840531 DOI: 10.1016/j.jacc.2012.01.077]

2 **Hillege HL**, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S, Granger CB, Michelson EL, Ostergren J, Cornel JH, de Zeeuw D, Pocock S, van Veldhuisen DJ; Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Investigators. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation* 2006; **113**: 671-678 [PMID: 16461840 DOI: 10.1161/CIRCULATIONAHA.105.580506]

3 **Hillege HL**, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, Hampton JR, van Veldhuisen DJ. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation* 2000; **102**: 203-210 [PMID: 10889132 DOI: 10.1161/01.cir.102.2.203]

4 **Ronco C**, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol* 2008; **52**: 1527-1539 [PMID: 19007588 DOI: 10.1016/j.jacc.2008.07.051]

5 **Felker GM**, Mentz RJ. Diuretics and ultrafiltration in acute decompensated heart failure. *J Am Coll Cardiol* 2012; **59**: 2145-2153 [PMID: 22676934 DOI: 10.1016/j.jacc.2011.10.910]

6 **Koniari K**, Nikolaou M, Paraskevaidis I, Parissis J. Therapeutic options for the management of the cardiorenal syndrome. *Int J Nephrol* 2010; **2011**: 194910 [PMID: 21197109 DOI: 10.4061/2011/194910]

7 **Geisberg C**, Butler J. Addressing the challenges of cardiorenal syndrome. *Cleve Clin J Med* 2006; **73**: 485-491 [PMID: 16708717 DOI: 10.3949/ccjm.73.5.485]

8 **Verbrugge FH**, Grieten L, Mullens W. Management of the cardiorenal syndrome in decompensated heart failure. *Cardiorenal Med* 2014; **4**: 176-188 [PMID: 25737682 DOI: 10.1159/000366168]

9 **Kumar U**, Wettersten N, Garimella PS. Cardiorenal Syndrome: Pathophysiology. *Cardiol Clin* 2019; **37**: 251-265 [PMID: 31279419 DOI: 10.1016/j.ccl.2019.04.001]

10 **Owan TE**, Chen HH, Frantz RP, Karon BL, Miller WL, Rodeheffer RJ, Hodge DO, Burnett JC Jr, Redfield MM. The effects of nesiritide on renal function and diuretic responsiveness in acutely decompensated heart failure patients with renal dysfunction. *J Card Fail* 2008; **14**: 267-275 [PMID: 18474338 DOI: 10.1016/j.cardfail.2007.12.002]

11 **Bart BA**, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, Redfield MM, Deswal A, Rouleau JL, LeWinter MM, Ofili EO, Stevenson LW, Semigran MJ, Felker GM, Chen HH, Hernandez AF, Anstrom KJ, McNulty SE, Velazquez EJ, Ibarra JC, Mascette AM, Braunwald E; Heart Failure Clinical Research Network. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med* 2012; **367**: 2296-2304 [PMID: 23131078 DOI: 10.1056/NEJMoa1210357]

12 **Fedele F**, Bruno N, Brasolin B, Caira C, D'Ambrosi A, Mancone M. Levosimendan improves renal function in acute decompensated heart failure: possible underlying mechanisms. *Eur J Heart Fail* 2014; **16**: 281-288 [PMID: 24464960 DOI: 10.1002/ejhf.9]

13 **Chen HH**, Anstrom KJ, Givertz MM, Stevenson LW, Semigran MJ, Goldsmith SR, Bart BA, Bull DA, Stehlik J, LeWinter MM, Konstam MA, Huggins GS, Rouleau JL, O'Meara E, Tang WH, Starling RC, Butler J, Deswal A, Felker GM, O'Connor CM, Bonita RE, Margulies KB, Cappola TP, Ofili EO, Mann DL, Dávila-Román VG, McNulty SE, Borlaug BA, Velazquez EJ, Lee KL, Shah MR, Hernandez AF, Braunwald E, Redfield MM; NHLBI Heart Failure Clinical Research Network. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. *JAMA* 2013; **310**: 2533-2543 [PMID: 24247300 DOI: 10.1001/jama.2013.282190]

14 **Inomata T**, Ikeda Y, Kida K, Shibagaki Y, Sato N, Kumagai Y, Shinagawa H, Ako J, Izumi T; Kanagawa Aquaresis Investigators. Effects of Additive Tolvaptan vs. Increased Furosemide on Heart Failure With Diuretic Resistance and Renal Impairment　- Results From the K-STAR Study. *Circ J* 2017; **82**: 159-167 [PMID: 28835586 DOI: 10.1253/circj.CJ-17-0179]

15 **Lannemyr L**, Ricksten SE, Rundqvist B, Andersson B, Bartfay SE, Ljungman C, Dahlberg P, Bergh N, Hjalmarsson C, Gilljam T, Bollano E, Karason K. Differential Effects of Levosimendan and Dobutamine on Glomerular Filtration Rate in Patients With Heart Failure and Renal Impairment:A Randomized Double-Blind Controlled Trial. *J Am Heart Assoc* 2018; **7**: e008455 [PMID: 30369310 DOI: 10.1161/JAHA.117.008455]

16 **Rangaswami J**, Bhalla V, Blair JEA, Chang TI, Costa S, Lentine KL, Lerma EV, Mezue K, Molitch M, Mullens W, Ronco C, Tang WHW, McCullough PA; American Heart Association Council on the Kidney in Cardiovascular Disease and Council on Clinical Cardiology. Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies: A Scientific Statement From the American Heart Association. *Circulation* 2019; **139**: e840-e878 [PMID: 30852913 DOI: 10.1161/CIR.0000000000000664]

17 **Palazzuoli A**, Pellegrini M, Ruocco G, Martini G, Franci B, Campagna MS, Gilleman M, Nuti R, McCullough PA, Ronco C. Continuous *vs* bolus intermittent loop diuretic infusion in acutely decompensated heart failure: a prospective randomized trial. *Crit Care* 2014; **18**: R134 [PMID: 24974232 DOI: 10.1186/cc13952]

18 **Ahmad T**, Jackson K, Rao VS, Tang WHW, Brisco-Bacik MA, Chen HH, Felker GM, Hernandez AF, O'Connor CM, Sabbisetti VS, Bonventre JV, Wilson FP, Coca SG, Testani JM. Worsening Renal Function in Patients With Acute Heart Failure Undergoing Aggressive Diuresis Is Not Associated With Tubular Injury. *Circulation* 2018; **137**: 2016-2028 [PMID: 29352071 DOI: 10.1161/CIRCULATIONAHA.117.030112]

19 **Mentz RJ**, Stevens SR, DeVore AD, Lala A, Vader JM, AbouEzzeddine OF, Khazanie P, Redfield MM, Stevenson LW, O'Connor CM, Goldsmith SR, Bart BA, Anstrom KJ, Hernandez AF, Braunwald E, Felker GM. Decongestion strategies and renin-angiotensin-aldosterone system activation in acute heart failure. *JACC Heart Fail* 2015; **3**: 97-107 [PMID: 25543972 DOI: 10.1016/j.jchf.2014.09.003]

20 **Ronco C**, Di Lullo L. Cardiorenal syndrome. *Heart Fail Clin* 2014; **10**: 251-280 [PMID: 24656104 DOI: 10.1016/j.hfc.2013.12.003]

21 **Marumo R**, Kaizuma S, Nogae S, Kanazawa M, Kimura T, Saito T, Ito S, Matsubara M. Differential upregulation of rat Na-K-Cl cotransporter, rBSC1, mRNA in the thick ascending limb of Henle in different pathological conditions. *Kidney Int* 1998; **54**: 877-888 [PMID: 9734612 DOI: 10.1046/j.1523-1755.1998.00051.x]

22 **Goldsmith SR**, Bart BA, Burnett J. Decongestive therapy and renal function in acute heart failure: time for a new approach? *Circ Heart Fail* 2014; **7**: 531-535 [PMID: 24847128 DOI: 10.1161/CIRCHEARTFAILURE.113.000828]

23 **Watanabe K**, Dohi K, Sugimoto T, Yamada T, Sato Y, Ichikawa K, Sugiura E, Kumagai N, Nakamori S, Nakajima H, Hoshino K, Machida H, Okamoto S, Onishi K, Nakamura M, Nobori T, Ito M. Short-term effects of low-dose tolvaptan on hemodynamic parameters in patients with chronic heart failure. *J Cardiol* 2012; **60**: 462-469 [PMID: 23068288 DOI: 10.1016/j.jjcc.2012.09.002]

24 **Salvador DR**, Rey NR, Ramos GC, Punzalan FE. Continuous infusion *vs* bolus injection of loop diuretics in congestive heart failure. *Cochrane Database Syst Rev* 2004: CD003178 [PMID: 14974008 DOI: 10.1002/14651858.CD003178.pub2]

25 **Ljungman S**, Kjekshus J, Swedberg K. Renal function in severe congestive heart failure during treatment with enalapril (the Cooperative North Scandinavian Enalapril Survival Study [CONSENSUS] Trial). *Am J Cardiol* 1992; **70**: 479-487 [PMID: 1642186 DOI: 10.1016/0002-9149(92)91194-9]

26 **Khan NA**, Ma I, Thompson CR, Humphries K, Salem DN, Sarnak MJ, Levin A. Kidney function and mortality among patients with left ventricular systolic dysfunction. *J Am Soc Nephrol* 2006; **17**: 244-253 [PMID: 16291840 DOI: 10.1681/ASN.2005030270]

27 **Ahmed A**, Fonarow GC, Zhang Y, Sanders PW, Allman RM, Arnett DK, Feller MA, Love TE, Aban IB, Levesque R, Ekundayo OJ, Dell'Italia LJ, Bakris GL, Rich MW. Renin-angiotensin inhibition in systolic heart failure and chronic kidney disease. *Am J Med* 2012; **125**: 399-410 [PMID: 22321760 DOI: 10.1016/j.amjmed.2011.10.013]

28 **O'Connor CM**, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, Heizer GM, Komajda M, Massie BM, McMurray JJ, Nieminen MS, Reist CJ, Rouleau JL, Swedberg K, Adams KF Jr, Anker SD, Atar D, Battler A, Botero R, Bohidar NR, Butler J, Clausell N, Corbalán R, Costanzo MR, Dahlstrom U, Deckelbaum LI, Diaz R, Dunlap ME, Ezekowitz JA, Feldman D, Felker GM, Fonarow GC, Gennevois D, Gottlieb SS, Hill JA, Hollander JE, Howlett JG, Hudson MP, Kociol RD, Krum H, Laucevicius A, Levy WC, Méndez GF, Metra M, Mittal S, Oh BH, Pereira NL, Ponikowski P, Tang WH, Tanomsup S, Teerlink JR, Triposkiadis F, Troughton RW, Voors AA, Whellan DJ, Zannad F, Califf RM. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med* 2011; **365**: 32-43 [PMID: 21732835 DOI: 10.1056/NEJMoa1100171]

29 **Wang DJ**, Dowling TC, Meadows D, Ayala T, Marshall J, Minshall S, Greenberg N, Thattassery E, Fisher ML, Rao K, Gottlieb SS. Nesiritide does not improve renal function in patients with chronic heart failure and worsening serum creatinine. *Circulation* 2004; **110**: 1620-1625 [PMID: 15337695 DOI: 10.1161/01.CIR.0000141829.04031.25]

30 **Yancy CW**, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; **128**: 1810-1852 [PMID: 23741057 DOI: 10.1161/CIR.0b013e31829e8807]

31 **Hauptman PJ**, Swindle J, Burroughs TE, Schnitzler MA. Resource utilization in patients hospitalized with heart failure: insights from a contemporary national hospital database. *Am Heart J* 2008; **155**: 978-985.e1 [PMID: 18513507 DOI: 10.1016/j.ahj.2008.01.015]

32 **Kass DA**, Solaro RJ. Mechanisms and use of calcium-sensitizing agents in the failing heart. *Circulation* 2006; **113**: 305-315 [PMID: 16418450 DOI: 10.1161/CIRCULATIONAHA.105.542407]

33 **Pataricza J**, Krassói I, Höhn J, Kun A, Papp JG. Functional role of potassium channels in the vasodilating mechanism of levosimendan in porcine isolated coronary artery. *Cardiovasc Drugs Ther* 2003; **17**: 115-121 [PMID: 12975592 DOI: 10.1023/a:1025331617233]

34 **Lilleberg J**, Laine M, Palkama T, Kivikko M, Pohjanjousi P, Kupari M. Duration of the haemodynamic action of a 24-h infusion of levosimendan in patients with congestive heart failure. *Eur J Heart Fail* 2007; **9**: 75-82 [PMID: 16829185 DOI: 10.1016/j.ejheart.2006.04.012]

35 **McLean AS**, Huang SJ, Nalos M, Ting I. Duration of the beneficial effects of levosimendan in decompensated heart failure as measured by echocardiographic indices and B-type natriuretic peptide. *J Cardiovasc Pharmacol* 2005; **46**: 830-835 [PMID: 16306809 DOI: 10.1097/01.fjc.0000189076.71730.f1]

36 **Poelzl G**, Zwick RH, Grander W, Metzler B, Jonetzko P, Frick M, Ulmer H, Pachinger O, Roithinger FX. Safety and effectiveness of levosimendan in patients with predominant right heart failure. *Herz* 2008; **33**: 368-373 [PMID: 18773157 DOI: 10.1007/s00059-008-3051-2]

37 **Russ MA**, Prondzinsky R, Carter JM, Schlitt A, Ebelt H, Schmidt H, Lemm H, Heinroth K, Soeffker G, Winkler M, Werdan K, Buerke M. Right ventricular function in myocardial infarction complicated by cardiogenic shock: Improvement with levosimendan. *Crit Care Med* 2009; **37**: 3017-3023 [PMID: 19661807 DOI: 10.1097/CCM.0b013e3181b0314a]

38 **Bragadottir G**, Redfors B, Ricksten SE. Effects of levosimendan on glomerular filtration rate, renal blood flow, and renal oxygenation after cardiac surgery with cardiopulmonary bypass: a randomized placebo-controlled study. *Crit Care Med* 2013; **41**: 2328-2335 [PMID: 23921271 DOI: 10.1097/CCM.0b013e31828e946a]

39 **Zager RA**, Johnson AC, Lund S, Hanson SY, Abrass CK. Levosimendan protects against experimental endotoxemic acute renal failure. *Am J Physiol Renal Physiol* 2006; **290**: F1453-F1462 [PMID: 16418300 DOI: 10.1152/ajprenal.00485.2005]

40 **Yilmaz MB**, Yontar C, Erdem A, Karadas F, Yalta K, Turgut OO, Yilmaz A, Tandogan I. Comparative effects of levosimendan and dobutamine on right ventricular function in patients with biventricular heart failure. *Heart Vessels* 2009; **24**: 16-21 [PMID: 19165563 DOI: 10.1007/s00380-008-1077-2]

41 **Packer M**, Colucci W, Fisher L, Massie BM, Teerlink JR, Young J, Padley RJ, Thakkar R, Delgado-Herrera L, Salon J, Garratt C, Huang B, Sarapohja T; REVIVE Heart Failure Study Group. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. *JACC Heart Fail* 2013; **1**: 103-111 [PMID: 24621834 DOI: 10.1016/j.jchf.2012.12.004]

42 **Elkayam U**, Tasissa G, Binanay C, Stevenson LW, Gheorghiade M, Warnica JW, Young JB, Rayburn BK, Rogers JG, DeMarco T, Leier CV. Use and impact of inotropes and vasodilator therapy in hospitalized patients with severe heart failure. *Am Heart J* 2007; **153**: 98-104 [PMID: 17174645 DOI: 10.1016/j.ahj.2006.09.005]

43 **Felker GM**, O'Connor CM. Inotropic therapy for heart failure: an evidence-based approach. *Am Heart J* 2001; **142**: 393-401 [PMID: 11526351 DOI: 10.1067/mhj.2001.117606]

44 **Ali SS**, Olinger CC, Sobotka PA, Dahle TG, Bunte MC, Blake D, Boyle AJ. Loop diuretics can cause clinical natriuretic failure: a prescription for volume expansion. *Congest Heart Fail* 2009; **15**: 1-4 [PMID: 19187399 DOI: 10.1111/j.1751-7133.2008.00037.x]

45 **Costanzo MR**, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, Jaski BE, Fang JC, Feller ED, Haas GJ, Anderson AS, Schollmeyer MP, Sobotka PA; UNLOAD Trial Investigators. Ultrafiltration *vs* intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol* 2007; **49**: 675-683 [PMID: 17291932 DOI: 10.1016/j.jacc.2006.07.073]

46 **Billings FT 4th**, Shaw AD. Clinical trial endpoints in acute kidney injury. *Nephron Clin Pract* 2014; **127**: 89-93 [PMID: 25343828 DOI: 10.1159/000363725]

47 **Ronco C**, Ronco F, McCullough PA. A Call to Action to Develop Integrated Curricula in Cardiorenal Medicine. *Blood Purif* 2017; **44**: 251-259 [PMID: 29065398 DOI: 10.1159/000480318]

**Footnotes**

**Conflict-of-interest statement:** The author declares no conflict of interests for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** December 25, 2020

**First decision:** May 6, 2021

**Article in press:** May 20, 2021

**Specialty type:** Medical laboratory technology

**Country/Territory of origin:** Malaysia

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Greenway SC **S-Editor:** Gao CC **L-Editor:** Filipodia **P-Editor:** Yuan YY

**Figure Legends**



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



**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.

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

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **Population** | **Sample size** | **Intervention** | **Duration of follow-up** | **Main findings** |
| Owan *et al*[10], 2008 | ADHF with renal dysfunction | 72 | Standard therapy *vs* 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 *et al*[11], 2012 | ADHF with worsened renal function | 188 | Ultrafiltration therapy *vs* stepped pharmacologic therapy (intravenous diuretics) | 96 h | Stepped pharmacologic-therapy with intravenous diuretics was superior to ultrafiltration |
| Fedele *et al*[12], 2014 | ADHF and renal impairment | 21 | Levosimendan (loading dose 6 μg/kg + 0.1 μg/kg per min) for 24 h *vs* placebo | 72 h | Levosimendan improves the laboratory markers of renal function and renal hemodynamic parameters |
| Chen *et al*[13], 2013 | AHF and renal dysfunction | 360 | Low dose dopamine (2 μg/kg per min for 72 h) *vs* low dose nesiritide (0.005 μg/kg per min for 72 h) *vs* placebo | 72 h | Neither low dose dopamine nor low dose nesiritide improved renal function when added to diuretic therapy |
| Inomata *et al*[14], 2017 | HF with diuretic resistance and renal impairment | 81 | Additive tolvaptan (≤ 15 mg/d) *vs* increased furosemide (≤ 40 mg/d) | 7 d | Additive tolvaptan increased urine volume compared with patients receiving an increased dose of furosemide |
| Lannemyr *et al*[15], 2018 | Chronic HF and impaired renal function | 32 | Levosimendan (loading dose 12 μg/kg + 0.1 μg/kg per min) *vs* 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.

**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 *et al*[10], 2008 | 1.85 ± 0.71 | 0.04 ± 0.44 | 44.8 ± 23.3 | -1.3 ± 12.8 | NA | NA | -2.75 ± 3.27 | NA |
| Owan *et al*[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 *et al*[13], 2013 | 1.65 | 0.02 | NA | NA | 1.66 | 0.07 | NA | 8574 |
| Chen *et al*[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 *et al*[14], 2017 | 1.6 | 0.20 ± 0.27 | NA | NA | NA | NA | 61 | -2.1 ± 2.6 | 1251 ± 540 | 79 ± 341 |

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 *et al*[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 | 1766.4 ± 514.2 | 2663.5 ± 721.2 |
| Fedele *et al*[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 *et al*[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.

**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** |
| Dopamine/dobutamine | Chen *et al*[13], 2013 (dopamine) | 1.59 | 0.00 | NA | NA | 1.71 | 0.12 | NA | NA | 8524 |
| Chen *et al*[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 *et al*[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 *et al*[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 m2)** | **Weight loss (Ib)** | **Urine output (mL/d)** |
| **Baseline** | **Mean changes** | **Baseline** | **Mean changes** | **Mean changes** | **Baseline** | **Mean changes** | **Baseline** | **Mean changes** |
| Ultrafiltration | Bart *et al*[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 *et al*[11], 2012 (pharmaco-logic 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.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2021 Baishideng Publishing Group Inc. All rights reserved.**