ACE INHIBITORS

Practical guidance on the use of ACE inhibitors in patients with HF due to left ventricular systolic dysfunction

Why?

Two major randomised trials (CONSENSUS I and SOLVD-T) and a meta-analysis of smaller trials have conclusively shown that ACE inhibitors increase survival, reduce hospital admissions and improve NYHA Class and quality of life in patients with all grades of symptomatic HF. Other major randomised trials in patients with systolic dysfunction or HF after acute myocardial infarction (SAVE, AIRE, TRACE) have shown that ACE inhibitors increase survival. In patients with heart failure (ATLAS), the composite end-point of death or hospital admission was reduced by higher doses of ACE inhibitor compared to lower doses. ACE inhibitors have also been shown to delay or prevent the development of symptomatic HF in patients with asymptomatic left ventricular systolic dysfunction (LVSD).

In whom and when?

Indications:

- Potentially all patients with HF
- 1st line treatment (along with beta-blockers) in patients with NYHA Class II–IV HF; start as early as possible in course of disease. ACE inhibitors are also of benefit in patients with asymptomatic LVSD (NYHA Class I).

Contraindications:

- History of angioneurotic oedema
- Known bilateral renal artery stenosis

Cautions/seek specialist advice:

- Significant hyperkalaemia (K^+>5.0 mmol/L)
- Significant renal dysfunction (creatinine >221 µmol/L or >2.5 mg/dL)
- Symptomatic or severe asymptomatic hypotension (systolic BP<90 mmHg)

Drug interactions to look out for:

- K^+ supplements/K^+ sparing diuretics e.g., amiloride and triamterene (beware combination preparations with furosemide), aldosterone antagonists (spironolactone, eplerenone), angiotensin receptor blockers, NSAIDS*
- "Low salt" substitutes with a high K^+ content

Where?

- In the community for most patients
- Exceptions – see Cautions/specialist advice above

Which ACE inhibitor and what dose?

	Starting dose	Target dose
Captopril	6.25 mg thrice daily	50 mg thrice daily
Enalapril	2.5 mg twice daily	10–20 mg twice daily
Lisinopril	2.5–5 mg once daily	20–35 mg once daily
Ramipril	2.5 mg once daily	5 mg twice daily or 10 mg once daily
Trandolapril	0.5 mg once daily	4 mg once daily

How to use?

- Start with a low dose (see above)
- Double dose slowly at not less than 2 weekly intervals+
- Aim for target dose (see above) or, failing that, the highest tolerated dose
- Remember some ACE inhibitor is better than no ACE inhibitor
- Monitor blood pressure and blood chemistry (urea/BUN, creatinine, K^+)
- Check blood chemistry 1–2 weeks after initiation and 1–2 weeks after final dose titration
- When to stop up-titration/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 up-titration

Advice to patient?

- Explain expected benefits (see Why?)
- Treatment is given to improve symptoms, to prevent worsening of HF leading to hospital admission and to increase survival
- Symptoms improve within a few weeks to a few months of starting treatment
- Advise patients to report principal adverse effects i.e., dizziness/symptomatic hypotension, cough – see Problem solving
- 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 dizziness, light-headedness and/or confusion and a low blood pressure reconsider need for nitrates, calcium channel blockers** and other vasodilators
- If no signs/symptoms of congestion consider reducing diuretic dose
- If these measures do not solve problem seek specialist advice

Cough:

- Cough is common in patients with heart failure, many of whom have smoking related lung disease, including cancer
- Cough is also a symptom of pulmonary oedema which should be excluded when a new or worsening cough develops
- ACE inhibitor induced cough rarely requires treatment discontinuation
- When a very troublesome cough does develop (e.g., one stopping the patient sleeping) and can be proven to be due to ACE inhibition (i.e., recurs after ACE inhibitor withdrawal and rechallenge) substitution of an angiotensin receptor blocker should be made (see Table 4)

Worsening renal function:

- Some rise in urea (blood urea nitrogen), 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 µmol/L (3 mg/dL), which ever 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 (e.g., NSAIDs*), other potassium supplements/retaining agents (triamterene, amiloride, spironolactone/eplerenone***) and, if no signs of congestion, reducing the dose of diuretic
- If greater rises in creatinine or potassium than those outlined above persist despite adjustment of concomitant medications, the dose of the ACE inhibitor should be halved and blood chemistry rechecked within 1–2 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 µmol/L (3.5 mg/dL) the ACE inhibitor should be stopped and specialist advice sought
- Blood chemistry should be monitored frequently and serially until potassium and creatinine have plateaued

NB: *it is very rarely necessary to stop an ACE inhibitor and clinical deterioration is likely if treatment is withdrawn – ideally, specialist advice should be sought before treatment discontinuation.*

* *Avoid unless essential.*

** *Calcium channel blockers should be discontinued unless absolutely essential (e.g., for angina or hypertension).*

*** *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 3 inhibitors of the renin-angiotensin-aldosterone system together is not recommended.*

+*Health care professionals with experience in the use of ACE inhibitors may wish to up-titrate the dose of ACE inhibitor more rapidly, taking account of the risk of adverse effects and the need for close monitoring of toleration and blood chemistry.*

BETA-BLOCKERS

Practical guidance on the use of beta-blockers in patients with HF due to left ventricular systolic dysfunction

Why?
Several major randomised controlled trials (i.e., USCP, CIBIS II, MERIT-HF, COPERNICUS) have shown, conclusively, that certain beta-blockers increase survival, reduce hospital admissions and improve NYHA Class and quality of life when added to standard therapy (diuretics, digoxin and ACE inhibitors) in patients with stable mild and moderate HF and in some patients with severe HF. In the SENIORS trial which differed substantially in design from the aforementioned studies (older patients, some patients with preserved left ventricular systolic function, longer follow-up), nebivolol appeared to have a smaller treatment effect, though direct comparison is difficult. One other trial (BEST) did not show a reduction in all cause mortality but did report a reduction in cardiovascular mortality and is otherwise broadly consistent with the aforementioned studies. The COMET trial showed that carvedilol was substantially more effective than short-acting metoprolol tartrate* (long acting metoprolol succinate was used in MERIT-HF).

In whom and when?
Indications:
- Potentially all patients with stable mild and moderate HF; patients with severe HF should be referred for specialist advice
- 1st line treatment (along with ACE inhibitors) in patients with stable NYHA Class II–III HF; start as early as possible in course of disease

Contraindications:
- Asthma

Cautions/seek specialist advice:
- Severe (NYHA Class IV) HF
- Current or recent (<4 weeks) exacerbation of HF e.g., hospital admission with worsening HF
- Heart block or heart rate <60/min
- Persisting signs of congestion, hypotension/low blood pressure (systolic <90 mmHg), raised juguiar venous pressure, ascites, marked peripheral oedema

Drug interactions to look out for:
- Verapamil/diltiazem (should be discontinued)**
- Digoxin, amiodarone

Where?
- In the community in stable patients (NYHA Class IV/severe HF patients should be referred for specialist advice)
- Not in unstable patients hospitalised with worsening HF
- Other exceptions – see Cautions/seek specialist advice

Which beta-blocker and what dose?

	Starting dose	Target dose
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25–50 mg twice daily
Metoprolol CR/XL	12.5–25 mg once daily	200 mg once daily*
Nebivolol	1.25 mg once daily	10 mg once daily

How to use?
- Start with a low dose (see above)
- Double dose at not less than 2 weekly intervals
- Aim for target dose (see above) or, failing that, the highest tolerated dose
- Remember some beta-blocker is better than no beta-blocker
- Monitor HR, BP, clinical status (symptoms, signs – especially signs of congestion, body weight)
- Check blood chemistry 1–2 weeks after initiation and 1–2 weeks after final dose titration
- When to stop up-titration/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 up-titration

Advice to patient?
- Explain expected benefits (see Why?)
- Treatment is given to improve symptoms, prevent worsening of HF leading to hospital admission and to increase survival
- Symptomatic improvement may develop slowly after starting treatment, taking 3–6 months or longer
- Temporary symptomatic deterioration may occur during initiation/up-titration phase; in long-term beta blockers improve well-being
- Advise patient to report deterioration (see Problem solving) and that deterioration (tiredness, fatigue, breathlessness) can usually be easily managed by adjustment of other medication; patients should be advised not to stop beta-blocker therapy without consulting their physician
- To detect and treat deterioration early, patients should be encouraged to weigh themselves daily (after waking, before dressing, after voiding, before eating) and to increase their diuretic dose should their weight increase, persistently (>2 days), by >1.5–2.0 kg.***

Problem solving
Worsening symptoms/signs (e.g., increasing dyspnoea, fatigue, oedema, weight gain):
- If increasing congestion increase dose of diuretic and/or halve dose of beta-blocker (if increasing diuretic doesn't work)
- If marked fatigue (and/or bradycardia – see below) halve dose of beta-blocker (rarely necessary)
- Review patient in 1–2 weeks; if not improved seek specialist advice
- If serious deterioration halve dose of beta-blocker or stop this treatment (rarely necessary); seek specialist advice

Low heart rate:
- If <50 beats/min and worsening symptoms – halve dose beta-blocker or, if severe deterioration, stop beta-blocker (rarely necessary)
- Review need for other heart rate slowing drugs e.g., digoxin, amiodarone, diltiazem/verapamil**
- Arrange ECG to exclude heart block
- Seek specialist advice

Asymptomatic low blood pressure:
- Does not usually require any change in therapy

Symptomatic hypotension:
- If dizziness, light-headedness and/or confusion and a low blood pressure reconsider need for nitrates, calcium channel blockers** and other vasodilators
- If no signs/symptoms of congestion consider reducing diuretic dose or ACE inhibitor
- If these measures do not solve problem seek specialist advice

NB: *beta-blockers should not be stopped suddenly unless absolutely necessary (there is a risk of a "rebound" increase in myocardial ischaemia/infarction and arrhythmias) – ideally specialist advice should be sought before treatment discontinuation.*

* *Metoprolol tartrate should not be used in preference to an evidence-based beta-blocker in HF.*

** *Calcium channel blockers should be discontinued unless absolutely necessary and diltiazem and verapamil are generally contraindicated in HF.*

*** *This is generally good advice for all patients with HF.*

ANGIOTENSIN RECEPTOR BLOCKERS

Practical guidance on the use of ARBs in patients with HF due to left ventricular systolic dysfunction

Why?

When added to standard therapy, including an ACE inhibitor, in patients with all grades of symptomatic HF, the ARBs valsartan and candesartan have been shown, in two major randomised trials (Val-HeFT and CHARM), to reduce HF hospital admissions, improve NYHA class and maintain quality of life. The two CHARM low LVEF trials (CHARM-Alternative and CHARM-Added) also showed that candesartan reduced all-cause mortality. In patients previously intolerant of an ACE inhibitor, candesartan has been shown to reduce the risk of the composite outcome of cardiovascular death or HF hospitalisation, the risk of HF hospital admission and to improve NYHA class. These findings in HF are supported by another randomised trial in patients with left ventricular systolic dysfunction, heart failure or both complicating acute myocardial infarction (VALIANT) in which valsartan was as effective as the ACE inhibitor captopril in reducing mortality and cardiovascular morbidity.

In whom and when?

Indications:

- Potentially all patients with HF
- 1st line treatment (along with beta-blockers) in patients with NYHA Class II–IV HF intolerant of an ACE inhibitor
- 2nd line treatment (after optimisation of ACE inhibitor and beta-blocker*) in patients with NYHA Class II–IV HF

Contraindications:

- Known bilateral renal artery stenosis

Cautions/seek specialist advice:

- Significant hyperkalaemia (K^+>5.0 mmol/L)
- Significant renal dysfunction (creatinine 221 µmol/L or >2.5 mg/dL)
- Symptomatic or severe asymptomatic hypotension (systolic BP<90 mmHg)

Drug interactions to look out for:

- K^+ supplements/K^+ sparing diuretics e.g., amiloride and triamterene (beware combination preparations with furosemide). Aldosterone antagonists (spironolactone, eplerenone), ACE inhibitors, NSAIDS**
- "Low salt" substitutes with a high K^+ content

Where?

- In the community for most patients
- Exceptions – see Cautions/specialist advice above

Which ARB and what dose?

	Starting dose	Target dose
Candesartan	4 or 8 mg once daily	32 mg once daily
Valsartan	40 mg twice daily	160 mg twice daily

How to use?

- Start with a low dose (see above)
- Double dose at not less than 2 weekly intervals
- Aim for target dose (see above) or, failing that, the highest tolerated dose
- Remember some ARB is better than no ARB
- Monitor blood pressure and blood chemistry (urea/BUN, creatinine, K^+)
- Check blood chemistry 1–2 weeks after initiation and 1–2 weeks after final dose titration
- When to stop up-titration/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 up-titration

Advice to patient?

- Explain expected benefits (see Why?)
- Treatment is given to improve symptoms, prevent worsening of HF leading to hospital admission and to increase survival
- Symptoms improve within a few weeks to a few months of starting treatment
- Advise patients to principal adverse effect i.e., report 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 dizziness, light-headedness and/or confusion and a low blood pressure reconsider need for nitrates, calcium channel blockers*** and other vasodilators
- 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 (blood urea nitrogen), creatinine and potassium is to be expected after initiation of an ARB; if the increase is small and asymptomatic no action is necessary
- An increase in creatinine of up to 50% above baseline, or 266 µmol/L (3 mg/dL), which ever 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 (e.g., NSAIDs**), other potassium supplements/retaining agents (triamterene, amiloride, spironolactone/eplerenone*) and, if no signs of congestion, reducing the dose of diuretic
- If greater rises in creatinine or potassium than those outlined above persist despite adjustment of concomitant medications, the dose of the ARB should be haived and blood chemistry rechecked within 1–2 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 µmol/L (3.5 mg/dL) the ARB should be stopped and specialist advice sought
- Blood chemistry should be monitored frequently and serially until potassium and creatinine have plateaued

NB: *it is very rarely necessary to stop an ARB and clinical deterioration is likely if treatment is withdrawn – ideally, specialist advice should be sought before treatment discontinuation.*

* *The safety and efficacy of an ARB used with an ACE inhibitor* ***and*** *spironolactone (as well as beta-blocker) is uncertain and the use of all 3 inhibitors of the renin-angiotensin-aldosterone system together is not recommended.*

** *Avoid unless essential.*

*** *Calcium channel blockers should be discontinued unless absolutely essential (e.g., for angina or hypertension).*

Practical guidance on the use of aldosterone antagonists in patients with HF due to left ventricular systolic dysfunction

Why?

The RALES study showed that low dose spironolactone increased survival, reduced hospital admissions and improved NYHA Class when added to standard therapy (diuretic, digoxin, ACE inhibitor and, in a minority of cases, a beta-blocker) in patients with severe (NYHA Class III or IV) HF. These findings in HF are supported by another randomised trial in patients with left ventricular systolic dysfunction and heart failure (or diabetes) complicating acute myocardial infarction (EPHESUS) in which another aldosterone antagonist, eplerenone, increased survival and reduced hospital admissions for cardiac causes.

In whom and when?

Indications:

- Potentially all patients with symptomatically moderately severe or severe HF (Class III/IV NYHA)
- Second line therapy (after ACE inhibitors and beta-blockers*) in patients with NYHA Class III–IV HF; there is no evidence of benefit in patients with milder HF

Cautions/seek specialist advice:

- Significant hyperkalaemia (K^+>5.0 mmol/L)**
- Significant renal dysfunction (creatinine >221 µmol/L or 2.5 mg/dL)**

Drug interactions to look out for:

- K^+ supplements/K^+ sparing diuretics e.g., amiloride and triamterene (beware combination preparations with furosemide). ACE inhibitors, ARBs, NSAIDS***
- "Low salt" substitutes with a high K^+ content

Where?

- In the community or in hospital
- Exceptions – see Cautions/seek specialist advice

How much?

	Starting dose	Target dose
Spironolactone	25 mg once daily or on alternate days	25–50 mg once daily
Eplerenone	25 mg once daily	50 mg once daily

How to use?

- Start with a low dose (see above)
- Check blood chemistry at 1, 4, 8 and 12 weeks; 6, 9 and 12 months; 6 monthly thereafter
- If K^+ rises above 5.5 mmol/L or creatinine rises to 221 µmol/L (2.5 mg/dL) reduce dose to 25 mg on alternate days and monitor blood chemistry closely
- If K^+ rises to ≥6.0 mmol/L or creatinine to >310 µmol/L (3.5 mg/dL) stop spironolactone immediately and seek specialist advice
- A specialist HF nurse may assist with patient education, follow-up (in person/by telephone), biochemical monitoring and dose up-titration

Advice to patient?

- Explain expected benefits (see Why?)
- Treatment is given to improve symptoms, prevent worsening of HF leading to hospital admission and to increase survival
- Symptom improvement occurs within a few weeks to a few months of starting treatment
- Avoid NSAIDs*** not prescribed by a physician (self-purchased "over the counter") and salt substitutes high in K^+
- If diarrhoea and/or vomiting occurs patients should stop spironolactone and contact their physician

Problem solving

Worsening renal function/hyperkalaemia:

- See How to use? section
- Major concern is hyperkalaemia (≥6.0 mmol/L); although this was uncommon in RALES it has been seen more commonly in clinical practice: conversely, a high normal potassium may be desirable in HF patients, especially if taking digoxin
- It is important to avoid other K^+ retaining drugs (e.g., K^+ sparing diuretics such as amiloride and triamterene) and nephrotoxic agents (e.g., NSAIDs***)
- The risk of hyperkalaemia and renal dysfunction when an aldosterone antagonist is given to patients already taking an ACE inhibitor and ARB is higher than when an aldosterone is added to just an ACE inhibitor or ARB given singly; close and careful monitoring is mandatory*
- Some "low salt" substitutes have a high K^+ content
- Male patients treated with spironolactone may develop breast discomfort and/or gynaecomastia (these problems are significantly less common with eplerenone)

* *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 3 inhibitors of the renin-angiotensin-aldosterone system together is not recommended.*

** *It is extremely important that these cautions and doses are adhered to in the light of recent evidence of serious hyperkalaemia with spironolactone in usual clinical practice in Ontario [36].*

*** *Avoid unless essential.*

Background to recommendations

The aim of this pocket guide is to summarise the published recommendations of an advisory group regarding the management of heart failure, in a format that clinicians can easily refer to.

The recommendations assume that a clinical diagnosis of heart failure has been established and that the physician may have already initiated diuretic therapy to treat the signs and symptoms of fluid overload.

The costs associated with the advisory group meeting were met by an unrestricted educational grant from AstraZeneca. However, the remit of the faculty was to review all the relevant published clinical trials and produce a set of clinical recommendations independent of any outside interests.

As approved labelling of products differs according to the regulatory requirements of a particular country, prescribers need to be aware of the relevant product prescribing information which applies in their country.

"Under-prescribing and under-dosing of some treatments which reduce both mortality and morbidity in patients with HF in controlled clinical trials is a persisting problem"

"The preparation of these concise and practical clinical recommendations for the prescribing of proven pharmacological treatments should provide doctors with the confidence to practise evidence-based medicine in their patients with HF whilst avoiding unnecessary toxicity"

Reference

McMurray J, Cohen-Solal A, Dietz R, Eichhorn E, Erhardt L, Hobbs R, 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;7:710–21.