Heart Failure

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GUIDELINES

Chronic kidney disease and kidney transplant recipients

a. We recommend that an angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist be prescribed for patients with chronic kidney disease (CKD) (or kidney transplant) and heart failure (1B).
b. We recommend that a beta-blocker be prescribed for patients with CKD (or kidney transplant) and heart failure (1B).
c. We suggest that patients with CKD or kidney transplant recipients who meet the criteria for an implantable device should be considered for such devices (2C).

Dialysis

d. We suggest that patients receiving dialysis who have heart failure should be prescribed an angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist (2D).
e. We suggest that patients receiving dialysis who have heart failure should be prescribed a beta-blocking agent (2C).
f. We suggest that an angiotensin receptor antagonist could be added to an angiotensin-converting enzyme inhibitor and beta-blocker in patients who continue to experience symptoms due to heart failure (2C).

UNGRADED SUGGESTIONS FOR CLINICAL CARE

Chronic kidney disease and kidney transplant recipients

- For patients with CKD (or kidney transplant) symptomatic on the recommended agents, the following therapies could be considered as a third agent (ungraded):
  - Aldosterone antagonists have mortality benefit in people without CKD, but this may be attenuated in CKD and offset by greater toxicity
  - Angiotensin receptor antagonist added to the angiotensin-converting enzyme inhibitor reduces hospitalisation but not mortality in people without CKD, but there is no data in CKD and potential increased toxicity
  - Polyunsaturated fatty acid (PUFA), vasodilators and digoxin have all been studied in heart failure patients, but there is insufficient data to recommend for or against their use in heart failure patients with CKD receiving angiotensin-converting enzyme inhibitor and beta-blocker therapy

- Diuretic therapy should be prescribed as required to control volume state with careful monitoring of kidney function and electrolytes (ungraded).

- Treatment of anaemia in people with CKD and heart failure should follow the KHA-CARI Guideline “Biochemical and Haematological Targets: Haemoglobin” without modification because of the presence of heart failure (ungraded).

Dialysis
- Treatment of anaemia in people requiring dialysis who have heart failure should follow the KHA-CARI Guideline "Biochemical and Haematological Targets: Haemoglobin" without modification because of the presence of heart failure (ungraded).

**IMPLEMENTATION AND AUDIT**

In order to be implemented, this guideline should be made accessible to both the nephrology and cardiology communities. Access via web link from the relevant society and guideline websites would be most effective.

Introduction of recording of heart failure status in the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry would enable measurement and monitoring of outcomes in dialysis and transplant patients with heart failure.

**BACKGROUND**

Chronic kidney disease (CKD) and chronic heart failure (CHF) frequently co-exist. The mechanisms for this [1], and a potential classification of this “cardiorenal syndrome” [2], have been reviewed in depth by others. Risk factors such as hypertension and diabetes are common to both CKD and CHF. Many current treatment recommendations for the management of CHF are based on the highest levels of evidence. However, most guidelines make no recommendations specific to patients with CKD. This guideline seeks to fill this gap.

Chronic kidney disease is defined as a glomerular filtration rate (GFR) less than 60mL/minute, unless otherwise stated. This is “moderate” (Stage 3 or worse) CKD according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) Clinical Practice Guidelines for Chronic Kidney Disease [3]. However, not all studies in this guideline meet the NKF KDOQI criteria of having two measures of kidney function at least 3 months apart.

The following definition of CHF stated in the National Heart Foundation (NHF) of Australia Guideline [4, 5] is used for this Guideline:

“A complex clinical syndrome with typical symptoms (e.g., dyspnoea, fatigue) that can occur at rest or on effort that is characterised by objective evidence of an underlying structural abnormality OR cardiac dysfunction that impairs the ability of the ventricle to fill with or eject blood (particularly during exercise).”

This guideline does not consider “heart failure with reduced ejection fraction” and “heart failure with preserved ejection fraction” separately.

The prevalence of CHF or reduced systolic function is increased in patients with CKD compared to people with normal kidney function. In the Chronic Renal Insufficiency Cohort, a history of CHF was reported by 15% of participants with a GFR<30mL/minute, compared to 5% in participants with GFR>60mL/minute [6]. Likewise, the prevalence of CKD is very high in CHF patients. In many trial cohorts, this prevalence is over one third and patients with CHF who also have CKD have a greater mortality risk than patients with CHF and normal kidney function [7-10]. In fact, reduced creatinine clearance was a stronger predictor of adverse outcome than reduced left ventricular ejection fraction (LVEF) in one study [11].

Heart failure is also a significant co-morbidity in end-stage kidney disease (ESKD). The prevalence of CHF has been reported in between 31-40% of patients commencing dialysis [12, 13], and patients receiving dialysis who have co-morbid CHF have a greater mortality than patients with no CHF [13, 14].

Heart failure may develop “de novo” after receiving a kidney transplant. Using United States Medicare Claims data, the cumulative incidence of de novo CHF was 10.2% after 12 months and 18.3% after 36 months compared to 12.0% and 32.3%, respectively for patients remaining on dialysis on the transplant waiting list [15]. The cumulative incidence of de novo CHF in patients who survived the first post-transplant year without CHF has been reported to be 3.6% at 5 years and 12.1% at 10 years [16].

The objectives of this guideline are to summarise the available evidence from randomised controlled trials (RCT) for treatment of CHF in patients with CKD. Data will be presented separately for patients in the following categories:
1. Patients with CKD defined by a GFR < 60 mL/minute not requiring dialysis, and kidney transplant recipients
2. Patients receiving dialysis

The following treatments will be considered:

1. Blockade of the renin-angiotensin system
2. Blockade of beta-adrenergic receptors
3. Aldosterone antagonists
4. Digoxin
5. Vasodilators (hydralazine and nitrates)
6. Treatment of anaemia
7. Strategies to control volume state
8. Use of Implantable Devices
9. Other therapies

The recommendations for patients with CKD and kidney transplant are grouped together because these patients are similar in terms of current actual kidney function, and there are no trials that specifically enrolled kidney transplant recipients with CHF to study a heart failure intervention. It is acknowledged that kidney transplant recipients will differ in many ways from CKD, including time receiving dialysis, presence of arteriovenous fistula and immunosuppression.

A number of RCTs have been performed in patients with CHF that provide a strong evidence base underpinning many guideline recommendations [4, 17, 18]. Evidence for each therapy in patients without kidney disease is presented in the section on “Patients with CKD and kidney transplant recipients”, along with a summary of the Australian National Heart Foundation Heart Failure Guideline [4, 18] before the evidence for patients with CKD. This is not re-stated in the “Dialysis” section.

The Tables of Included Studies include only those with data on patients with CKD or dialysis that is discussed in the text and do not include all of the RCTs discussed in this guideline.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for kidney disease, and renal replacement therapy were combined with MeSH terms for cardiovascular disease and all of the drugs used to treat cardiovascular disease – beta-adrenergic antagonists, angiotensin converting enzyme inhibitors, angiotensin receptor antagonists, digoxin, nitrates, calcium antagonists and alpha-antagonists. The Cochrane search strategy for RCTs was also applied. These were then combined with the following search terms to define cardiac failure: Heart Failure, Left Ventricular Dysfunction, and Dilated Cardiomyopathy; systolic dysfunction, congestive cardiac failure and congestive heart failure were searched as “text words”. Ovid MEDLINE was the database searched.

Date of search/es: 19 September 2007 and updated search 23 February 2011 and April 2013.

WHAT IS THE EVIDENCE?

1. Patients with CKD (GFR<60mL/minute) and kidney transplant recipients

1A. Blockade of the renin-angiotensin system

Evidence from studies of patients without CKD

In patients with CHF, including those patients with heart failure after acute myocardial infarction, treatment with an angiotensin-converting enzyme (ACE) inhibitor reduced the risk of death by 20% (odds ratio 0.80, 95% confidence interval 0.74-0.87, p<0.001) [19]. Re-infarction, admission for heart failure or a composite of these events with mortality were also reduced. Angiotensin receptor blockers also reduce mortality when compared to placebo, but not when compared directly to ACE inhibitors [20], and may reduce hospital admissions for heart failure when added to ACE inhibitors compared to ACE inhibitors alone [20, 21].

National Heart Foundation guideline for the general population: [5]
- ACE inhibitors are recommended in systolic heart failure (LVEF<40%) at all levels of symptoms (Grade A) and at maximum tolerated dose (Grade B)
- Angiotensin receptor antagonists are recommended as an alternative where ACE inhibitors are not tolerated, or in addition to ACE inhibitors where patients remain symptomatic (Grade A)

**Evidence in CKD patients from randomised controlled trials**

There are no RCTs examining blockade of the renin angiotensin system specifically in patients with reduced kidney function and CHF and hence the only evidence is from subgroup or post hoc analyses of other randomised controlled trials. Whilst trials have reported that reduced kidney function [8, 10], worsening kidney function [22] and proteinuria [23-25] are associated with increased mortality in patients with CHF, few have actually reported the effect of the intervention in the patients with CKD.

Of all the trials of drugs that inhibit the renin-angiotensin system, four reported subgroup analyses of patients with CKD. In one of the earliest studies of ACE inhibitors in CHF, the Cooperative North Scandinavian Enalapril Survival (CONSENSUS) Study [26], patients with a serum creatinine above the median value of 123 μmol/L who received enalapril had a six month cumulative mortality of 28% compared to 55% in patients receiving placebo (p=0.004) [27]. Crude mortality was reported in a separate publication [28]. The Studies of Left Ventricular Dysfunction (SOLVD) Treatment trial randomised 2,569 ambulatory patients with heart failure and a left ventricular ejection fraction 35% to enalapril or placebo [29]. A recent post hoc analysis of 1,036 participants who had an estimated GFR<60mL/minute/1.73m2 at baseline demonstrated a 12% (95% CI 27 to -6, p=0.16) reduction in mortality with enalapril treatment [30]. This was consistent with the reduction in mortality in all patients, and there was no interaction based on CKD status (p=0.615). Hospitalisation was significantly reduced in the CKD subgroup. In patients with reduced LVEF following myocardial infarction in the Survival and Ventricular Enlargement (SAVE) Study [31], mortality was reduced by treatment with captopril compared to placebo by 28% (95% confidence interval [CI] 6-45) in patients with GFR<60mL/minute. Cardiovascular mortality and morbidity was reduced by 31% (95% CI 14-45) in this subgroup, and there was no significant interaction between effect of captopril and level of kidney function. Whilst the relative benefit was similar, the absolute benefit of treatment with captopril was greater in patients with GFR<60mL/minute. In patients with CHF randomised to the angiotensin receptor blocker valsartan or placebo in addition to an ACE inhibitor in the Valsartan in Heart Failure (Val-HeFT) trial [32], 58% had a GFR below 60mL/minute at baseline [25]. This subgroup received no mortality benefit but there was a significant reduction in first morbid event with valsartan treatment (hazard ratio 0.86, 95% CI 0.74-0.99). The interaction between valsartan therapy and CKD status was not significant.

In a combined analysis of studies of candesartan in CHF patients, 36% of participants analysed had a GFR below 60mL/minute [8]. Lower GFR was strongly associated with cardiovascular mortality and heart failure hospitalisation. Whilst outcome by treatment assignment was not specifically reported, the authors reported no interaction between treatment effect of candesartan and level of GFR (p for interaction=0.88). Although the various Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme studies performed subgroup analyses of a number of pre-specified subgroups, level of kidney function was not one of them [33-35]. A limitation of applying results of these subgroup or post hoc analyses is that the definition of CKD was based on a single serum creatinine measurement to estimate GFR and not two measurements three months apart that would ensure the participant has chronic kidney disease.

**Addition of angiotensin receptor antagonist to angiotensin-converting enzyme inhibitor**

In people with CHF, the addition of an angiotensin receptor antagonist to therapy with an ACE inhibitor significantly reduces heart failure hospitalisation (odds ratio 0.77, 95% CI 0.69-0.87) but not all-cause mortality (odds ratio 0.97, 95% CI 0.87-1.08) [20]. The largest studies in this meta-analysis were the Val-HeFT [32] and CHARM-Added [35] Studies. The subgroup analysis of Val-HeFT is discussed above; there was no CKD subgroup reported for CHARM or the meta-analysis.

The possible harms of adding an angiotensin receptor antagonist to an ACE inhibitor have not been studied in CHF patients with CKD, but were reported in patients at high cardiovascular risk in the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial [36]. Patients receiving telmisartan and ramipril had a hazard ratio for dialysis, doubling of serum creatinine and death of 1.09 (95% CI 1.01-1.18) compared to patients receiving ramipril alone. The greatest difference was seen in the need for acute dialysis. A subsequent analysis however did not demonstrate that these adverse events were increased in patients with lower GFR [37].
Thus, there is insufficient evidence that the benefits of addition of an angiotensin receptor antagonist to ACE inhibitor therapy in patients with CKD and CHF outweigh the potential harms.

Results of other studies

Some studies in different CKD populations have demonstrated that blockade of the renin-angiotensin system reduces de novo CHF in patients without known CHF at baseline. The Efficacy of Candesartan on Outcome in Saitama Trial in Renal Disease (E-COST-R) Study randomised 141 non-diabetic hypertensive patients age 60-75 years with creatinine between 106 and 177 μmol/L to open-label candesartan or conventional therapy [38]. In the 71 patients with pre-existing cardiovascular disease, combined cardiovascular events were reduced, mainly because CHF occurred in 4/33 treated with candesartan compared to 13/38 treated with conventional therapy. These events were not clearly defined and not adjudicated in a blind fashion.

In a RCT of the angiotensin receptor blocker losartan in patients with diabetic nephropathy (the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study), first hospitalisation for heart failure was a pre-specified and adjudicated secondary endpoint [39]. Patients treated with losartan had a 32% reduction in risk of first hospitalisation for heart failure from 16.7% to 11.9% (p=0.005). Similarly, in the Irbesartan Diabetic Nephropathy Trial (IDNT) that randomised patients to irbesartan, placebo or amlodipine, patients receiving irbesartan had a lower incidence of the secondary adjudicated outcome of first congestive heart failure episode compared to the other two groups [40]. In contrast, ramipril did not reduce the incidence of CHF in patients with diabetes and microalbuminuria or proteinuria compared to placebo in the type 2 DIABetes, Hypertension, Cardiovascular Events and Ramipril (DIABHYCAR) Study [41]. These patients had lower serum creatinine than the RENAAL and IDNT patients.

Adverse effects

One of the potential limiting factors to the therapeutic blockade of the renin-angiotensin system in patients with CKD is concern regarding adverse effects. In the SAVE Study, 12% of participants developed worsening of kidney function defined by a rise in serum creatinine of 23μmol/L, but there was no difference between those receiving captopril or placebo [22]. The Assessment of Lisinopril and Survival (ATLAS) Study compared low dose to high dose lisinopril in patients with CHF and reported on adverse events in patients with a serum creatinine above or below 132.6μmol/L [42]. In the group receiving high dose lisinopril, 3.7% of patients with creatinine ≥132.6μmol/L withdrew due episodes of hypotension or dizziness compared 1.0% in the group with a serum creatinine below this level. For the outcome of renal dysfunction or hyperkalaemia, the corresponding proportions were 6.0% compared to 0.8%, respectively. Whilst there was a relative increase in these adverse events in patients with reduced kidney function, the authors concluded that high doses are well tolerated in most patients. The statistical or clinical significance of these differences in proportions, or relative risks, were not reported. The Evaluation of Losartan in the Elderly (ELITE) Study compared losartan to captopril in patients with CHF aged 65 years or more, and the primary endpoint of this tolerability study was a persisting rise in serum creatinine of ≥26.5 μmol/L [43]. Patients had a mean (± standard deviation) serum creatinine of 106±35 μmol/L but a specific subgroup with reduced kidney function was not reported. There was no difference between groups, with 10.5% of patients reaching this primary endpoint in each group, although 32% of participants with an initial rise in serum creatinine did not have a confirmatory measure performed.

Summary

In patients with CHF, post hoc analyses of two trials suggest that patients with CKD receive the same, or possibly greater, reduction in mortality with an ACE inhibitor. One post hoc analysis demonstrated no benefit when an angiotensin receptor blocker was compared to placebo. The reported increase in adverse effects in patients with reduced kidney function suggests careful monitoring is required but does not justify withholding this treatment.

1B. Blockade of beta-adrenergic receptors

Evidence from studies of patients without CKD
In patients with CHF, therapy with one of three beta-blockers receives the strongest recommendation (Class I) based on the highest level of evidence (Level A) [17]. This is because this therapy reduces mortality by 35% and the number needed to treat for one year to prevent one death is only 20 [44].

**National Heart Foundation guideline for the general population:**

- Beta-blockers are recommended for patients with systolic heart failure on appropriate doses of ACE inhibitor (Grade A), including patients with advanced heart failure (Grade B)

**Evidence in CKD patients from randomised controlled trials**

There are no RCTs that specifically recruited patients with CKD, but five trials report post hoc subgroup analyses of patients with GFR (or creatinine clearance) less than 60mL/minute. The Cardiac Insufficiency Bisoprolol study II (CIBIS II) used bisoprolol [45], the Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT HF) used metoprolol succinate [46], the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) used nebivolol [9], and the Carvedilol Post-infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) Study and the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study both used carvedilol [47]. These studies reported between 21 and 40% reduction in all-cause mortality with beta-blocker therapy that was statistically significant in three of the four reports. There was no significant interaction between beta-blocker therapy and level of kidney function for all-cause mortality in these studies. When the outcome of all-cause mortality was combined with hospitalisation for worsening heart failure in MERIT-HF, the P for interaction of 0.011 suggested increasing benefit at lower GFR [46]. A systematic review of the CKD subgroups in these studies demonstrated an overall 28% reduction in all-cause mortality with beta-blocker therapy in these trials with no evidence of any heterogeneity [48].

**Results of other studies**

Not discussed.

**Adverse effects**

In MERIT HF, reported adverse events included cardiac failure, fatigue, bradycardia, dizziness and hypotension. In the metoprolol succinate group, the incidence of adverse events increased as the GFR declined, being 8.4 per 100 patient years, 13.6 and 16.9 for GFR>60 mL/minute, GFR 45-60 mL/minute and GFR<45 mL/minute, respectively [46]. In the systematic review of the CKD subgroups, hypotension and bradycardia were five times more likely to occur in the patients randomised to beta-blocker therapy than placebo [48].

**Summary**

The reduction in mortality achieved by therapy with four different beta-blockers in patients with CHF is at least as much in patients with reduced kidney function as with normal kidney function. However, the majority of patients in these trials had CKD Stage III and the low number of patients with GFR<30mL/minute in these trials makes application of the results to these patients less certain.

1C. Aldosterone antagonists

**Evidence from studies of patients without CKD**

In patients with severe heart failure symptoms, classified as New York Heart Association (NYHA) Class III or IV, or recently hospitalised with heart failure, the addition of the aldosterone antagonist spironolactone to an ACE inhibitor, diuretics and digoxin reduced all-cause mortality by 30% and hospitalisation for heart failure by 35% over 2 years [49]. The proportion of patients receiving beta-blocking agents was 10-11% in this trial. In patients with acute myocardial infarction complicated by heart failure, the addition of the aldosterone antagonist eplerenone reduced all-cause mortality by 15% [50]. The proportion of patients receiving beta-blocking agents was 75% in this trial. These treatments are given a “Class I” recommendation in guidelines, provided that kidney function and serum potassium can be monitored [17]. In addition, the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) demonstrated a 37% reduction in cardiovascular death or first
hospitalization for heart failure in patients with CHF and mild symptoms (NYHA Class II), although the mean LVEF was 26% [51].

**National Heart Foundation guideline for the general population[4]:**

- Treatment with the aldosterone antagonist spironolactone is recommended for patients who remain severely symptomatic on appropriate doses of ACE inhibitor and diuretics (Grade B)
- Treatment with the aldosterone antagonist eplerenone is recommended for patients who remain mildly symptomatic on appropriate doses of ACE inhibitor and beta-blockers (Grade B), and in patients with left ventricular systolic dysfunction and symptoms of heart failure in the early post-myocardial infarction period (Grade B)

**Evidence in CKD patients from randomised controlled trials**

In the RCTs of more severe CHF, a pre-specified subgroup analysis based on the serum creatinine was reported in the original publications [49, 50]. In the Randomised Aldactone Evaluation Study (RALES), the relative risk of all-cause mortality in patients with serum creatinine≥106μmol/L receiving spironolactone was 0.8 (95% CI 0.65-0.95) compared to placebo [49], and in the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), the relative risk of all-cause mortality in patients with serum creatinine≥96μmol/L receiving eplerenone was 0.9 (95% CI 0.8-1.1) compared to placebo [50]. In both studies, patients with higher serum creatinine derived less benefit from the aldosterone antagonist and in EPHESUS, a significant interaction was demonstrated (p=0.03) between serum creatinine and treatment assignment. Patients with reduced kidney function were at greater risk of hyperkalaemia, but it is not clear whether this group derived less benefit because of increased toxicity or because of other factors. A post hoc analysis of RALES demonstrated that almost half of the participants had an eGFR<60mL/minute/1.73m2 [52]. In contrast to the subgroup analysis by serum creatinine in the primary report, baseline eGFR did not modify the risk of death by treatment arm, with a 30% risk reduction in participants with either eGFR<60mL/minute/1.73m2 or eGFR≥60mL/minute/1.73m2 who received spironolactone. This analysis also demonstrated a significant increase in mortality in patients who had worsening renal function (defined by a 30% or greater decline in eGFR) who received placebo but not increased mortality in patients receiving spironolactone whose kidney function worsened. However, hyperkalaemia occurred significantly more frequently in patients receiving spironolactone. A post hoc analysis of EPHESUS demonstrated that 33% of participants with available serum creatinine had an estimated GFR<60mL/minute/1.73m2 [53]. This analysis did not report whether the effect of treatment differed in patients with and without CKD, but analysed the effect of eplerenone on kidney function. An early reduction in eGFR of >20% was seen in 16% of all participants and was more frequent in patients receiving eplerenone. Baseline eGFR<60mL/minute was not a risk factor for early reduction in eGFR, and eplerenone therapy was still beneficial in participants who experienced an early reduction in eGFR. In EMPHASIS-HF, the benefit of eplerenone was similar in the one third of participants with a GFR<60mL/minute [51]. Only graphical data was provided for this subgroup analysis.

**Results of other studies**

One RCT has been performed in patients with stage II and III CKD that compared spironolactone to placebo and evaluated left ventricular mass and aortic stiffness [54]. These patients had preserved LVEF and although this was not a heart failure trial, it did demonstrate a significant reduction in left ventricular mass index as well as measures of aortic stiffness. In an earlier cohort, these investigators demonstrated that these cardiac abnormalities are similar to that seen in patients with CHF and preserved ejection fraction [55].

**Adverse effects**

The main adverse effects of spironolactone reported in RALES were breast pain or gynaecomastia in males (10% in the spironolactone group compared to 1% in the placebo group, p=0.001), and hyperkalaemia (serum potassium≥6.0mmol/L) occurred in 1-2% of participants and was no different between spironolactone and placebo [49]. An analysis of healthcare databases demonstrated that the prescription rate for spironolactone in patients aged 66 or over and treated with an ACE inhibitor after a heart failure hospitalisation increased 5-fold after the publication of RALES [56]. The rate of hospital admission involving a diagnosis of hyperkalaemia (defined by International Classification of Disease 9 code 276.7, not by serum potassium level) increased 3-fold, in-hospital death increased, and admissions for “renal insufficiency” (not defined) also increased. In EPHESUS, where eplerenone was compared to placebo, gynaecomastia occurred in less than 1% of participants and did not differ by
treatment assignment [50]. Hyperkalaemia (serum potassium $\geq 6.0$ mmol/L) occurred in 5.5% of participants receiving eplerenone and 3.9% receiving placebo (p=0.002). The proportion of participants who developed hyperkalaemia and were receiving eplerenone was 10.1% if creatinine clearance was less than 50mL/minute, compared to 4.6% if creatinine clearance was 50mL/minute or greater and by logistic regression, the risk of hyperkalaemia was significantly greater with lower baseline kidney function. In EMPHASIS-HF, hyperkalaemia (not defined) was twice as frequent in the participants randomised to eplerenone (8%) compared to placebo (4%), but only 1% in each group actually discontinued therapy because of this. Episodes of renal failure were also similar between groups.

Summary

Trials comparing aldosterone antagonism to placebo demonstrate unclear clinical benefit in patients with reduced kidney function and potentially greater toxicity. These agents should therefore be used with caution in such patients until more evidence becomes available.

1D. Digoxin

Evidence from studies of patients without CKD

Treatment with digoxin in patients with CHF had no effect on mortality but significantly reduced hospitalisations for heart failure, a secondary endpoint, by 28% in the large Digitalis Intervention Group Study [57]. These patients were receiving angiotensin converting enzyme inhibitors and diuretics, but not beta-blockers. Two RCTs randomised patients to maintaining digoxin therapy versus withdrawal of digoxin therapy. The Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED) Study demonstrated a reduction in maximal exercise capacity and an increase in treatment failures in patients with CHF treated with digoxin and diuretics that were randomised to digoxin withdrawal [58]. The Randomized Assessment of Digoxin on Inhibitors of the Angiotensin-Converting Enzyme (RADIANCE) Study enrolled patients with CHF treated with diuretics, digoxin and an ACE inhibitor [59]. Patients randomised to withdrawal of digoxin had a six-fold increase in worsening of heart failure and a reduction in maximal exercise duration compared to those maintained on digoxin. The randomised phases of these studies were only three months duration and therefore mortality could not be assessed.

National Heart Foundation guideline for the general population:

- Digoxin is considered a second line agent for patients with advanced heart failure to improve symptoms and reduce hospitalisations (Grade B)

Evidence in CKD patients from randomised controlled trials

A post hoc analysis from the Digitalis Intervention Group Study analysed patients according to estimated GFR levels $>60$mL/minute per 1.73m2 (n=3643), GFR $30-60$mL/minute per 1.73m2 (n=2939) and GFR<30mL/minute per 1.73m2 (n=218) [7]. Although mortality increased as GFR declined, therapy with digoxin did not reduce mortality in the groups with GFR$\leq 60$mL/minute per 1.73m2, but did reduce the secondary outcome of all-cause mortality plus heart failure hospitalisation in patients with GFR 30-60mL/minute per 1.73m2 (hazard ratio for digoxin versus placebo 0.84, 0.76-0.93). An interaction between level of kidney function and effect of digoxin was not demonstrated (p=0.54 for interaction term).

Results of other studies

No other RCTs of digoxin in patients with CHF have either been performed in patients with CKD or reported on a subgroup of patients with CKD within a larger trial.

Adverse effects

Patients with reduced kidney function received lower doses of digoxin, but attained higher levels. Adverse effects of digoxin were not reported in the subgroup analysis, and in the main trial, supraventricular arrhythmia and second or third degree atrioventricular block occurred 2 to 3-fold more frequently in participants on digoxin as compared to placebo [57]. A subsequent analysis of this trial examined the effect of hypokalaemia on outcomes [60]. Serum potassium was less than 4.0mmol/L in 19% of participants with GFR$<60$mL/minute and compared to normokalaemia (4.0-4.9mmol/L), all-cause mortality and other adverse outcomes were significantly increased in participants with hypokalaemia. Randomisation to digoxin had no significant effect on this association.

Summary
Digoxin may reduce a combined outcome of all-cause mortality and heart failure hospitalisation in patients with GFR 30-60mL/minute, but the risk of adverse effects, particularly in patients with serum potassium <4mmol/L, should be carefully considered.

1E. Vasodilators

Evidence from studies of patients without CKD

In male patients receiving diuretics and digoxin in the era before ACE inhibitors, the combination of hydralazine and isosorbide dinitrate reduced mortality in the first 2 years by 34% (95% confidence interval 4-54, p<0.028) compared to placebo [61]. The reduction in mortality was not statistically significantly different over the whole study period (Log rank p=0.093). This Veterans Administration Vasodilator Heart Failure Trial (V-HeFT) had a third arm that received prazosin, and the mortality in the prazosin group was similar to placebo. A second RCT by this group that again enrolled only male patients, V-HeFT-II, compared the ACE inhibitor enalapril to the hydralazine/isosorbide dinitrate combination [62] and demonstrated a 28.2% reduction in mortality in the enalapril group compared to the hydralazine/isosorbide dinitrate combination (p=0.016) that did not attain statistical significance over the whole period of follow up (p=0.08). A subsequent study enrolling African American patients (male and female), the African American Heart Failure Trial (A-HeFT), demonstrated a reduction in absolute mortality from 10.2% in patients randomised to placebo to 6.2% in patients randomised to the hydralazine/isosorbide dinitrate combination (p=0.02) [63]. Most patients were receiving ACE inhibitors and beta-blockers in this study.

National Heart Foundation guideline for the general population:

- Hydralazine–isosorbide dinitrate should be reserved for patients who are truly intolerant of ACEIs and angiotensin receptor antagonists, or for whom these agents are contraindicated and no other therapeutic option exists (Grade B).

Evidence in CKD patients from randomised controlled trials

No measure of kidney function was reported in the original report of V-HeFT [61] or V-HeFT-II [62], or in subsequent reports on the influence of pre-randomisation variables in both studies [64, 65]. In A-HeFT, a subgroup analysis demonstrated no differences in treatment effect of the hydralazine/isosorbide dinitrate combination compared to placebo between patients with a “history of chronic renal insufficiency” and those without such a history. This subgroup was defined by the patients’ medical history and not by any measure of kidney function.

Results of other studies

Other studies are not discussed.

Adverse effects

The main adverse effect reported in these studies was headache.

Summary

Hydralazine–isosorbide can be considered in patients who do not tolerate ACE inhibitors or angiotensin receptor blockade, but there is no data to support its use specifically in patients with CKD.

1F. Treatment of anaemia

Evidence from studies of patients without CKD

Just as CHF and CKD are common co-morbidities, anaemia is also a common co-morbidity in both conditions. The risk of death increases as the number of these co-morbidities present increases [66]. In addition to possible benefits from raising haemoglobin, there are potential non-haemopoietic effects of erythropoiesis stimulating agents (ESA) that might benefit patients with CHF, such as reducing cardiac myocyte apoptosis and fibrosis, and neovascularisation mediated by vascular endothelial
growth factor [66]. Some investigators have suggested that anaemia should be corrected with available tools (erythropoiesis stimulating agents and iron supplementation) in patients with CKD and CHF [67]. The Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure (FAIR-HF) Study randomised patients with CHF and iron deficiency (with or without anaemia) to infusions of ferric carboxymaltose or saline placebo [68]. Patients randomised to ferric carboxymaltose improved on the Self-Reported Patient Global Assessment and improved NYHA Class after 24 weeks. Exercise tolerance and quality of life were also improved.

Only one trial is seeking to study the effects of treatment with an ESA in patients with co-morbid CHF, CKD (GFR 20-70mL/minute) and mild anaemia (Clinical Trials.gov NCT00356733) [69]. However, clinical events will not be assessed.

**National Heart Foundation guideline for the general population:**

- Iron deficiency should be treated to improve symptoms, exercise tolerance and quality of life (Grade B)
- The possibility of anaemia correction with ESAs is acknowledged but no formal recommendation is made

In the absence of a specific RCT, this guideline presents data from either RCTs in patients with CHF and anaemia, in which data on a CKD subgroup was available, or data from RCTs in patients with CKD and anaemia, in which data on CHF was available.

**Evidence in CKD subgroups of randomised controlled trials designed specifically for heart failure patients**

A number of RCTs have been performed in patients with anaemia and CHF. Two meta-analysis of the same seven trials demonstrated no reduction in mortality but significantly reduced heart failure hospitalisation with ESA therapy [70], and improved LVEF and exercise capacity [71]. All but one of these trials was placebo-controlled. A Cochrane Review of ESA therapy in patients with CHF reported 11 RCTs ranging in size from 15 to 319 participants [72]. The mean baseline serum creatinine was abnormal in almost all studies, and the baseline haemoglobin ranged from 10.1-11.8g/dL. Meta-analysis demonstrated that ESA therapy was superior to placebo for improvements in exercise tolerance and duration by various measures, improved LVEF, improvement in NYHA Class, but reported variable results on Quality of Life measures. For all of these outcomes, there was substantial heterogeneity demonstrated. However, there was also a favourable risk ratio for all-cause mortality (0.61, 95% CI 0.37-0.99) and heart failure hospitalisation (0.62, 95% CI 0.44-0.87) with no heterogeneity for these outcomes.

The Reduction of Events by Darbepoetin Alfa in Heart Failure (RED-HF) trial evaluated the effect of darbepoetin alfa compared to placebo on morbidity and mortality in CHF patients with anaemia (haemoglobin 9.0-12.0g/dL) [73]. Although patients with a serum creatinine >265 μmol/L were excluded, 1645 out of 2278 participants (72%) had a GFR<60mL/minute/1.73m². In the trial overall, and in this subgroup with CKD, correction of anaemia with darbepoetin alfa did not reduce the primary outcome of death or hospitalisation for heart failure. As in previous erythropoiesis stimulating agent trials for other patient groups, there was an increase in thrombo-embolic adverse events in patients receiving darbepoetin alfa (13.5% versus 10%, p=0.009).

In addition, 40% of participants in the FAIR-HF Study had a GFR<60mL/minute/1.73m² and subgroup analysis demonstrated no difference in the effect of ferric carboxymaltose compared to placebo on the Self-Reported Patient Global Assessment and change in NYHA Class after 24 weeks in this group compared to participants with GFR above this level [68].

**Evidence in heart failure subgroups of randomised controlled trials designed specifically for CKD patients**

In contrast to the CHF studies, the RCTs of erythropoiesis stimulating agents that have been performed in patients with CKD have predominantly compared high versus low haemoglobin targets, and only one is placebo-controlled. Meta-analyses of these studies have been performed at strategic time points and point estimates for clinical outcomes such as mortality and vascular access thrombosis have consistently favoured the lower haemoglobin target groups [74-76]. Heart failure subgroups were not reported. The major trials of patients with CKD not requiring dialysis are presented below, with a focus on patients with CHF.
The Canadian Multicentre Randomised Trial included 172 participants with a calculated creatinine clearance between 15-79mL/minute and randomised them to achieve a haemoglobin level of 120-140g/L or 90-115g/L using erythropoietin alfa [77]. Less than 10% of patients had symptomatic CHF at baseline. Treating to higher haemoglobin had no benefit on the primary outcome of change in left ventricular mass index.

An Australian trial of similar design randomised 155 patients with calculated creatinine clearance of 15-50mL/minute to a haemoglobin target of 90-100g/L compared to 120-130g/L, maintained by treatment with erythropoietin alfa [78]. Patients with NYHA Class III or IV CHF were excluded and treatment did not affect the development of left ventricular hypertrophy.

The Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) Study randomised 603 participants with an estimated GFR of 15-35mL/minute to high versus low haemoglobin targets with erythropoietin beta [79]. Congestive heart failure was an exclusion criteria but this was presumably only NYHA Class III or IV CHF as patients with NYHA Class I or II CHF made up 27% of participants who underwent a baseline echocardiogram in a subsequent report [80]. In the subgroup of patients with eccentric left ventricular hypertrophy, there were more cardiovascular events (including acute heart failure) at 4 years in patients randomised to the higher haemoglobin target compared to patients randomised to the lower haemoglobin target.

The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) Study randomised 715 patients with an estimated GFR of 15-50mL/minute to achieve a haemoglobin of 113g/L (n=717) compared to 135g/L with erythropoietin alfa [81]. Congestive heart failure was present in 22.9% and 24.4% in these groups, respectively. The primary composite endpoint of death, myocardial infarction, hospitalisation for heart failure and stroke was increased in the high haemoglobin target group, and heart failure hospitalisation was the most frequent component of this primary endpoint (45.5% of events). There was a significant interaction between treatment allocation and baseline history of CHF in that treating to the higher haemoglobin target had no effect on the primary outcome in patients with a history of CHF, but resulted in increased events in patients with no history of CHF (p for interaction=0.028) [82].

The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) randomised 2012 patients with diabetes and an estimated GFR of 20-60mL/minute to darbepoetin alfa with target haemoglobin 130g/L, and 2026 to placebo with rescue darbepoetin alfa if the haemoglobin fell below 90g/L [83]. Heart failure was present at baseline in 31.5% and 35.2% in these groups, respectively (p=0.01). There was no difference in the composite endpoint of death or non-fatal cardiovascular events, and no difference in each individual component of the primary event (including heart failure), except that the risk of stroke was almost two-fold higher in the patients receiving darbepoetin alfa. A subgroup analysis according to baseline CHF was not reported.

Results of other studies

Other studies are not discussed.

Adverse effects

Potential adverse effects of therapy with ESAs in patients with CKD and CHF are those reported in the meta-analyses: hypertension, stroke, and vascular access thrombosis [76].

Summary

Currently, there is no evidence that correcting anaemia in patients with CKD and CHF reduces clinical events. There is a discrepancy between the reduction in mortality in the meta-analysis of CHF RCTs [72] and the increase in mortality in the CKD RCTs [76]. Erythropoiesis stimulating agents should be used with caution in patients with both CHF and CKD and the potential harms should be carefully weighed against the potential to ameliorate symptoms attributable to anaemia in the individual patient.

1G. Strategies to control volume state

Evidence from studies of patients without CKD

Diuretic therapy is important in the management of symptomatic patients with CHF in order to control the extracellular fluid volume expansion and relieve pulmonary congestion. Randomised controlled evidence for alteration of disease progression is lacking [84].
The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) recruited patients aged 55 years or over with at least one cardiovascular risk factor but excluded patients with CHF at baseline [85]. There were significantly less episodes of de novo fatal heart failure in patients randomised to the thiazide diuretic chlorthalidone compared to a calcium channel antagonist, angiotensin converting enzyme inhibitor or alpha-receptor blocker. When heart failure was divided into preserved ejection fraction and reduced ejection fraction, chlorthalidone was superior in all comparisons except when compared to the angiotensin converting enzyme inhibitor for the outcome of heart failure with reduced ejection fraction, where the therapies were equivalent [86]. In the Blood Pressure Lowering Triallist’s Collaboration meta-analysis, diuretics were combined with beta-blockers and this combination was no different to inhibition of the renin angiotensin system, but superior to calcium antagonists with respect to reducing heart failure hospitalisations [87]. There are no long-term RCTs of diuretic therapy with important clinical outcomes in CHF patients and thus all guideline recommendations regarding diuretics are based upon the lowest levels of evidence [4, 17].

**National Heart Foundation guideline for the general population:**

- Diuretics are recommended to achieve euvoelma but should not be considered as monotherapy in patients with systolic dysfunction (Grade D)

**Evidence in CKD patients from randomised controlled trials**

There is no evidence in this group.

**Results of other studies**

In patients with reduced kidney function, higher doses of loop diuretics are often required and thiazide diuretics are much less effective when the GFR falls below 30mL/minute [88].

**Adverse effects**

The main adverse effects of diuretic therapy are excessive volume depletion, leading to worsening kidney function and neurohormonal activation, and electrolyte abnormalities, such as hypokalaemia, hypomagnesaemia and hyponatraemia [17]. The activation of both the sympathetic nervous and renin-angiotensin-aldosterone systems may have deleterious effects in people with CHF. Accurate assessment of volume state is thus critical to effective use of diuretics and avoidance of these important adverse effects [89]. Idiosyncratic reactions can also occur.

**Summary**

Diuretic therapies are useful and necessary to treat states of volume excess, but there is no data in patients with CKD to either recommend them or discount them as a long term therapy to improve prognosis. Clinical volume state, kidney function and electrolytes must be carefully monitored.

1H. Implantable devices

**Evidence from studies of patients without CKD**

Implantable cardioverter defibrillators (ICD) reduced mortality by 23% compared to placebo in patients with a previous episode of unprovoked ventricular arrhythmia, or with LVEF less than 35% and NYHA Class II or III symptoms in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) [90]. Patients randomised to amiodarone in this study had similar mortality to placebo. Cardiac dyssynchrony refers to regional delays in myocardial activation and contraction due to intraventricular conduction delays that impair systolic function. The Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial enrolled patients with NYHA Class III or IV symptoms, an ejection fraction below 35%, and with a prolonged QRS (≥120ms) [91]. Cardiac resynchronisation therapy (CRT) reduced mortality with a hazard ratio of 0.76 (95% CI 0.58-1.01) compared to pharmacological therapy whereas CRT plus ICD significantly reduced mortality with a hazard ratio of 0.64 (95% CI 0.48-0.86). The Cardiac Resynchronisation – Heart Failure (CARE-HF) trial compared pharmacological therapy to CRT without a defibrillator [92]. CRT reduced mortality compared to pharmacological therapy with a hazard ratio of 0.64 (95% CI 0.48-0.85).
National Heart Foundation guideline for the general population:

- Implantable cardioverter defibrillators should be considered for patients with symptomatic heart failure (i.e. NYHA functional class II–III) and LVEF ≤35% (Grade A); other criteria are also listed in guidelines.
- Cardiac resynchronisation therapy, with or without ICD, should be considered in patients with symptomatic heart failure (i.e. NYHA functional class II–IV) who meet specific criteria (Grade A); criteria listed in guidelines and update.

Evidence in CKD patients from randomised controlled trials

The Multicentre Automatic Defibrillator Implantation Trial II (MADIT-II) demonstrated a 30% reduction in mortality in patients who had a LVEF ≤30% within a month following a myocardial infarction [93]. These investigators subsequently reported a subgroup analysis based on blood urea nitrogen dichotomised at 25mg/dL (8.9mmol/L) as a measure of heart failure severity, rather than kidney function [94]. Mortality was greater in these patients with higher urea, but there was no interaction between therapy with an ICD and level of blood urea nitrogen. A meta-analysis of CRT studies that included COMPANION and CARE-HF demonstrated a reduction in mortality of 22% in patients with NYHA Class III and IV symptoms, but noted that there was insufficient data to examine a CKD subgroup [95]. In CARE-HF, half of participants had a GFR<60mL/minute/1.73m2 and there was no heterogeneity in the effect of CRT on the primary endpoint of death or unplanned cardiovascular hospitalisation between the CKD subgroups defined this way [92].

Results of other studies

A meta-analysis of observational studies has demonstrated that patients who receive an ICD have an approximately three-fold greater mortality if they have CKD compared to if they have better kidney function [96]. In a retrospective case control study that identified patients between 1998 and 2008, 33 patients had a LVEF ≤35% and a GFR below 60mL/minute [97]. The two year survival of patients who received an ICD was 80%, compared to 61% in those who did not (p=0.027). Another analysis divided 441 patients who had an ICD inserted between 1994 and 2002 according to their kidney function. Mean survival was 86 months, 60 months and 38 months for patients with GFR<60mL/minute, GFR<60mL/minute and patients receiving dialysis, respectively [98].

Adverse effects

Adverse effects of ICD or CRT have not been reported specifically in patients with CKD.

Summary

Studies of ICD and CRT have not been reported specifically in patients with CKD. Patients with CHF and reduced kidney function derived similar benefit from CRT to those with normal kidney function in the CARE-HF Study and thus CRT should be considered in appropriate patients.

1. Other therapies

Inotropic therapy

Inotropic therapies may be used in patients with severe acute decompensation of heart failure. The major inotropic therapies currently in use are 1) the β1-adrenergic receptor agonist dobutamine; 2) the dopaminergic receptor agonist dopamine, which stimulates β1 and α1 receptors at progressively higher doses; phosphodiesterase 3 inhibitors that increase intracellular cAMP (for example milrinone; and 4) the calcium sensitiser levosimendan.

By improving stroke volume and cardiac output, these agents may improve symptoms and renal perfusion. However, available data suggests no reduction, and a possible increase, in mortality. A systematic review of intravenous dobutamine or high dose dopamine demonstrated an increase in mortality with use of these agents compared to placebo or control that was not statistically significant (odds ratio 1.50, 95% CI 0.51-3.92) [99]. A systematic review of phosphodiesterase 3 inhibitors also demonstrated an increased mortality with this therapy as compared to placebo (relative risk 1.17, 95% CI 1.06-1.30) [100]. A more recent large RCT comparing the phosphodiesterase 3 inhibitor enoximone...
to placebo in patients with advanced CHF, the Studies of Oral Enoximone Therapy in Advanced HF (ESSENTIAL) programme, demonstrated no benefit or harm with enoximone [101]. In a meta-analysis of 19 studies, levosimendan was not superior to placebo but was superior to intravenous dobutamine with regard to mortality [102]. Levosimendan also improved various haemodynamic parameters. Apart from the increase in mortality, the main adverse effect with this type of therapy is arrhythmia.

**National Heart Foundation guideline for the general population:**

- The NHF guideline makes no recommendation regarding the use of positive inotropic agents other than stating that inpatient or ambulatory infusions of inotropes such as dobutamine may be used for severe heart failure for specific reasons and levosimendan should be reserved for those who do not respond to or tolerate dobutamine.

**Summary**

Whilst the potential improvements in renal perfusion might benefit patients with CKD, the above studies did not report specifically on patients with CKD and therefore no recommendation regarding the use of these agents in this group can be made.

**Polyunsaturated fatty acid (PUFA)**

In a single large RCT (n=6975), treatment with n-3 PUFA (eicosapentaenoic acid and docosahexaenoic acid) at a dose of 1g daily led to a modest reduction in mortality when compared to placebo (27.3% versus 29.1%; absolute risk reduction 1.8%, 95% CI 0.3-3.9) [103]. Subgroup analysis was performed, but not by level of kidney function. There was no increase in adverse events compared to placebo.

**National Heart Foundation guideline for the general population:**

- This therapy is recommended as a second-line agent for patients symptomatic on ACE inhibitors (or Angiotensin receptor antagonists) and beta-blockers (Grade B).

**Summary**

In the absence of specific data in CKD, a recommendation cannot be made.

**Direct sinus node inhibition**

The Systolic Heart failure treatment with the If inhibitor ivabradine Trial (SHIFT) demonstrated a significant reduction in cardiovascular death and heart failure hospitalisation in patients with CHF in sinus rhythm with a heart rate above 70 beats per minute (Hazard Ratio for ivabradine versus placebo: 0·82, 95% CI 0.75–0.90) [104]. Although GFR was measured and reported at baseline, subgroup analysis by this variable was not reported.

**National Heart Foundation guideline for the general population:**

Direct sinus node inhibition with ivabradine should be considered for patients with impaired systolic function and a recent heart failure hospitalisation who are in sinus rhythm with heart rate > 70 bpm despite maximal beta-blockade

**Summary**

A CKD subgroup is yet to be reported and there are no other data for patients with CKD to determine the role for this agent in CHF patients with CKD.

**Ligation of the arteriovenous fistula**

A unique contributing factor to CHF in patients with CKD is the cardiac effects of shunting blood from the arterial to the venous system through the arteriovenous fistulae for vascular access. Cases of arteriovenous fistula-related high-output cardiac failure that has improved with ligation of the fistula have been reported [105]. Ligation of the arteriovenous fistula in 20 kidney transplant recipients without CHF resulted in a reduced left ventricular end-diastolic diameter and left ventricular mass index [106].

Because successful kidney transplantation makes ligation of the arteriovenous fistula possible, this is mentioned here as a therapeutic option in kidney transplant recipients. However, the benefits and
harms of ligation of arteriovenous fistulae in kidney transplant recipients with CHF have not been studied in any systematic way.

2. Patients receiving dialysis

2A. Blockade of the renin-angiotensin system

Evidence from randomised controlled trials

Four RCTs of blockade of the renin-angiotensin system in patients requiring dialysis have been published.

Cice et al randomised 332 haemodialysis patients at 30 centres to telmisartan or placebo [107]. All patients had dialysis four times a week and all received therapy with an ACE inhibitor. All had CHF defined by NYHA Class II or III symptoms and a LVEF ≤40%. Other therapies included carvedilol (60%) and digoxin (50%). The primary outcome of all-cause mortality occurred in 35.1% of participants receiving telmisartan after a median of 36 months compared to 54.4% receiving placebo (p<0.001), and the adjusted hazard ratio for this outcome was 0.51. Cardiovascular deaths and admissions for heart failure were also significantly reduced in patients receiving telmisartan.

Two other studies examined angiotensin receptor antagonists in patients undergoing dialysis, but CHF was not an inclusion criteria. Suzuki et al randomised 366 patients on haemodialysis to open-label angiotensin receptor blocker or no therapy [108]. Approximately 15% of participants had CHF at baseline and in this study. There was no difference in mortality but cardiovascular events were reduced by 49% and the most frequently reported component of this composite endpoint was heart failure. Although said to be defined by American College of Cardiology and American Heart Association guidelines, the adjudication of this outcome was not clear. Eighty patients receiving haemodialysis who did not have CHF were randomised to candesartan or no therapy and followed for a mean of 19 months [109]. Few were on ACE inhibitors or beta-blockers. There were 17 cardiovascular events in the control group and 7 in the candesartan group. Eleven of the events in the control group were attributed to heart failure (presumably de novo). However, the sample size was small, events few in number and although endpoints were assessed blinded to treatment, the definition of heart failure admission described only NYHA classification and no other clinical features.

The ACE inhibitor fosinopril was compared to placebo in a study of 397 haemodialysis patients whose main entry criteria was left ventricular hypertrophy [110]. The proportion with CHF at baseline was not reported and patients were followed for 24 months. There was no difference in the primary composite endpoint of cardiovascular events, including hospitalisation for heart failure, between therapy with fosinopril and placebo.

An important limitation of these studies, particularly the ones that relied on admission for heart failure as an outcome is the difficulty in defining what constitutes an admission for heart failure in patients undergoing dialysis.

Results of other studies

The US Renal Data System (USRDS) Dialysis Morbidity and Mortality Study (DMMS) Wave 2 reported the effects of beta-blocking agents in patients on dialysis who commenced dialysis in 1996 [111]. In this cohort, between 21 and 26% of participants was receiving ACE inhibitor therapy, and the use of ACE inhibitors did not reduce either time to de novo heart failure, or time to a composite of de novo heart failure or death in the Cox regression models reported. In an earlier analysis that examined hospitalisation for heart failure, ACE inhibitors were included but not retained in multivariable models with hospitalisation for heart failure as the outcome [112]. In a single centre analysis of 126 patients on haemodialysis, the use of ACE inhibitors was associated with improved survival and this effect was essentially confined to the patients under the age of 65 years [113]. Heart failure was reported in 35% of this cohort at baseline.

The most beneficial effect in observational studies appears to be with the use of ACE inhibitors following myocardial infarction. Using data from a national database of acute myocardial infarction, the Cooperative Cardiovascular Project demonstrated in patients with ESKD that the in-hospital mortality of patients considered “ideal” for receiving an ACE inhibitor was 17.9% in patients who received an ACE inhibitor compared to 33.6% in those who did not (P=0.007) [114]. Heart failure was present in 40% at baseline and the main criteria, other than contraindications, for being considered an “ideal” ACE inhibitor candidate was a LVEF less than 40%. An analysis of 368 patients with ESKD treated in a single coronary care unit from 1990-1998 compared patients prescribed an ACE inhibitor to those not
prescribed an ACE inhibitor [115]. Heart failure was diagnosed in 69% of patients prescribed an ACE inhibitor and 47% of patients not prescribed an ACE inhibitor and treatment with an ACE inhibitor was associated with a 37% reduction in mortality over more than 5 years of follow up. Although supportive of a role for ACE inhibitors in this clinical setting in patients with ESKD, these studies were not specifically in patients with CHF and the observational nature of these studies makes them prone to sources of bias such as confounding by indication.

Adverse effects

In the study of telmisartan versus placebo in patients with CHF already receiving an ACE inhibitor, 19 patients failed the run-in and this was because of hypotension in 7 [107]. Discontinuation of study drug occurred in 27 (16.3%) of patients receiving telmisartan compared to 18 (10.7%) receiving placebo (p<0.01), with hypotension being the predominant reason in both groups. Hypotension was more common in participants receiving telmisartan.

Summary

There are no RCTs comparing ACE inhibitor or angiotensin receptor antagonists to placebo in patients receiving dialysis who have CHF. Angiotensin receptor antagonist added to an ACE inhibitor appeared to reduce mortality compared to placebo in one trial of patients receiving dialysis who have CHF.

2B. Blockade of beta-adrenergic receptors

Evidence from randomised controlled trials

One RCT of beta-blocker therapy in patients receiving dialysis who have CHF has been published. This study randomised 114 patients with symptomatic heart failure (NYHA Class II or III) and a LVEF <35%. All patients were receiving either an ACE inhibitor (96.9%) or angiotensin receptor blocker (3.1%), all were receiving digoxin and all were receiving dialysis 4 times per week. The first report of this study reported an improvement in ejection fraction at 12 months from 26% to 36% in the patients receiving carvedilol compared to no improvement in the placebo arm [116]. During this phase of the study, participants, investigators and outcome assessors were blinded to treatment allocation. These investigators subsequently reported mortality and cardiovascular events after a further 12 months in which blinding was not maintained [117]. In this analysis, all-cause mortality was reduced by 49% (hazard ratio 0.51, 95% confidence interval 0.32-0.82) and hospitalisation for heart failure by 81% (hazard ratio 0.19, 95% confidence interval 0.09-0.41). These were secondary endpoints in this study, and how the outcomes were adjudicated was unclear. It is interesting to note that there were only 3 deaths reported in the first 12 months, and then 71 deaths after 24 months.

Results of other studies

In observational data, beta-blockers do reduce mortality in patients with ESKD although there are few studies specific to patients with CHF. In the Cooperative Cardiovascular Project, patients considered “ideal” for a beta-blocker, essentially those without a contra-indication, the 30-day mortality following myocardial infarction was 20.7% in those receiving a beta-blocker compared to 31.2% in those not prescribed a beta-blocker (P<0.001) [114]. Heart failure was present in 40% of these patients at baseline. In the USRDS DMMS Wave 2 cohort patients without CHF at baseline who received beta-blockers had a reduced risk of de novo heart failure (hazard ratio 0.69, 95% confidence interval 0.52-0.91) and composite of de novo heart failure and cardiac death (hazard ratio 0.77, 95% confidence interval 0.61-0.97) [111]. However, patients with CHF at baseline who were receiving beta-blockers had no reduction in recurrent heart failure or mortality.

Adverse effects

Permanent treatment withdrawal was similar between carvedilol and placebo groups in Cice’s study [117]. Eighteen of an initial 132 patients were excluded in the run-in phase predominantly due to predictable side effects such as hypotension, bradycardia, worsening heart failure and bronchospasm.

Summary

The reduction in mortality and other events achieved by therapy with carvedilol in the sole study of beta-blocker therapy in patients requiring dialysis who have CHF is impressive, but limitations such as small sample size and lack of blinding in the second 12 months indicate that a larger trial is required to confirm these results. However, this is consistent with reports of CKD subgroups in CHF trials [48].
2C. Aldosterone antagonists

*Evidence from randomised controlled trial subgroup or post hoc analyses in heart failure populations*

Most studies of aldosterone antagonism in patients undergoing haemodialysis examined safety, particularly in relation to hyperkalaemia.[118] Sixteen patients receiving haemodialysis with heart failure (NYHA Class II or IV symptoms and a mean LVEF between 31 and 34%) were randomised to spironolactone or placebo [119]. Left ventricular ejection fraction increased by 6% in patients receiving spironolactone compared to 0.8 in the placebo group (p=0.046), there was a significant reduction in cardiovascular hospitalisations in the spironolactone group but an increase in admissions for infections. This same group randomised 18 patients receiving peritoneal dialysis who had heart failure to receive spironolactone 25mg daily or placebo and measured potassium, haemoglobin and LVEF up to 6 months [120]. There was no difference in any of these parameters between treatment groups.

*Results of other studies*

A study of 108 patients undergoing haemodialysis who had left ventricular hypertrophy on echocardiogram and BNP>200pg/mL randomised participants to carvedilol and spironolactone in a 2x2 factorial design [121]. Patients with severe heart failure (NYHA Class IV) were excluded. The mean LVEF was over 50% in these patients. Whilst there may have been a benefit from the combination of carvedilol and spironolactone in reducing cardiac events compared to monotherapy, no benefit of spironolactone monotherapy was demonstrated. One patient developed hyperkalaemia that required treatment.

*Adverse effects*

An uncontrolled study of 50 haemodialysis patients demonstrated that spironolactone 25mg daily could be administered to patients undergoing haemodialysis without severe hyperkalaemia (K>6.8mmol/L) [122]. Three of 50 participants withdrew due to gynaecomastia.

*Summary*

Aldosterone antagonism at doses equivalent to spironolactone 25 mg daily may be prescribed for patients undergoing dialysis where potassium is closely monitored. Severe hyperkalaemia is a rare event in the studies to date. Evidence of clinical benefit is lacking.

2D. Digoxin

*Evidence from randomised controlled trial subgroup or post hoc analyses in heart failure populations*

There are no RCTs or post hoc analyses examining the use of digoxin in patients undergoing dialysis who have CHF.

*Results of other studies*

A very large retrospective cohort study from Fresenius Medical Care North America analysed outcomes in patients receiving digoxin and adjusted for co-morbidities using propensity score analysis [123]. Patients receiving digoxin who had coexistent CHF had an 18% increased risk of mortality, even after adjustment for other covariates and the propensity score. This risk was similar if they had co-existing atrial fibrillation. Furthermore, high serum levels of digoxin, and low pre-dialysis serum potassium levels were also associated with greater mortality.

*Adverse effects*

Specific adverse effects were not analysed in the Fresenius Medical Care North America study.

*Summary*

There is no evidence of benefit of digoxin in patients receiving dialysis who have CHF, and a non-randomised analysis suggests significant harm. If digoxin is used in such patients, careful monitoring of serum potassium in peritoneal dialysis patients and careful attention the potassium concentration of the dialysate in haemodialysis patients is necessary to avoid hypokalaemia.
2E. Vasodilators

**Evidence from randomised controlled trials**

No randomised controlled trial has examined the use of either nitrates or hydralazine in patients undergoing dialysis who have CHF.

**Results of other studies**

No other studies have addressed the use of vasodilators in patients undergoing dialysis who have CHF.

**Adverse effects**

Theoretically, vasodilators could contribute to intra-dialytic hypotension in patients undergoing haemodialysis. However, there is no data to support this from studies of the use of these agents.

**Summary**

There is insufficient data of the use of vasodilators in patients undergoing dialysis to recommend for or against their use.

2F. Treatment of anaemia

**Evidence from randomised controlled trials**

A number of RCTs of ESAs enrolled patients undergoing dialysis with CHF or ischaemic heart disease, but none were exclusively in patients with CHF. All compared different haemoglobin targets and none randomised patients to ESA versus placebo.

In the most recent meta-analysis of ESAs in patients with CKD, including those undergoing dialysis, higher haemoglobin targets were associated with a significantly increased risk of stroke, hypertension and vascular access thrombosis, and an increased risk of mortality that was not statistically significant [76]. No interaction was demonstrated between patients with CKD not requiring dialysis and those requiring dialysis for these outcomes (except vascular access thrombosis).

The largest and most relevant RCT (n=1233) enrolled patients with either CHF or ischaemic heart disease who were undergoing haemodialysis and the Data Monitoring Committee recommended that the trial be stopped after the third interim analysis [124]. The risk of death or non-fatal myocardial infarction was increased in patients randomised to a haematocrit of 42% compared to 30% (risk ratio 1.3, 95% confidence interval 0.9-1.9). The incidence of vascular access thrombosis was 39% in the high haematocrit group compared to 29% in the low haematocrit group (p=0.001). A sub-study of 28 participants of this trial from one centre demonstrated no difference in ambulatory blood pressure between the two groups, although may have been subject to Type II error [125].

A study of 146 patients with either left ventricular concentric hypertrophy or dilatation, 76 of whom had left ventricular dilatation, were randomised to achieve a haemoglobin target of 10g/dL compared to 13.5g/dL using epoetin α and changes in left ventricular parameters were measured [126]. Left ventricular cavity volume index was not different between the groups after 48 weeks.

**Results of other studies**

In early observational data of patients with mean haemoglobin of 8.8g/dL, lower haemoglobin was associated with an increased risk of de novo and recurrent heart failure, independent of age, diabetes and ischaemic heart disease [127].

**Adverse effects**

Similar adverse effects were seen with high haemoglobin targets – an increase in the risk of death and non-fatal myocardial infarction that did not reach statistical significance, and an increase in vascular access thrombosis.

**Summary**

Despite early observational data that anaemia is significantly associated with CHF, there is no evidence that correction of anaemia reduces heart failure events and there is some evidence of harm.
2G. Strategies to control volume state

There are no RCTs of the use of diuretics in patients requiring dialysis for the treatment of CHF. Intuitively, maintenance of “euvolaemia” with dialysis therapy is an important component of heart failure therapy in patients undergoing dialysis. However, studies of maintenance of euvolaemia (or indeed defining “euvolaemia”) in patients undergoing dialysis with CHF are lacking.

2H. Implantable devices

Evidence from randomised controlled trials

There are no RCTs specifically in patients undergoing dialysis. A RCT is underway in the Netherlands to randomise patients undergoing dialysis aged 55 to 80 to ICD therapy or not [128]. In the Implantable Cardioverter Defibrillators in Dialysis patients (ICD2) Trial (ISRCTN20479861), heart failure is not a specific inclusion criteria and NYHA Class IV heart failure is an exclusion criteria. This trial is scheduled to finish in 2012.

Results of other studies

Patients undergoing dialysis who received an ICD for any indication in one centre over a 14-year period (n=50) were compared to contemporaneous patients receiving dialysis at another centre who did not receive an ICD but had a LVEF<35% (n=50), the most common indication for receiving an ICD. Forty-three patients received the ICD based on their LVEF (“primary prevention”), and 7 received the ICD following cardiac arrest or syncope (“secondary prevention”) [129]. The median survival was 8 years with an ICD versus 2.5 years without and the hazard ratio adjusted for beta-blocker and amiodarone use (which were both greater in the ICD group) and other things demonstrated a 60% reduction in mortality with an ICD (hazard ratio 0.40; 95% confidence interval 0.19-0.82, p=0.01). However, this analysis may be subject to considerable residual confounding. In a retrospective analysis from a single centre that compared 31 patients receiving dialysis who had a LVEF<35% who did not receive an ICD to patients who did and demonstrated no difference in survival by ICD status [97].

In an analysis of the United States Medicare database, 30,518 patients receiving dialysis had a cardiac arrest or ventricular tachyarrhythmia between 1996 and 2001, but only 6,042 were still alive 30 days after the index event [130]. One year survival was 71% in the 460 patients who received an ICD (7.6%) compared to 49% in patients who did not receive an ICD. The association with survival was the same across tertiles of propensity scores.

Because ICD therapy comes with a considerable cost, some authors question the wisdom of treating patients with an ICD if such a therapy might be futile in the context of their overall risk of death [131]. In support of this argument, comparison of patients with ICD who are, or are not, receiving dialysis has been performed. A meta-analysis of such studies identified 89 patients receiving dialysis from 7 studies of 2,516 patients who received an ICD [132]. Despite the ICD, mortality was 2 to 3-fold greater in patients undergoing dialysis.

Adverse effects

Adverse effects of ICD in patients undergoing dialysis have not been reported in RCTs. In an observational study, there were more major complications in patients undergoing dialysis compared to patients not undergoing dialysis [133]. Importantly, 4 of 41 patients receiving dialysis had thrombosis of vascular access veins ipsilateral to the device.

Summary

The use of ICD therapy in patients receiving dialysis who have CHF cannot be routinely recommended. The decision to use ICD therapy in a patient receiving dialysis should balance the potential benefit to the individual patient with the risk of complications, particularly thrombosis of vascular access veins if the ICD is implanted on the same side as the vascular access.

2I. Other therapies

Inotropic therapy
There are no RCTs with clinical outcomes of the use of inotropic therapy in patients undergoing dialysis. Therefore, the role of these agents in this group of patients cannot be defined.

**Polyunsaturated fatty acid (PUFA)**

There are no studies of PUFA in patients undergoing dialysis that examined clinical outcomes in patients with CHF. Therefore, the role of these agents in this group of patients cannot be defined.

**Direct sinus node inhibition**

There are no studies of this agent in patients undergoing dialysis. Two studies from the same centre are registered in patients undergoing dialysis but both exclude CHF patients (Clinical Trials.gov NCT01364077 and NCT01425164).

**Kidney transplant**

Restoring kidney function with transplantation may improve cardiac function in patients requiring dialysis. In patients with CHF and LVEF≤40%, LVEF improved from 31.6±6.7% before, to 52.2±12.0% after receiving a kidney transplant (p=0.002) [134]. In a pivotal observational study of cardiac structure and function in 433 patients with ESKD, all 12 patients with systolic dysfunction before kidney transplant had normal systolic function on echocardiograms following their transplant [135]. Other studies have demonstrated improvements in left ventricular volumes and function following transplantation [136-138], including as early as 3 months following the procedure [139]. However, patients receiving dialysis who have a LVEF≤45% had between 2 to 5 times greater death, cardiac death and cardiac complications than patients with LVEF above this level after receiving a kidney transplant [140]. Although not considered a heart failure therapy, the potential beneficial effects of kidney transplant on cardiac function should be carefully considered in patients with CHF who are being evaluated for kidney transplant.

**SUMMARY OF EVIDENCE**

A number of RCTs have been performed in patients with CHF that provide a strong evidence base underpinning many guideline recommendations for the general population [4, 17, 18]. The recommendations for patients with CKD are based on post hoc analyses of randomised controlled trials of therapies in patients with heart failure. Although these are post hoc analyses, a large proportion of patients in these studies had an eGFR<60mL/minute/1.73m2 so the results of these trials can be applied to CKD Stage 3. However, fewer patients in the trials had an eGFR<30mL/minute/1.73m2 so this should be borne in mind when applying these guidelines to such patients. There are no data specifically for kidney transplant recipients but it is considered reasonable to apply the CKD recommendations to this group, acknowledging this lack of specific data. For dialysis patients, there are smaller trials of lower quality but these data are generally consistent with the CKD and general population data.

**WHAT DO THE OTHER GUIDELINES SAY?**

**INTERNATIONAL GUIDELINES:**

**Kidney Disease: Improving Global Outcomes (KDIGO):**

No Heart Failure Guideline.

**Kidney Disease Outcomes Quality Initiative:**

This guideline addresses “Cardiomyopathy (Systolic or diastolic dysfunction)” in patients undergoing dialysis with regard to both diagnosis and management and was published in 2005 [141]. This guideline recommends:

- “Maintenance of euvolaemia” as the cornerstone of therapy
- Beta-blocking agents are preferred based on data that is “moderately strong” (the single Carvedilol study)
- ACE inhibitors should be used although the data is “weak”
- Digitalis should be considered as third line therapy (no data referred to)
- Aldosterone antagonists should be used with “great caution, or not at all” (based on “weak” data)
This NKF KDOQI Guideline is the only “renal” guideline to address heart failure and this CARI Guideline would concur with most of the recommendations above. The major exception is the recommendation of digoxin as a third line agent. Recent observational data regarding the potential toxicity of digoxin and the single RCT of telmisartan as add-on therapy to ACE inhibitor in dialysis patients with CHF indicate that digoxin may not be the most appropriate agent.

**UK Renal Association:**
No Heart Failure Guideline.

**Canadian Society of Nephrology:**
No Heart Failure Guideline.

**European Best Practice Guidelines:**
No Heart Failure Guideline.

**SUGGESTIONS FOR FUTURE RESEARCH**

1. A RCT of an agent to treat heart failure specifically in patients with CKD with heart failure. Although there are limitations to the evidence for ACE inhibitors and beta-blocking agents in CKD, it would be hard to justify withholding these agents in a placebo controlled trial and thus a study of a third agent may be more appropriate.

2. A RCT of an agent to treat heart failure specifically in patients receiving dialysis with heart failure. Again, it would be difficult to justify withholding either an ACE inhibitor or beta-blocking agent and thus a third agent or different haemodialysis schedule such as nocturnal haemodialysis or short daily haemodialysis could be studied.

3. Introduction of recording of heart failure status in the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry would also provide opportunities for research in patients with heart failure undergoing renal replacement therapy.

**CONFLICT OF INTEREST**

Matthew Roberts has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.
REFERENCES


## APPENDICES

### Table 1. Characteristics of included studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>N</th>
<th>Study design</th>
<th>Description - Participants and Interventions</th>
<th>Follow up (months)</th>
<th>Comments and results</th>
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<tbody>
<tr>
<td><strong>1A: Blockade of the renin-angiotensin system</strong></td>
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| CONSENS US [26-28] | 253 | RCT | Patients with severe CHF (NYHA Class IV) on digitalis and diuretics. Excluded if serum creatinine >300 µmol/L. | Mean = 6 | Crude mortality at 6 months for patients above and below the baseline median serum creatinine of 123 µmol/L
- Placebo:
  - High creatinine – 50%
  - Low creatinine – 38%
- Enalapril:
  - High creatinine – 24% (52% reduction P=0.002)
  - Low creatinine – 29% (24% reduction P=0.12)
Limitations: Trial discontinued early. Serum creatinine only available at baseline. No sub group analysis available on basis of CKD. |
| SOLVD [29, 30] | 2,569 eGFR<60mL/min/1.73m²: 1,036 | RCT | Patients with CHF and LVEF≤35% not receiving ACEi. Excluded if serum creatinine >221µmol/L | Mean=41.4 | Hazard Ratio for mortality for enalapril versus placebo:
- CKD: 0.88 (0.73, 1.06)
- No CKD: 0.82 (0.69, 0.98)
P for interaction=0.615 |
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<tr>
<th>Study ID</th>
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| SAVE [22, 31] | 2,231 eGFR<60mL/min/1.73m²: 719 | RCT, Multicentre (US and Canada) | Acute myocardial infarction with LVEF≤40% Excluded if serum creatinine >221μmol/L Captopril versus placebo WRF defined as an increase in serum creatinine >27μmol/L 2 weeks after baseline Multiple outcomes: all-cause mortality, major cardiovascular events, development of CHF. | 42                | Risk reduction for mortality for captopril versus placebo:  
  • CKD: 13% (-11, 21)  
  • No CKD: 28% (6, 45)  
  P for interaction=0.30  
  No difference in WRF between captopril (6.4%) and placebo (5.7%), p=0.38.  
  WRF was associated with an increased risk of death compared to those without WRF:  
  • HR 1.46 (1.05, 2.02)  
  Development of CHF not significantly greater.  
  Limitation: WRF defined at 2 weeks post baseline and is thus an unreliable indicator of adverse effects over the study follow up period. There are many potential causes of worsening renal function following myocardial infarction. |
| Val-HeFT [25, 32] | 5010 eGFR ml/min/1.73 m²  
  • <60 (2916)  
  • >60 (2086) | Sub group analysis of a randomised controlled trial. Multi-centre (Nth America) | Patients with NYHA Class II-IV heart failure and LVEF≤40% at least 3 months prior. Excluded if serum creatinine >221μmol/L Valsartan versus placebo, in addition to ACE inhibitor in both groups Primary outcome: mortality and composite of mortality and morbidity. | Mean =23 (0 to 38) | The beneficial effects of valsartan on mortality did not differ between those with low and high eGFR ml/min/1.73 m²:  
  • <60: HR(adj) 1.01 (0.85,1.20)  
  • >60: HR(adj) 0.91 (0.69,1.25)  
  Limitations: Excluded severe CKD. Relied on dip stick analysis for proteinuria. Potential for residual confounding associated with sub group analysis. |
<table>
<thead>
<tr>
<th>Study ID</th>
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| CHARM Studies [8] | 2743, subgroup of 7099 participants in the CHARM studies. | Sub group analysis of 3 randomised controlled trials. Multi-centre (international). This sub-group analysis includes only Nth American participants. | Patients with NYHA Class II-IV for at least 4 weeks duration. Excluded if serum creatinine >265µmol/L. Candesartan versus placebo. Primary outcome: CV death or unplanned hospitalisation for worsening CHF. | Median = 34.4 (1 day to 45.2 months) | Adjusted HR (95% CI) for all-cause mortality according to eGFR ml/min/1.73 m²:  
- <45 (n=419): 1.91 (1.42-2.58)  
- 59.9-45.0 (n=547): 1.50 (1.12-2.00)  
- 74.9-60.0 (n=618): 1.14 (0.85-1.54)  
- 89.9-75.0 (n=519): 1.13 (0.83-1.54)  
- >90.0 (n=507): 1.00  
Limitations: Reliance on baseline serum creatinine, which was missing in 61 (2.2%). Sub group analysis of Nth American cohort. Potential for residual confounding associated with sub group analysis. The 3 studies had different inclusion criteria and treatment schedule. |
| E-COST-R (2005) [38] | 141 | Open label randomised controlled trial. Multi-centre (Japan) | Adult (60 to 75 years) patients with hypertension and creatinine 106-177µmol/L. Excluded patients with heart failure. Candesartan versus conventional antihypertensive agents. Primary outcomes: fatal and non-fatal, stroke, MI and CHF. | Mean = 3.1±0.4 years | RR (95%CI) of CHF for participants treated with candesartan compared to conventionally treated group:  
- Previous history of cardiovascular events: 0.35 (0.13, 0.98).  
- No history of cardiovascular events: 1.65 (0.53, 5.14).  
| RENAAL (2001) [39] | 1513 | Double blind placebo controlled randomised trial (primary report) Multi-centre (international) | Patients with type 2 diabetes and nephropathy. Irbesartan versus placebo. Primary outcome: time to first event of the composite of doubling of the serum creatinine, ESRD or death. | Mean 3.4 years | First hospitalisation for heart failure after randomisation in the losartan treated group compared to placebo:  
- Risk ratio: 0.71 (95%CI 0.55, 0.91).  
- Risk reduction: -0.05 (95%CI -0.10, -0.01)  
Limitations: Study discontinued early. Discontinuation rates of 53.5% in placebo vs. 46.5% in irbesartan group. Limited to patients with type 2 diabetes patients. Heart failure reported as part of a secondary composite outcome of cardiovascular events. CHF endpoint not defined. |
<table>
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<tr>
<th>Study ID</th>
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| IDNT (2003) | 1715  | Double blind placebo controlled randomised trial (post hoc analysis)          | Patients with type 2 diabetes and overt nephropathy and hypertension.                                        | Mean 2.6 years    | Risk for episode of CHF:  
  - Irbesartan vs. placebo: HR 0.72 (95%CI 0.52,1.00)  
  - Amlodipine vs. placebo: HR 1.11 (0.83-1.50)  
  - Irbesartan vs. amlodipine: HR 0.65 (0.48,0.87)  

Limitations: Limited to patients with type 2 diabetes. Use of multiple antihypertensive agents across treatment groups. Heart failure reported as part of a secondary composite outcome of cardiovascular events. |
| DIABHYCAR (2003) | 4912 | Double blind randomised controlled trial (post hoc analysis). Multi-centre (Europe and Nth Africa) | Patients with type 2 diabetes aged ≥50 years. With urine albumin concentration (UAC) >20mg/L and serum creatinine ≤150 µmol/L. Ramipril versus placebo. Primary outcome: composite of death, MI, stroke and requirement for RRT. | Mean 47±16        | Multivariate analysis of factors predicting CHF development:  
  - Ramipril vs. placebo. HR 0.76 (95%CI 0.54,1.07)  

Limitations: Limited to patients with type 2 diabetes. Analysis at a cohort level rather than by treatment. Heart failure was a secondary outcome. |
<table>
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<tr>
<th>Study ID</th>
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| ATLAS (2001)[42] | 3164 | Double blind randomised controlled trial (post hoc analysis of safety outcome). Multi-centre (international). | Patients with CHF NYHA Class II-IV. Excluded if serum creatinine >221µmol/L. Randomised those who showed tolerability in open label assessment. High dose versus low dose lisinopril. Primary outcome: all-cause mortality. Primary safety outcome included a composite of renal dysfunction and hyperkalaemia. | 54                | Incidence of renal dysfunction/hyperkalaemia:  
  - Any occurrence:  
    - SCr ≥ 133µmol/L 40.2% in HD and 31.8% in LD  
    - SCr < 133µmol/L 15.7% in HD and 10.0% in LD  
  - Classified as serious:  
    - SCr ≥ 133µmol/L 15.6% in HD and 15.6% in LD  
    - SCr < 133µmol/L 5.4% in HD and 4.1% in LD  
Limitations: High rate of treatment discontinuation (30% low dose and 27% in high dose). No statistical analysis of adverse outcomes including renal dysfunction and insufficient data provided to allow assessment. Basis for assessment of renal dysfunction not provided. |
| ELITE (1997)[43] | 722  | Double blind placebo controlled randomised trial. Multi-centre (international) | Older (≥65 years) patients with NHYA Class II-IV who had never received ACEi. Excluded if serum creatinine ≥221µmol/L. Captopril versus losartan Primary outcome: Persistent increase in serum creatinine of ≥27µmol/L from baseline. | 12                | Primary outcome occurred in 10.5% in the losartan group compared to 10.5% in captopril:  
Limitations: High rate of withdrawal (18% captopril and 30% losartan). Exclusion of patients with renal insufficiency. Restricted to patients 65 years of age or older. |

1B: Blockade of beta-adrenergic receptors
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<tr>
<th>Study ID</th>
<th>N</th>
<th>Study design</th>
<th>Description - Participants and Interventions</th>
<th>Follow up (months)</th>
<th>Comments and results</th>
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</table>
| CIBIS II, (1999) [45, 142, 143] | 2657      | Double blind placebo controlled randomised trial. | NYHA Class III-IV heart failure, LVEF≤35%, on ACE inhibitor Excluded if serum creatinine ≥300μmol/L Bisoprolol versus placebo Primary outcome was all-cause mortality | 15.6              | Adjusted HR (95% CI) for all-cause mortality (bisoprolol versus placebo) according to eGFR ml/min/1.73 m²  
  • <45 (n=450): 0.71 (0.48, 1.05)  
  • 59.9-45.0 (n=669): 0.69 (0.46, 1.04)  
  • 74.9-60.0 (n=640): 0.53 (0.34, 0.82)  
  • >75.0 (n=863): 0.64 (0.42, 0.99)  
  P for interaction=0.81  
  This trial was stopped prematurely after the second interim analysis demonstrated a significant mortality benefit |
| MERIT-HF, (1999) [46, 144]    | 3991      | Double blind placebo controlled randomised trial. | NYHA Class II-IV heart failure, LVEF≤40%, on ACE inhibitor No renal exclusion criteria Metoprolol succinate versus placebo Two primary outcomes: all-cause mortality and all-cause mortality plus hospital admission | 12                | Adjusted HR (95% CI) for all-cause mortality (metoprolol succinate versus placebo) according to eGFR ml/min/1.73 m²  
  • <45 (n=493): 0.41 (0.25, 0.68)  
  • 59.9-45.0 (n=976): 0.68 (0.45, 1.02)  
  • >60.0 (n=2496): 0.71 (0.54, 0.95)  
  P for interaction=0.095  
  This trial was stopped prematurely after the second interim analysis demonstrated a significant mortality benefit |
| SENIORS, (2005) [9, 145]      | 2112      | Double blind placebo controlled randomised trial. | Age≥70 years, NYHA Class II-IV heart failure, heart failure admission or LVEF≤35% Excluded if serum creatinine ≥250μmol/L Nebivolol versus placebo Primary outcome was composite of all-cause mortality plus cardiovascular hospital admission | 21±9              | Adjusted HR (95% CI) for all-cause mortality (nebivolol versus placebo) according to eGFR tertile:  
  • <55.5 (n=704): 0.76 (0.56, 1.03)  
  • 55.5-72.8 (n=704): 1.14 (0.78, 1.66)  
  • >72.8 (n=704): 0.82 (0.53, 1.25)  
  P for interaction=0.521 |
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<th>Study ID</th>
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<th>Comments and results</th>
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<tr>
<td>CAPRICORN N (2001) [146] and COPERNICUS (2002) [147] Pooled Analysis (2011) [47]</td>
<td>CAPRICORN =1959 COPERNICUS=2289 Pooled analysis: 4217 of whom 2566 had eGFR&lt;60 ml/min/1.73 m²</td>
<td>Both double blind placebo controlled randomised trials. Both multi-centre (international)</td>
<td>CAPRICORN Myocardial infarction within 3-21 days, LVEF≤40%, on ACE inhibitor No renal exclusion criteria COPERNICUS Symptoms at rest or minimal exertion, LVEF≤25%, on ACE inhibitor Excluded if creatinine&gt;247.5 μmol/L Primary outcome was all-cause mortality or hospital admission for cardiovascular problems in both trials.</td>
<td>13.6 ±7.9 for whole group</td>
<td>Adjusted HR (95% CI) for all-cause mortality (carvedilol versus placebo) according to eGFR ml/min/1.73 m² ≤60 (n=2566): 0.76 (0.63, 0.93) &gt;60.0 (n=1651): 0.59 (0.43, 0.81) P for interaction not significant</td>
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1C: Aldosterone antagonists
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<th>Study ID</th>
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<th>Study design</th>
<th>Description - Participants and Interventions</th>
<th>Follow up (months)</th>
<th>Comments and results</th>
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</table>
| RALES (1999) [49, Vardeny 2012][52] | 1663 | Pre-specified sub group analysis of a double blind placebo controlled randomised trial. Multi-centre (international)         | Patients with CHF NYHA Class III or IV at the time of enrolment and Class IV symptoms within 6 months prior to enrolment. Excluded if serum creatinine >221µmol/L. Spironolactone versus placebo. Primary outcome: all-cause mortality. | 24 (median)      | Relative risk of all-cause mortality in spironolactone treatment group compared to placebo:  
  - 0.70 (95%CI 0.60, 0.82), (placebo event rate 46%).  
  Significant reduction in all-cause mortality in the low and high serum creatinine groups (<106µmol/L and ≥106µmol/L), however risk reduction values not reported.  
  Post hoc Relative risk of all-cause mortality in spironolactone treatment group compared to placebo by eGFR:  
    - eGFR<60: 0.68 (0.56-0.84)  
    - eGFR>60: 0.71 (0.57-0.90)  
  Post hoc Relative risk hyperkalaemia by eGFR:  
    - eGFR<60: Placebo 8.5%, Spironolactone 25.2%  
    - eGFR>60: Placebo 6.0%, Spironolactone 15.4%  
  Adjusted hazard ratio for death associated with worsening renal function by treatment group:  
    - Placebo: 1.9 (1.3-2.6)  
    - Spironolactone: 1.1 (0.79-1.5, p for interaction=0.009)  
  Limitations: Trial stopped early due to meeting pre-specified criteria. High treatment discontinuation rate (26% treatment, 24% placebo). Sub group data provided graphically only. Proportion of patients with high versus low serum creatinine not provided. Likely to be few patients with eGFR<30mL/minute therefore results may not apply to more severe chronic kidney disease. |
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<th>Study ID</th>
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<th>Follow up (months)</th>
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<tr>
<td>EPHESUS (2003) [50, 53, 54]</td>
<td>6,632</td>
<td>Pre-specified sub group analysis of a double blind placebo controlled randomised trial. Multi-centre (international)</td>
<td>Patients with acute MI, left ventricular dysfunction and clinical features of heart failure. Excluded if serum creatinine &gt;221µmol/L. Eplerenone versus placebo. Primary outcomes: time to death from any cause and time to death from cardiovascular causes or first hospitalisation for a cardiovascular event.</td>
<td>16 (median)</td>
<td>Relative risk of all-cause mortality in eplerenone treatment group compared to placebo: 0.85 (95%CI 0.75 - 0.96). (placebo event rate 17%). Significant reduction in all-cause mortality for low (&lt;96µmol/L) serum creatinine group and non-significant reduction in high group (p for interaction=0.03), however risk reduction values not provided. Post hoc analysis of effect of treatment on kidney function: Mean difference in GFR eplerenone versus placebo: -1.4±0.3mL/minute Proportion with &gt;20% fall in GFR: 16.9% in eplerenone versus 14.7% in placebo, p=0.017 Limitations: Discontinuation rate of 15%. Sub group data provided graphically only. No analysis on basis of GFR. Proportion of patients with high versus low serum creatinine not provided. Serum creatinine measured at baseline. Sub group analysis for patients with renal dysfunction.</td>
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<td>Edwards et al (2009)[54]</td>
<td>112</td>
<td>Double blind placebo controlled randomised trial. Single centre (UK)</td>
<td>Adult (18 to 80 years) with stages 2 or 3 CKD. Treatment with an ACEi or ARB for at least 6 months. Excluded if CHF. Spironolactone versus placebo. Primary outcomes: Change in LV mass and arterial stiffness.</td>
<td>9</td>
<td>Change in LV mass from baseline to 9 months: Spironolactone: 119g (±34) to 105g (±30) – decrease of 12% Placebo: 110g (±26) to 113g (±28) – increase of 4% Spironolactone had no effect on left ventricular ejection fraction; however, left ventricular ejection fraction was normal at study entry Limitations: Excluded CHF patients. Single centre.</td>
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1D: Digoxin
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<th>Study ID</th>
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<th>Study design</th>
<th>Description - Participants and Interventions</th>
<th>Follow up (months)</th>
<th>Comments and results</th>
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</table>
| DIG (2004) [7, 60] | 6,800 eGFR ml/min/1.73 m²  
| |   | Double blind placebo controlled randomised trial (post hoc sub-group analyses).  
| |   | Multi-centre (North America) | Adult patients (>21 years) with heart failure and LV ejection fraction ≤0.45. Excluded if serum creatinine >265µmol/L.  
| |   | Digoxin versus placebo | Primary outcome: all-cause mortality.  
| |   | | A second post hoc analysis examined outcome in patients with GFR<60mL/minute who had serum potassium <4mmol/L (n=527) compared to serum potassium 4.0-4.9mmol/L (n=2266) | 37 (mean) | Adjusted hazard ratio (HR) for all-cause mortality in patients treated with digoxin vs placebo according to GFR (ml/min/1.73 m²) sub groups:  
| |   | |   |   | >60 – 1.01 (95%CI 0.89,1.14)  
| |   | |   |   | 30-60 – 0.95 (95%CI 0.85,1.07)  
| |   | |   |   | <30 – 0.93 (95%CI 0.65,1.35)  
| |   | | There was no interaction of kidney function and therapy (p=0.19) | Hazard ratios (HR) in propensity score matched cohort of patients with hypokalaemia (n=522) compared to those with normokalaemia (n=522):  
| |   | |   |   | All-cause mortality - 1.56 (95%CI 1.25, 1.95)  
| |   | |   |   | Cardiovascular mortality – 1.65 (95%CI 1.29, 2.11)  
| |   | |   |   | Progressive HF– 1.82 (95%CI 1.28, 2.57)  
| |   | | There was no significant difference between digoxin and placebo groups. | Limitations: Post hoc subgroup analysis. Imprecise measures of renal function. Exclusion of patients with high serum creatinine. |

1E: Vasodilators

| | | Multi-centre (US) | Adult (>18 years) African Americans with NYHA Class III or IV.  
| | | | Fixed-dose isosorbide dinitrate and hydralazine (FDC I/H) versus placebo.  
| | | | Primary outcome: Composite score weighted for all-cause mortality, first hospitalisation for HF, and change in QoL at 6 months. | 20 | No significant difference in treatment effect between patients with a history chronic renal insufficiency and those without.  
| | | | Relative risk for composite of all-cause mortality or first hospitalisation for heart failure in participants with chronic renal insufficiency compared to those without:  
| | | |   |   | 1.62 (95%CI 1.29, 2.03)  
| | | | Limitations: Subgroup analysis. “Chronic renal insufficiency” defined by history and not by any measure of kidney function. Restricted to African Americans. Trial stopped early in accordance with predefined requirements. Renal insufficiency defined by medical records. |

1F: Treatment of anaemia
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<tr>
<th>Study ID</th>
<th>N</th>
<th>Study design</th>
<th>Description - Participants and Interventions</th>
<th>Follow up (months)</th>
<th>Comments and results</th>
</tr>
</thead>
</table>
| RED-HF (2013)[73] | 2278    | Double blind placebo controlled randomised trial. | Patients with CHF NYHA Class II-IV, LVEF≤40% and haemoglobin 9.0-12.0g/dL  
Darbepoetin alfa versus placebo aiming for a target haemoglobin of 13.0g/dL  
Primary outcome: All-cause death or hospitalisation for heart failure | 28 (median)      | Hazard ratio for the primary outcome darbepoetin alfa versus placebo:  
- All patients: 1.01 (0.90-1.13, p=0.87)  
  - GFR<60: 0.90 (0.90-1.16)  
  - GFR>60: 0.94 (0.71-1.25, p for heterogeneity=0.75)  
Thromboembolic adverse events  
- Darbepoetin alfa: 153 (13.5%)  
- Placebo: 114 (10.0%)  
- Risk difference 3.5% (0.9-6.5, p=0.009) |
| FAIR-HF (2009)[68] | 459     | Double blind placebo controlled randomised trial. | Ambulatory patients with CHF NYHA Class II or III, Hb at screening between 95 and 135 g/L and iron deficient. Excluded if “significantly impaired renal function”.  
Ferric carboxymaltose versus placebo.  
Primary outcome: Self-reported Patient Global Assessment (PGA) and NYHA Class at 24 weeks. | 6                | Mean eGFR (ml/min/1.73 m²) at baseline:  
- FC group 63.8 (SD 21.2); placebo group 64.8 (SD 25.3).  
Odds ratio at 24 weeks in FC treated group compared to placebo:  
- PGA: 2.51 (95%CI 1.75, 3.61)  
- NYHA Class I or II – 2.40 (95%CI, 1.55,3.71)  
No significant difference between subgroups with GFR <60 and >60 ml/min/1.73 m² (P for interaction of kidney function and treatment assignment=0.22)  
No significant differences in adverse events and side effects between treatment groups.  
Limitations: Criteria for significantly impaired renal function not defined. Withdrawal from FC treatment 7%, withdrawal from placebo 10%. Graphical presentation of OR for subgroup analysis. |
<table>
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</tr>
</thead>
</table>
| CHOIR (2006) [81, 82] | 1432 | Heart failure at baseline: 375 | Open label randomised controlled trial (post hoc analysis). Multi-centre (US) Adults (>18 years) with CKD (eGFR 15-50 ml/min/1.73m²) not on dialysis and Hb <11.0 g/dL. High Hb target (13.5 g/dL) versus low Hb target (11.3 g/dL). Hb control using subcutaneous epoetin alfa. Primary outcome: Time to composite of death, MI, hospitalisation for CHF or stroke. | 16 (median) | HR's for high Hb group compared to low Hb group.  
- Primary composite endpoint - 1.34 (95% CI 1.03,1.74), low Hb rate 13.5%  
- All-cause death - 1.48 (95% CI 0.97,2.27), low Hb rate 5.0%  
- Hospitalisation due to HF - 1.41 (95% CI 0.97,2.05), low Hb rate 6.6%  
Adjusted HR's for subgroups with and without HF at baseline in high Hb group vs low Hb group:  
- Primary composite endpoint no previous HF – 1.86 (95% CI 1.21,2.85)  
- Primary composite endpoint previous HF – 0.99 (95% CI 0.68,1.43)  
(P for interaction of baseline HF and treatment assignment=0.028)  
Limitations: Early termination on basis of predefined criteria. Post hoc subgroup analysis for baseline heart failure. High withdrawal rate, 38% in high Hb group and 38% in low Hb group. Self-reported history of HF for baseline determination. |
| TREAT (2009) [83] | 4047 | Heart failure at baseline: 1347 | Double blind placebo controlled randomised trial. Multi-centre (international) Patients with type 2 diabetes and eGFR between 20 and 60 ml/min/1.73 m² and Hb ≤11.0g/dL. Darbepoetin alfa versus placebo. Primary outcome: composite of all-cause death or a cardiovascular event. | 29.1 (median) | HF at baseline:  
- 31.5% in darbepoetin alfa group and 35.2% in placebo group (P=0.01). HR's for darbepoetin alfa compared to placebo group:  
- Composite outcome – 1.05 (95% CI 0.94-1.17), placebo event rate 29.7%  
- All-cause death – 1.05 (95% CI 0.92-1.21), placebo event rate 19.57%  
- Episode of Heart failure – 0.89 (95% CI 0.74-1.08), placebo event rate 11.3%  
Limitations: restricted to patients with Type 2 diabetes. No sub group analysis for baseline HF. Baseline differences between treatment groups, for HF, eGFR, HbA1C. |

**1G: Strategies to control volume state**

No data

**1H: Implantable devices**
<table>
<thead>
<tr>
<th>Study ID</th>
<th>N</th>
<th>Study design</th>
<th>Description - Participants and Interventions</th>
<th>Follow up (months)</th>
<th>Comments and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADITII (2002)[93, 94]</td>
<td>1232 Serum urea&gt;8.9mmol/L: 368</td>
<td>Open label randomised trial (post hoc analysis). Multi-centre (US and Europe)</td>
<td>Adults (&gt;21 years) who had an MI ≥one month before study entry and ejection fraction ≤30%. Implantable defibrillator versus conventional medical therapy. Primary outcome: All-cause death.</td>
<td>20 (mean)</td>
<td>HR for all-cause death in defibrillator group compared to medical therapy: 0.69 (95%CI 0.51-0.93), control rate 20%. Adjusted HR's for all-cause mortality for defibrillator compared to medical therapy: Serum urea ≤8.9mmol/L - 0.65 (95%CI 0.44,0.96) Serum urea &gt; 8.9mmol/L - 0.71 (95%CI 0.48,1.06) P value for interaction = 0.74 Limitations: Cross over rate defibrillator to medical therapy 2.8%, medical therapy to defibrillator 4.5%. No estimate of CKD.</td>
</tr>
</tbody>
</table>
| CARE-HF (2005) [92, 96, 97] | 813 | Open label randomised trial. Multi-centre (International) | Adults (>18 years) with HF NYHA Class III or IV, LV ejection fraction <35%, QRS duration>120msec on ECG plus other ECG criteria. Implantable defibrillator and medication vs. medication alone. Primary outcome: composite of all-cause death or unplanned hospitalisation for major cardiovascular event. | 29.4 (mean) | Median eGFR at baseline similar in both groups: 61 ml/min/1.73m² (interquartile range 46-73). HR defibrillator treatment group compared to medication therapy alone according to pre-specified eGFR subgroup analysis: All-cause death or unplanned hospitalisation  
  - eGFR <60.3: 0.67 (95%CI 0.50-0.89)  
  - eGFR ≥60.3: 0.57 (95%CI 0.40-0.80) There was no heterogeneity between these groups. Limitations: Subgroup analysis. Limited to baseline assessment of eGFR. |
<p>| Korantzopoulos et al (2009)[96] | 11 observational studies (3010 participants) | Systematic review and meta-analysis of observational studies. | Prospective or retrospective observational studies with a primary objective of analysis of the association between CKD and mortality in patients with ICDs. | NA | Adjusted HR for effects of CKD on all-cause mortality in patients with ICD: Any definition of CKD - 3.44 (95%CI 2.82,13.88) Based on eGFR of 60 – 3.06 (95%CI 2.31,4.04) Limitations: Meta-analysis is largely of retrospective observational studies with only 2 of 11 studies were prospective. Variable definition of CKD. |</p>
<table>
<thead>
<tr>
<th>Study ID</th>
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</tr>
</thead>
</table>
| Khan et al (2010)[97] | 78    | Retrospective case control study based. Single centre (US) | Patients with a diagnosis of CKD and LV ejection fraction <35%. Cases were defined by ICD therapy, controls had no ICD therapy. | 2.7 ± 2.3 years (mean) | Two year survival:  
- CKD with ICD 80%, CKD no ICD 61% (P=0.027)  
- Dialysis with ICD 55%, dialysis no ICD 42% (P=0.754)  
Multivariate OR for risk of death in non-dialysis CKD patients.  
- ICD – 0.23 (95% CI 0.06-0.85), P=0.03.  
Limitations: Retrospective observational study. Medical record review. CKD measured at baseline. Cause of death not able to be determined for a number of patients. Single centre and small sub-group numbers. |
| Cheema et al (2010) [98] | 441 eGFR ml/min/1.73 m²  
- <60 (257)  
- >60 (162)  
- HD (22) | Retrospective medical records review. Single centre (US) | Consecutive ICD patients from 1994-2002. | Up to 10 years | Overall survival:  
- <60 – 60.3 (95% CI 51.0,69.5) months  
- >60 - 85.9 (95% CI 77.4,94.3) months  
- HD - 37.8 (95% CI 22.8,52.8) months  
Limitations: Retrospective observational study. Medical record review. CKD measured at baseline. Single centre. Standard of care for both medical therapy and ICD therapy may have changed over the course of the study. |
| Cice et al (2010)[107] | 332   | Double blind placebo controlled randomised trial. Multi-centre (Italy) | Adult HD patients with NYHA Class II and III symptoms, ejection fraction ≤40% and taking an ACEi. Excluded patients with low tolerance to telmisartan during run in period. “Add on” telmisartan versus placebo. (i.e. telmisartan in addition to standard CHF medication that included an ACEI) Primary outcome: all-cause mortality. | 3 years | Adjusted HR for telmisartan compared to placebo.  
- All-cause mortality – 0.51 (95% CI 0.32-0.82), control rate 54%.  
- Hospital admission for CHF – 0.38 (95% CI 0.19,0.51)  
- Cardiovascular deaths – 0.42 (95% CI 0.30-0.61)  
Limitations: The population had a very high mortality and morbidity rate. Dropout rate of 16% for telmisartan and 11% for placebo. Patients received haemodialysis 4x/week.  
Greater risk of hypotension with telmisartan than placebo. |
<table>
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<tr>
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</table>
Multi-centre (Japan) | Hypertensive adult (30 to 80 years) patients receiving HD 2-3x/week. Excluded if receiving an ACEi or ARB.  
ARB* versus no ARB. *(type as selected by clinician).  
Primary outcome: composite of fatal and nonfatal cardiovascular events. | CHF at baseline 16% in ARB and 15% in control groups. RR for ARB group compared to control:  
- Primary endpoint (fatal and non-fatal CV events) - 0.58 (95% CI 0.40, 0.83)  
- Non-fatal episode of CHF - 0.48 (95% CI 0.26, 0.88)  
- All-cause death - 0.66 (95% CI 0.42, 1.04)  
Limitation: Not a CHF population and no subgroup analysis. Lack of baseline assessment of a number of factors contributing to CVD. Multiple ARBs used for treatment. Open label design. Limited definition of CHF as an outcome. |
Single centre (Japan) | Adult (≥35 years) HD patients stable for at least 6 months. Excluded if they had CHF.  
Candesartan versus control.  
Primary outcome: Overall incidence of CV events. | 19.4 (mean) | RR of HF in candesartan group compared to control.  
- 0.39 (95% CI 0.15, 1.02)  
Limitation: CHF excluded. Small numbers, single centre. Limited clinical definition of HF. |
Multi-centre (France) | Adult (50-80 years) HD patients (for at least 6 months) and LVH.  
Fosinopril versus placebo.  
Primary outcome: Cardiovascular event (cardiovascular death, non-fatal MI, unstable angina, stroke, revascularisation, hospitalisation for HF, and resuscitated cardiac arrest) | 24 | No significant difference between treatment groups. Given problem with randomisation, only conducted cohort analyses. 1 year event rate for HF hospitalisation was 6.5%.  
Limitations: Not a CHF study. Study population and CHF at baseline not reported. Trial ended up being underpowered for main clinical outcome due to imbalance in randomisation. |
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</table>
  • ACEi – 0.97 (95%CI 0.76,1.23) –  
  • Beta blockers – 0.69 (95% CI 0.52-0.91)  
Limitations: Retrospective analysis of dialysis registry. Restricted to Medicare claim patients. |
| Efrati et al (2002) [113] | 126 | Retrospective medical record review. Single centre (Israel) | HD patients between 1994 and 2000. Outcome: All-cause mortality. | NA | At start of dialysis, 66 (52%) were treated with ACEi with 32% having CHF compared to 38% in those not treated with ACEi. Adjusted RR for all-cause mortality associated with ACEi treatment:  
  • 0.48 (95% CI 0.25-0.91) caused mainly by decrease in cardiovascular death.  
Limitations: Retrospective medical records review. Single centre small cohort. |
| Berger et al (2003)[114] | Not receiving dialysis: 145,740  Receiving Dialysis: 1,025 | Retrospective registry review. US - Cooperative Cardiovascular Project matched with USRDS | Patients >65 years presenting with clinical evidence of AMI. Primary outcome 30 day mortality post AMI. | NA | CHF was present in 40% of dialysis patients at baseline; therefore, not a pure CHF population.  
30 day mortality in all patients:  
  • Dialysis 29.0%, non ESKD 18.3% (P<0.001)  
RRR in 30 day mortality with beta-blocker use:  
  • Dialysis 40% (P<0.001), non ESKD 56% (P<0.001)  
RRR in 30 day mortality with ACEi use:  
  • Dialysis 48% (P<0.001), non ESKD 27% (P<0.001)  
No adverse events reported.  
Limitations: bias associated with retrospective review of medical registry. Short term outcomes assessment. |
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</table>
| McCullough et al (2002)  | 527        | Retrospective registry review.                    | Adult (>20 years) HD patients admitted to the coronary care unit following a cardiac event. ACEi treatment (n=143) compared to no ACEi treatment (n=225). Primary outcome: Arrhythmic, haemodynamic and death.                                                    | NA                | Proportion of CHF in treatment groups:  
  - ACEi – 66%; no ACEi – 40%.  
  Adjusted RR for all-cause death after discharge in ACEi treated group compared to no ACEi:  
  - 0.63 (95%CI 0.47,0.83)  
  Limitations: Retrospective review of medical register. Not a pure CHF population. Mismatches between CHF in ACEi group and no ACEi group. Single centre.                                                                                                                                |
|                          | (complete records 368) | Single centre (US) |                                                                                                                                      |                   |                                                                                                                                                                                                                                           |
| Cice et al (2001) and Cice et al (2003) | 114 | Double blind placebo controlled randomised trial. | HD patients with NYHA Class II to III symptoms and LVEF <35%. Patients received HD 4x/week. Carvedilol versus placebo  
Outcomes first 12 months (blinded): Changes in LV measurements and symptoms of CHF.  
Outcomes second 12 months (unblinded): all-cause mortality, hospitalisation, cardiovascular death, | 24                | LV ejection fraction:  
Placebo: 26±8% at baseline, 26±8% at 12 months  
Carvedilol: 26±8% at baseline, 36±11% at 12 months  
HR at 24 months associated with carvedilol treatment compared to placebo:  
  - All-cause mortality – 0.51 (95%CI 0.32,0.82) – control rate 73%  
  - All-cause hospitalisation – 0.44 (95%CI 0.25,0.77) – control rate 59%  
  - Cardiovascular death – 0.32 (95%CI 0.18,0.57) - control rate 68%  
Limitations: Un-blinded after first 12 months. Change from very low mortality rate at 12 months to very high at 24 months. Adjudication of secondary outcomes not detailed. Single centre study. |
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</table>
| Taheri et al (2009) [119] | 16    | Placebo controlled double blind randomised trial. | HD patients with heart failure (NHYA Class III or IV) treated with an ACEi or an ARB. Spironolactone versus placebo  
Outcomes: change in LV ejection fraction and LV mass at 6 months | 6                 | Mean difference in change in outcomes from baseline between spironolactone compared to placebo:  
- LV ejection fraction: +5.37% (95%CI 1.79, 8.95)  
- LV mass: -11.4 (95%CI -17.82, -4.98)  
Limitations: Single centre small numbers. High dropout rate (30%). |
| Taheri et al (2012) [120] | 18    | Placebo controlled double blind randomised trial. | CAPD patients with heart failure (NHYA III or IV) treated with an ACEi or an ARB and serum K<5.5mmol/L. Spironolactone 25mg daily versus placebo  
Outcomes: change in K, Hb and LV ejection fraction | 6                 | No difference in any outcome.                                                                                                                                                                                                 |
Primary outcome: Composite of cardiovascular death, non-fatal MI and stroke. | 24 (median)       | Data regarding CHF not reported in Abstract.  
RR for combined therapy compared to monotherapy:  
- All cardiac events – 0.89 (95%CI 0.78, 0.98)  
All other endpoints non-significant.  
Limitations: Not a CHF population. Severe HF (NHYA Class IV) excluded. Published in Abstract form only; thus limited description of all aspects. |
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</table>
| Matsumoto et al (2009)[122] | 61    | Prospective cohort. Multicentre (Japan) | Oliguric HD patients aged >30years  
Spironolactone at a dose of 25 mg/day for 6 months. No control.  
Primary outcome: Serum potassium. | 6     | Serum potassium levels 4.96±0.72 at baseline and 5.18±0.72 at 6 months  
Limitations: Small observational study without a control group. Not a CHF population. Withdrawal rate of 18%. Power of study unknown. Limited baseline characteristics provided. |
Incident HD patients from 2001 to 2006.  
Patients classified by with digoxin treatment status.  
Primary outcome: mortality. | Maximum 4 years. | Patients with CHF comprised 21% of this cohort  
Association between digoxin use and mortality:  
- All patients – HR (adj) 1.28 (95%CI 1.25-1.31).  
- Patients with CHF – HR (adj) 1.18 (95%CI 1.13-1.23).  
Mortality HR increases with increasing serum digoxin concentrations  
Mortality risk for high digoxin level (>2.2ng/L versus <0.6ng/L):  
HR 2.53 when serum potassium<4.3mmol/L  
HR 0.86 when serum potassium>4.6mmol/L (P for interaction =0.04)  
Limitation: Medical records review. Observational study. Digoxin and non-digoxin ‘users’ significantly different in risk factors for mortality. Lack of structural cardiac parameters. Confounding by indication for digoxin use (although used propensity score) |

2E: Vasodilators  
No data  

2F: Treatment of anaemia
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Besarab et al (1998) and Berns et al (1999) [124, 125] comment</td>
<td>1233</td>
<td>Open label randomised controlled trial Multicentre (US)</td>
<td>HD patients with CHF or ischaemic heart disease. Excluded inpatients with NHYA Class IV symptoms. Normal versus low haematocrit target. Primary outcome: Length of time to death or a first nonfatal MI.</td>
<td>29</td>
<td>CHF present in 44% (normal haematocrit) and 47% (low haematocrit) at baseline RR in normal compared to low haematocrit:  - Primary composite endpoint - 1.3 (95%CI 0.9,1.9)  - All-cause mortality - 1.21 (95%CI 1.01,1.46)  CHF requiring hospitalisation in normal versus low haematocrit groups: HR 0.88 (0.67,1.17), low haematocrit rate 15%, Limitations: Trial terminated early.</td>
</tr>
<tr>
<td>Foley et al (1996) [127]</td>
<td>432</td>
<td>Prospective cohort study Single centre (US)</td>
<td>Dialysis patients who had survived for at least 6 months and technically satisfactory Echocardiogram within 1 year of starting dialysis.</td>
<td>41 (mean)</td>
<td>HF identified at baseline in 31% of cohort. Independent impact of anaemia (effect of a decrease in mean Hb of 1 g/dL):  - De novo HF - RR 1.28 (P=0.017) – rate 24%.  - Death – RR 1.14 (P=0.024) – rate 32%. Limitations: Observational from a single centre. Study commenced in 1982 and thus not representative of current management with respect to dialysis or heart failure. Definition of HF subject to bias. Treatment associated with individual cases of anaemia is unknown.</td>
</tr>
</tbody>
</table>

**2G: Strategies to control volume state**

No data

**2H: Implantable devices**
<table>
<thead>
<tr>
<th>Study ID</th>
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</thead>
<tbody>
<tr>
<td>Hiremath et al (2010) [129]</td>
<td>50 ESRD with ICD 50 ESRD no ICD</td>
<td>Retrospective case control study. Two centres (US) – cases with ICD (US) and controls with no ICD(Canada)</td>
<td>Cases: Patients receiving dialysis for at least 3 years identified from an ICD Registry. Controls: Patients receiving dialysis at a Canadian hospital with no ICD but LVEF &lt;35%.</td>
<td>7 years</td>
<td>OR for all cause-death for ICD group compared to no ICD: 0.48 (95%CI 0.22-1.07). Median survival: ICD group 8.0 years, No ICD group 2.5 years (P=0.015) Adjusted HR for survival in ICD compared to no ICD groups: 0.40 (95%CI 0.19-0.82). Limitations: Retrospective analysis of cases from one centre and controls from another. Case and controls not matched for diabetes (70% in ICD vs. 50% in no ICD) or prior CAD (68% in ICD and 92% in no ICD). No centre specific mortality rates.</td>
</tr>
<tr>
<td>Herzog et al (2005) [130]</td>
<td>6,042</td>
<td>Retrospective review of medical claims database (US).</td>
<td>Prevalent dialysis patients (1996-2001) who were hospitalised with an index event of cardiac arrest or ventricular fibrillation/flutter (n=30,518) and who survived at least 30 days after discharge (n=6,173).</td>
<td>NA</td>
<td>Of the 6,042 surviving at least 30 days after discharge 460 (7.6%) had an ICD implanted within 30 days of admission. Estimated survival: 1 year – 71% ICD, 49% no ICD 3 years – 36% ICD, 23% no ICD 5 years – 22% ICD, 12% no ICD Independent association of ICD with death: RR 0.58 (95%CI 0.50,0.66) Overall, 56% of patients had CHF. Limitations: Retrospective review of medical claims database with limited clinical data in relation to severity of HF and CAD. No data on use of cardiovascular medications.</td>
</tr>
<tr>
<td>Study ID</td>
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</tbody>
</table>
Controls randomly selected for age, sex and type of device at a ratio of 3 controls to every 1 ESRD.  
Primary outcome: Any adverse unexpected peri-procedure event including death. | NA                | Of the ESRD patients, 95% were on HD, with a mean time on dialysis of 35±40 months.  
There were no fatal complications in either group.  
Unadjusted OR for patients experiencing complications in ESRD patients compared to non ESRD:  
- Major complications: 8.07 (95%CI 2.79-23.1) – control rate 5%.  
Conditional logistic regression indicated that ESRD was associated with major complications:  
- ESRD: 5.06 (95%CI 2.1-12.0)  
4 dialysis patients (10%) had thrombosis of vascular access ipsilateral to the device. Controls had no vascular access.  
Limitations: Retrospective review of medical records. Small number of cases from a single centre. Low rate of specific complication types. Uncertainty in assigning complications to CRMD. Analysis based on incidence of patients experiencing complications rather than total number of complications. |
Table 2. Quality of randomised trials

<table>
<thead>
<tr>
<th>Study ID (author, year)</th>
<th>Method of allocation concealment *</th>
<th>Blinding</th>
<th>Intention-to-treat analysis †</th>
<th>Loss to follow up (%)</th>
<th>Limitations of study design</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(participants)</td>
<td>(investigators)</td>
<td>(outcome assessors)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONSENSUS (1987) [26-28]</td>
<td>Central</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td>SOLVD [29, 30]</td>
<td>Computer generated assignment</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td>SAVE [22, 31]</td>
<td>Computer generated assignment</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6 (0.3%)</td>
</tr>
<tr>
<td>Val-HeFT [25, 32]</td>
<td>Central</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes – all patients appear to be included</td>
</tr>
<tr>
<td>CHARM Studies [8]</td>
<td>Central</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>E-COST-R (2005) [38]</td>
<td>Sealed envelopes randomly assigned to treatments</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>20%</td>
</tr>
<tr>
<td>RENAAL (2001) [39]</td>
<td>Computer generated random allocation</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes 0% (however high treatment discontinuation rate).</td>
</tr>
<tr>
<td>IDNT (2003) [40]</td>
<td>Central</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>DIABHYCAR (2003) [41]</td>
<td>Central</td>
<td>Yes</td>
<td>Unclear</td>
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<td>ATLAS (2001) [42]</td>
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<td>0% (however high rate of treatment discontinuation)</td>
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<td>ELITE (1997) [43]</td>
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<td>CIBIS II, (1999) [45, 142, 143]</td>
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<td>MERIT-HF, (1999) [46, 144]</td>
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<td>Study ID (author, year)</td>
<td>Method of allocation concealment *</td>
<td>Blinding (participants)</td>
<td>Blinding (investigators)</td>
<td>Blinding (outcome assessors)</td>
<td>Intention-to-treat analysis †</td>
</tr>
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<td>SENIORS, (2005) [9, 145]</td>
<td>Central</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
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<td>CAPRICORN (2001) [146] and COPERNICUS (2002) [147] Pooled Analysis (2011) [47]</td>
<td>CAPRICORN: Central</td>
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<td>Yes</td>
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<td>COPERNICUS: Unclear</td>
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<td>RALES (1999) [49]</td>
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<td>Edwards et al (2009) [54]</td>
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<td>DIG (2004) [7, 60]</td>
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<td>A-HeFT (2007) [63, 148]</td>
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<td>FAIR-HF (2009) [68]</td>
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<td>RED-HF (2013) [73]</td>
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<td>CHOIR (2006) [81, 82]</td>
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<td>Study ID (author, year)</td>
<td>Method of allocation concealment *</td>
<td>Blinding (participants)</td>
<td>Blinding (investigators)</td>
<td>Blinding (outcome assessors)</td>
<td>Intention-to-treat analysis †</td>
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<td>Suzuki et al (2008) [108]</td>
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