

Annex 3

Practical guidance: Use of angiotensin receptor blockers in patients with heart failure with reduced ejection fraction⁶⁰

Indications

- First-line treatment (along with beta blockers) in patients with NYHA Class II-IV HF intolerant of an ACE inhibitor.
- Second-line treatment (after optimisation of ACE inhibitor and beta blocker) in patients with NYHA Class II-III HF who cannot take a mineralocorticoid receptor antagonist. The safety and efficacy of spironolactone used with an ACE inhibitor and an ARB (as well as beta blocker) is uncertain and the use of all three inhibitors of the renin–angiotensin–aldosterone system together is not recommended.

Contraindications

- known bilateral renal artery stenosis.

Cautions/seek specialist advice

- significant hyperkalaemia ($K^+ >5.0$ mmol/l)
- significant renal dysfunction (creatinine >221 micromol/l)
- symptomatic or severe asymptomatic hypotension (systolic BP <90 mm Hg).

Drug interactions to look out for

- K^+ supplements/ K^+ sparing diuretics
- 'low salt' substitutes with a high K^+ content.

Starting and target doses

ARB	Starting dose	Target dose
candesartan	4 or 8 mg once daily	32 mg once daily
valsartan	40 mg twice daily	160 mg twice daily

Candesartan is the only ARB which is licensed for use in patients with HF. Valsartan is the only ARB which is licensed for use in patients following MI with HF or LVSD or both.

How to use angiotensin receptor blockers

- Start with a low dose (*see starting and target doses*) and double the dose at not less than two-weekly intervals.
- Aim for the target dose or, failing that, the highest-tolerated dose.
- Monitor blood pressure and blood chemistry (urea, creatinine, and electrolytes).
- Check blood chemistry one to two weeks after initiation and one to two weeks after each dose titration.
- When to stop uptitration/reduce dose/stop treatment (*see problem solving*).
- A specialist HF nurse may assist with patient education, follow up (in person/by telephone), biochemical monitoring and dose uptitration.

Advice to the patient

- Explain the expected benefits, ie treatment is given to improve symptoms, to prevent worsening of HF thereby avoiding hospital admission and to increase survival.
- Symptoms should improve within a few weeks to a few months of starting treatment.
- Advise patients to report principal adverse effects, ie dizziness/symptomatic hypotension.
- Advise patients to avoid NSAIDs not prescribed by a physician (self purchased 'over the counter') and salt substitutes high in K^+ .

Problem Solving

Asymptomatic low blood pressure

- Does not usually require any change in therapy.

Symptomatic hypotension

- If the patient has dizziness, light headedness and/or confusion and low blood pressure reconsider the need for nitrates, calcium channel blockers and other vasodilators. Calcium channel blockers should be discontinued unless absolutely essential (eg, for angina or hypertension).
- If no signs/symptoms of congestion consider reducing diuretic dose.
- If these measures do not solve problem seek specialist advice.

Worsening renal function

- Some rise in urea, creatinine and potassium is to be expected after initiation of an ACE inhibitor; if an increase is small and asymptomatic no action is necessary.
- An increase in creatinine of up to 50% above baseline, or 266 micromol/l whichever is the smaller, is acceptable.
- An increase in potassium to ≤ 5.5 mmol/l is acceptable.
- If urea, creatinine or potassium do rise excessively consider stopping concomitant nephrotoxic drugs (eg NSAIDs), other potassium supplements/retaining agents (triamterene, amiloride, spironolactone/ eplerenone) and, if there are no signs of congestion, reducing the dose of diuretic. The safety and efficacy of an ACE inhibitor used with an ARB and spironolactone (as well as beta blocker) is uncertain and the use of all three inhibitors of the renin-angiotensin-aldosterone system together is not recommended.
- If greater rises in creatinine or potassium than those outlined above persist despite adjustment of concomitant medications, the dose of the ARB should be halved and blood urea, creatinine and electrolytes rechecked within one to two weeks; if there is still an unsatisfactory response specialist advice should be sought.
- If potassium rises to >5.5 mmol/l or creatinine increases by $>100\%$ or to above 310 micromol/l the ARB should be stopped and specialist advice sought.
- Blood urea, creatinine and electrolytes should be monitored frequently and serially until potassium and creatinine have plateaued.

Reproduced from McMurray J, Cohen-Solal A, Dietz R, Eichhorn E, Erhardt L, Hobbs FD, et al. Practical recommendations for the use of ACE inhibitors, beta blockers, aldosterone antagonists and angiotensin receptor blockers in heart failure: putting guidelines into practice. Eur J Heart Fail. 2005;7(5):710-21, with permission from John Wiley and Sons⁶⁰