

**Chronic heart failure: management of chronic heart failure in
adults in primary and secondary care**
A clinical guideline for the NHS in England and Wales

APPENDIX J: EVIDENCE TABLES

**Section 7.2: Pharmacological treatment of heart failure
due to LV systolic dysfunction -
Aldosterone Antagonists**

Pharmacological therapy

Aldosterone antagonists: Spironolactone

Experimental Studies

Paper	Pitt, B., Zannad, F., Remme, W. J., Cody, R., Castaigne, A., Perez, A., Palensky, J., & Wittes, J. 1999, "The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators.", <i>New England Journal of Medicine</i> , vol. 341, pp. 709-717.
Description	Randomised controlled trial
N=	n=1663, spironolactone =822, placebo =841 Age =65yrs, Male =73%, NYHA class III ~70%, class IV ~30%, Ischaemic origin HF =55%, LV ejection fraction =25% International study
Intervention	Oral spironolactone at mean 26mg /day was given and compared with placebo in HF patients NYHA classes III-IV on standard medication with diuretic, ACEi and mostly digoxin, as a continuous treatment
Outcomes	Primary endpoint was all cause mortality, with secondary evaluation of cardiac death, hospitalisation, and a combination of the above, also changes in NYHA class studied all to a mean 24 months. Six pre-specified subgroup analyses were undertaken with respect to age, LV ejection fraction, cause of HF, serum creatinine concentration and use of ACEi and digitalis at baseline
Results	<ul style="list-style-type: none"> • All cause mortality was reduced in the spironolactone arm Vs placebo RR 0.70 (95% CI 0.60 – 0.82) (p<0.001) • Similarly cardiac cause mortality was reduced RR 0.69 (0.58 – 0.82) (p<0.001) • The reduction in the risk of death was similar in all six subgroups • The reduction in the risk of hospitalisation for cardiac causes was pronounced with spironolactone RR 0.70 (0.59 – 0.82) (p<0.001) • Unsurprisingly the composite mortality / hospitalisation due to cardiac causes was similarly improved on spironolactone. • There was a significant improvement in NYHA class (p<0.001), however this was biased toward improvement with class IV patients unable to deteriorate other than death. • Side effect of hyperkalaemia was not significantly different between trial groups, but careful monitoring maybe necessary especially in elderly or diabetics. • There was significantly more gynaecomastia with patients on spironolactone (p<0.001)
Comments	<p>Only patients with severe heart failure and LV ejection fraction <35% can be sure to be seen to be applied to the intervention and the benefits described</p> <p>Patients with a serum creatinine concentration >2.5 mg/decilitre, and potassium >5.0 mmol/l were exclusion criteria</p> <p>Only severe HF patients included and high placebo mortality rate 46% at mean 2 years</p> <p>Reduction in risk of death was observed at 2 to 3 months and continued through the study</p> <p>The exact mechanism for risk of death not certain but may be due to ability of spironolactone to reduce myocardial and vascular fibrosis</p>
Reference	92

Paper	Ramires, F. J., Mansur, A., Coelho, O., Maranhao, M., Gruppi, C. J., Mady, C., & Ramires, J. A. 2000, "Effect of spironolactone on ventricular arrhythmias in congestive heart failure secondary to idiopathic dilated or to ischemic cardiomyopathy", <i>American Journal of Cardiology</i> , vol. 85, no. 10, pp. 1207-1211.
Description	Randomised controlled trial
N=	n= 35, spironolactone =19, no treatment =16 Age =48yrs, Male =91%, Ischaemic HF origin =86%, LV ejection fraction =33% Brazil
Intervention	An intervention of Spironolactone at 50mg/day for 12 weeks then 25mg/day for 4 weeks Vs normal therapy in patients with moderate HF
Outcomes	Evaluations of serum electrolyte concentrations and Arrhythmia evaluation were conducted at weeks 4, 12 and 16.
Results	<ul style="list-style-type: none"> • There were significant effects in the increase of sodium (140mmol/l Vs 137 at baseline) ($p<0.001$), potassium (3.8mmol/l Vs 3.2 at baseline) ($p<0.0001$) and • in Magnesium (0.9mmol/l Vs 0.6 at baseline) ($p<0.0001$) when on spironolactone, with little change in patients in control arm • There was a significant decrease in the frequency of VPCs in patients on spironolactone decreased significantly ($p<0.0001$) with no statistical change in the control group. • The number of VT episodes decreased in both groups.
Comments	Most patients with moderate symptomatic HF (NYHA class III) can be seen to be suitable for the intervention The two trial arms were similar in most characteristics at baseline except for a higher level of serum Digoxin the in the control group 2.5 Vs 2.3 nmol/l ($p<0.01$) Use of intervention to curtail arrhythmic events. Benefits on mortality will require further study.
Reference	93

Aldosterone antagonists: Eplerenone

Experimental studies

Paper	Pitt, B., Williams, G., Remme, W., Martinez, F., Lopez-Sendon, J., Zannad, F., Neaton, J., Roniker, B., Hurley, S., Burns, D., Bittman, R., & Kleiman, J. 2001, "The EPHEsus trial: eplerenone in patients with heart failure due to systolic dysfunction complicating acute myocardial infarction. Eplerenone Post-AMI Heart Failure Efficacy and Survival Study.", <i>Cardiovascular Drugs & Therapy</i> , vol. 15, no. 1, pp. 79-87.
Description	Randomised Controlled Trial
N=	Planning to recruit approximately 6200 patients Will be international study
Intervention	Eplerenone will be given at a target of 50mg/day Vs placebo
Outcomes	Primary endpoints will be cardiovascular mortality or cardiovascular morbidity leading to hospitalisation., with secondary endpoints of all cause hospitalisation, or this combined with all cause mortality, at up to 2.5 yrs
Results	N/A
Comments	<ul style="list-style-type: none">• The study results will be applicable only to post MI HF patients with LV dysfunction• Subgroup analyses pre-specified to include race, age, presence of diabetes, ejection fraction, and use of concomitant medicines

Paper	Williams, E. S. & Miller, J. M. 2002, "Results from late-breaking clinical trial sessions at the American College of Cardiology 51st Annual Scientific Session", <i>Journal of the American College of Cardiology</i> , vol. 40, no. 1, pp. 1-18.
Description	Randomised Controlled Trial
N=	n=202, eplerenone =64, enalapril =71, combined therapy =67 Demographic characteristics of the patients are not included, but all had diastolic BP of >90 and <140 mmHg and systolic BP of >140 and <200 mmHg at baseline and echocardiographic evidence of LV hypertrophy USA
Intervention	Interventions of eplerenone at 200 mg/day, enalapril at 40mg/day and combination eplerenone 200mg/day plus enalapril 10mg/day were compared as a continuous treatment for 9 months
Outcomes	Main outcome measures are changes in LV mass and blood pressure markers all at 9 months, and adverse events noted
Results	<ul style="list-style-type: none"> • The mean change in LV mass was -14.5g in the eplerenone group, -19.7g with enalapril, and -27.2g for the combined therapy all (p<0.05 from baseline) , which showed a significantly greater effect with combination therapy over eplerenone (p=0.007) • Blood pressure reductions were statistically similar in each of the three groups • The urinary albumin -creatinine ratio was reduced more with the combined therapy than with eplerenone alone (p=0.001) or enalapril only (p=0.038) • An adverse event of cough was reported more commonly in the enalapril group (14.1%) than eplerenone group (3.1%) (p=0.05) but no significant difference was seen with the combination therapy arm (9.0%) • Additional blood pressure medications were required significantly more often in the enalapril group than in the eplerenone group
Comments	Only patients surviving MI with LV hypertrophy can be seen to be directly relevant to the outcomes of this trial Eplerenone alone or in combination with ACEi is effective for cardiac protection and blood pressure control in patients with essential hypertension and LV hypertrophy.