Medicines Advice Initiative Australia

Pharmaceutical Society of Australia

Pharmacist quick reference guide to:
Four pillars for the treatment of heart failure with reduced ejection fraction (HFrEF)

Principles of pharmacological management[1,2]

Start all four classes of medicines within 2–4 weeks of diagnosis.

Aim to achieve target doses (maximally tolerated doses) within 2-3 months.

Monitor signs and symptoms of HF, functional status, fluid status, kidney function, BP, HR and electrolyte concentrations. Daily weight recommended.

Continue all four pillars of HFrEF treatment even if LVEF improves

Table 1: Pharmacist's role in the pharmacological management of HFrEF

	RAS inhibitors ACEI, ARNI (sacubitril + valsartan) and ARB	**HF specific beta-blockers** bisoprolol, carvedilol, MR metoprolol and nebivolol	**MRAs** eplerenone and spironolactone	**SGLT2 inhibitor** dapagliflozin and empagliflozin
Provide evidence-based counselling focusing on clinical outcomes.	Recommended for **all** HFrEF patients. Either an ARNI or ACEI (ARNI preferred) is recommended to decrease mortality and HF hospitalisations. Refer to PBS website for current eligibility criteria. Note: ACEI or ARNI preferred over ARB as none of the HF ARB studies demonstrated a reduction in all-cause mortality.[5]	Recommended for all clinically stable and euvolaemic patients with HFrEF (including older patients and those with peripheral vascular disease, erectile dysfunction, diabetes, interstitial lung disease or COPD). Reduces the symptoms of HF, improves LVEF, and reduces hospitalisation and mortality (including sudden death).	Recommended for all HFrEF patients. Low-dose spironolactone (up to 25–50 mg orally once daily) and low-dose eplerenone (up to 25–50 mg orally once daily) reduces risk of death and hospitalisation and improves symptoms.	Recommended for all HFrEF patients, regardless of diabetes status. Reduces cardiovascular mortality and hospitalisation. Refer to PBS website for current eligibility criteria.
Inform GPs when and why dosage adjustments are required.	Start with a low dose (especially if elderly or concomitant diuretic therapy) and double the dose every two weeks to the highest tolerated dose within the recommended range. ARNI: 24+26 mg orally twice daily increasing to maximum 97+103 mg orally twice daily.	Start therapy with a very low dose, when the patient is clinically stable and euvolaemic. Double the dose every 2–4 weeks to the highest tolerated maintenance dose within the recommended range. Switch patients already taking a beta blocker for a comorbidity (e.g. angina, hypertension) to a HF specific beta blocker on diagnosis of HFrEF.	Start with 25 mg orally once daily for spironolactone or eplerenone and increase to target dose of 50 mg orally once daily at 4-8 weeks, if tolerated. Avoid (use cautiously) in patients with stage 4 or 5 CKD or serum K > 5 mmol/L.	SGLT2I can be initiated at diagnosis or within 2-4 weeks of diagnosis. No additional dose titration required. *dapagliflozin* 10 mg orally once daily *empagliflozin* 10 mg orally once daily. Consider reducing the dose of concomitant loop diuretics when starting an SGLT2 inhibitor if the patient is euvolaemic.
Advise of adverse effects or poor response to therapy.	Elderly may be more predisposed to side effects which include hypotension, headache, dizziness, hyperkalaemia, fatigue, nausea and renal impairment. *Angioedema:* if previously experienced with an ACEI or ARB, ARNI therapy is contraindicated. When switching agents stop the ACEI at least 36 hours before starting ARNI. Cease RAS inhibitor if angioedema is suspected and seek specialist advice. *Cough:* if thought to be related to ACEI and impacting quality of life, switch to ARB.	May precipitate bronchospasm or heart failure if patient is fluid overloaded. Can decrease HR and BP.	*Hyperkalaemia:* risk increased in those with renal impairment and those taking other medicines that may increase K concentrations including ACEI, ARB, ARNIs and trimethoprim. Note: manufacturer of eplerenone contraindicates use with K-sparing diuretics. If K 5.5–5.9 mmol/L, reduce dose by half. If K > 6 mmol/L, stop MRA and seek specialist advice. Gynaecomastia: switch to eplerenone.	*Ketoacidosis* (with or without accompanying hyperglycaemia). Withhold if other risk factors present including acute serious illness, prolonged fasting, bowel preparation, low carbohydrate intake and excessive alcohol intake. *Genitourinary infections:* including vulvovaginal candidiasis, balanitis, bacterial UTIs and rarely Fournier's gangrene. *Volume depletion:* Elderly are at increased risk of adverse effects related to volume depletion including hypotension and fainting.
Recommend appropriate monitoring.	BP, volume status, serum K and renal function should be reviewed on initiation, after 1–2 weeks, at each dose escalation and 6–monthly longer term. Consider dose adjustment of diuretics and other antihypertensives or withholding diuretics for 24 hours before starting. Review and cease NSAIDs.	HR, BP and clinical evaluation of volume status following initiation, after 1–2 weeks, at each dose escalation and 6–monthly longer term.	BP, volume status, serum K and renal function should be reviewed on initiation, after 1–2 weeks, every 4 weeks for 12 weeks, at 6 months and then 6–monthly longer term.	Monitor fluid balance and consider reducing diuretic dose in euvolaemic patients. Check renal function before starting treatment and then periodically as clinically indicated (at least annually).

TG[1], AMH[2], Guidelines for heart failure in Australia 2018[4]

Tips to titrate the four pillars

Dose reduction or cessation of therapy is generally not required for[1,4]:

- asymptomatic hypotension
- rise in serum creatinine of up to 30%
- rises in serum K (but within the normal range)

Table 2: Managing issues during medicine up-titration

Clinical issue	Recommended management
Hyperkalaemia	For serum potassium > 5.5mmol/L • Assess volume status • Review need for other medicines that impact K levels and do not improve HF outcomes. Review diet. • Decrease the MRA and/or RAS inhibitor dose. For serum potassium > 6.0mmol/L • Review need for other medicines that impact K levels and do not improve HF outcomes. Review diet. • Stop the MRA and seek specialist advice.
Symptomatic hypotension (dizziness, light-headedness, confusion)	• Review volume status and other medical therapy. • Review treatments that reduce BP but have not been shown to improve HF outcomes (e.g. CCB) • If no signs or symptoms of congestion present, reduce diuretic dose. • Change the timing of doses (e.g. split into morning and night). • Temporarily reduce the dose of the RAS inhibitor. • Reduce the beta blocker dose and seek specialist advice. Avoid abrupt cessation.
Deterioration of kidney function	A decline in eGFR up to 30% is acceptable if stabilised within 2 weeks (or 4–12 weeks for SGLT2 inhibitor). If greater than 30% decline: • Review the volume status and medical therapy. • Review and cease nephrotoxic medicines including NSAIDs. • If no signs or symptoms of congestion, reduce or withhold the loop diuretic • Decrease the dose of the RAS inhibitor or MRA.
Fluid balance	Daily monitoring of weight is recommended. Ensure the patient understands their fluid plan. Weight changes +/- 2 kg or more should prompt clinical review. SGLT2 inhibitors, MRAs and ARNIs have a mild diuretic effect. In volume depletion: • Assess volume status before commencing or adjusting doses. • Reduce the dose of loop diuretic in euvolaemic patients, if required.[3]
Symptomatic bradycardia	Assess fluid status. If HR < 50 bpm, review the need for other drugs that slow heart rate (e.g., digoxin, amiodarone) and arrange ECG to exclude heart block. Consider reducing beta-blocker (avoiding abrupt cessation) and seek specialist advice.
Congestion	Review fluid action plan. Usually managed by increasing the diuretic dose. Occasionally may require a reduction in the beta blocker dose or temporary withdrawal.

TG[1], AMH[2], Guidelines for heart failure in Australia 2018[4]

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Table 3: Medicines that may exacerbate heart failure

- NSAIDs (including COX-2 selective)
- centrally acting CCB
- tricyclic antidepressants
- medicines that prolong the QT interval
- corticosteroids
- saxagliptin
- moxonidine

TG[1], Guidelines for heart failure in Australia 2018[4]

Abbreviations:

HF – heart failure; HFrEF – heart failure with reduced ejection fraction; LVEF – left ventricular ejection fraction; SGLT2 – sodium glucose cotransporter 2; ACEI – angiotensin converting enzyme inhibitors, HR – heart rate; ARB – angiotensin II receptor blockers; ARNI – angiotensin-receptor/ neprilysin inhibitor; MRA – mineralocorticoid receptor antagonists; MR – modified release; RAS – renin-angiotensin system; CKD – chronic kidney disease; K – potassium; eGFR – estimated glomerular filtration rate; BP – blood pressure; BPM – beats per minute; ECG – electrocardiogram, UTI – urinary tract infection; CCB – calcium channel blocker; NSAIDs – non-steroidal anti-inflammatory drugs; COX – cyclo-oxygenase.

References:

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5. Sindone A, De Pasquale C, Amerena J et al. Consensus statement on the current pharmacological prevention and management of heart failure. MJA 2022;217(4):212–217.

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