Clinical Review

Management of Acute Admissions of Heart Failure Patients with Kidney Disease

J Junarta, A Banerjee, R Lowe-Jones & D Banerjee

Abstract

Acute heart failure (HF) admissions are common. They are often associated with prolonged hospitalisations and poor outcomes. One-third of chronic HF patients also suffer from chronic kidney disease (CKD). Hence, acute admissions of HF with CKD are common and are associated with longer length of stay and increased mortality. Hyperkalaemia and acute on chronic renal impairment are important challenges in the management of these cases. Cautious introduction of high-dose diuretic therapy, followed by the re-commencement of renin-angiotensin-aldosterone (RAAS) inhibitors, improves length of stay, quality of life, and prognosis. During an admission on to the medical assessment unit careful monitoring and management of the patient's clinical condition and biochemistry is essential.

Keywords

heart failure, kidney disease, acute kidney injury, spironolactone, ACE inhibitor

Key messages

- CKD and AKI are both common in acute HF patients and are associated with poor prognosis. Functional transient worsening of renal function with initiation of RAASi should be distinguished from persistent AKI.
- Managing fluid overload and related symptoms requires careful diuretic therapy
- ACEi should be used in all patients with HFrEF and CKD with dose modification if necessary
- Life prolonging RAASi therapy can be limited due to rising creatinine and potassium
- Careful monitoring of electrolytes is essential during IV diuretic therapy
- Small changes in creatinine and electrolyte concentrations can be tolerated
- Collaborative working amongst acute physicians, cardiologists, and nephrologists is essential for symptom control, avoiding unnecessary hospital stay, and improving quality of life

Joey Junarta
BSc[1,3]

Anita Banerjee
FRCP[2]

Racquel Lowe-Jones
MBBS[1]

Debasish Banerjee
FRCP FASN[1,3]

Institutions:
[1] Renal and Transplantation Unit, St Georges University Hospital NHS Foundation Trust
[2] Diabetes and Endocrinology Department, Guys and St Thomas' NHS Foundation Trust
[3] Cardiology Clinical Academic Group, Molecular and Clinical Sciences Research Centre, St Georges University of London

Correspondence
Debasish Banerjee
MD FRCP FASN
Consultant Nephrologist
Reader
St Georges University Hospital
Grosvenor Wing
Room no G2.113
Blackshaw Road Tooting
London SW17 0QT UK

Introduction

Acute heart failure (HF) admissions can often be a challenge to manage as demonstrated by the following two cases. The fluid overload causing symptoms needs urgent attention with the paradigm of the electrolyte abnormalities limiting the use of diuretics and RAAS inhibitors, which are known to improve long term prognosis.

Case 1

The first case was a 65-year old Caucasian male who presented with increasing shortness of breath and leg swelling. He was a known type 2 diabetic for 18 years with a previous myocardial infarction requiring percutaneous coronary intervention, congestive HF with low ejection fraction (EF) of 35%, and chronic kidney disease (CKD). On examination, he was breathless, had feet and leg oedema, raised jugular venous pressure (JVP), pulse 60 beats per minute (BPM), blood pressure 138/90 mmHg, respiratory rate 20/minute, oxygen saturation 92%, and few bi-basal chest crepitations. His regular medications included candesartan 32 mg daily, furosemide 40 mg daily, atenolol 100 mg daily, aspirin 75 mg daily, atorvastatin 10 mg daily, and spironolactone 25 mg daily. His blood tests showed sodium 131 mmol/L (N: 133-146 mmol/L), potassium 5.8 mmol/L (N: 3.5-5.3 mmol/L), which was previously 5.1 mmol/L, urea 18 mmol/L (N: 2.5-7.8 mmol/L), creatinine 270 µmol/L which was previously 210 µmol/L (N: 64-104 µmol/L), N-terminal-pro-brain natriuretic peptide (NT-pro-BNP) 16,000 ng/L (N: <125 ng/L), troponin T 18 ng/L (N: <14 ng/L). His ECG showed Q waves in leads V1, V2, and V3.

The admitting team started intravenous (IV) furosemide 80 mg twice a day for fluid removal and discontinued his candesartan and spironolactone due to rising serum potassium and creatinine.

Case 2

The second case was a 59-year old Afro-Carribean female with a long history of poorly controlled hypertension, she presented with chest pain and breathlessness. On examination, she was breathless with leg oedema, raised JVP, pulse 80 BPM, blood pressure 190/104 mmHg, respiratory rate 18/min, oxygen saturation 94%, weight 104 kg, and bi-basal crepitations. Her regular medications were ramipril 5 mg daily, nifedipine (long-acting) 60 mg daily, and bendroflumethiazide 2.5 mg daily. Her ECG showed

© 2019 Rila Publications Ltd.

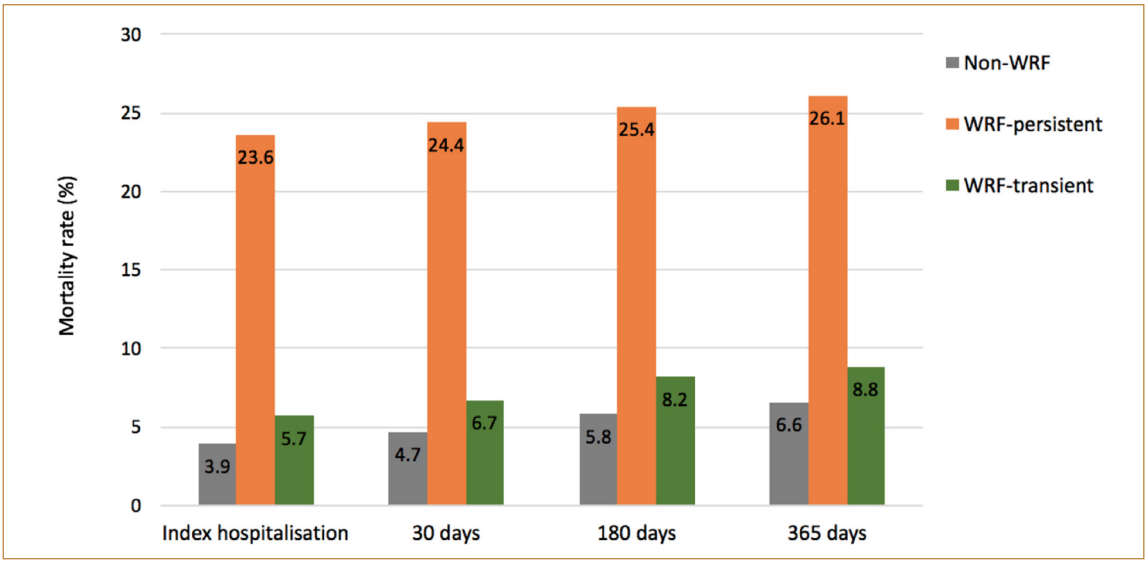


Figure 1. Comparison of all-cause mortality rate by patient cohort.[3]
WRF worsening renal failure

T wave inversion in leads V5 and V6 with a QRS duration of 0.16s. The blood tests showed sodium 135 mmol/L (N: 133-146 mmol/L), potassium 3.5 mmol/L (N: 3.5-5.3 mmol/L), creatinine 176 µmol/L (N: 49-90 µmol/L), which was previously 130 µmol/L, troponin T 14 ng/L (N: <14 ng/L), N-terminal-pro-brain natriuretic peptide (NT-pro-BNP) 11,000 ng/L (N: <125 ng/L).

The admitting team started her on IV furosemide 40 mg twice a day, spironolactone 25 mg daily, and stopped ramipril and bendroflumethiazide.

These cases demonstrate the therapeutic options for acute HF-CKD admissions, the challenge of using high-dose diuretic therapy with its possible impact on kidney function and electrolytes, discontinuation of RAAS inhibition (RAASi), the life-prolonging drugs, and not knowing when they can be restarted, with caution. Often determination of acute versus chronic kidney failure is difficult with slightly different implications. Interpretation of troponin and BNP levels with renal failure are problematic due to their elevated levels related to kidney injury itself.[1] Device therapy, when indicated as in the second case, is difficult to decide, particularly with a higher risk of infections.[1] Maintenance of serum potassium and sodium within a safe range is difficult and requires close monitoring.

Epidemiology of Renal Impairment in Heart Failure Patients

The most important co-morbidity in HF patients is renal impairment. Renal impairment may be an already existing, baseline reduction in glomerular filtration rate (GFR) i.e. CKD or new onset reduction in renal function as time progresses. The new onset reduction in GFR could be due to a persistent acute kidney injury (AKI) related to sepsis, etc.; or functional reduction in GFR caused by initiation of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), usually transient, also called "worsening renal failure" in the cardiology literature. Both entities are common in acute and chronic HF and are associated with adverse outcomes.

In an unselected real-world cohort of 1056 admissions of 851 patients with acute HF, the prevalence of CKD stage 3A/B (moderate) was 36% whilst stage 4/5 (severe) was 11%.[2] Importantly, both severe CKD and acute kidney injury (AKI) were associated with greater inpatient mortality and length of stay compared to patients who had no or mild CKD (stage 0-2).[2]

In a large meta-analysis (excluding registry studies), the prevalence of CKD at baseline was associated with higher mortality, 16% versus 11%; unadjusted odds ratio (OR) for mortality of 2.34 (95% confidence interval [CI] 2.20-2.50; *P*=0.001).[3] From 28 studies that included 49,890 patients, the prevalence of WRF was associated with higher mortality, 36% versus 32%; combined unadjusted OR for mortality of 1.81 (95% CI 1.55-2.12).[3] HF patients on haemodialysis have a very poor outcome. In a large registry study with 310,456 patients, the 5-year survival rate was 12.5%.[4]

The Difference between Worsening of Renal Function with Renin-Angiotensin-Aldosterone System Inhibition Compared to Other Causes of Persistent Acute Kidney Injury

The dynamic changes in renal function frequently observed in acute HF patients are important for

© 2019 Rila Publications Ltd.

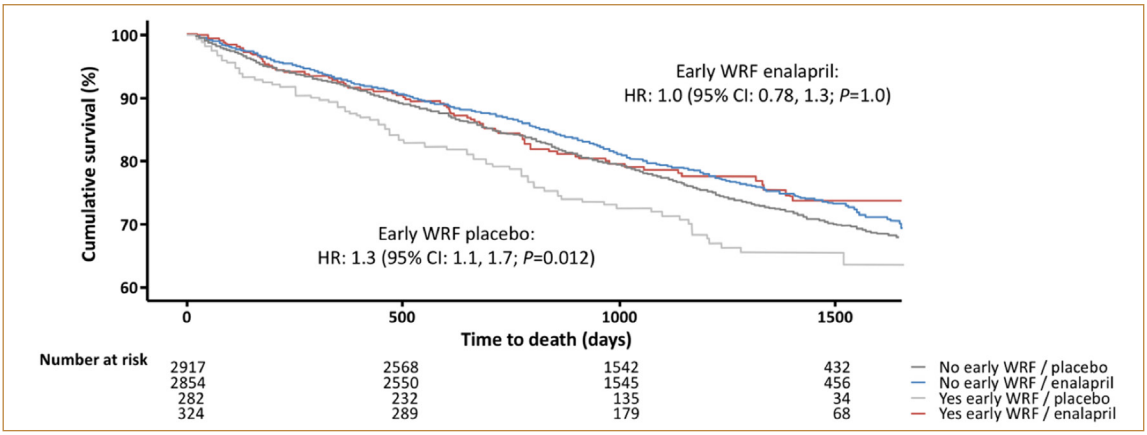


Figure 2. Kaplan-Meier curves grouped by absence or presence of early worsening renal function and randomisation to enalapril or placebo.[11]

guiding treatment and monitoring treatment effectiveness. A rise of even 17 μmol/L (0.2 mg/dL) in serum creatinine has been shown to be associated with adverse outcomes.[5] Most early reports define WRF or AKI as an increase in serum creatinine by ≥26.5 μmol/L (0.3 mg/dL), however, there remains limited consensus on the best definition.[6]

It is important to emphasise that WRF or AKI are not prognostically uniform syndromes. Research suggests that the mechanism underlying the deterioration in GFR may be more important for patient outcomes rather than the direct reduction in GFR itself.

WRF can be classified as transient (WRFt) or persistent (WRFp) (or persistent AKI). Palmer et al. conducted a retrospective analysis comparing the effect of WRFt and WRFp on outcomes in patients hospitalised with acute HF.[7] Importantly, the all-cause mortality rate in those with WRFp was strikingly higher compared to WRFt and non-WRF patients (Figure 1).[7] Indeed, another study also found that those with WRFp to have 46% higher risk of 90-day all-cause mortality compared with WRFt patients.[8] In the DOSE trial, the authors found that a degree of WRFt with high dose IV diuretics to be tolerable in acute HF patients, and that it was not associated with poor outcomes.[9]

In the study by Palmer et al., patients with WRFp (or peristent AKI) had significantly higher rates of sepsis, chronic liver disease, impaired immune function, and cancer.[7] They also used less ACEis, ARBs, and β-blockers compared to patients with WRFt. These observations support the notion that the predominant risk associated with pWRF is a reflection of underlying disease and hence cause of AKI.

RAASi drugs reduces GFR, hence, increased frequency of WRF has been reported whilst using these agents. However, WRF in the setting of RAASi is mechanistically distinct from spontaneously occurring WRF and appears to be benign. The SOLVD trials were randomised placebo-controlled trials of enalapril in patients with cardiac dysfunction.[10, 11] In study participants randomised to enalapril, early WRF in this group lacked adverse prognostic significance (Figure 2).[12] In contrast, early WRF in participants randomised to placebo was associated with significantly increased mortality (Figure 2). Importantly, at 1 year, recovery in renal function in patients with early WRF in both placebo and enalapril-treated groups was significant and levels were similar. Moreover, the survival benefit imparted by enalapril remained in the group that developed early WRF.[12] Ultimately, these results indicate that even relatively large reductions in GFR (≈30%) after starting ACEis may not lead to poor clinical outcomes or that patients will not benefit from the continuation of it. As such, the data provides evidence suggesting that RAASi should not be withdrawn when it causes moderate WRF.

Intravenous Diuretics in Acute Heart Failure Patients with Kidney Disease

Diuretics are pivotal for the treatment and prevention of fluid overload in HF and CKD patients. Thiazide diuretics may be beneficial for those with chronic HF and CKD stages 1-3. For patients with CKD stages 4-5, loop diuretics may be needed as thiazide diuretics are less effective in eGFR <30 ml/min/1.73m^2. Loop diuretics are useful in alleviating RAASi-induced hyperkalaemia, but challenges exist in using them, including changes in creatinine and electrolyte levels.

Both continuous and bolus IV loop diuretic therapy are equally effective for symptomatic control in acute decompensated HF.[9] The treatment of choice for relieving congestion in acute decompensated HF is adequate diuretic therapy combining different

© 2019 Rila Publications Ltd.

agents such as furosemide with metolazone; better than to ultrafiltration.[13] In advanced CKD, the combination of a loop diuretic and potassium-sparing diuretic may prevent hypokalaemia.

Diuretic therapy causes haemoconcentration due to loss of plasma water, which is associated with improved symptoms and even improved outcomes. A >3% rise (Q4) in 1684 patients with EF<40% and were post discharge improved mortality, cardiovascular mortality and HF admissions in placebo arm of the EVEREST trial.[14]

HF patients on dialysis may have very limited urine output and diuretics may be ineffective. The excess fluid needs removal with dialysis. Rapid fluid removal on dialysis patients with HF is often associated with symptomatic intradialytic hypotension. Cases such as these may require daily isolated ultrafiltration. The other option is peritoneal dialysis, which removes fluid in a gentler way and may be useful. Limited evidence suggests that peritoneal dialysis may be associated with less frequent hospital admissions and improved quality of life.[15]

Renal Venous Congestion in Heart Failure and its Management

In HF, the degree of renal impairment has been shown to be associated with the severity of congestion, estimated from elevated JVP, oedema, ascites and orthopnoea.[16] Venous congestion has long been suspected as being a cause of renal dysfunction. However, despite extensive research on the concept for more than a century, the exact pathophysiology of it is unknown.

Early experiments demonstrated that partial occlusion of the renal vein in animals led to reductions in renal blood flow and GFR, and that these abnormalities were reversed when congestion was relieved.[17, 18] The popular initial explanation for this was that a reduction in perfusion pressure (arterial pressure - venous pressure) caused the organ dysfunction.[17] However, the relationship between venous congestion and renal dysfunction is more complex than originally thought. The pathophysiology of it seems to involve much more than a direct hydraulic effect of decreased perfusion pressure enabling organ dysfunction.[17]

An increase in renal vascular resistance appears to be one of the primary mechanisms explaining venous congestion. This mechanism likely involves activation of the sympathetic nervous system, as intra-renal infusion of phentolamine or renal denervation abrogates the effect.[19, 20] Another explanation that has been proposed is the direct effect of increased renal interstitial pressure causing tubular collapse and opposition of flow into Bowman's space.[21]

However, it is important to realise that venous congestion in human HF is significantly more complicated than the congestion generated in animal experiments. In these experiments, the renal veins are often constricted selectively. In contrast, the entire venous system is overloaded in human HF. Here, pro-natriuretic/renal-preserving effects of global venous and cardiac volume overload may counterbalance the local effects of selective renal congestion; by decreasing sympathetic activity in the kidneys and increasing natriuretic peptide secretion.[17] The situation becomes more complex when we consider each patient's specific HF profile, their treatment plan, disease severity, and co-morbidities.[17] These factors contribute to an individual's level of renal function and will obviously vary across patients and populations.

Regardless, it seems that addressing venous congestion in patients with HF can be important in preserving renal function. Aronson et al. assessed the association between net fluid loss, central venous pressure (CVP), and renal function in patients with acute decompensated HF.[22] They found a strong graded association between increased fluid removal in the first 24 hours of hospitalisation and a lower incidence of WRF, suggesting but not proving the beneficial impact of treatment of congestion. Equally, however, it may be possible that patients who did not respond to treatment initially were sicker and hence were predisposed to developing WRF as treatment was escalated.[17] Importantly, the authors found that right atrial pressure was not a reliable surrogate marker for the degree of congestion and risk of WRF, which agrees with findings from the ESCAPE trial.[22, 23] Pressure weakly correlates with volume in the venous system possibly due to high compliance; large changes in blood volume are associated with small changes in pressure. Thus, although decongestion is associated with diminished risk of WRF, CVP is not a reliable marker to monitor the effectiveness of decongestion.[22] Considering these findings, the focus of managing venous congestion in acute HF admissions should lie in preventing renal injury as opposed to following a protocol driven by diuretics.

The management of venous congestion first begins with prevention, initially through salt and water restriction. Salt restriction should be to 2 grams/day. Intravenous loop diuretics are the first line treatment in relieving symptoms of congestion and fluid overload in acute decompensated HF. Recommended starting IV dose of a loop diuretic is double the oral pre-admission dose, with reassessment in 1-2 hours for response.[18] The dose should be increased until sufficient diuresis occurs or the maximum recommended dose is reached if no response occurs with the initial dose. To prevent

© 2019 Rila Publications Ltd.

a rebound increase in sodium absorption, the use of single daily dosing of loop diuretics should be avoided.[18] IV loop diuretics are preferred over oral formulations in acute decompensated HF to overcome decreased absorption caused by splanchnic congestion.[18] The addition of a non-loop diuretic may be useful in patients who fail to respond to loop diuretic therapy alone.[24] Large doses of loop diuretics e.g. furosemide 750 mg daily combined with a thiazide diuretic e.g. metolazone 5 mg twice a day has been successfully used in trials and shown to be better than machine ultrafiltration. However, this requires careful monitoring of electrolytes, avoiding hyponatraemia and hypokalaemia.

Sympathetic overactivity and diuretic use in acute HF leads to RAAS activation, leading to salt and water retention, worsening venous congestion. Thus, RAASi using ACEis or ARBs is important. However, combining aggressive diuresis with these medications in the acute setting may cause WRF. The therapeutic window is narrow, which requires renal function to be monitored closely and adjustments in doses of both types of drugs to be made.[18, 25] Often, it may be necessary to withhold ACEis and ARBs in patients at high risk of developing WRF. Currently, large-scale randomised trials are lacking to guide the use of mineralocorticoid receptor antagonists (MRA) in preventing WRF in acute HF, however, they are used in combination with loop diuretics in the presence of hypokalaemia.

Machine ultrafiltration removes isotonic sodium and water, reducing fluid overload. In cases where diuretic therapy is refractory, ultrafiltration and peritoneal dialysis may be utilised in collaboration with intensive care and renal physicians. The UNLOAD trial compared the treatment of acute decompensated HF using ultrafiltration versus IV diuretics.[26] It was found that those treated with ultrafiltration had greater fluid loss and less HF re-hospitalisations compared to those treated with IV diuretics. However, the study did not assess outcomes beyond 90 days and lacked hard clinical endpoints. Peritoneal dialysis with 1-4 exchanges daily has also been shown to reduce the number and duration of hospitalisations and improve congestive symptoms.[27] Once-daily exchanges with icodextrin improves symptoms in acute decompensated HF and can sustain peritoneal ultrafiltration for up to 12 hours.[28]

Management of Hypokalaemia and Hyperkalaemia in Heart Failure Patients with Kidney Disease

In HF patients with CKD, the occurrence of hypokalaemia is often due to diuretics and/or poor nutrition and can be associated with arrhythmias. The first step in its management is to remove the insulting agent if present. The second step involves providing dietary therapy to increase potassium levels. Potassium-sparing diuretics can be added to further increase potassium levels. Amiloride is useful to control blood pressure simultaneously whilst spironolactone can be used concomitantly for its cardioprotective effects. Oral potassium supplementation can be started if needed but carries the risk of subsequent hyperkalaemia. Frequent monitoring is important to ensure that hyperkalaemia does not develop with the addition of a potassium-sparing diuretic and/or potassium supplementation.

RAAS inhibitors and potassium-sparing diuretics are common causes of hyperkalaemia. The incidence of hyperkalaemia with RAAS monotherapy in hypertensive patients is below 2%.[29] In patients with HF or CKD, the incidence ranges from 5-10%.[29] Hyperkalaemia is first managed with removal of the insulting agent and dietary potassium restriction. Thereafter, the correction of acidosis with sodium bicarbonate can be done, which also prevents the progression of CKD itself.[30] Where bicarbonate is less than 22 mmol/L, sodium bicarbonate can be given with a dose of 500 mg twice daily. Larger doses can be used but will often need an accompanying increase or addition of a loop diuretic dose.

Sodium zirconium cyclosilicate is a cation exchanger that entraps potassium in the intestine preventing absorption. In the HARMONIZE trial, open-label sodium zirconium cyclosilicate lowered serum potassium to normal levels within 48 hours and by 0.5 mmol/L in 4 hours, among outpatients with hyperkalaemia, hence can be started immediately in moderate hyperkalaemia.[31] 5 g, 10 g, and 15 g doses of the agent daily resulted in a higher proportion of patients with normal potassium levels for up to 28 days compared to placebo.

Patiromer, another potassium binding agent, has been shown to reduce potassium levels in CKD patients with hyperkalaemia with or without other co-morbidities, including HF, hypertension, and/or diabetes mellitus. In 306 patients with diabetic kidney disease treated with RAAS blockade (ACEi or ARB with or without spironolactone), the use of patiromer resulted in a significant and sustained decrease in serum potassium over 52 weeks.[32] In 237 CKD patients, patiromer reduced serum potassium by 1 mmol/L over 4 weeks.[33] In another study of 243 hyperkalaemic patients with CKD and HF, the use of patiromer achieved an approximately 1 mmol/L reduction in serum potassium over 4 weeks, reducing recurrent hyperkalaemia.[34] A recent study by Pitt et al. showed that patiromer initiated at a starting dose of 16.8 g/day followed by individual dose titration was able to maintain serum potassium within a target range of 3.5-5.5 mEq/L in 90.5%

© 2019 Rila Publications Ltd.

of study participants.[35] This occurred even against a background of diuretic therapy in over 80% of patients. This study recruited 63 patients with CKD and chronic HF and all but one was on one or more RAAS inhibitors at baseline. spironolactone was also initiated with patiromer at 25 mg/day and up-titrated to 50 mg/day. The incidence of hypokalaemia (1.6%) and serum magnesium below the lower limit of normal (<1.8 mg/dL) was lower in this study compared with rates in the PEARL-HF study (7% and 24% respectively) that used a higher fixed dose of patiromer at 25.2 g/day.[35, 36] This suggests that patiromer initiated at a lower dose of 16.8 g/day with personalised dose titrations may be more effective in preventing hypokalaemia and serum magnesium below the lower limit of normal. However, it is important to emphasize that the trials discussed above were of short duration and that the use of ACEi or ARB facilitated with patiromer has not been shown to improve cardiovascular morbidity or mortality.

Management of Hyponatraemia and Hypernatraemia in Heart Failure Patients with Kidney Disease

CKD patients may be more susceptible to developing dysnatraemias as their ability to maintain salt and water homeostasis is diminished. In a cohort of 655,493 non-dialysis dependent CKD patients, 13.5% had hyponatraemia and 2% had hypernatraemia at baseline and both conditions were associated with higher mortality.[37] Over a median follow up of 5.5 years, 26% developed at least one episode of hyponatraemia and 7% had at least one episode of hypernatraemia.[37] Hypernatraemia occurs in these patients usually because of volume depletion due to over diuresis. In this case, fluid therapy, preferably sodium chloride 0.9%, corrects the abnormality.

Chronic HF is characterised by a decrease in cardiac output, which causes an increase in the secretion of renin and vasopressin. This eventually leads to hypervolemic hyponatraemia. Diuretic use in acute decompensated HF is also important in causing hyponatraemia. The Hyponatremia Registry for Patients with Euvolemic and Hypervolemic Hyponatremia (HN Registry) is a prospective, observational, study of patients hospitalised with hyponatraemia (defined as [Na^+] ≤130 mEq/l), euvolemic or hypervolemic, in the United States (146 sites) and with euvolemic hyponatraemia in Europe (79 sites).[38] In an analysis of a subset of patients in the registry who had hypervolemic HF with hyponatraemia, fluid restriction was found to be the most commonly prescribed initial monotherapy for hyponatraemia (44%), followed by no specific treatment beyond the treatment of congestion (23%), prescription of isotonic saline (5%), tolvaptan (4%), loop diuretics (3%), hypertonic saline (2%), and salt tablets (1%). The effect of fluid restriction on [Na^+] was found to be modest, causing only a median increase of 2 mEq/L in the first 24 hours.[38] Importantly, there was no difference in the rate of change in [Na^+] between patients receiving fluid restriction and no specific treatment. Indeed, in another study of 28 patients with hypervolemic and euvolemic hyponatraemia, fluid restriction of 1200 ml/day resulted in a mean change of only 0.7 ± 2.1 mEq/L in [Na^+] on day 5 of treatment.[39] These findings challenge current recommendations for fluid restriction as initial therapy for hyponatraemia. The American College of Cardiology/American Heart Association guidelines states that fluid restriction of 1.5 to 2 L/day is reasonable in stage D to reduce congestive symptoms, especially in those with hyponatraemia.[40] This recommendation is classified as class IIa, Level of Evidence C.[40] The use of tolvaptan, isotonic saline, and hypertonic saline resulted in a faster rate of change in [Na^+] than fluid restriction or no specific treatment. [Na^+] increased by ≥5 mEq/L in the majority of patients treated with these agents compared to the minority who received fluid restriction or no specific treatment. However, it has been shown that simultaneous administration of IV fluids and diuretics during the first 48 hours of hospitalisation in acute decompensated HF patients was associated with worse outcomes, including greater rates of critical care admission, renal replacement therapy, and in-hospital death compared to patients receiving only diuretics.[41] In the EVEREST trial, tolvaptan initiated within 48 hours of hospitalisation to treat acute HF improved dyspnoea, oedema, body weight, and [Na^+].[42] [Na^+] was shown to significantly increase among patients with baseline [Na^+] <134 mEq/L. Short-term reductions in body weight were sustained throughout the duration of the trial. Importantly, renal function was preserved while this effect on fluid balance occurred. Despite this, treatment with tolvaptan did not improve all-cause mortality and the study's combined end-point of cardiovascular mortality and rates of hospitalisation for HF. Nonetheless, considering the significant benefits in improved morbidity along with the neutral survival effect, tolvaptan is a potentially useful agent for treating patients with acute decompensated HF, including to address the problem of hyponatraemia commonly encountered. Thiazide diuretics, a common cause of hyponatraemia may need to be stopped to correct serum sodium, more so in patients with chronic HF.

The treatment of hyponatraemia should be guided by severity, duration and symptoms. Acute or

© 2019 Rila Publications Ltd.

symptomatic, severe hyponatraemia (<125 mmol/L) is a medical emergency, and is best managed in the intensive therapy unit, but uncommon in HF. Mild (<135 mmol/L) or moderate (<130 mmol/L) or chronic severe hyponatraemia is best managed by fluid restriction, or vaptans.

Use of Renin-Angiotensin-Aldosterone-System Inhibitors in Chronic Kidney Disease Patients

The management of chronic HF patients with CKD requires careful use of ACEis/ARBs, β-blockers, and MRAs whilst monitoring serum creatinine and potassium. Often, large doses of diuretics are needed for the management of acute decompensated HF, along with the cautious use of ACEis/ARBs or MRAs. Again, this necessitates regular monitoring of serum creatinine and electrolytes. Clinical trials evaluating the utility of these agents in HF patients often include patients with stage 1-3 CKD by chance. However, stage 4-5 CKD and dialysis patients are routinely excluded. Hence, there is some evidence to support the use of these guideline-recommended medications in stage 1-3 CKD, but such evidence in stage 4-5 CKD, dialysis, and post-kidney transplant recipients is alarmingly lacking.

Sub-group analysis of multiple randomised controlled trials has demonstrated benefits of using ACEis in patients with HF and CKD. Reductions in mortality and hospitalisations with enalapril and lisinopril have been shown in patients with eGFR <60 ml/min/1.73m^2 and <45 ml/min/1.73m^2.[43] For patients with CKD stages 1-3, ACEis should be used in all patients with HF with reduced ejection fraction (HFrEF), with monitoring of creatinine and potassium. For patients with CKD stages 4-5, they may be used in HFrEF and dose modifications may be necessary. Monitoring of creatinine and potassium is paramount in these patients. ARBs may be used in all patients with CKD stages 1-3 and HFrEF with caution.[44, 45] For patients with CKD stages 4-5, they may be used in HFrEF with monitoring of creatinine and potassium.[44, 45] MRAs are proven to be beneficial in patients with CKD and HFrEF who remain symptomatic after treatment with ACEi and β-blockers. Almost 50% of study participants in a large randomised controlled trial of spironolactone and 1/3 of participants in a trial of eplerenone had eGFR <60 ml/min/1.73m^2 at baseline and benefitted from therapy.[46, 47] Thus, MRAs should be used in all CKD stages 1-3 patients with HFrEF along with careful monitoring of potassium. For those with CKD stages 4-5, they may be used in HFrEF patients with caution and close monitoring of potassium.

Sacubitril/valsartan (neprilysin-angiotensin receptor inhibitor), an increasingly used therapy in HF, was recently tested in CKD patients with eGFR 20-60 ml/min/1.73m^2.[48] It was found to be safe, improved cardiac biomarkers, and blood pressure.[48] In a post-hoc analysis of the PARADIGM-HF trial, sacubitril/valsartan compared with enalapril led to a slower rate of decrease in eGFR and improved cardiovascular outcomes in HFrEF patients with CKD (eGFR <60 ml/min/1.73m^2).[49] Currently, there is insufficient evidence to guide the use of sacubtril/valsartan for different stages of CKD, especially in the context of acute HF admissions.

Device Therapy in Heart Failure Patients with Chronic Kidney Disease

Both HF and CKD carry significant risk for left ventricular dysfunction and arrhythmogenesis.[50] When these entities are combined, the risk is substantially increased. Device therapies including cardiac resynchronisation therapy (CRT) and implantable cardioverter defibrillators (ICDs) are proven treatment for improving clinical outcomes in select patients with HF. This section summarises existing evidence for the role of CRT and ICDs in patients with both CKD and HF.

In a retrospective subgroup analysis of the MADIT-II study, patients with eGFR ≥35 ml/min/1.73 m^2 who received ICD therapy demonstrated an overall risk reduction for all-cause mortality and sudden cardiac death (SCD) by 32% and 66%, respectively.[51] However, ICD therapy in patients with an eGFR <35 ml/min/1.73 m^2 was not associated with any survival benefit.[51] In another retrospective cohort study, end-stage renal disease (ESRD) patients with left ventricular dysfunction receiving ICD therapy had significantly less all-cause mortality compared to those who did not undergo ICD placement (hazard ratio [HR]: 0.40).[52] The median survival in the ICD group was 8 years while it was 3.1 years in the non-ICD group.[52] The retrospective study by Herzog et al. supports the use of ICDs in secondary prevention of SCD in dialysis patients, as ICD implantation was independently associated with a 42% reduction in mortality risk.[53] In a meta-analysis of 3 randomised controlled trials, ICD placement in patients with ESRD was associated with an increase in overall survival compared to those without ICD therapy (OR: 2.25; 95% CI 1.87-2.69; P<0.001).[54] However infection risks are very high as shown in a retrospective analysis of 9528 dialysis patients.[55]

A retrospective subgroup analysis of the Multicenter InSync Randomized Clinical Evaluation study demonstrated eGFR improvement in patients with eGFR 30-60 ml/min/1.73 m^2 receiving CRT compared to those who did not (6.4 ± 2.4 ml/min/1.73 m^2 vs. -1.1 ± 1.5 ml/min/1.73 m^2; P=0.008).[56] However, no difference was observed in patients with eGFR ≥60 ml/min/1.73 m^2. One meta-

© 2019 Rila Publications Ltd.

analysis evaluated the impact of baseline renal function on all-cause mortality in patients who underwent CRT.[57] They found that each 10-unit increment in GFR was associated with a 19% decrease in all-cause mortality, showing that baseline renal dysfunction had an adverse effect on all-cause mortality in those receiving CRT.[57] The CARE-HF study assessed the efficacy of optimal medical therapy with CRT.[58] The authors found no difference in all-cause mortality or unplanned hospitalisation for a major cardiovascular event in patients with eGFR ≥60 mL/min/1.73 m^2 compared to those with eGFR ≤60 mL/min/1.73 m^2. In a post-hoc analysis of the COMPANION trial, CRT candidates with baseline renal dysfunction had a significantly higher risk of SCD (HR: 1.69; 95% CI 1.06-2.65; *P*=0.03).[59] In the study by Cleland et al., CRT combined with medical therapy compared with medical therapy alone demonstrated a 33% lower hazard for death or hospitalisations in CKD patients.[60] Pooled analyses by Garg et al. demonstrated significant improvements in left ventricular EF (mean difference 6.24%; 95% CI 3.46-9.07) and eGFR (mean difference 2.30 ml/min/1.73 m^2; 95% CI 0.33-4.27) after CRT in CKD.[61]

Unfortunately, most evidence guiding the use of device therapy in HF patients with CKD is based on retrospective data, which are prone to various biases, including selection bias. Hence, due to the paucity of evidence, clearly defined guidelines for the use of device therapy in these patients does not exist. Thus, the risk/benefit ratio of device therapy for a patient must be assessed on an individual basis.

Conclusion

The management of acute HF-CKD admissions is difficult and requires attention to multiple factors. Challenges exist in implementing diuretic therapy and RAASi considering its impact on kidney function and electrolytes. Furthermore, although device therapy has been shown to be effective in select HF patients, there is limited research to guide its use in HF-CKD. This review summarises the most relevant literature to guide the management of acute admissions of HF patients with kidney disease.

Conflict of interest

DB has received honorarium from Viforpharma, Astrazeneca, Pfizer

References

1. Shurrab M, Ko DT, Zayed Y, *et al.* Outcomes of ICDs and CRTs in patients with chronic kidney disease: a meta-analysis of 21,000 patients. *J Interv Card Electrophysiol.* 2018 Oct;**53(1)**:123-9.
2. Jenkins R, Mandarano L, Gugathas S, *et al.* Impaired renal function affects clinical outcomes and management of patients with heart failure. *ESC Heart Fail.* 2017 Nov;**4(4)**:576-84.
3. Damman K, Valente MA, Voors AA, *et al.* Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J.* 2014 Feb;**35(7)**:455-69.
4. Banerjee D, Ma JZ, Collins AJ, *et al.* Long-term survival of incident hemodialysis patients who are hospitalized for congestive heart failure, pulmonary edema, or fluid overload. *Clin J Am Soc Nephrol.* 2007 Nov;**2(6)**:1186-90.
5. Gottlieb SS, Abraham W, Butler J, *et al.* The prognostic importance of different definitions of worsening renal function in congestive heart failure. *J Card Fail.* 2002 Jun;**8(3)**:136-41.
6. Damman K, Testani JM. The kidney in heart failure: an update. *Eur Heart J.* 2015 Jun 14;**36(23)**:1437-44.
7. Palmer JB, Friedman HS, Waltman Johnson K, *et al.* Association of persistent and transient worsening renal function with mortality risk, readmissions risk, length of stay, and costs in patients hospitalized with acute heart failure. *Clinicoecon Outcomes Res.* 2015 Jun 19;**7**:357-67.
8. Krishnamoorthy A, Greiner MA, Sharma PP, *et al.* Transient and persistent worsening renal function during hospitalization for acute heart failure. *Am Heart J.* 2014 Dec;**168(6)**:891-900.
9. Felker GM, Lee KL, Bull DA, *et al.* Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med.* 2011 Mar 3;**364(9)**:797-805.
10. SOLVD Investigators, Yusuf S, Pitt B, *et al.* Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med.* 1991 Aug 1;**325(5)**:293-302.
11. SOLVD Investigators, Yusuf S, Pitt B, *et al.* Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med.* 1992 Sep 3;**327(10)**:685-91.
12. Testani JM, Kimmel SE, Dries DL, *et al.* Prognostic importance of early worsening renal function after initiation of angiotensin-converting enzyme inhibitor therapy in patients with cardiac dysfunction. *Circ Heart Fail.* 2011 Nov;**4(6)**:685-91.
13. Bart BA, Goldsmith SR, Lee KL, *et al.* Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med.* 2012 Dec 13;**367(24)**:2296-304.
14. Greene SJ, Gheorghiade M, Vaduganathan M, *et al.* Haemoconcentration, renal function, and post-discharge outcomes among patients hospitalized for heart failure with reduced ejection fraction: insights from the EVEREST trial. *Eur J Heart Fail.* 2013 Dec;**15(12)**:1401-11.
15. Lu R, Mucino-Bermejo MJ, Ribeiro LC, *et al.* Peritoneal dialysis in patients with refractory congestive heart failure: a systematic review. *Cardiorenal Med.* 2015 Apr;**5(2)**:145-56.
16. Damman K, Voors AA, Hillege HL, *et al.* Congestion in chronic systolic heart failure is related to renal dysfunction and increased mortality. *Eur J Heart Fail.* 2010 Sep;**12(9)**:974-82.
17. Testani JM, Damman K. Venous congestion and renal function in heart failure ... it's complicated. *Eur J Heart Fail.* 2013 Jun;**15(6)**:599-601.
18. F Gnanaraj J, von Haehling S, Anker SD, *et al.* The relevance of congestion in the cardio-renal syndrome. *Kidney Int.* 2013 Mar;**83(3)**:384-91.
19. Dilley JR, Corradi A, Arendshorst WJ. Glomerular ultrafiltration dynamics during increased renal venous pressure. *Am J Physiol.* 1983 Jun;**244(6)**:F650-8.
20. Abildgaard U, Amtorp O, Agerskov K, *et al.* Renal vascular adjustments to partial renal venous obstruction in dog kidney. *Circ Res.* 1987 Aug;**61(2)**:194-202.
21. Braam B, Cupples WA, Joles JA, *et al.* Systemic arterial and venous determinants of renal hemodynamics in congestive heart failure. *Heart Fail Rev.* 2012 Mar;**17(2)**:161-75.
22. Aronson D, Abassi Z, Allon E, *et al.* Fluid loss, venous congestion, and worsening renal function in acute decompensated heart failure. *Eur J Heart Fail.* 2013 Jun;**15(6)**:637-43.
23. Nohria A, Hasselblad V, Stebbins A, *et al.* Cardiorenal interactions:

© 2019 Rila Publications Ltd.

insights from the ESCAPE trial. *J Am Coll Cardiol.* 2008 Apr 1;**51(13)**:1268-74.
24. Dormans TP, Gerlag PG. Combination of high-dose furosemide and hydrochlorothiazide in the treatment of refractory congestive heart failure. *Eur Heart J.* 1996 Dec;**17(12)**:1867-74.
25. Knight EL, Glynn RJ, McIntyre KM, *et al.* Predictors of decreased renal function in patients with heart failure during angiotensin-converting enzyme inhibitor therapy: results from the studies of left ventricular dysfunction (SOLVD). *Am Heart J.* 1999 Nov;**138(5 Pt 1)**:849-55.
26. Costanzo MR, Guglin ME, Saltzberg MT, *et al.* Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol.* 2007 Feb 13;**49(6)**:675-83.
27. Sanchez JE, Rodriguez C, Gonzalez I, *et al.* Analysis of the advantages of peritoneal dialysis in the treatment of chronic refractory heart failure. *Nefrologia.* 2010;**30(5)**:487-9.
28. Khalifeh N, Vychytil A, Horl WH. The role of peritoneal dialysis in the management of treatment-resistant congestive heart failure: A European perspective. *Kidney Int Suppl.* 2006 Nov;**(103)**:S72-5. doi(103):S72-5.
29. Weir MR, Rolfe M. Potassium homeostasis and renin-angiotensin-aldosterone system inhibitors. *Clin J Am Soc Nephrol.* 2010 Mar;**5(3)**:531-48.
30. de Brito-Ashurst I, Varagunam M, Raftery MJ, *et al.* Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J Am Soc Nephrol.* 2009 Sep;**20(9)**:2075-84.
31. Kosiborod M, Rasmussen HS, Lavin P, *et al.* Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. *JAMA.* 2014 Dec 3;**312(21)**:2223-33.
32. Bakris GL, Pitt B, Weir MR, *et al.* Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalemia and Diabetic Kidney Disease: The AMETHYST-DN Randomized Clinical Trial. *JAMA.* 2015 Jul 14;**314(2)**:151-61.
33. Weir MR, Bakris GL, Bushinsky DA, *et al.* Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med.* 2015 Jan 15;**372(3)**:211-21.
34. Pitt B, Bakris GL, Bushinsky DA, *et al.* Effect of patiromer on reducing serum potassium and preventing recurrent hyperkalaemia in patients with heart failure and chronic kidney disease on RAAS inhibitors. *Eur J Heart Fail.* 2015 Oct;**17(10)**:1057-65.
35. Pitt B, Bushinsky DA, Kitzman DW, *et al.* Evaluation of an individualized dose titration regimen of patiromer to prevent hyperkalaemia in patients with heart failure and chronic kidney disease. *ESC Heart Fail.* 2018 Jun;**5(3)**:257-66.
36. Pitt B, Anker SD, Bushinsky DA, *et al.* Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. *Eur Heart J.* 2011 Apr;**32(7)**:820-8.
37. Kovesdy CP, Lott EH, Lu JL, *et al.* Hyponatremia, hypernatremia, and mortality in patients with chronic kidney disease with and without congestive heart failure. *Circulation.* 2012 Feb 7;**125(5)**:677-84.
38. Dunlap ME, Hauptman PJ, Amin AN, *et al.* Current Management of Hyponatremia in Acute Heart Failure: A Report From the Hyponatremia Registry for Patients With Euvolemic and Hypervolemic Hyponatremia (HN Registry). *J Am Heart Assoc.* 2017 Aug 3;**6(8)**:10.1161/JAHA.116.005261.
39. Gheorghiade M, Gottlieb SS, Udelson JE, *et al.* Vasopressin v(2) receptor blockade with tolvaptan versus fluid restriction in the treatment of hyponatremia. *Am J Cardiol.* 2006 Apr 1;**97(7)**:1064-7.
40. Yancy CW, Jessup M, Bozkurt B, *et al.* 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013 Oct 15;**62(16)**:e147-239.
41. Bikdeli B, Strait KM, Dharmarajan K, *et al.* Intravenous fluids in acute decompensated heart failure. *JACC Heart Fail.* 2015 Feb;**3(2)**:127-33.
42. Konstam MA, Gheorghiade M, Burnett JC, *et al.* Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA.* 2007 Mar 28;**297(12)**:1319-31.
43. Bowling CB, Sanders PW, Allman RM, *et al.* Effects of enalapril in systolic heart failure patients with and without chronic kidney disease: insights from the SOLVD Treatment trial. *Int J Cardiol.* 2013 Jul 15;**167(1)**:151-6.
44. Ahmed A, Fonarow GC, Zhang Y, *et al.* Renin-angiotensin inhibition in systolic heart failure and chronic kidney disease. *Am J Med.* 2012 Apr;**125(4)**:399-410.
45. Ahmed A, Rich MW, Zile M, *et al.* Renin-angiotensin inhibition in diastolic heart failure and chronic kidney disease. *Am J Med.* 2013 Feb;**126(2)**:150-61.
46. Vardeny O, Wu DH, Desai A, *et al.* Influence of baseline and worsening renal function on efficacy of spironolactone in patients With severe heart failure: insights from RALES (Randomized Aldactone Evaluation Study). *J Am Coll Cardiol.* 2012 Nov 13;**60(20)**:2082-9.
47. Rossignol P, Cleland JG, Bhandari S, *et al.* Determinants and consequences of renal function variations with aldosterone blocker therapy in heart failure patients after myocardial infarction: insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study. *Circulation.* 2012 Jan 17;**125(2)**:271-9.
48. Haynes R, Judge PK, Staplin N, *et al.* Effects of Sacubitril/Valsartan Versus Irbesartan in Patients With Chronic Kidney Disease. *Circulation.* 2018 Oct 9;**138(15)**:1505-14.
49. Damman K, Gori M, Claggett B, *et al.* Renal Effects and Associated Outcomes During Angiotensin-Neprilysin Inhibition in Heart Failure. *JACC Heart Fail.* 2018 Jun;**6(6)**:489-98.
50. Turakhia MP, Blankestijn PJ, Carrero JJ, *et al.* Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Eur Heart J.* 2018 Jun 21;**39(24)**:2314-25.
51. Goldenberg I, Moss AJ, McNitt S, *et al.* Relations among renal function, risk of sudden cardiac death, and benefit of the implanted cardiac defibrillator in patients with ischemic left ventricular dysfunction. *Am J Cardiol.* 2006 Aug 15;**98(4)**:485-90.
52. Hiremath S, Punnam SR, Brar SS, *et al.* Implantable defibrillators improve survival in end-stage renal disease: results from a multi-center registry. A*m J Nephrol.* 2010;**32(4)**:305-10.
53. Herzog CA, Li S, Weinhandl ED, *et al.* Survival of dialysis patients after cardiac arrest and the impact of implantable cardioverter defibrillators. K*idney Int.* 2005 Aug;**68(2)**:818-25.
54. Chen TH, Wo HT, Chang PC, *et al.* A meta-analysis of mortality in end-stage renal disease patients receiving implantable cardioverter defibrillators (ICDs). *PLoS One.* 2014 Jul 18;**9(7)**:e99418.
55. Charytan DM, Patrick AR, Liu J, *et al.* Trends in the use and outcomes of implantable cardioverter-defibrillators in patients undergoing dialysis in the United States. *Am J Kidney Dis.* 2011 Sep;**58(3)**:409-17.
56. Boerrigter G, Costello-Boerrigter LC, Abraham WT, *et al.* Cardiac resynchronization therapy improves renal function in human heart failure with reduced glomerular filtration rate. *J Card Fail.* 2008 Sep;**14(7)**:539-46.
57. Bazoukis G, Letsas KP, Korantzopoulos P, *et al.* Impact of baseline renal function on all-cause mortality in patients who underwent cardiac resynchronization therapy: A systematic review and meta-analysis. *J Arrhythm.* 2017 Oct;**33(5)**:417-23.
58. Richardson M, Freemantle N, Calvert MJ, *et al.* Predictors and treatment response with cardiac resynchronization therapy in patients with heart failure characterized by dyssynchrony: a pre-defined analysis from the CARE-HF trial. *Eur Heart J.* 2007 Aug;**28(15)**:1827-34.
59. Saxon LA, Bristow MR, Boehmer J, *et al.* Predictors of sudden cardiac death and appropriate shock in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial. *Circulation.* 2006 Dec 19;**114(25)**:2766-72.
60. Cleland JG, Daubert JC, Erdmann E, *et al.* The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med.* 2005 Apr 14;**352(15)**:1539-49.
61. Garg N, Thomas G, Jackson G, *et al.* Cardiac resynchronization therapy in CKD: a systematic review. *Clin J Am Soc Nephrol.* 2013 Aug;**8(8)**:1293-303.

© 2019 Rila Publications Ltd.