# Invited Review

## Title: Management of heart failure patient with chronic kidney disease

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### Abstract

Chronic Kidney Disease (CKD) is common in heart failure patients, associated with high mortality and morbidity, and worse on dialysis. Despite increasing use of evidence-based drug and device therapy in heart failure patients in the general population, CKD patients have not benefitted. This review discusses prevalence and evidence of drug, device and kidney replacement therapy of heart failure in CKD.

Evidence for beta-blocker, ACE inhibitor, angiotensin-receptor blocker, angiotensin-receptor-neprilysin-inhibitor and sodium-glucose co-transporter inhibitor therapy in mild to moderate CKD has emerged from general population studies in heart failure patients with reduced ejection fraction (HFrEF). Beta-blockers have been shown to improve outcomes in HFrEF patients with all stages of CKD, including patients on dialysis. Whereas ACE-inhibitor studies of HFrEF selected patients with creatinine <200µmol/L, <265µmol/L for angiotensin-receptor blocker studies and <220µmol/L for mineralocorticoid-receptor antagonist studies; excluding severe CKD patients. Angiotensin-receptor-neprilysin-inhibitor therapy was successfully used in randomised trials in patients with eGFR as low as 20ml/min/1.73m2. Hence benefits of renin-angiotensin-aldosterone-axis-inhibitor therapy patients with mild to moderate CKD has been demonstrated, yet such therapy is not utilised in all suitable patients due to fear of hyperkalaemia and worsening kidney function. Sodium-glucose co-transporter inhibitor therapy improved mortality and hospitalisation in CKD 3,4 (eGFR>20ml/min/1.73m2) patients with HFrEF. High-dose and combination diuretic therapy, often necessary, may be complicated with worsening kidney function and electrolyte imbalances, but has been used successfully in CKD3 and 4 patients. Intravenous iron improved symptoms in heart failure patients with CKD3; and high-dose reduced the heart failure hospitalisations by 44% in dialysis patients. Cardiac-resynchronisation therapy reduced death and hospitalisations in heart failure patients with CKD3. Peritoneal dialysis in patients with symptomatic fluid-overload improved symptoms and prevented hospital admissions. Evidence suggest combined cardiology-nephrology clinics may help improve management of HFrEF patients with CKD. A multidisciplinary approach may be necessary for implementation of evidenced-based therapy.

Key words: Chronic Kidney Disease, Heart Failure, Drug therapy, Device therapy, Dialysis, Multidisciplinary care.

### Epidemiology of CKD in heart failure

Patients with heart failure frequently suffer from co-existing chronic kidney disease (1). Large meta-analysis suggests approximately half (49%) of the patients with heart failure suffer from CKD (excluding registry studies) (2). The incidence of heart failure in CKD patients was 18 per 1000 person-years in large population based study from the USA (3). Prevalence of heart failure increases with decreasing kidney function, and approximately 44% of dialysis patients suffer from heart failure, half with reduced ejection fraction (1). The prognosis of heart failure patients with CKD is poor and worsens with deteriorating kidney function with a higher mortality; (odds ratio 2.34, 95% CI 2.20–2.50, p<0.001) (4). The coexisting CKD is usually caused by diabetes, hypertension or ischaemic kidney disease (see case in table 1). Consider a 54-year-old man with diabetes, hypertension and heart failure due to severe coronary artery disease who presents with fluid overload and near end stage kidney disease. In patients like these, prognosis is poor and management is difficult. The CKD patients were older in most studies which may be due to age related decline in GFR; however presence of CKD was independent prediction of mortality adjusted for age (5). In addition, a significant number of heart failure patients also suffer from acute kidney injury (AKI) due to a variety of reasons such as sepsis, kidney hypo-perfusion and drug toxicity with significant adverse outcomes (6). However the worsening of estimated glomerular filtration rate (eGFR) due to initiation of renin-angiotensin-aldosterone-system inhibitors (RAASi) does not bear the same long-term consequences as persistent AKI due to sepsis or hypovolemia (7,8).

### The interdependence of heart and kidney

The heart and the kidney are interlinked in physiological states to maintain salt-water homeostasis and normal blood pressure. In health, the crosstalk between the two organs help the body to respond to changes in kidney perfusion due to volume depletion or overload to maintain appropriate blood flow to vital organs: avoiding ischaemia or hyperperfusion injury. In disease, the kidney and heart can affect each other’s function adversely (9). On one hand inability to excrete salt and water and abnormal renin secretion by the diseased kidney increases cardiac preload, afterload and heart failure; on the other hand poor kidney perfusion due to low cardiac output and renal venous congestion due to right heart failure causes kidney failure . When both organs are diseased, they adversely affect each other’s function, which poses significant challenges with management of patients with compromised heart and kidney function. Common pathologic mechanisms may affect both organs and cause simultaneous dysfunction of the kidney and the heart. (10)

The neurohumoral interactions between the two organs are complex in disease states as follows:

The natriuretic peptides, which induce diuresis with cardiac volume overload are up regulated with kidney disease to help with associated fluid retention; but can be elevated due to poor elimination of the peptide molecules by the kidneys themselves. During treatment of heart failure with diuretics, while congestive symptoms and Brain Natriuretic Peptide (BNP) concentrations improves, the kidney function may worsen due to reduction in kidney plasma flow. (11) Stopping of diuretics may improve kidney function but worsen cardiac volumes and levels of BNP.

The renin, angiotensin and aldosterone levels increase with hypotension, in response to low kidney perfusion, in HFrEF, to improve GFR by efferent arteriolar vasoconstriction and increase systemic blood pressure. However the excess fluid retention due to the increased levels of renin, angiotensin and aldosterone may increase the volume overload of the heart and further deterioration of heart failure.

Treatment with ACEi/ARB lowers intraglomerular pressure due to efferent arteriolar vasodilatation and apparent worsening of kidney function, which causes anxiety in treating physicians. However with ACEi eGFR decline upto 35% was associated with improved heart failure hospitalisation rates (12).

Progression of CKD in heart failure patients is perhaps faster than in non-heart failure patients in the absence of AKI, for example in the recently completed EMPEROR-reduced trial the eGFR declined by 4.2 ml/min/1.73m2 (95% CI 3.1-5.3) over a median follow-up of 16 months, in the placebo arm with most patients on ACEi and baseline eGFR 62±21 ml/min/1.73m2(13).

### Acute Kidney Injury in patients with heart failure and CKD

The incidence of acute kidney injury in patients with heart failure is high. Incidence of acute kidney injury among acute heart failure admissions at St George’s Hospital was 17% in 1,094 patients admitted with acute decompensated heart failure and inpatient mortality was 21% with stage 1, 36% with stage 2 and 48% with Stage 3 AKI (p<0.001) (6). In a meta-analysis of 28 trials with 49,890 patients the incidence of AKI or worsening of kidney function was 23% and the mortality was higher odds ratio of 1.81 [1.55-2.12; p<0.001] over 488±569 days (2). In a unique situation in cardiology where the kidney insult is known, and preventive measures are used i.e. with coronary angiogram the incidence was 7.1% in 985,737 US patients undergoing per cutaneous coronary interventions and was higher with presence of CKD and heart failure (14). The other causes of AKI in heart failure patients are infection, sepsis, volume depletion, drug toxicity and obstruction of the urinary tract in older men with enlarge prostate.

Certain classes of drugs decrease kidney function at therapy initiation which is distinguished from “true AKI” by the term “permissive AKI” or “hemodynamic AKI”. The angiotensin converting enzyme inhibitor and angiotensin receptor blockers as mentioned above works by dilating the efferent arteriole and thereby the lowering of intra-glomerular pressure and preventing long-term harmful effects of hyperfiltration in individual nephrons causing glomerulosclerosis, in patients with chronic kidney disease. The Sodium-glucose-cotransporter 2 inhibitors (SGLT2i), a recently introduced class of oral hypoglycemics causes a drop in estimated glomerular filtration (eGFR) at therapy initiation. With canagliflozin a SGLT2i in the CREDENCE study (baseline eGFR 56 ml/min/1.73m2) the initial drop of eGFR was followed by a slowing of progression of chronic kidney disease and improvement in heart failure outcomes. The drop in eGFR at 3 weeks with Canagliflozin arm was 3.17 ml/min/1.73m2 (95% CI 3.87 to 2.47) more than placebo, yet the decline in eGFR with longer time was less (15). The drop in eGFR in the first 4 weeks was similar with empagliflozin in the heart failure trial where the baseline eGFR was 62±22 ml/min/1.73m2(13). The initial worsening of glomerular filtration rate is likely, due to increased delivery of salt and water to the distal tubule, which in turn decreases glomerular filtration pressure through the crosstalk between the distal tubule and efferent arteriole of the same nephron by a mechanism known as ‘tubulo-glomerular feedback’.

## Therapy of heart failure in patients with CKD

Management of chronic heart failure in the general population has changed over the last three decades. Novel agents such as ivabradine, angiotensin receptor neprilysin inhibitor, mineralocorticoid receptor inhibitors, Cardiac resynchronization therapy has improved survival. Many of the trials included patients with mild to moderate CKD and evidence has emerged for newer agents in heart failure patients with CKD which is discussed below, summarized in table 2 and figure 1 (1).

### Diuretic therapy

As seen in the case in table 1, water retention and lung congestion in CKD heart failure patients causes breathlessness, poor exercise tolerance, multiple hospital admissions - resulting in poor quality of life. Diuretic therapy is challenging in these patients due to the need for higher doses, frequently causing transient worsening kidney function, electrolyte imbalances such as hyponatraemia and hypokalaemia (16). These challenges results in the patients needing to visit a variety of specialty doctors, each changing diuretic agents and diuretic doses, often to minimise adverse electrolyte and creatinine changes and resulting in poor symptom control for the volume-overloaded patient. Renal venous congestion and consequent kidney dysfunction due to elevated right heart pressure is an often mentioned, poorly understood, difficult to manage condition requiring careful escalation of diuretic doses with close monitoring of weight, electrolytes and creatinine (17). With appropriate use of diuretic therapy, working on different segments of the nephron, symptoms can be controlled and survival may be better. The commonly used thiazide diuretics may not be effective and loop diuretics are often used with metolazone as necessary. Intravenous diuretics are used for admitted patients with acute decompensated heart failure. However there is no significant difference between continuous infusion or bolus administration of intravenous diuretics (16). Spironolactone in acute heart failure patient can be natriuretic and relieve congestion without significant adverse effect on serum potassium levels (18). A study by the NHLBI Heart Failure Clinical Research Network have demonstrated that rapid diuresis in acute heart failure patients of 8425 ml (6341-10528) over 72 hours with 560 mg (300-815) of Furosemide in 360 patients with CKD 3,4 and acute heart failure was safe, not associated with elevation of markers of tubular injury despite some worsening of creatinine (19). Aggressive diuresis may be useful provided the patient is adequately decongested as evidenced by improvement of physical symptoms, deceased BNP and hemoconcentration; despite the rise in creatinine (20).

### RAAS inhibitor therapy of heart failure with reduced ejection fraction in CKD

Randomised controlled trials have shown improvement of survival of heart failure patients with use of ACEi (or ARB) and mineralocorticoid receptor antagonists. Most of these studies included patients with mild to moderate (i.e. stages 1,2 and 3) CKD (21). Severe CKD patients have been excluded from most ACEi inhibitor studies (see tables 2 and 3 and figure 1).

MRA Therapy has been associated with improved survival of symptomatic heart failure patients. 50% of the patients in a randomised control trial of spironolactone had a GFR of less than 60 ml/min/1.73m2, hence the benefits of the trial extended in CKD patients. Similarly, eplerenone was beneficial in patients with post myocardial infarction heart failure in CKD patients. However, hyperkalaemia was not infrequent and was associated with discontinuation of therapy.

The use of ACEi inhibitors and MRAs, particularly in CKD patients is often associated with hyperkalaemia and rising creatinine. Rising creatinine has been observed in ACEi trials upto 40% without significant impact of long-term outcomes (12,22). A rise upto 30% can be viewed as due to haemodynamic changes due to RAASi (23). In fact, such a change may be beneficial and named “permissive AKI” as opposed to “true AKI” due to other reasons in HFrEF patients, which requires careful history taking and physical examination (7). The RAASi drugs should be held when kidney blood flow autoregulation is necessary in the patient e.g. with diarrhoea causing volume depletion.

Patients are referred back and forth between nephrologists and cardiologists with RAASi initiation induced changes creatinine and potassium, resulting in multiple hospital attendances and often discontinuation of the RAASi. Analysis of 194,456 patient records showed increasing frequency of hyperkalemia, up to 30% in CKD stages 4-5 if measured >4 times a year; and discontinuation of ACEi/ARB in 24% (24). Nephrologists traditionally have managed hyperkalaemia with judicious use of diuretics and correction of acidosis, but the oral potassium binders such as patiromer or sodium zirconium cyclosilicate may be useful (25). Randomised controlled studies of new potassium binders for maximisation of RAASi therapy in advanced CKD patients with heart failure are necessary. A close collaboration between nephrologists and cardiologists is necessary for successful initiation and continuation of RAASi in CKD patients with heart failure.

### Angiotensin receptor and Neprilysin inhibitor therapy of heart failure with reduced ejection fraction in CKD

The large randomised controlled trial of dual angiotensin receptor and Neprilysin inhibitor (ARNI) therapy excluded patients with eGFR<30 ml/min/1.73 m2, (see tables 2 and 3 and figure 1) however included patients with only mild CKD (26). A randomised controlled trial of ARNI including patients with eGFR as low as 20 ml/min/1.73m2 demonstrated safety and efficacy similar to irbesartan (27). More recently ARNI therapy has been shown to slow the progression of CKD in HFpEF patients, better than valsartan. (28) The recommended starting dose for patients with eGFR<60 ml/min/1.73m2 is 24 mg Sacubitril and 26 mg valsartan twice a day, at least 36 hours after stopping ACEi or ARB; and dose increased with careful monitoring of creatinine, potassium and blood pressure.

### Ivabradine and beta-blocker therapy of Heart Failure with reduced ejection fraction in patients with CKD

Beta-blockers have been proven beneficial in HFrEF patients with CKD from trials with CKD and general population studies including CKD patients (see tables 2,3 and figures 1 and 2) (29-33). Carvedilol has been shown to be beneficial in patients with heart failure with CKD 5 on dialysis (34).

The SHIFT study demonstrated improved hospitalisation and deaths due to heart failure with Ivabradine in HFrEF patients with heart rate above 70 beats per minute despite betablocker therapy, which included patients with creatinine<220 µmol/L. The study included 1589 patients with CKD 3 and benefits in CKD were similar to non-CKD patients (35). Ivabradine is metabolized by the CYP3A4 enzyme in liver and gut and renal elimination is minimal. The dose is 2.5 to 7.5 mg twice a day and does not require dose adjustment with creatinine clearance of >15ml/min.

### Sodium Glucose Cotransporter 2 inhibitor therapy of heart failure with reduced ejection fraction in CKD

The SGLT2i therapy in heart failure patients has been recently shown to reduce mortality and hospitalisations. The recently completed dapagliflozin study included 1926 CKD 3 patients and was able to achieve a risk reduction for composite endpoints of 28% versus 24% in patients with eGFR>60 ml/min/1.73m2 (see tables 1 and 2). Adverse kidney events with dapagliflozin was not higher compared to placebo (36). More recently empaglifozin was shown to reduce heart failure hospitalisation and eGFR decline, including patients with eGFR as low as 20ml/min/1,73m2 (48% eGFR<60 ml/min/1.73m2) (13). The DAPA-CKD trial has reported lower heart failure admissions in CKD patients (eGFR >25 but <75 ml/min/1.73m2) and proteinuria.

### Management of iron deficiency and anaemia of heart failure with reduced ejection fraction in CKD

Nephrologists has been using intravenous iron for the last three decades to treat renal anaemia in predialysis and dialysis patients with CKD. A recent study from UK have shown benefits of high dose intravenous iron in dialysis patients in reducing mortality and morbidity, together with heart failure hospitalisations by 44% (37). A previous trial of benefits of intravenous iron in the HFrEF patients included patients with early stages of CKD (38). A collaboration between cardiologists and nephrologists may assist the management of iron deficiency in HFrEF patients CKD.

### Kidney replacement therapy

CKD is a progressive disease with declining kidney function over time, causing frequent episodes of fluid overload, hyperkalaemia, further complicated by episodes of AKI. With eGFR less than 20 ml/min/1.73m2, decisions need to be made, in discussion with the patient, about indications, appropriateness and modality of kidney replacement therapy (RRT). Careful consideration of patient expectations, co-morbidities, frailty and quality of life are necessary factors to consider in starting RRT. Patients with heart failure on dialysis has very poor prognosis with a 5-year survival of 12.5% (39). There may be symptomatic relief and decreased hospitalisation with peritoneal dialysis in carefully selected patients (40). In a study of 118 heart failure patients with CKD peritoneal dialysis was associated with improvement in quality of life and NYHA class (41). A metanalysis of 23 studies demonstrated benefits of peritoneal dialysis in heart failure patients with CKD with improved hospitalisation rates and heart function (42). In patients with refractory heart failure overnight ultrafiltration with icodextrin solution improved quality of life, heart function and NYHA class (43). Haemodialysis may be tricky in patients with low blood pressure, but more frequent dialysis and longer nocturnal dialysis may be useful for fluid removal. However, creation of artrerio-venous fistula or graft for haemodialysis may cause dilatation of left atrium and right ventricle and associated heart failure (44). For acute heart failure patients with low blood pressure slow ultrafiltration with continuous kidney replacement therapy may be useful.

### Device therapy

Rate of CKD progression to dialysis, associated blood stream infection, patient’s age and general health determines the benefits of other treatments such as use of cardiac resynchronisation therapy and implantation of defibrillators. Cardiac synchronisation therapy was beneficial in CKD 3 patients in a Canadian study which included more than half patients with eGFR<60 ml/min/1.73m2 (45). In a meta-analysis of 5 retrospective studies defibrillator therapy was associated with improvement of mortality in patients at high risk of sudden cardiac death (46). Defibrillator therapy in dialysis was associated with high infection rates and a recent randomised trial in haemodialysis patients has failed to show any significant benefit (47,48).

### Heart failure with preserved ejection fraction in CKD patients

The diagnosis of HFpEF in patients with CKD may be challenging. The brain natriuretic peptide levels may be elevated due to CKD and may not be diagnostic. The fluid overload may be due to CKD itself. These patients have similar risk of poor outcomes and suffer frequent hospital admissions due to fluid overload similar to heart failure patients with reduced ejection function (49). Careful use of diuretics is necessary to control the symptoms of volume overload. NSAIDS should be avoided which can cause AKI and fluid retention in CKD patients and mimic HFpEF. There is no compelling evidence of effective therapy in HFpEF to improve outcomes such as cardiovascular mortality or heart failure hospitalizations. However, large trials are underway, such as FINEARTS-HF (NCT04435626), a randomized controlled of finerenone (a non-steroidal MRA) in CKD patients with HFpEF.

### Multidisciplinary care

The CKD - heart failure patients need multidisciplinary care to minimise the number of healthcare visits. A close working relationship between nephrologists and cardiologists is the key to control symptoms and prolonging life where possible; with diuretics, ACEi and MRA, while avoiding electrolyte abnormalities and AKI; and advising appropriately for dialysis and device therapy (see figure 2) (1). In a recent study in St George’s Hospital multidisciplinary care was associated with improvement in iron stores and RAASi use in 124 patients with CKD and heart failure (50). A multidisciplinary cardiology-nephrology service with doctors and specialist nurses in the UK has demonstrated better utilisation of evidence-based therapy and healthcare resources (51). A similar multidisciplinary meeting for pre-kidney transplant patients with cardiologists, nephrologists, transplant surgeons and specialist nurses showed that high cardiac risk patients can be safely transplanted (52).

### Way forward

To achieve appropriate therapy and hence the best possible outcome , combined cardiology – nephrology clinics are necessary as demonstrated by the success of the kidney failure heart failure clinic at St George’s hospital which manages kidney and heart care, together with intravenous iron and advice on dialysis therapy (50). Patients appreciate the multiple benefits from a single visit and provide excellent feedback. The multidisciplinary “one stop shop” clinic is very patient centred and helps with decision on RAASi, device therapy and intravenous iron administration simultaneously, but requires proper resources including the presence of nephrologist, cardiologist, anaemia nurse and appropriate space all at the same time. However, once economic and outcome benefits of a combined clinic is established, such clinics need to be replicated in other institutions. With improved knowledge among cardiologists and nephrologists, multidisciplinary approach, evidenced-based therapy can be implemented in early and moderate CKD patients. However we recognise more studies are necessary to strengthen evidence base in advanced CKD patients.

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## Tables

Table 1: Case discussion

|  |
| --- |
| Presentation |
| A 54-year-old man was referred to a joint cardiology-nephrology clinic due to progressive oedema, increasing breathlessness (NYHA class 3), decreased urine output and stage 5 chronic kidney disease. On examination he had leg oedema, weight since last hospital visit had increased by 9 Kg, blood pressure was 158/70 mm Hg, pulse rate was 74/min, jugular venous pressure was elevated and bibasilar chest crepitations were audible. He had no ascites. Four years ago, he was diagnosed with biopsy proven, stage 3, diabetic nephropathy; multi-vessel, inoperable coronary artery disease and heart failure with reduced ejection fraction. He suffered from hypertension and hypercholesterolemia. |
| Investigation |
| His echocardiogram showed reduced ejection fraction of 20%, ECG showed sinus rhythm with QRS duration of 100 ms. His blood tests showed: sodium 130 mmol/L, potassium 5.7 mmol/L, creatinine 4.2 mg/dL (372 µmol/L), eGFR 15 ml/min/1.73m2, and N Terminal pro B type natriuretic peptide (NT pro BNP) 2742 ng/L. |
| Management  |
| He was previously treated with aspirin, clopidogrel, bisoprolol, ramipril, atorvastatin, metformin and insulin; and hospital admissions were prevented using variable doses furosemide, intermittent metolazone with careful monitoring of weight and electrolytes. In the joint clinic his furosemide dose was increased, metolazone started daily, betablocker dose increased, intravenous iron given and metformin stopped. He was informed about long-term kidney replacement therapy and visited the peritoneal dialysis unit. All of this was only possible because he was seen in a joint CKD-Heart Failure clinic with access to specialist nurses. |

Table 2: Heart failure studies in general population with clinical characteristics including creatinine or eGFR based inclusion criterion

|  |  |  |
| --- | --- | --- |
| **TRIAL (year)** | **Age & Diabetes** | **<Creatinine or >GFR****(mean)** |
| ACE inhibitor |
| SAVE 1992(53) | 59y 29% | <2.5 mg/dl |
| SOLVD 1991 (54) | 61y 26% | <2.5 mg/dl (1.2 mg/dL) |
| SOLVD prevent 1992(55) | 59y 15% | <2.5 mg/dl (1.2mg/dL) |
| Angiotensin Receptor Blocker |
| CHARM 2003(56)  | 66y 28% | <3 mg/dL [265 µmol/L] |
| Βeta Blocker |
| CIBIS II 1997(30) | 61y | <3.4 mg/dL [300 µmol/L] |
| COPERNICUS 2001(31) | 63y | <2.8 mg/dL [247 µmol/L] [1.4 mg/dL (134)] |
| MERIT HF 1999(29) | 63y 25% | - |
| SENIORS(32) | 76y 27% |  <2.8 mg/dL [250 µmol/L] 1.15 mg/dL [102 µmol/L] |
| Mineralocorticoid antagonists |
| RALES 1999(57) | 65y | <2.5 mg/dL [221 µmol/L] |
| EMPHASIS 2011(58) | 69y 34% | >30 ml/min (1.1 mg/dL) |
| EPHESUS 2003(59) | 64y 32% | <2.5 mg/dL [220 µmol/L] (1.1 mg/dL) |
| Angiotensin Receptor Blocker Neprilysin Inhibitor |
| PARADIGM HF 2014(26). | 64y 35% |  >30 ml/min (1.1 mg/dL) |
| Ivabradine |
| SHIFT 2010(60) | 61y 30% |  - (74 ml/min/1.73m2) |
| Cardiac Resynchronisation Therapy |
| RAFT 2010(45) | 66y 30% | -\*51% patients<60ml/min/1.73m2 |
| SGLT2 inhibitor |
| DAPA-HF 2019(36) | 66 y 41% | >30ml/min/1.73m2 |
| EMPEROR-reduced 2020 | 67 y 50% | >20ml/min/1.73m2 |

Legend: Table includes pivotal studies which has helped us to draw our conclusions on therapy of HFrEF patients with CKD (particularly stage 3). The table highlights that patients included in these studies had relatively high creatinine and low eGFR due to the fact that CKD is common in heart failure patients. Hence significant numbers of CKD patients were included. Studies included significant proportion of diabetes patients. \*51% of the included patients had eGFR<60ml/min/1.73m2

Table 3: Pharmacotherapy of heart failure in patients with CKD

|  |  |  |
| --- | --- | --- |
| Agents | CKD stages 1,2,3 | CKD stages 4,5 |
| ACE inhibitors | Should be used in all patients with HFrEF, with monitoring of creatinine and potassium | May be used in HFrEF with monitoring of creatinine and potassium. Dose modification may be necessary |
| Beta Blockers | Should be used all HFrEF | May be used in HFrEF |
| Minerelocorticoid receptor antagonists | Should be used in HFrEF with careful monitoring of potassium | May be used in HFrEF patients with caution and monitoring of potassium |
| Angiotensin receptor blockers | Should be used in all HFrEF with caution  | May be used in HFrEF with monitoring of creatinine and potassium |
| Ivabradine  | May be used in HFrEF with sinus rhythm and stable on beta blockers | Unknown effects |
| Angiotensin Receptor and Neprilysin inhibitor | May be used in HFrEF patients instead of ACEi/ARB | Unknown effects |
| Sodium Glucose Co-Transporter inhibitor | Can be used HFrEF patients with or without diabetes | Unknown effects  |
| Hydralazine and Isosorbide dinitrate  | Should be considered in HFrEF patients intolerant to ACE/ARB | May be considered in HFrEF patients intolerant to ACE/ARB |

## Figures Title and Legends

Figure 1 The evidence of heart failure management in patients with chronic kidney disease with different levels of kidney function

Legend: Adapted from KDIGO consensus conference report. The increasing levels of evidence for improved outcomes (mortality and hospitalizations) is shown for each therapy on the Y axis with increasing levels of GFR on the X axis. Evidence is strong for BB, ACEi, ARB, MRA and moderate for CRT and Ivabradine for eGFR> 30 ml/min/1.73m2. ACEi,angiotensin-converting enzyme inhibitor;ARB, angiotensin II receptor blocker; BB,b-blocker; CKD G5D, chronic kidney disease glomerular filtration rate category 5 patient on dialysis; CKD G5 ND, chronic kidney disease glomerular filtration rate category 5 patient not on dialysis; CRT, cardiac resynchronization therapy; EF, ejection fraction; eGFR, estimated glomerularfiltration rate; GFR, glomerularfiltration rate; H-ISDN, hydralazine-isosorbide dinitrate; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; MRA, mineralocorticoid receptor antagonist.

Figure 2 Management strategy for patients with heart failure in CKD patients including kidney replacement therapy

Legend: Adapted from KDIGO consensus conference report. Stepwise, evidence-based, drug therapy (increasing levels of evidence from top to bottom of the pyramid) is shown in the middle. The bars on either side of the pyramid shows relevant supportive treatement. ACEi, angiotensin-converting enzyme inhibitor; AF, atrialfibrillation; AKI, acutekidney injury; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor;CKD-MBD, chronic kidney disease–mineralbone disorder; CRT, cardiac resynchronization therapy; CRRT, continuous kidney replacement therapy; H-ISDN, hydralazine-isosorbide dinitrate;ICD,implantable cardioverter-defibrillator; NSAID, nonsteroidal anti-inflammatory drug; RAASi, renin-angiotensin-aldosterone system inhibitor.