Prescribing aldosterone antagonists for patients with heart failure due to left ventricular systolic dysfunction

NHS South London Cardiovascular and Stroke Network

The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Rationale: Evidence from clinical trials has shown that the use of an aldosterone antagonist in addition to optimal ACE inhibitor and beta-blocker therapy can reduce mortality and hospitalisations in selected patients with heart failure due to left ventricular systolic dysfunction (LVSD).

Place in Therapy

NICE recommendations:

1. **Aldosterone antagonists should be considered for all patients with left ventricular systolic dysfunction (LVSD) (ejection fraction ≤ 35%) who remain symptomatic despite optimal therapy with an ACE inhibitor (ACEI) and a beta-blocker (both at maximum tolerated doses) and a diuretic.**
2. **In line with NICE Post-MI Secondary Prevention guidance, an aldosterone antagonist should be prescribed within 3–14 days of myocardial infarction (MI), preferably after initiation of ACE inhibitor therapy, for patients with symptoms and/or signs of heart failure and left ventricular systolic dysfunction (LVSD) and an ejection fraction (EF) ≤40%**

Choice of agent and current licensed indications:

- Spironolactone is licensed for use in patients with severe heart failure (NYHA Class III-IV):
- Eplerenone is licensed for use in adult patients with NYHA class II (chronic) heart failure and left ventricular systolic dysfunction (LVEF ≤30%); and also in stable patients with left ventricular dysfunction (LVEF ≤ 40 %) and clinical evidence of heart failure after recent myocardial infarction.
- In addition, eplerenone may be used as an alternative to spironolactone in moderate to severe heart failure if the patient experiences intolerable side effects with spironolactone. This is an unlicensed use.

Contra-indications	Cautions
- Anuria - Acute renal impairment or severe impairment of renal function (baseline Serum Cr >200µmol/L or eGFR <30mls/min) - Hyperkalaemia (K+ >5.0mmol/L at initiation) - Addison's disease - Hypersensitivity to specific aldosterone antagonist or excipients - Hyponatraemia (Na+<135mmol/L) - Co-prescription of potassium sparing diuretics, potassium supplements. - Co-prescription of eplerenone with strong CYP3A4 enzyme inhibitors – see 'interactions' overleaf - Severe hepatic impairment Childs Pugh Class C - In addition to the combination of both an ACEI and an ARB	- Porphyria (spironolactone only) - Pregnancy and lactation - Hepatic impairment (Child Pugh Class A & B, monitor electrolytes closely) - Moderate to severe renal impairment (serum Cr>150 µmol/L or eGFR< 50mls/min) - Diabetic microalbuminuria - Elderly - monitor potassium carefully. - Drug/Food interactions (see listed overleaf)

Consider referral prior to initiation:

- Hyponatraemia (Na<135mmol/L)
- Pregnancy and lactation
- Symptomatic hypotension or severe asymptomatic hypotension (systolic BP<90mmHg)
- Significant renal dysfunction / renovascular disease e.g. creatinine > 150 µmol/L or eGFR<50ml/min or hyperkalaemia

Initiation and Monitoring

- Check baseline blood chemistry. (e.g. serum creatinine, urea, potassium, sodium and eGFR and liver function tests) Aldosterone antagonists should not be started in patients with a serum K+ > 5.0mmol/L.
- Recheck blood chemistry at 1, 4, 8, 12 weeks, 6, 9 and 12 months and then 6 monthly thereafter throughout therapy

Spironolactone: Initiate at a dose of 25mg once daily - for elderly patients use either 12.5mg daily or 25mg on alternate days). If the patient remains symptomatic at 6 weeks, consider increasing the dose to 50mg daily (or 25mg if started at lower dose); after checking renal function and potassium level

Eplerenone: Initiate at a dose of 25mg once daily, increasing to target dose of 50mg once daily within 4 weeks according to potassium level.

Managing Hyperkalaemia

Serum potassium (mmol/L)	Action	Dose adjustment
5.0 - 5.4	Maintain dose	• No dose adjustment
5.5 – 5.9	Decrease dose	• 50mg daily to 25mg daily • 25mg daily to 25mg every other day • 25mg every other day to withhold drug
≥ 6.0	Withhold drug and seek specialist advice	• N/A

Other Problem Solving	
Sodium / water depletion or hypovolaemia	Consider a reduction in the concomitant diuretic dose e.g. bumetanide or furosemide; recheck blood chemistry. If persistent, consider reducing the dose or stopping aldosterone antagonist
Symptomatic hypotension	Measure blood chemistry. Assess fluid intake. Consider a reduction in the diuretic dose or omit one to two days of diuretic therapy. Advise about avoiding abrupt postural changes. Review in 1-2 days. If symptoms persist or are severe, seek specialist advice.
GI upset	Reduce dose or discontinue therapy
Hyponatraemia	Serum Na< 135mmol/L, stop aldosterone antagonist and seek specialist advice
Gynaecomastia	Can occur during therapy with spironolactone - usually reversible on cessation of therapy Eplerenone may be considered as an alternative to spironolactone for patients with severe LVSD, where spironolactone is indicated but has not been tolerated usually due to the development of gynaecomastia. This is an unlicensed use.

Common Drug interactions (for full list of interacting drugs see BNF / SPC)	
Interacting Drug	**Mechanism of action/Significance and Action to be taken**
ACEI / ARB Or Aliskiren	Increased risk of hyperkalaemia. Monitor serum K+ levels closely if combination therapy used especially with any changes in treatment or in the patient's clinical condition. Combination of ACEI & ARB and an aldosterone antagonist is contra-indicated.
Cardiac glycosides	May increase digoxin levels. Monitor for signs of digoxin toxicity. Dose adjustment may be required.
Ciclosporin, tacrolimus	Risk of hyperkalaemia and renal dysfunction. Concurrent use to be avoided. If concurrent use essential, monitor K+ levels and renal function closely.
Drosperinone	Increased risk of hyperkalaemia. Monitor serum K+ during first cycle
Glucocorticoids, tetracosactide	May precipitate sodium and fluid retention - monitor carefully.
Lithium	May affect lithium levels • No additional monitoring required with spironolactone but ensure the patient is aware to report symptoms of lithium toxicity • Co-administration of eplerenone and lithium should be avoided. If this combination appears necessary, lithium plasma concentrations should be monitored
NSAIDs / High dose aspirin	Caution with combination use. Patients should be well hydrated and have their renal function checked before starting this combination.
Potassium and other potassium sparing diuretics	Concurrent use contraindicated as can lead to severe and even life threatening hyperkalaemia. Potassium containing salt substitutes can be hazardous as potassium supplements.
Potassium rich foods e.g. spinach, mangos bananas	Increased risk of hyperkalaemia. Monitor K+ levels closely
Tricyclic anti-depressants, neuroleptics, amifostine, baclofen	Co-administration of these drugs with eplerenone may potentially increase antihypertensive effects and risk of postural hypotension.
Trimethoprim	Increased risk of hyperkalaemia. Monitor carefully, particularly in patients with renal impairment and in the elderly.
Strong CYP3A4 inhibitors: such as ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin, telithromycin and nefazadone	Risk of increased plasma concentration of eplerenone - concomitant use is contra-indicated.
Mild to moderate CYP3A4 inhibitors: erythromycin, saquinavir, amiodarone, diltiazem, verapamil, and fluconazole	Risk of increased plasma concentration of eplerenone. Eplerenone dosing should not exceed 25mg.
CYP3A4 inducers: rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort	Risk of decreased eplerenone efficacy. Concomitant use not recommended.
Coumarins, such as warfarin	May affect INR. Monitor carefully especially at initiation or cessation.

As a black triangle drug for this indication all adverse effects should be reported to the CSM using the yellow card system, even if well documented, in addition to any local reporting arrangements

Patient information

- This treatment is given to improve symptoms, prevent worsening of heart failure, reduce hospitalisations and to prolong life
- Symptom improvement should occur a few weeks or months after starting treatment
- Spironolactone should be taken with food
- Aldosterone antagonists can cause dizziness or lightheadedness and, if affected, you should not drive
- Avoid salt substitutes (such as LO-SALT) and over the counter cystitis remedies which are high in potassium
- Avoid anti-inflammatory painkillers (NSAIDS) such as ibuprofen (including over the counter products)
- If dehydration, diarrhoea or vomiting occurs, do not to take your aldosterone antagonist and seek advice medical advice

References

- Chronic Heart Failure. NICE clinical Guideline CG108. Issued Aug 2010 Available from http://guidance.nice.org.uk/CG108/Guidance
- ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. Available from http://www.escardio.org/guidelines-surveys/esc-guidelines/Pages/acute-chronic-heart-failure.aspx
- Summary of product characteristics for Aldactone. Available online at www.medicines.org.uk
- Summary of product characteristics for Inspira. Available online at www.medicines.org.uk

Acknowledgments to Northampton General Hospital, Kings College Hospital, St George's Hospital and Gloucestershire Countrywide Primary Care Heart Failure Guidelines