# Invited review

# Title: Personalising heart failure management in CKD patients

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## Abstract

CKD in heart failure patients is common, present in 49%, associated with higher mortality [Hazard ratio, 2.34 (95% CI2.20–2.50,P<0.001) and multiple hospital admissions. The management of heart failure in CKD can be challenging due to drug induced electrolyte and creatinine changes; resistance to diuretics and infections related to device therapy. Evidence for improvement in mortality and heart failure hospitalisations exists in HFrEF stage 3 CKD patients from randomised controlled trials of ACE-inhibitor and mineralocorticoid receptor antagonist therapy; but not in dialysis patients where higher doses can cause hyperkalaemia. Evidence on improvement of cardiovascular death and heart failure hospitalisations has emerged with angiotensin blocker-neprilysin inhibitor, ivabradine and more recently with sodium-glucose cotransporter inhibitors in HFrEF patients with CKD stages 1,2, and 3. However these studies have excluded CKD 4,5 patients. Evidence for betablocker therapy exists in CKD stages 1,2 and 3 and separately in haemodialysis patients. Cardiac resynchronisation therapy reduces heart failure hospitalisations and mortality in patients with CKD 1,2,3 but not in CKD stages 4,5 or dialysis patients. Internal cardioverter and defibrillator therapy in HFrEF patients have been shown to be beneficial in CKD 3 patients, not in dialysis patients where it is associated with high rates of infection. For HFpEF patients with CKD therapy is symptomatic as there is no proven therapy for improvement in survival or hospitalisations. Heart failure patients with end-stage-kidney disease with fluid overload may benefit from peritoneal dialysis. A multidisciplinary, personalised approach has been associated with better care and improved patient satisfaction.

## Introduction

Patients with heart failure and chronic kidney disease are often frail and elderly, with very different needs, depending on age, co-existing comorbidities and expectations. An elderly multimorbid individual with CKD and heart failure may be keen on enjoying their remaining life free from symptoms and hospital admissions; whereas a young individual with the same condition may wish to live longer and contribute positively at home and work. A personalised, collaborative management approach tailored to the patient’s needs and life goals should be the way forward. This review describes the burden of heart failure with CKD, the updated evidence behind therapy together with the benefits of a patient-centred multidisciplinary approach. “We conducted a literature search using MESH terms heart failure and kidney disease or kidney failure, particularly looking for randomised controlled trial evidence. The search resulted in 260 studies which were reviewed for the purpose of the manuscript. Studies mentioned in the recent consensus reports were also reviewed.”

## Epidemiology of heart failure with CKD and vice versa

The results from meta-analyses of cohort, registry and randomised-controlled heart failure studies indicated that 32% suffered from CKD, but the prevalence of CKD was higher (49%) on excluding the two specific registry studies [1]. The prevalence of CKD was observed to be higher in acute heart failure patients (53%) compared to chronic heart failure patients (42%) [1]. In our own experience of acute heart failure patients, the incidence was around 47% [2].

The common causes of CKD in patients with heart failure are hypertension, diabetes and atherosclerotic-renovascular disease [3]. In normal physiological state, the heart and kidney are interdependent for their functions and in disease states they adversely affect each other's function [4]. The poorly pumping heart fails to deliver adequate oxygen to the kidney causing ischaemic injury, and a failing kidney retains salt and water to add to the burden on the heart (see Figure 1)

## Prognosis of heart failure patients with CKD

Clinically important adverse outcomes to be considered in patients with heart failure include number and duration of hospitalisations, mortality and poor quality of life and functional status due to symptoms. The prognosis of heart failure has improved over time but remains poor compared to other chronic conditions. In the recently completed EMPEROR reduced trial in patients with NYHA class II-IV, heart failure with reduced ejection fraction (HFrEF) treated with placebo (age 66±11 years, ejection fraction (EF) 27±6%, diabetes 50%, 70% on ACE inhibitor or angiotensin receptor blocker (ARB), 73% on mineralocorticoid receptor antagonist (MRA), 95% on betablockers, 44% on device therapy) all-cause mortality was 10.7%/year and hospitalisations were 71%/year [5] In meta-analysis of acute and chronic heart failure patients, co-existing CKD was associated with higher risk of death. The mortality was higher with CKD patients compared to non-CKD patients, hazard ratio being 2.34 (95% CI 2.20–2.50, P<0.001), when followed for a mean of 361±333 days for acute heart failure patients and 942±802 days for chronic heart failure patients [1].

## Principles of management of heart failure patients with CKD

The goal of treatment for heart failure patients is not only to improve survival but also to improve functional status and quality of life. Better symptom control and quality of life may often be a higher priority over prolong survival in multimorbid heart failure-CKD patients. Recurrent hospitalisations are undesirable as it impacts patients’ life goals and quality of life and hence prevention of hospitalisation is an important treatment outcome. A common indication for hospitalisation is breathlessness and oedema, which often requires carefully managed diuretic therapy as discussed below. Both established and newer drug and device therapies that have been shown to improve survival and reduce hospitalisation rates in HFrEF patients with CKD are discussed below [figure 2].

## Challenges in management of heart failure patients with CKD

There are several challenges in management of heart failure in the presence of kidney disease including abnormalities of drug pharmacokinetics, altered drug pharmacodynamics, biochemical abnormalities of electrolytes, and infections with device therapy. Abnormalities of drug pharmacokinetics due to poor kidney function:

Concentrations of certain drugs increase in the blood in CKD due to decreased kidney elimination. In addition, CKD causes abnormalities, such as of p-glycoprotein function increasing bioavailability of digoxin; and cytochrome P 450 group of enzyme function decreasing clearance of carvedilol and verapamil. Often the available evidence of the exact impact of CKD on drug pharmacokinetics is limited and dose adjustments are difficult.

#### Diuretic resistance:

The effects of diuretic therapy decrease with worsening kidney function, but the term diuretic resistance is not very well defined. Thiazide diuretics are often ineffective in CKD stages 4 and 5. Loop diuretics are more effective with lower eGFR however higher doses are necessary with lower glomerular filtration rates. Loop diuretics work by acting on the Sodium-potassium-cotransporters (NKCC) on the luminal side of tubular cells in the ascending limb of loop of Henle. Decreased function of organic anion transporters prevents secretion of loop diuretics into the tubular lumen thereby preventing their action [6].

#### Initial rise in serum creatinine with initiation of ACEi/ARB and Sodium glucose cotransporter 2 inhibitor (SGLT2i) therapy:

Studies have shown that the initiation of ACEi therapy may be associated with an initial decline in kidney function before slowing in the progression of kidney disease in both heart failure and non-heart failure patients.

In the SOLVD trial 606 patients (9.5%) experienced worsening kidney function between baseline and 14 days post randomization with a mean decrease in eGFR of 29.2 ± 9.8% in the enalapril group and 28.9 ± 9.3% in the placebo group. Patients experiencing early worsening kidney failure (WKF) at 14 days had a significant recovery of kidney function by one year (p<0.0001) and the degree of recovery was similar between those assigned to enalapril or placebo (16.0 ± 34.1% vs. 18.2 ± 38.0%, p=0.52). However patients with a worsening kidney function with enalapril had no increase in mortality (HR=1.0, 95% CI 0.78–1.3, p=1.0) as opposed to placebo patients with worsening kidney failure (HR=1.3, 95% CI 1.1–1.7, p=0.012) [7]. More recently reanalysis of the SOLVD trial, compared to zero percent eGFR decline in the placebo arm as the reference, up to a 10% decline in eGFR with enalapril was associated with survival benefit (HR 0.87 [95% CI 0.77, 0.99]) while up to a 35% decline in eGFR was associated with decreased risk of heart failure hospitalization (HR 0.78 [95% CI 0.61, 0.98]) [8].

The early worsening of kidney function is related to the efferent arteriolar vasodilation and decrease in filtration pressure at each individual nephron. The lower intraglomerular pressure prevents hyperfiltration in each nephron and protects the glomerulus in the longer term.

A similar observation was noted with SGLT2i trials. In a trial of 4744 heart failure patients randomised to Dapagliflozin or placebo, there was a higher initial decline in eGFR in the dapagliflozin group than in the placebo group (–3.97±0.15 vs. –0.82±0.15 ml/min/1.73 m2) [9]. However, thereafter, the annual change in the mean eGFR was smaller with dapagliflozin than with placebo (–1.67±0.11 and –3.59±0.11 ml/min/1.73 m2, respectively), for a between-group difference of 1.92 ml/min/1.73 m2 per year (95% CI, 1.61 to 2.24) .

The early worsening of kidney function at 2 weeks is consistent among different SGLT2i. This is probably due to tubuloglomerular feedback whereby increased salt and water delivery to the periglomerular distal tubule causes afferent arteriolar vasoconstriction and decline in filtration pressure in each glomerulus. The low intraglomerular pressure protects the glomerulus from hyperfiltration.

#### Hyperkalaemia due to ACEi, ARB, MRA

Hyperkalaemia is an uncommon side-effect of renin-angiotensin-aldosterone-system inhibitor (RAASi) therapy in heart failure with CKD. The incidence of serum potassium >5.5 mmol/L with enalapril is 6.4%. The mean eGFR in the trial was 65 ± 19 ml/min/1.73m2 (creatine 1.2±0.3) [10]. Use of ACEi benazepril in advanced CKD was associated with higher incidence of potassium >6.0 mmol/L (5%) with baseline eGFR 37±6 ml/min/1.73m2[11]. Therapy with spironolactone in RALES study resulted in serious hyperkalaemia in 3.9% (>6.0mmol/L) and 19% (>5.5mmol/L) [12]. Incidence of hyperkalaemia is perhaps higher in haemodialysis patients as discussed below.

#### Lack of evidence of drug therapy in advanced CKD

Most clinical trials of heart failure excluded subjects with advanced chronic kidney disease (eGFR < 30ml/min per 1.73m2). The exclusion criterion in earlier studies were creatine >177 µmol/L or >221 µmol/L [10]. More recently the exclusion criterion has been either eGFR <30 ml/min/1.73m2 or eGFR<20 ml/min/1.73m2  [5]. Hence patients with CKD stages 4,5 were mostly excluded in randomised controlled trials of heart failure.

## Lifestyle changes for management of heart failure patients with CKD

Exercise helps with improvement of quality of life in patients with HFrEF as demonstrated in a randomised controlled study with 2332 patients exercising 36 sessions over 3 months [13]. The mean creatinine was 1.2 mg/dL, hence significant proportion had CKD. Salt restriction is recommended for patients particularly with fluid overload, but randomised controlled trial evidence is lacking.

## Drug therapy for heart failure with reduced ejection fraction and CKD (Table 1)

#### Beta-blockers:

Subgroup analysis of general population studies suggested survival benefits with beta-blockers use in subjects with HFrEF and CKD [14-18]. Carvedilol therapy has been shown to improve mortality in HFrEF patients on haemodialysis [19]. The same study suggested improvement in sudden death, which is common in dialysis and advanced CKD patients [19, 20].

#### ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB):

There is positive evidence for CKD 1-3 subjects from general population studies such as SOLVD and SAVE on mortality and hospitalisations in heart failure with CKD. The SAVE trial randomised 2231 patients with a creatinine level up to 221 µmol/L showing an improvement in all-cause mortality with captopril compared to placebo [21]. The SOLVD trial randomised 2569 patients with a creatinine up to 177 µmol/L showing an improvement in all-cause mortality with enalapril compared to placebo [10]. These drugs caused a decline in kidney function which was not associated with adverse outcome. Hyperkalaemia is an infrequent side effect, the incidence of which increased with worsening kidney function. However, these trials excluded subjectss with advanced CKD. The effects of ACEi/ARB in patients on dialysis subjects remains controversial with one randomised trial suggesting beta-blocker atenelol being better than ACEi lisinopril [22, 23] and another trial (FOSIDIAL) did not show any difference in survival between ACEI treatment Fosinopril versus placebo over 3 years follow up [24].

#### Mineralocorticoid receptor inhibitor (MRA):

There is evidence for benefit in CKD 1-3 subjects from general population studies such as RALES, EMPHASIS, EPHESIS on mortality and hospitalisations. In RALES, 48% of the 1658 patients had eGFR <60 ml/min/1.73m2, the risk reduction of death and heart failure hospitalisation was similar for subjects with eGFR < 60 or > 60ml/min per 1.73m2 [25]. Hyperkalaemia occurred more often in patients with eGFR<60 ml/min/1.73m2 than those > 60 [26]. Deterioration of kidney function was a problem as evidenced by more than 30% decline in eGFR in 14% patients in the trial of Eplerenone in Mild Heart Failure Patients for Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) [27]. Evidence for MRA in CKD 4,5 is lacking.

In two recent small randomised controlled trials in haemodialysis patients there was higher incidence of hyperkalaemia (>6.5 mmol/L) with spironolactone, and more so with a dose of 50 mg (e.g 8 out of 32 patients) than 25 mg daily (e.g 4 out of 26 patients) [28, 29]. Incidence of hyperkalaemia (>6.5 mmol/L) was also higher (11%) with eplerenone compared to placebo (2%) in 154 patients on haemodialysis [30].

#### Diuretics:

Diuretic therapy can cause adverse effects on blood concentrations of urea, creatinine, sodium and potassium in heart failure patients with CKD [31]. The changing creatinine and electrolytes may require decreased dose or cessation of diuretics which in turn causes fluid overload and hospitalisations.

Kidney venous congestion and consequent kidney dysfunction due to elevated right heart pressure is poorly understood and difficult to manage condition requiring escalation of diuretic doses with close monitoring of volume status, body weight, and creatinine [32]. The commonly used thiazide diuretics are not effective with advanced CKD and loop diuretics are often used with metolazone as necessary for adequate diuresis. Intravenous diuretics are used for acute decompensated heart failure. Spironolactone in acute heart failure patients can be natriuretic and help relieve congestion without significant adverse effect on serum potassium levels [33]. In carefully conducted study rapid diuresis was safe in CKD 3,4 patients with decompensated heart failure with high urine volumes 8425 ml (6341-10528) over 72 hours using furosemide 560 mg (300-815) and not associated with markers of tubular injury despite mild rise in serum creatinine [34].

#### Angiotensin receptor and neprilysin inhibitor (ARNI):

Trials from the general population showed benefits in mortality and hospitalisation with confirmed safety in CKD patients with eGFR >= 30 ml/min/1.73m2.The benefits of ARNI, was demonstrated for the first time in a large RCT of 8842 HFrEF patients, eGFR>30 ml/min/1.73m2 with a reduction in cardiovascular death and heart failure hospitalisation HR 0.80 (95%CI 0.73-0.87;p<0.001) [35]. There is evidence that ARNI may slow progression of CKD as compared with ACEi alone. Side effects such as hyperkalaemia are less common compared to ACEi or ARB. A meta-analysis of all trials suggested a lower incidence of serious hyperkalaemia (defined as K > 6.0mmol/L) with ARNI compared to enalarpil or valsartan with pooled relative risk of 0.76 (95%CI 0.65–0.89, P<0.007) and a lower incidence of worsening kidney function RR of 0.79 (95%CI 0.67–0.95, P < 0.010) [36].

#### Ivabradine:

Ivabradine a I(f) current inhibitor when used in 6658 clinically stable, beta-blocked, HFrEF patients, creatinine<220µmol/L improved cardiac death and heart failure hospitalisations [37]. This study included significant number of CKD 3 patients who benefitted with risk reduction ratio 0·82 (95% CI 0·75–0·90, p<0·0001). The safely and efficacy of Ivabradine in CKD 4,5 patients is unknown.

#### Sodium glucose cotransporter 2 inhibitor (SGLT2i):

The EMPEROR reduced trial included patients with HFrEF and CKD eGFR>20ml/min/1.73m2. 1799 out of 3730 (48%) patients had CKD eGFR<60 ml/min/1.73m2. Cardiovascular death and heart failure hospitalisations were reduced by 25% (hazard ratio, 0.75; 95%CI, 0.65 to 0.86; P<0.001) in the whole population of which 50% were diabetics and 73% had EF<30% [5]. The eGFR decline was slower with empagliflozin compared to placebo (–0.55 vs. –2.28 ml/minute/1.73 m2/year), for a between-group difference of 1.7ml/minute/1.73 m2/year (95% CI, 1.10 to 2.37; P<0.001). The primary endpoint was reached in 202/893 with empagliflozin compared to 237/906 in placebo among patients with eGFR<60. There was a 50% (95%CI 32-77) reduction in incidence of RRT or sustained loss of eGFR [5].

The DAPA-HF trial included patients with eGFR >30 ml/min/1.73m2 and EF<40%. The primary endpoint (worsening heart failure or CV death) was reduced by 26% (95% CI 65-85%). 40.6% (1926/4744) patients had eGFR <60ml/min/1.73m2) [9]. The reduction in primary endpoint was similarly observed in CKD and non-CKD patients hazard ratio 0.72 (95% CI 0.59-0.86) and 0.76 95% CI 0.63-0.92). Serious kidney adverse events occurred in 38 patients (1.6%) in the dapagliflozin group and in 65 patients (2.7%) in the placebo group (P = 0.009).

## Device therapy for heart failure with reduced ejection fraction and CKD

#### Cardiac Resynchronisation Therapy (CRT)

The benefits of CRT (with ICD) in patients with eGFR<60 ml/min/1.73m2 was similar to patients with eGFR>60ml/min/1.73m2. This was demonstrated in 1798 HFrEF patients with QRS duration more than 120 ms, eGFR 30-59 in 43% and <30 ml/min/1.73m2 in 7% of ICD patients, with reduction in death and hospitalisation for heart failure HR 0.75 (95%CI 0.64 to 0.87; P<0.001) [38]. The benefits in CKD stage 4,5 and on dialysis are unknown.

#### Internal Cardioverter and defibrillator (ICD)

Sudden Cardiac Death rates in patients on dialysis and with advanced CKD is high and even higher with heart failure [20]. There is some evidence of ICD in primary prevention of sudden cardiac death in HFrEF patients as demonstrated in a trial including CKD 3 patients [39]. However, the risk of infection is high in dialysis patients and recently completed trial in dialysis patient it provided no added benefit in prevention of sudden cardiac death (SCD) in patients with ejection fraction more than 35% [40].

## Management of heart failure with preserved ejection fraction and CKD

HFpEF patients with CKD can be diagnostically challenging as advanced CKD itself can present with fluid retention and high BNP levels. Presence of significant diastolic dysfunction on echocardiogram helps with confirmation of diagnosis. These patients may suffer from multiple hospital admissions due to fluid overload requiring high doses of diuretics. There is no proven treatment of HFpPF and CKD which may prolong life or reduce hospitalisation and treatment is mainly symptomatic [41].

## Multidisciplinary management

The heart failure patients with CKD are often frail elderly patients with complex medical needs. They visit multiple health professionals resulting in fragmented care and conflicting advice. This often results in not starting and/or discontinuation of proven therapy. Hence multidisciplinary care at the point of delivery is necessary particularly having the cardiologist and nephrologist together in one clinic.

We designed a multidisciplinary clinic with cardiologist, nephrologist [figure 3] attending the patient in the same room and the anaemia nurse providing intravenous iron and erythropoietin as necessary as we know that intravenous iron improves symptoms in HFrEF patients including patients with CKD 3 [42]. The first 124 relatively elderly [78.5 years (IQR 68.1–84.4years)] patients, over 234 days (IQR121–441days) had an improvement in RAASi therapy [43]. Proportions of heart failure with CKD patients on no RAASi decreased from 41.2% to 29.9% and those on single or dual RAASi therapy increased from 45.4% to 50.5% and 13.4% to 19.6%, respectively (p=0.03). This was not associated with significant changes in serum potassium or creatinine. Serum ferritin improved 131.0 to 267.5μg/L; P≤0.001) and number of patients with iron deficiency decreased from 56.7% to26.8%, P=0.002. In patients with iron deficiency at baseline, 43.6% received IV iron at the same clinic visit, with a significant increase in ferritin level (67.0 to 185.0 μg/L; P<0.001). The informal feedback from patients were very positive [44].

## Peritoneal Ultrafiltration in heart failure patients

Peritoneal dialysis or ultrafiltration has been used as an alternative strategy to treat subjects with NYHA class III and IV heart failure or endstage heart failure and chronic kidney disease refractory to maximally tolerated medical therapy. Different case series suggested that peritoneal ultrafiltration significantly reduced hospital stay, improved symptoms, functional class and quality of life [45-48]. A previous systematic review of 14 observational studies with 471 patients (average age 71.6 years; diabetes mellitus 47%; NYHA class III 38.9%-class IV 59.8%; ischemic cardiopathy 67.8%; mean LVEF 35%) suggested significant improvement in NYHA class and reduction in hospitalisations. Survival at 12 months varied between 47 and 95%. Mortality appeared to be associated with diabetes, higher basal eGFR, less change in EF after peritoneal ultrafiltration and less use of icodextrin [49]. Another systematic review of 31 observational studies with 902 diuretic-resistant HF subjects showed similar findings that peritoneal ultrafiltration improved left ventricular EF, NYHA Class and reduced hospitalisation frequency and duration compared to diuretic therapy alone. With follow-up > 1 year, the overall mortality was 48.3%. Survival was 42.1% with peritoneal dialysis and 45.0% with extracorporeal therapy [50].

However, there was so far no randomized controlled trial that evaluated whether peritoneal dialysis or ultrafiltration may impact clinical outcomes and quality of life in these patients. The Peritoneal Dialysis for Heart Failure (PDHF) study was a multicenter prospective randomised-controlled trial in subjects with severe diuretic-resistant NYHA Class III/IV heart failure and chronic kidney disease stage 3/4 already received optimal medical treatment being randomised to either continuation of conventional heart failure treatment or to additionally receiving peritoneal ultrafiltration with 1 overnight icodextrin exchange. The primary study endpoint was to examine change in 6-minute walk test between baseline and 28 weeks. Secondary outcomes were changes in patient reported quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire, short form 36 health survey results, hospitalisation, and mortality. The trial aimed to recruit 130 subjects but was stopped early due to inadequate recruitment. Over a 2-year period, 290 patients were screened from which only 20 met inclusion criteria and 10 were recruited. Reasons for ineligibility were fluctuating eGFR, suboptimal heart failure treatment, frailty, and patients being too unwell for randomization and patients’ unwillingness to engage in an invasive therapy, and suboptimal coordination between cardiology and kidney services, showing the challenges in performing clinical trials in this vulnerable group of subjects [51].

The peritoneal dialysis regimen performed for ultrafiltration purpose were very variable. Some reports used 1 - 3 daily continuous ambulatory peritoneal dialysis exchanges for ultrafiltration while others did 2 – 4 sessions weekly using automated peritoneal dialysis. The types of peritoneal dialysis fluid used were also very variable from standard glucose solutions to hypertonic glucose solutions or icodextrin. Icodextrin solution has the advantage of being glucose sparing and allowing once daily nocturnal exchange to be performed in these patients. Peritoneal ultrafiltration has also been used successfully in elderly subjects with refractory heart failure [52].

## Ongoing research and trials

The therapy of heart failure in CKD patients remains challenging and requires more research with established and novel therapies. The evidence for life-prolonging therapy CKD 4, 5 and dialysis patients with heart failure is lacking. Future studies should include such patients with advanced CKD and on kidney replacement to minimise unexpected deaths and hospitalisations. Safety and efficacy of Sacubitril/Valsartan is being test in dialysis patients in “The Effect of Sacubitril/Valsartan on Cardiovascular Events in Dialysis Patients and Efficacy Prediction of Baseline LVEF Value” study (NCT04572724).

Evidence of life-prolonging treatment of HEpEF in early and advanced CKD is lacking. Ongoing studies which may benefit include FINEARTS-HF (NCT04435626), a randomized controlled of finerenone (a non-steroidal MRA) in CKD patients with HFpEF. The “Phase IIb Safety and Efficacy Study of Different Oral Doses of BAY94-8862 in Subjects With Worsening Chronic Heart Failure and Left Ventricular Systolic Dysfunction and Either Type 2 Diabetes Mellitus With or Without Chronic Kidney Disease or Chronic Kidney Disease Alone (ARTS-HF)” is recruiting CKD 3 patients. Novel MRA therapy trial “Efficacy, Safety and Tolerability of AZD9977 (the novel MRA) and Dapagliflozin in Participants With Heart Failure and Chronic Kidney Disease (MIRACLE)” will include at least 30% of patients with eGFR<30 ml/min/1.73m2. (NCT04595370).

Empagliflozin is tested in acute heart failure patients with eGFR >20 ml/min/1.73m2 in “A Study to Test the Effect of Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure” (NCT04157751) with kidney failure as a secondary outcome.

The possible efficacy of peritoneal ultrafiltration is proposed to be tested in “Peritoneal Ultrafiltration in Cardio Renal Syndrome. (PURE)” study (NCT03994874) which may provide further insight in CKD 4 and 3 patients.

## Conclusion

Heart failure patients with CKD are common, difficult to treat, despite evidence in HFrEF with CKD1-3. Multidisciplinary approach with personalised care is the way forward.

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## Table 1

Title: Drug and device therapy for HFrEF in patients with CKD, based on available evidence

|  |  |  |  |
| --- | --- | --- | --- |
| Agents | CKD stages 1,2,3 | CKD stages 4,5 | Dialysis |
| Beta Blockers   | Should be used | May be used  | Should be used |
| ACE inhibitors | Should be used, with monitoring of creatinine and potassium | May be used with monitoring of creatinine and potassium. Dose modification may be necessary | No proven benefit, limited evidence  |
| Mineralocorticoid receptor antagonists | Should be used with careful monitoring of potassium | May be used with caution and monitoring of potassium | No proven benefit, may cause hyperkalaemia with high dose  |
| Angiotensin receptor blockers | Should be used with caution  | May be used with monitoring of creatinine and potassium | No proven benefits, may cause hyperkalaemia |
| Ivabradine  | May be used with sinus rhythm and stable on beta blockers | Unknown effects | Unknown effect |
| Angiotensin Receptor and Neprilysin inhibitor | May be used instead of ACEi/ARB | No proven benefit  | No proven benefits |
| Sodium Glucose Co-Transporter inhibitor\* | Should be used with or without diabetes | Unknown effects  | No proven benefits |
| Hydralazine and Isosorbide dinitrate  | Should be considered intolerant to ACE/ARB | May be considered intolerant to ACE/ARB | No proven benefits |
| Cardiac Resynchronisation therapy | Should be offered to patients with wide QRS | No proven benefit\*\*  | No proven benefits, increased risk of infections |
| Internal Cardioverter Defibrillator therapy | Should be offered patients | No proven benefit  | No benefit in dialysis patients with EF>35%, increased risk of infections\*\*\* |

Legend: Most evidence is from heart failure trials which included patients with CKD stages 1,2,3 in HFrEF patients with improvement in cardiovascular mortality and heart failure hospitalisations. \*SGLT2i has significant renal benefits, \*\* few patients were included in the trials, \*\*\* based on Randomised Trial in dialysis patients with ejection fraction more than 35%

## Figures

Figure 1: The interdependence of kidney and heart in heart failure patients with CKD

Figure 2: The treatment options for heart failure in CKD patients

Legend : The figure shows the treatment choices for heart failure in CKD patients including life prolonging therapy for HFrEF in CKD 1,2,3 as the base, decongestion therapy on the right, choices for kidney replacement therapy on the left. It also highlights the importance of close collaboration between primary care, heart failure nurses, cardiologists and nephrologists and close monitoring of blood pressure, weight, fluid balance and laboratory parameters. ACEi=Angiotensin converting enzyme inhibitor, ARB=Angiotensin Receptor Blocker, ARNI=Angiotensin Receptor Neprilysin Inhibitor, MRA=Mineralocorticoid antagonist, CRT=cardiac Resynchronisation therapy.

Figure 3: The delivery and benefits of multidisciplinary clinic for CKD patients with heart failure

Legend: The figure shows the care givers, therapy delivered and possible benefits of multidisciplinary CKD heart failure clinic in a tertiary care centre [43].