Heart Failure

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GUIDELINES

CKD and kidney transplant recipients

a. We recommend that an angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist be prescribed for patients with CKD (or kidney transplant) and heart failure (1B). The evidence of benefit in the general population is strong and there is reasonable data to suggest that these effects are similar in CKD.
b. We recommend that a beta-blocker be prescribed for patients with CKD (or kidney transplant) and heart failure (1B). The evidence of benefit in the general population is strong and there is strong data to suggest that these effects are similar in CKD.
c. There is insufficient evidence that the benefits of aldosterone antagonists in patients with CKD and heart failure outweigh the harms. Therefore we do not suggest that this therapy should be prescribed for all patients (ungraded).
d. The anaemia of people with CKD and heart failure should be treated according to the CARI Guideline "Biochemical and Haematological Targets: Haemoglobin". There is no evidence this should be modified for patients with heart failure (ungraded).
e. The role of diuretic therapy in heart failure is to control the disturbance in extracellular fluid volume and there is no evidence of benefit in terms of cardiovascular outcomes (ungraded).
f. In the absence of any evidence, patients with CKD or kidney transplant recipients who meet the criteria for an implantable device should be considered for such devices (ungraded).

Dialysis

a. We suggest that patients receiving dialysis who have heart failure be prescribed an angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist (ungraded). This is based on there being strong evidence in the general population as there are no trials comparing these agents to placebo in patients undergoing dialysis.
b. In the absence of *high-quality* evidence, we suggest that patients receiving dialysis who have heart failure be prescribed a beta-blocking agent (2C). This is based on there being strong evidence in the general population, strong data to suggest similar effects in CKD, and one randomised controlled trial in patients undergoing dialysis consistent with these data.
c. The anaemia of people requiring dialysis who have heart failure should be treated according to the CARI Guideline "Biochemical and Haematological Targets: Haemoglobin". There is no evidence this should be modified for patients with heart failure (ungraded).

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 heart failure 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.

The prevalence of heart failure 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 heart failure was reported by 15% of participants with a GFR<30mL/minute, compared to 5% in participants with GFR>60mL/minute [3]. Likewise, the prevalence of CKD, defined as a glomerular filtration rate (GFR) less than 60mL/minute, is very high in heart failure patients. In many trial cohorts, this prevalence is over one third and patients with heart failure who also have CKD have a greater mortality risk than patients with heart failure and normal kidney function [4]. In a randomised controlled trial population with severe heart failure, 50% of participants had a creatinine clearance less than 60mL/minute and reduced creatinine clearance was a stronger predictor of outcome than reduced left ventricular ejection fraction (LVEF) [5].

Heart failure is also a significant co-morbidity in end-stage kidney disease (ESKD). The prevalence of heart failure has been reported in between 31-40% of patients commencing dialysis [6, 7], and patients receiving dialysis who have co-morbid CHF have a greater mortality than those who don't have CHF [7, 8]. Patients receiving dialysis who have heart failure who receive a kidney transplant are at increased risk of adverse outcomes in the post-transplant period. Of 653 patients who had cardiac nuclear imaging before kidney transplant, 18% had a LVEF≤45% and these patients had between 2 to 5 times greater death, cardiac death and cardiac complications than patients with LVEF above this level [9].

Heart failure may also develop "de novo" after receiving a kidney transplant. Using United States Medicare Claims data, the incidence of de novo heart failure was estimated to be 10.2% at 12 months and 18.3% at 36 months [10]. For patients remaining on dialysis on the transplant waiting list, these incidences were 12.0% and 32.3%, respectively. In a retrospective study that used a clinical definition of heart failure, the cumulative incidence of de novo heart failure in patients who survived the first post-transplant year without heart failure was 3.6% at 5 years and 12.1% at 10 years [11].

However, the presence of heart failure or concerns about the development of heart failure should not preclude patients with ESKD from being considered for transplantation, because restoring kidney function with transplantation actually may improve cardiac function in such patients. In patients with heart failure and LVEF≤40% who received a kidney transplant at a single centre, LVEF improved from 31.6±6.7% before to 52.2±12.0% after receiving a kidney transplant (p=0.002) [12]. In a pivotal observational study of change in cardiac structure and function in 433 patients with ESKD from the 1980s, all 12 patients with systolic dysfunction before transplant had normal systolic function on echocardiograms following their transplant

[13]. Other studies have demonstrated improvements in left ventricular volumes and function following transplantation [14-16], including as early as 3 months following the procedure [17].

A unique contributing factor to heart failure in patients with ESKD is the cardiac effects of shunting blood from the arterial to the venous system through the arteriovenous fistulae for vascular access. Because successful kidney transplantation makes ligation of the arteriovenous fistula possible, this may be a therapeutic option in kidney transplant recipients. Ligation of the arteriovenous fistula in 20 kidney transplant recipients without heart failure resulted in a reduced left ventricular end-diastolic diameter and left ventricular mass index [18]. Cases of arteriovenous fistula-related high-output cardiac failure that has improved with ligation of the fistula have been reported [19]; however, the benefits of ligation of arteriovenous fistulae in kidney transplant recipients with heart failure have not been studied in any systematic way.

The objectives of this guideline are to summarise the available evidence from randomised controlled trials for treatment of heart failure *in patients with chronic kidney disease*. 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. Treatment of anaemia with erythropoiesis stimulating agents
6. Strategies to control volume state including diuretics
7. Use of Implantable Devices

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 heart failure to study a heart failure intervention. It is accepted that they will be different in many ways such as time already spent undergoing dialysis and immunosuppression.

A number of randomised controlled trials have been performed in patients with heart failure that provide a strong evidence base underpinning many guideline recommendations [20-22]. Evidence for each therapy in patients without kidney disease is presented in the first section on "**Patients with CKD and kidney transplant recipients**", along with a summary of the Australian National Heart Foundation Heart Failure Guideline [21, 22] for the respective therapies. This is not re-stated in the "**Dialysis**" section.

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 randomised controlled trials 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 (1950-March 2008) was the database searched.

Date of searches: 19 March 2008

What is the evidence?

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

1. Blockade of the renin-angiotensin system

Evidence from studies of patients without CKD

In patients with heart failure, including those patients with heart failure after acute myocardial infarction, treatment with an angiotensin-converting enzyme inhibitor reduced the risk of death by 20% (odds ratio 0.80, 95% confidence interval 0.74-0.87, p<0.001) [23]. Reinfarction, 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 angiotensin-converting enzyme inhibitors [24], and may reduce hospital admissions for heart failure when added to angiotensin-converting enzyme inhibitors compared to angiotensin-converting enzyme inhibitors alone [24, 25].

National Heart Foundation guideline for the general population:

- 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 randomised controlled trials examining blockade of the renin angiotensin system specifically in patients with reduced kidney function *and* heart failure 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 [4, 26], worsening kidney function [27] and proteinuria [28-30] are associated with increased mortality in patients with heart failure , few have actually reported the effect of the intervention in the patients with chronic kidney disease.

Of all the trials of drugs that inhibit the renin-angiotensin system, three reported subgroup analyses of patients with chronic kidney disease (Table 1). In one of the earliest studies of angiotensin-converting enzyme inhibitors in heart failure [31], 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) [32]. Crude mortality was reported in a separate publication [33]. In patients with reduced left ventricular ejection fraction following myocardial infarction in the Survival and Ventricular Enlargement (SAVE) Study [34],

mortality was reduced by treatment with captopril compared to placebo by 28% (95% confidence interval 6-45) in patients with GFR<60mL/minute. Cardiovascular mortality and morbidity was reduced by 31% (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 heart failure randomised to the angiotensin receptor blocker valsartan or placebo, 58% had a GFR below 60mL/minute at baseline [30]. This subgroup received no mortality benefit but there was a significant reduction in first morbid event with valsartan treatment (hazard ratio 0.86, 0.74-0.99). The interaction term was not significant.

In a combined analysis of studies of candesartan in heart failure patients, 36% of participants analysed had a GFR below 60mL/minute [4]. 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 CHARM studies performed subgroup analyses of a number of pre-specified subgroups, level of kidney function was not one of them [35-37].

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. Furthermore, the mode of action of blockers of the renin-angiotensin system may in itself result in a rise in serum creatinine that does not of itself represent kidney disease.

Results of other studies

Some studies in different CKD populations have demonstrated that blockade of the renin-angiotensin system reduces de novo heart failure in patients without known heart failure at baseline. The E-COST 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 heart failure 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 randomised controlled trial of the angiotensin receptor blocker losartan in patients with diabetic nephropathy (RENAAL), 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 a randomised controlled trial comparing irbesartan to placebo or amlodipine in patients with diabetic nephropathy (IDNT), 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 heart failure in patients with diabetes and microalbuminuria or proteinuria compared to placebo in another large randomised controlled trial [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 sytem in patients with CKD is concern regarding adverse effects. In the Survival and Ventricular Enlargement (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 [27]. The Assessment of Lisinopril and Survival (ATLAS) Study compared low dose to high dose lisinopril in patients with heart failure 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 heart failure 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 heart failure, post hoc analyses of two trials suggest that patients with CKD receive the same, or possibly greater, reduction in mortality with an angiotensin-converting enzyme 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.

2. Beta-blocker therapy

Evidence from studies of patients without CKD

In patients with heart failure, therapy with one of three beta-blockers receives the strongest recommendation (Class I) based on the highest level of evidence (Level A) [20]. 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 randomised controlled trials that specifically recruited patients with CKD, but five trials report post hoc subgroup analyses of patients with glomerular filtration rate (or creatinine clearance) less than 60mL/minute

(**Table 1**). These studies used bisoprolol (CIBIS II) [45], metoprolol succinate (MERIT HF) [46], nebivolol (SENIORS) [47], and carvedilol (two studies: CAPRICORN, COPERNICUS) [48]. 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 the mortality outcome in these studies. For the outcome of all-cause mortality 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 these studies demonstrated an overall 28% reduction in all-cause mortality with beta-blocker therapy in these trials with no evidence of any heterogeneity (Badve et al. JACC, in press).

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, hypotension and bradycardia were five times more likely to occur in the patients randomised to beta-blocker therapy than placebo (Badve et al. JACC, in press).

Summary
The reduction in mortality achieved by therapy with four different beta-blockers in patients with heart failure 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.

3. Aldosterone antagonists

Evidence from studies of patients without CKD
In patients with severe heart failure symptoms (New York Heart Association Class III or IV) or recently hospitalised with heart failure, the addition of the aldosterone antagonist spironolactone to an angiotensin-converting enzyme 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 eplenerone 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 [20]. 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 heart failure and mild symptoms (NYHA Class II), although the mean left ventricular ejection fraction was 26% [51].

National Heart Foundation guideline for the general population:

- 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 randomised controlled trials of more severe heart failure, a pre-specified subgroup analysis based on the serum creatinine was reported in the original publications [49, 50], but no post hoc analysis according to GFR has been reported. 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 (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 eplenerone was 0.9 (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. In EMPHASIS-HF, benefit was similar in the one third of participants with a GFR<60mL/minute [51].

Results of other studies

One randomised controlled trial has been performed in patients with stage II and III chronic kidney disease that compared spironolactone to placebo and evaluated left ventricular mass and aortic stiffness [52]. These patients had preserved left ventricular ejection fraction 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 heart failure and preserved ejection fraction [53].

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]. In EPHESUS, where eplenerone was compared to placebo, gynaecomastia occurred in less than 1% of participants and did not differ by treatment assignment [50]. Hyperkalaemia (serum potassium≥6.0mmol/L) occurred in 5.5% of participants receiving eplenerone and 3.9% receiving placebo (p=0.002). The proportion of participants who developed hyperkalaemia and were receiving eplenerone 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 eplenerone (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.

4. Digoxin

Evidence from studies of patients without CKD
Treatment with digoxin in patients with heart failure had no effect on mortality but significantly reduced hospitalisations for heart failure, a secondary endpoint, by 28% in the large Digitalis Intervention Group Study [54]. These patients were receiving angiotensin converting enzyme inhibitors and diuretics, but not beta-blockers.

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 MDRD eGFR levels >60mL/minute per 1.73m^2 (n=3643), eGFR 30-60mL/minute per 1.73m^2 (n=2939) and eGFR<30ml/minute per 1.73m^2 (n=218) [55]. Although mortality increased as GFR declined, therapy with digoxin did not reduce mortality in the groups with GFR≤60mL/minute per 1.73m^2, but did reduce the secondary outcome of all-cause mortality plus heart failure hospitalisation in patients with eGFR 30-60mL/minute per 1.73m^2 (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 randomised controlled trials of digoxin in patients with heart failure have either been performed in patients with chronic kidney disease or reported on a subgroup of patients with chronic kidney disease 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 [54]. A subsequent analysis of this trial examined the effect of hypokalaemia on outcomes [56]. Serum potassium was less than 4.0mmol/L in 19% of participants with eGFR<60mL/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 eGFR 30-60mL/minute, but the risk of adverse effects, particularly in patients with serum potassium <4mmol/L, should be carefully considered.

5. Erythropoiesis stimulating agents

Evidence from studies of patients without CKD
Just as heart failure 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 [57]. In addition to possible benefits from raising haemoglobin, there are potential non-haemopoietic effects of erythropoiesis stimulating agents (ESA) that might benefit patients with heart failure, such as reducing cardiac myocyte apoptosis and fibrosis, and neovascularisation mediated by vascular endothelial growth factor [57]. Some investigators have suggested that anaemia should be corrected with available tools (erythropoiesis stimulating agents and iron supplementation) in patients with CKD and heart failure [58].
Only one trial is seeking to study the effects of treatment with an ESA in patients with co-morbid heart failure, CKD (GFR 20-70mL/minute) and mild anaemia (Clinical Trials.gov NCT00356733) [59]. However, clinical events will not be assessed.

National Heart Foundation guideline for the general population:

- The possibility of anaemia correction with ESAs is acknowledged but no formal recommendation is made

In the absence of a specific randomised controlled trial, this guideline presents data from either randomised controlled trials in patients with heart failure and anaemia, in which data on a CKD subgroup was available, or data from randomised controlled trials in patients with CKD and anaemia, in which data on heart failure was available.

Evidence in CKD subgroups of randomised controlled trials designed specifically for heart failure patients
A number of randomised controlled trials have been performed in patients with anaemia and heart failure. A meta-analysis of seven trials demonstrated no reduction in mortality with treatment with ESA but there was significantly reduced heart failure hospitalisation [60], and a separate meta-analysis of the same studies reported improved left ventricular ejection fraction and exercise capacity [61]. All but one of these trials was placebo-controlled. The mean baseline haemoglobin was above 10g/dL in these studies, and the mean baseline serum creatinine ranged from 115μ/L up to 221μmol/L, suggesting that CKD was prevalent in these patients. A large randomised controlled trial is underway to evaluate the effect of darbepoeitin alfa compared to placebo on morbidity and mortality in heart failure patients with anaemia (Clinical Trials.gov NCT00358215) [62]. Patients with a serum creatinine greater than 265 μmol/L will be excluded, but it is likely that there will be a substantial subgroup with CKD. It is hoped that the investigators will report on this subgroup.

Evidence in heart failure subgroups of randomised controlled trials designed specifically for CKD patients
In contrast to the heart failure studies, the randomised controlled trials 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 [63-65]. 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 heart failure.

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 [66]. Less than 10% of patients had symptomatic heart failure 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 [67]. Patients with New York Heart Association (NYHA) grade III or IV heart failure were excluded and treatment did not affect the development of left ventricular hypertrophy.

A study that randomised 390 patients with an estimated glomerular filtration rate between 25 and 60mL/minute to high versus low haemoglobin targets, maintained with erythropoietin alfa was terminated prematurely by the sponsor because of the emerging concerns regarding pure red cell aplasia at that time [68]. The primary outcome was rate of GFR decline and patients with NYHA grade III or IV heart failure were excluded from this study.

A Scandinavian study that enrolled 416 participants included 72 patients with creatinine clearance less than 30mL/minute but not on dialysis (the rest of the participants were receiving dialysis) [69]. Only three of the 72 participants had heart failure and in response to the report of a study in patients undergoing dialysis [70], the protocol was amended to make NYHA grade III or IV heart failure an exclusion criterion.

The CREATE Study randomised 603 participants with an estimated glomerular filtration rate of 15-35mL/minute to high versus low haemoglobin targets with erythropoietin beta [71]. Congestive heart failure was an exclusion criteria but this was presumably only NYHA grade III or IV heart failure as patients with NYHA grade I or II heart failure made up 27% of participants who underwent a baseline echocardiogram in a subsequent report [72]. 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 CHOIR Study randomised 715 patients with an estimated glomerular filtration rate of 15-50mL/minute to achieve a haemoglobin of 113g/L (n=717) compared to 135g/L with erythropoietin alfa [73]. 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 heart failure in that treating to the higher haemoglobin target had no effect on the primary outcome in patients with a history of heart failure, but resulted in increased events in patients with no history of heart failure (p for interaction=0.028) [74].

The TREAT Study randomised 2012 patients with diabetes and an estimated glomerular filtration rate of 20-60mL/minute to darbepoetin alfa with target haemoglobin 130g/L, and 2026 to placebo with rescue daprbepoetin alfa if the haemoglobin fell below 90g/L [75]. 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 heart failure was not reported.

Results of other studies
Other studies are not discussed.

Adverse effects
Potential adverse effects of therapy with erythropoiesis stimulating agents in patients with CKD and heart failure are those reported in the meta-analyses: hypertension, stroke, vascular access thrombosis. The risk of death, cardiovascular events and end-stage kidney disease was less in the low haemoglobin arms but these were not statistically significant [65].

Summary
Currently, there is no evidence that correcting anaemia in patients with CKD and heart failure reduces clinical events. Erythropoiesis stimulating agents should be used with caution in patients with both heart failure and CKD and the potential harms demonstrated in the CKD studies should be carefully weighed against the potential to ameliorate symptoms attributable to anaemia in the individual patient.

6. Diuretics to reduce extracellular fluid volume

Evidence from studies of patients without CKD
Diuretic therapy is important in the management of symptomatic patients with heart failure in order to control the extracellular fluid volume expansion and relieve pulmonary congestion. Randomised controlled evidence for alteration of disease progression is lacking [76].

The ALLHAT randomised controlled trial recruited patients aged 55 years or over with at least one cardiovascular risk factor but excluded patients with heart failure at baseline [77]. 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 [78]. In the Blood Pressure Lowering Trialist'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 anatagonists with respect to reducing heart failure hospitalisations [79]. There are no long-term randomised controlled trials of diuretic therapy with important clinical outcomes in heart failure patients and thus all guideline recommendations regarding diuretics are based upon the lowest levels of evidence .[20, 22].

National Heart Foundation guideline for the general population:

- Diuretics are recommended to achieve euvolaemia 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 glomerular filtration rate falls below 30mL/minute [80].

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 [20]. Accurate assessment of volume state is thus critical to effective use of diuretics and avoidance of these important adverse effects [81]. 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 must be carefully monitored.

7. Implantable devices

Evidence from studies of patients without CKD
Implantable cardioverter defibrillators (ICD) reduced mortality by 23% in patients with a previous episode of unprovoked ventricular arrhythmia, or with left ventricular ejection fraction less than 35% and NYHA Class II or III symptoms [82]. Similarly, cardiac resynchronisation therapy (CRT) reduced mortality plus hospital admission by 20% in patients with NYHA Class III or IV symptoms, an ejection fraction below 35%, and with a prolonged QRS (≥120ms) [83]. A meta-analysis of CRT studies

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

Subgroups with chronic kidney disease were not reported in the above studies. The Multicentre Automatic Defibrillator Implantation Trial II demonstrated a 30% reduction in mortality in patients who had a left ventricular ejection fraction ≤30 % within a month following a myocardial infarction [84]. These investigators subsequently examined three subgroups, one of which was blood urea nitrogen [85]. Although a measure of renal function, blood urea nitrogen was considered by these investigators as a measure of severity of heart failure and dichotomised at 25mg/dL (8.9mmol/L) based on previous data, and 30% of participants had blood urea nitrogen above this level. Mortality was greater in these patients, but there was no interaction between therapy with an ICD and level of blood urea nitrogen. A meta-analysis of CRT demonstrated a reduction in mortality of 17% in patients with NYHA Class I and II symptoms and 22% in patients with NYHA Class III and IV symptoms, but noted that there was insufficient data to examine a chronic kidney disease subgroup [86].

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 [87]. In a retrospective case control study that identified patients between 1998 and 2008, 33 patients had a left ventricular ejection fraction ≤35% and a GFR below 60mL/minute [88]. 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 [89].

Adverse effects

Adverse effects of ICD 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 receiving dialysis

1. Blockade of the renin-angiotensin system

Evidence from randomised controlled trials

Four randomised controlled trials 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 [90]. All patients had dialysis four times a week and all received therapy with an ACE inhibitor. All had heart failure defined by NYHA Class II or II symptoms and a left ventricular ejection fraction ≤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 (**Table 2**). 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 heart failure was not an inclusion criteria. Suzuki et al randomised 366 patients on haemodialysis to open-label angiotensin receptor blocker or no therapy [91]. Approximately 15% of participants had heart failure 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 heart failure were randomised to candesartan or no therapy and followed for a mean of 19 moths [92]. 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 [93]. The proportion with heart failure at baseline was not reported and patients were followed for 24 months. There was no difference in the primary composite endpoint of cardiovascular events that included 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 [94]. 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 [95]. 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 [96]. 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 end-stage kidney disease 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) [97]. 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 left ventricular ejection fraction less than 40%. An analysis of 368 patients with end-stage kidney disease treated in a single coronary care unit from 1990-1998 compared patients prescribed an ACE inhibitor to those not prescribed an ACE inhibitor [98]. 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 end-stage kidney disease, these studies were not specifically in patients with heart failure 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 heart failure already receiving an ACE inhibitor, 19 patients failed the run-in and this was because of hypotension in 7 [90]. 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 randomised controlled trials comparing ACE inhibitor or angiotensin receptor antagonists to placebo in patients receiving dialysis who have heart failure. Angiotensin receptor antagonist added to an ACE inhibitor appeared to reduce mortality compared to placebo in one trial of patients receiving dialysis who have heart failure.

2. Beta-blocker therapy

Evidence from randomised controlled trials
One randomised controlled trial of beta-blocker therapy in patients receiving dialysis who have heart failure has been published. This study randomised 114 patients with symptomatic heart failure (NYHA II or III) and a left ventricular ejection fraction <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 [99]. 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 [100]. 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 end-stage kidney disease although there are few studies specific to patients with heart failure. 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) [97]. Heart failure was present in 40% of these patients at baseline. In the USRDS DMMS Wave 2 cohort patients without heart failure 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). However, patients with heart failure 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 [100]. 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 heart failure 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 heart failure trials (Badve et al. JACC, in press).

3. 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.[101]. Sixteen patients receiving haemodialysis with heart failure (NYHA Class II or IV symptoms and a mean left ventricular ejection fraction between 31 and 34%) were randomised to spironolactone or placebo [102]. 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.

Results of other studies

A study of 108 patients undergoing haemodialysis who had LVH on echocardiogram and BNP>200pg/mL randomised participants to carvedilol and spironolactone in a 2x2 factorial design (Nakao N, Hasegawa H, Fujimori A, Seno H, Toriyama T, Kawahare H. Effects of Combined B-blockade and anti-aldosterone antagonist treatment for cardiovascular prevention in patients receiving maintenance dialysis. J Am Soc Nephrol S 2007; 18:709A). Patients with severe heart failure (NYHA Class IV) were excluded. The mean left ventricular ejection fraction 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 monotherpay 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) [103]. 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.

4. Digoxin

Evidence from randomised controlled trial subgroup or post hoc analyses in heart failure populations
There are no randomised controlled trials or post hoc analyses examining the use of digoxin in patients undergoing dialysis who have heart failure.

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 [104]. Patients receiving digoxin who had coexistent heart failure 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 heart failure, 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.

5. Erythropoiesis stimulating agents

Evidence from randomised controlled trials

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

In the most recent meta-analysis of ESAs in patients with chronic kidney disease, 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 [65]. No interaction was demonstrated between patients with CKD not requiring dialysis and those requiring dialysis for these outcomes (except the vascular access thrombosis). The largest and most relevant RCT (n=1233) enrolled patients with either heart failure or ischaemic heart disease who were undergoing haemodialysis and the Data Monitoring Committee recommended that the trial be stopped after the third interim analysis [70]. 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 [105]. 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 [106]. 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 [107].

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 heart failure, there is no evidence that correction of anaemia reduces heart failure events and there is some evidence of harm.

6. Diuretics to reduce extracellular fluid volume

There are no randomised controlled trials of the use of diuretics in patients requiring dialysis for the treatment of heart failure.

7. Implantable devices

Evidence from randomised controlled trials

There are no randomised controlled trials specifically in patients undergoing dialysis. A randomised controlled trial is underway in the Netherlands to randomise patients undergoing dialysis aged 55 to 80 to ICD therapy or not [108]. 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

Some observational studies demonstrate benefit of ICD therapy in primary prevention in patients with LVEF<35%, as well as in secondary prevention in patients who have survived a cardiac arrest or ventricular tachyarrhythmia.

Patients undergoing dialysis who received an ICD in one centre over a 14 year period (n=50) were compared to contemporaneous patients receiving dialysis at another centre who 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") [109]. 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 [88].

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 [110]. On 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 [111]. 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 [112]. 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 randomised controlled trials. In an observational study, there were more major complications in patients undergoing dialysis compared to patients not undergoing dialysis [113]. 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 heart failure cannot be routinely recommended and consideration should be given to balance the

potential benefit to the individual patient where this benefit may be less than that of someone not requiring dialysis, with the heightened risk of complications, particularly thrombosis of vascular access veins if the ICD is implanted on the same side as the vascular access.

INTERNATIONAL GUIDELINES:

Kidney Disease Outcomes Quality Initiative

This guideline addresses "Cardiomyopathy (Systolic or diastolic dysfunction)" with regards to both diagnosis and management. This guideline recommends "maintenance of euvolaemia" as the cornerstone of therapy, and that treatment should be similar to the non-dialysis population with the exception that dosing schedules may need to be modified in haemodialysis. They suggest beta-blocking agents are preferred based on data that is "moderately strong" (the single carvedilol study), that ACE inhibitors be used although the data is "weak", and that digitalis be considered as third line therapy (no data referred to). They also recommend that aldosterone antagonists be used with "great caution, or not at all" (based on "weak" data). (KDOQI CVD Guidelines, AJKD 2005)

UK Renal Association:
No guideline addressing heart failure (Nephron Clin Pract 2011; 118(suppl 1).

Canadian Society of Nephrology:

European Best Practice Guidelines:

Implementation and audit

Suggestions for future research

1.

2.

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Appendices

Table 1. Characteristics of included studies

Study ID: author, year, acronym (other publication)	N (N with CKD)	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
CKD and Transplant								
Swedberg, 1987, CONSENSUS [31] (Swedberg 1988, 1990)	253	RCT	35 centres in Scandinavia	NYHA Class IV heart failure on digitalis and diuretics	Enalapril 5mg bd titrated to 20mg bd	Identical placebo	Mean=6	Terminated early by Ethical Review Committee; Excluded if creatinine>300µmol/L
Pfeffer, 1992, SAVE [114] (Tokmakova 2004)	2231 (719)	RCT	45 centres in the USA and Canada	Acute myocardial infarction LVEF≤40%	Captopril 12.5mg tds titrated up to 50mg tds	Identical placebo	Mean = 42±10	Excluded if creatinine>221µmol/L
Cohn, 2001, Val-HeFT [115] (Anand, 2009)	5010 (2916)	RCT	302 international centres	NYHA Class II-IV heart failure, LVEF≤40%	Valsartan 40mg bd titrated to 160mg bd	Identical placebo	Mean =23 (0 to 38)	93% on ACE inhibitor Excluded if creatinine>221µmol/L
CIBIS II, 1999 [116] (Erdmann, 2001; Castagno, 2010)	2657 (849)	RCT	274 centres in Europe	NYHA Class III-IV heart failure, LVEF≤35%, on ACE inhibitor	Bisoprolol 1.25mg daily titrated to 10mg daily	Identical placebo	Mean=15.6	Terminated early by Advisory and Safety Committee; Excluded if creatinine>300µmol/L
MERIT-HF, 1999 [117] (Ghali, 2009)	3991 (1469)	RCT	313 international centres	NYHA Class II-IV heart failure, LVEF≤40%, on ACE inhibitor	Metoprolol CR/XL 12.5 or 25mg daily titrated to 200mg daily	Identical placebo	Mean=12	Terminated early by Independent Safety Committee; No exclusion based on serum creatinine
Flather, 2005, SENIORS [118] (Cohen-Solal, 2009)	2135 (704)	RCT	11 European countries	Age≥70 years, heart failure admission or LVEF≤35%	Nebivolol 1.25mg daily titrated to 10mg daily	Identical placebo	Mean = 21±9	Excluded if "significant renal dysfunction" defined in methods paper as creatinine>250µmol/L
Dargie, CAPRICORN, 2001 [119] (Wali, 2011)	1959	RCT	163 international centres	Myocardial infarction within 3-21 days, LVEF≤40%, on ACE inhibitor	Carvedilol 6.25mg bd titrated to 25mg bd	Identical placebo	Mean=15.6	No exclusion based on serum creatinine
Packer, COPERNICUS, 2001 [120] (Wali, 2011)	2289	RCT	334 international centres	Symptoms at rest or minimal exertion, LVEF≤25%, on ACE inhibitor	Carvedilol 3.125mg bd titrated to 25mg bd	Identical placebo	10.4	Terminated early by Data Safety Monitoring Board; Excluded if creatinine>247.5 µmol/L

CAPRICORN+COPERNICUS [48]	4217 (2566)							31 participants from the above 2 studies not included in this analysis
Pitt, RALES, 1999 [49]	1663 (not stated)	RCT	195 international centres	NYHA Class III-IV heart failure, LVEF≤35%, on ACE inhibitor	Spironolactone 25mg daily titrated to 50mg daily	Identical placebo	24	Terminated early by Data Safety Monitoring Board; Excluded if creatinine>221µmol/L or K>5.0mmol/L
Pitt, EPHESUS, 2003 [50]	6642	RCT	674 international centres	Myocardial infarction within 3-14 days, LVEF≤40%, clinical features of heart failure	Eplerenone 25mg daily titrated to 50mg daily	Identical placebo	16 (0-33)	Excluded if creatinine>220µmol/L or K>5.0mmol/L
Zannad, EMPHASIS-HF, 2011 [51]	2737 (912)	RCT	278 international centres	Age≥55 years, NYHA Class II, LVEF≤30%, on maximal therapy	Eplerenone 25mg daily titrated to 50mg daily (25mg second daily titrated to 25mg daily if eGFR 30-50mL/minute)	Identical placebo	Median=21	Excluded if eGFR<30mL/minute or K>5.0mmol/L
DIG Trial, 1997 [54] (Shlipak, 2004)	6800 (3157)	RCT	302 centres in the USA and Canada	Clinical heart failure with LVEF≤45%, in sinus rhythm	Digoxin titrated according to an algorithm	Identical placebo	Mean=37 (28-58)	Excluded if creatinine>265µmol/L; 94% received ACE inhibitor, beta-blocker use not stated
Dialysis								
Cice, 2010 [90]	332	RCT	30 Italian centres	Haemodialysis 4X per week, NYHA Class II-III heart failure, LVEF≤40%, on ACE inhibitor	Telmiartan 20mg daily titrated up to 80mg daily	Identical placebo	Mean=35.5±8.5 (2-40)	Approximately 60% on beta-blockers; 19/351 enrolled patients (5.4%) failed run-in
Cice, 2001, 2003 [99, 100]	114	RCT	Italy (number of centres not stated)	Haemodialysis 4X per week, NYHA Class II-III heart failure, LVEF≤35%,	Carvedilol 3.125mg bd titrated up to 25mg bd	Identical placebo	24 months (first 12 months for blinded echo outcomes, second 12 months unblended)	All on ACE inhibitor or ARB and digitalis; 18/132 (13.6%) failed the run-in

CONSENSUS=Cooperative North Scandinavian Enalapril Survival Study; SAVE=Survival and Ventricular Enlargement; Val-HeFT=Valsartan in Heart Failure Trial; CIBIS II=Cardiac Insufficiency Bisoprolol Study II; MERIT-HF=Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; SENIORS=Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure; CAPRICORN= Carvedilol Post-Infarct Survival Control in LV Dysfunction; RALES= Randomized Aldactone Evaluation Study; EPHESUS=Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; EMPHASIS-HF=Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; DIG=Digitalis Intervention Group;

Table 2. Quality of randomised trials

Study ID (author, year)	Method of allocation concealment *	Blinding			Intention-to-treat analysis †	Loss to follow up (%)	Quality Score
		(participants)	(investigators)	(outcome assessors)			
Swedberg, 1987, CONSENSUS [31]	Central	Yes	Yes	Yes	Yes	0	High
Pfeffer, 1992, SAVE [114] (Tokmakova 2004)	Central	Yes	Yes	Yes	Yes	6/2231 (<1%)	High
Cohn, 2001, Val-HeFT [115] (Anand, 2009)	Central	Yes	Yes	Yes	Yes – all patients appear to be included	None stated (8 had no baseline serum creatinine)	High
CIBIS II, 1999 [116] (Erdmann, 2001; Castagno, 2010)	Central	Yes	Yes	Yes	Yes	6/2647 (<1%)	High
MERIT-HF, 1999 [117] (Ghali, 2009)	Central	Yes	Yes	Yes	Yes	None stated (26 had no baseline serum creatinine)	High
Flather, 2005, SENIORS [118] (Cohen-Solal, 2009)	Central	Yes	Yes	Yes	Stated, but 7 randomised patients excluded from analysis (6 protocol violations in 1 centre, 1 did not receive study drug)	37/2128 (1.7%)	Medium
Dargie, CAPRICORN, 2001 [119] (Wali, 2010)	Central	Yes	Yes	Yes	Yes	None stated	High
Packer, COPERNICUS, 2001 [120] (Wali, 2010)	Central	Yes	Yes	Yes	Yes	0	High
Pitt, RALES, 1999 [49]	Not stated	Yes	Yes	Yes	Yes	None stated	High
Pitt, EPHESUS, 2003 [50]	Central	Yes	Yes	Yes	Stated, but 10 excluded from one site due to data quality	17/6642 (<1%)	High

Zannad, EMPHASIS-HF, 2011 [51]	Central	Yes	Yes	Yes	Yes	32/2737 (1.2%)	High
DIG Trial, 1997 [54] (Shlipak, 2004)	Central	Yes	Yes	Yes (Note that Investigators were outcome assessors)	Yes	93/6800 (1.4%)	High
Cice, 2010 [90]	Central	Yes	Yes	Yes (Not clear who assessed outcomes)	Yes	0	High
Cice, 2001, 2003 [99, 100]	Unclear	Yes	Yes	Yes (Not clear who assessed outcomes)	Yes	0	Low – reduced by unblinding for the second 12 months and apparent lack of independent assessment of outcomes

Table 3a. Results for dichotomous outcomes: all-cause mortality in CKD and transplant

Study ID (author, year, acronym)	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]	Comment
RAS antagonist					
Swedberg, 1988, CONSENSUS [33]	24%	50%	52% reduction (p=0.002	NR	Crude mortality in patients with creatinine>120µmol/L (the median). Numbers not provided.
Tokmakova, 2004, SAVE [34]	96/359 (26.7%)	127/360 (35.3%)	"Relative Risk reduction" 28% (6-45)	NR	
Anand, 2009, Val-HEFT [30]	362/1477 (24.5%)	341/1439 (23.7%)	1.01 (0.8501.20)	NR	Time to first morbid event significantly different
Beta-blocker					
Erdmann, 2001, CIBIS II [45]	67/434	97/415	0.66 (0.50-0.87)	NR	
Ghali, 2009, MERIT-HF [46]	63/735	105/734	0.60 (0.45-0.80)	NR	Numbers presented separately for GFR<45 and GFR 45-60. Number are the sum of these.
Cohen-Solal, 2009, SENIORS [47]	71/348	92/356	0.79 (0.60-1.04)	NR	
Wali, 2011, CAPRICORN and COPERNICUS [48]	181/1293	233/1273	0.76 (0.64-0.91)	NR	
Badve (JACC, In press), Systematic Review	382/2810	527/2778	0.72 (0.64-0.81)		P for heterogeneity=0.435, I^2=0%

Aldosterone antagonist					
Pitt, RALES, 1999 [49]	Not stated	Not stated	0.8 (0.65-0.95)	NR	Patients with creatinine≥106µmol/L (inferred from Figure 2 of paper)
Pitt, EPHESUS, 2003 [50]	Not stated	Not stated	0.9 (0.8-1.1)	NR	Patients with creatinine≥96µmol/L (inferred from Figure 2A of paper)
Zannad, EMPHASIS-HF, 2011 [51]	Not stated	Not stated	0.70 (0.55-0.85)	NR	Patients with eGFR<60mL/minute (inferred from Figure 2 of paper)
Digoxin					
DIG Trial, 1997 [54] (Shlipak, 2004)	Not stated	Not stated	0.95 (0.85-1.07) for GFR 30-60 0.93 (0.65 to 1.35) for GFR<30		N=2,939 with GFR 30-60mL/min N=218 with GFR<30mL/min
ESA					
Volume state					
Implantable devices					

Table 3b. Results for dichotomous outcomes: all-cause mortality in dialysis

Study ID (author, year, acronym)	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]	Comment
RAS antagonist					
Cice, 2010 [90]	58/165	91/167	0.51; 95% CI: 0.32 to 0.82		Adjusted hazard ratio for mortality
Beta-blocker					
Cice, 2001, 2003 [99, 100]	30/58	41/56	0.51 (0.32-0.82)		Adjusted hazard ratio for mortality
Aldosterone antagonist					
Digoxin					
ESA					

Volume state					
Implantable devices					