South East London Area Prescribing Committee:

Pharmacological management of Heart Failure June 2017

Developed by Kings Health Partners in conjunction with the SEL Cardiovascular Disease Working Group on behalf of the SEL APC. If you have any queries or comments on this guideline please contact: LAMCCG.medicinesoptimisation@nhs.net

Date approved: June 2017 **Review date: June 2019 or sooner if evidence/practice changes**

Pharmacological management of Heart Failure

Acknowledgements

Developed By

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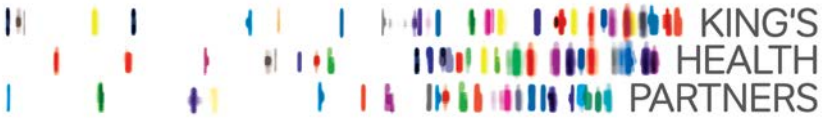
IN HEALTH



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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.
These guidelines are not intended for acute care and are only to be used after a heart failure diagnosis has been made.

Overview of Pharmacological management of Heart Failure
Please see attached flowcharts for specific details on medications, dosing and cautions etc.

Heart Failure (HF)

- •Manage co-morbid conditions – Hypertension, Ischaemic Heart Disease (IHD), Diabetes Mellitus (DM)
- •Cardiac Rehab
- •Education

Patients may require **diuretics** for symptomatic relief at any stage, depending on symptoms

HFpEF (Heart Failure with Preserved Ejection Fraction)
(Left Ventricular Ejection Fraction (LVEF) >40%)

No evidence for disease modifying therapies in HFpEF

Diuretics to relieve symptoms & signs of congestion and management of co-morbidities

HFrEF (Heart Failure with Reduced Ejection Fraction)/LVSD (Left Ventricular Systolic Dysfunction)(LVEF ≤40%)

1st line – ANGIOTENSIN CONVERTING ENZYME INHIBITOR (ACE-I) e.g. Ramipril
AND BETA-BLOCKERS (BB) e.g. Bisoprolol

Consider **ANGIOTENSIN II RECEPTOR BLOCKER** (ARB) e.g. Candesartan - if intolerant of ACE-I
Up titrate to maximum tolerated dose of both drugs

IF REMAINS SYMPTOMATIC despite maximal therapy with ACE-I/ARB and BB

2nd line – MINERALOCORTICOID RECEPTOR ANTAGONISTS (MRA)/ ALDOSTERONE ANTAGONISTS (AA) e.g. Spironolactone/ Eplerenone
Up titrate to maximum tolerated dose

IF REMAINS SYMPTOMATIC SEEK SPECIALIST ADVICE for consideration of:

- •Sacubitril/Valsartan
- •Ivabradine
- •Digoxin
- •Hydralazine + Nitrate
- •Device therapy
- •Transplant

Prescribing Loop Diuretics in heart failure (all heart failure)

See overleaf for more detailed information

Most patients with HF will require treatment with loop diuretics for symptom control. SEE **BOX 1** (overleaf) FOR IMPORTANT INFORMATION AND CONTRAINDICATIONS

Examination of Fluid Status: Blood Pressure (BP), Heart Rate (HR), Jugular Venous Pressure (JVP), and Weight

Fluid overload

One or more of the following:

- Weight ↑ >1.5kg above dry weight/rapid weight gain over 2-3 days
- ↑dyspnoea / ↑peripheral oedema or sacral oedema / orthopnoea and/or paroxysmal nocturnal dyspnoea (PND)

Dehydration

Two or more of the following:

- Weight ↓ >1.5kg below dry weight over 2-3 days
- No symptoms of ↑ dyspnoea or peripheral oedema
- Symptoms of thirst, dizziness, or feeling washed out

Baseline checks: BLOODS – U&Es (Ur, Cr, K^+, Na^+), eGFR

Start furosemide 40mg daily or increase diuretic dose as below

EITHER Furosemide

Current TOTAL dose:	Increase to:
40mg/day	80mg/day
80mg/day	120mg/day (split dose)
120mg/day	160mg/day(split dose)*

OR Bumetanide

Current TOTAL dose:	Increase to:
1mg/day	2mg/day
2mg/day	3mg/day (split dose)
3mg/day	4mg/day (split dose)*

*if not responding to high dose loop diuretic consider addition of thiazide with advice from community HF Team/secondary care team and/or referral to acute services for intravenous (IV) diuretics

Review symptoms in 3-5 days or sooner where clinically indicated and repeat baseline checks. SEE **BOX 2** (overleaf) FOR ADVERSE EFFECTS/PROBLEM SOLVING

Still fluid overloaded?

Yes

No

Continue higher dose and monitor for dehydration/check U&Es and BP

Decrease diuretic dose

EITHER Furosemide

Current TOTAL dose:	Decrease to:
160mg/day	120mg/day (split dose)
120mg/day	80mg/day
80mg/day	40mg/day
40mg/day	20mg/day or stop

OR Bumetanide

Current TOTAL dose:	Decrease to:
5mg/day	4mg/day (split dose)
4mg/day	3mg/day (split dose)
3mg/day	2mg/day
2mg/day	1mg/day
1mg/day	0.5mg/day or stop

Review symptoms in 3-5 days or sooner where clinically indicated SEE **BOX 2** (overleaf) FOR ADVERSE EFFECTS/PROBLEM SOLVING

Still dehydrated?

Continue to reduce dose and monitor for signs of fluid overload

No

Yes

Patient information

- Avoid taking a dose after 4pm as this can lead to nocturia
- Report dizziness/light-headedness as this may be indicative of over treatment
- Report sudden or sustained weight increase or decrease (more than 1kg over 3 days) to a community HF team or GP. Weigh after waking and voiding but before breakfast and dressing.

Primary care to carry out 6 monthly medical review for all HF patients (please see General Practice Six Month Review template on local prescribing system)

For support with education and management please contact your local community HF team (see **appendix** for details)

Prescribing Loop Diuretics in heart failure (all heart failure)

See overleaf for flow chart

BOX 1: FOR IMPORTANT INFORMATION AND CONTRAINDICATIONS

•The cause of fluid retention should be investigated and treated as appropriate (i.e. non-adherence, infection, atrial fibrillation (AF), excess intake of salt or fluid).
•The diuretic of choice would be furosemide, with bumetanide reserved for those patients unresponsive to furosemide.
•When changing from furosemide to bumetanide the conversion should be furosemide 40mg to bumetanide 1mg.
•There is no evidence to support a particular dose of a diuretic; the dose should be increased gradually to control symptoms [see flow chart] and consider dose increase for 3-5 days at a time.
•Use the lowest dose of furosemide or bumetanide necessary to relieve fluid overload, oedema and breathlessness without causing dehydration or risking renal dysfunction or hypotension. The dose required will vary between patients.
•All patients should be counselled to limit salt and fluid intake (1.5 to 2 litres per day), monitor their weight daily, how to identify changing symptoms and report any changes to the prescriber.
•Serum potassium (K^+) should be monitored, especially after a dose adjustment, and maintained in the range 3.6-5.0mmol/L.
•Dose regime of loop diuretics should be discussed with the patient and can be adjusted to suit the patient's lifestyle to improve adherence, within safe limits and avoiding large single doses. Total daily doses are given on the flow chart.
•Doses lower than stated in flowchart can be considered after clinical assessment.

CONTRAINDICATIONS

•Hypersensitivity to loop diuretics or excipients
•Hypovolaemia
•Dehydration
•Severe hypokalaemia: serum $K^+ < 3.3$ mmol/L
•Severe hyponatraemia: serum sodium (Na^+) < 130 mmol/L
•Comatose or precomatose states associated with liver cirrhosis
•Anuria
•Renal failure due to nephrotoxic or hepatotoxic drugs
•Addison's disease
•Breast feeding
•Digitalis intoxication

CAUTIONS

•Hypotension
•Prostatic enlargement or impaired micturition
•Gout
•Diabetes
•Hepatic impairment
•Renal Impairment
•Pregnancy
•Pancreatitis/history of pancreatitis
•Systemic lupus erythematosus
•Hypoparathyroidism
•Hypokalaemia
•Drug interactions . See list in British National Formulary (BNF)

BOX 2: ADVERSE EFFECTS/PROBLEM SOLVING

Over diuresis:
•Signs of dizziness/light headedness/fatigue/uraemia/hypotension and gout.
•Exclude and/or treat dehydration caused by other factors such as diarrhoea, vomiting, fasting and hot weather.
•Review diuretics and reduce dose [see flow chart].
•Reassess and if no improvement seek advice from community HF team or HF consultant.

Unresponsive to increase in diuretics:
•Check medication adherence and fluid intake.
•Consider switching from furosemide to bumetanide.
• Consider addition of a thiazide diuretic (e.g. metolazone) with advice from community HF team or HF consultant.
•Reassess and if no improvement seek advice from community HF team or HF consultant.

Hypokalaemia:
•Consider increasing ACE-I/ARB if possible or replace with Sando K (usual dose 2 three times a day for 3 days).
•Advise increase in dietary potassium
•Discuss addition of MRA/AA, if clinically indicated.

Hyponatraemia:
•Fluid restriction.
•Reduce or stop diuretics if possible.
•Seek advice if serum Na^+ falls below 130 mmol/L [this is a poor prognostic indicator].

Hyperuricaemia / gout:
•For acute gout attacks treat with Colchicine and avoid Non-Steroidal Anti-Inflammatory Drugs (NSAIDS).
•For frequent gout attacks consider prophylaxis with Allopurinol.

Renal failure:
•Check for hypovolaemia / dehydration.
•Exclude other nephrotoxic agents e.g. NSAIDs, Trimethoprim.
•Review and discuss adjustment of other nephrotoxic drugs e.g. ACE-I, ARBs and Spironolactone.

Symptomatic hypotension (SBP<100mmHg associated with dizziness, fainting and confusion): seek advice regarding fluid and electrolyte replacement from community HF team or HF consultant.
•Check blood chemistry.
•Encourage fluid intake.
•Withhold one to three diuretic doses and lower doses by one step [see flow chart].
•Counsel patient to avoid abrupt postural changes.
•Reassess BP and hypotensive symptoms in 3 days.
•If patient remains symptomatic, review vasodilators e.g. if taking ramipril once a day, consider splitting dose to twice a day. If symptoms persist consult community HF team or HF consultant .

Photosensitivity:
•Advise on protective measures (sunscreen, clothing) against exposure to UV light or sunlight.

Prescribing ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACE-I) in patients with LVSD/HFrEF (LVEF≤40%)
read code 585f
See overleaf for more detailed information

ACE-I should be offered to ALL patients with LVSD (LVEF≤40%)
SEE **BOX 1** (overleaf) FOR IMPORTANT INFORMATION AND CONTRAINDICATIONS

Baseline

- BLOODS – U&Es (Ur, Cr, K^+, Na^+), eGFR
- BP

Initiation

- Start at LOWEST dose and titrate up
  - RAMIPRIL* 1.25mg daily
  - LISINOPRIL 2.5 - 5mg daily
  - ENALAPRIL 2.5mg twice daily

*ACE-I of choice in LVSD

Patient information

- ACE-I will improve symptoms, prevent HF worsening, reduce risk of hospital admissions and prolong life
- It may take a few weeks to start showing an effect
- Hypotension and dizziness are the most common side effects
- Report any dry cough to GP/ HF team
- Avoid any Over The Counter (OTC) anti-inflammatories (NSAIDS)

- Review other medications such as NSAIDs/ nephrotoxic drugs/ diuretics/ K^+ sparing diuretics etc
- Stop K^+ supplements

Up titration

- Aim for TARGET dose or Maximum Tolerated Dose
  - RAMIPRIL 5mg twice daily OR 10mg daily
  - LISINOPRIL 30 – 35mg daily
  - ENALAPRIL 10 – 20mg twice daily
- Double dose at 2-4 weekly intervals

SEE SUGGESTED UP TITRATION SCHEDULE

- Repeat baseline checks within 1-2 weeks of initiation and before/after any dose changes
- More frequent monitoring may be required if patient is on combined loop and thiazide diuretic therapy, or MRA/AA.

SEE **BOX 2** (overleaf) FOR ADVERSE EFFECTS/ PROBLEM SOLVING

SUGGESTED UP TITRATION SCHEDULE
Some ACE-I is better than no ACE-I

Preferred ACE-I for LVSD (LVEF≤40%):
1st line - RAMIPRIL
2nd line - LISINOPRIL
3rd line - ENALAPRIL
If already on a ACE-I switch to one licensed for LVSD (LVEF≤40%)

DRUG / Week	Week 0-2	Week 2-4	Week 4-6	Week 6-8	Week 8-12
RAMIPRIL	1.25MG OD	1.25MG BD	2.5MG BD	5MG BD	
LISINOPRIL	2.5MG OD	5MG OD	10MG OD	20MG OD	30-35MG OD
ENALAPRIL	2.5mg BD	5MG BD	10MG BD	20MG BD	

Note: OD= daily; BD=twice daily

Monitoring

- Stable dose – 6 monthly review

SEE **BOX 3** (overleaf) FOR RECOMMENDATIONS WHEN MONITORING

Primary care to carry out 6 monthly medical review for all HF patients (please see General Practice Six Month Review template on local prescribing system**)**
For support with education and management please contact your local community HF team (see **appendix** for details)

Prescribing ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACE-I) in patients with LVSD/HFrEF (LVEF≤40%)

Read code 585f

See overleaf for flow chart

BOX 1: FOR IMPORTANT INFORMATION AND CONTRAINDICATIONS

Evidence from clinical trials demonstrates that patients with HF, due to left ventricular dysfunction, show an improvement in symptom control and a reduction in morbidity and mortality when treated with an ACE-I. Therefore, all patients diagnosed with HF due to LVSD (LVEF ≤ 40%) should be considered for an ACE-I and up titrated to maximum tolerated dose to improve outcome.

CONTRAINDICATIONS

- **Concomitant use of sacubitril valsartan (Entresto) - Discontinue sacubitril valsartan (Entresto) at least 36 hours prior to starting an ACE-I**
- Haemodynamically relevant bilateral renal artery stenosis
- Renal artery stenosis in a single functioning kidney
- Aortic or mitral valve stenosis or outflow obstruction – except under specialist supervision
- Known hypersensitivity to any ACE-I or excipients
- History of angioedema (hereditary, idiopathic or previous angioedema with ACE -I)
- Pregnancy
- Baseline K^+ > 5.5 mmol/L

CAUTIONS

- Symptomatic or severe asymptomatic hypotension (systolic BP <90 mmHg)
- Patients with a documented intolerance of ACE-I due to symptomatic hypotension – consider re-challenging with a longer acting ACE-I (such as ramipril)
- Patients on high dose diuretics (i.e. furosemide > 80mg daily) – increased risk of hypotension and renal dysfunction
- Breastfeeding – seek specialist advice
- Impaired liver function
- Moderate to severe renal impairment: creatinine > 150 micromol/L or eGFR < 50 ml/min. See individual summary of product characteristics (SPCs) for dose adjustment requirements
- Baseline serum K^+ between 5 to 5.5 mmol/L
- Drug interactions – see British National Formulary (BNF) for list

Seek specialist advice prior to initiation:

- Hypertrophic cardiomyopathy
- Hyponatraemia (serum Na^+ <135 mmol/L)
- Symptomatic or severe asymptomatic hypotension (systolic BP<90 mmHg)
- Significant renal dysfunction or renovascular disease e.g. creatinine >150 micromol/L or eGFR <50 ml/min or hyperkalaemia (serum K^+>5.0 mmol/L)
- Renovascular disease (diagnosed as well as undiagnosed and clinically silent disease) e.g. peripheral vascular disease (PVD) or severe generalised atherosclerosis
- Patients undergoing dialysis/extracorporeal treatments or having desensitisation with wasp or bee venom

BOX 2: ADVERSE EFFECTS/PROBLEM SOLVING

- **Angioedema:** Rare but life threatening. Discontinue therapy and seek urgent medical advice.
- **Symptomatic hypotension:**
  - Consider dehydration and address as appropriate - review diuretic dose with a view to decreasing dose if patient free of symptoms suggestive of fluid retention
  - If dizziness, light-headedness and/or confusion occur in the setting of low BP, reduce dose of ACE-I (back to last tolerated dose), and review use of other vasodilators (e.g. nitrates, calcium channel blockers (CCB)). Monitor closely and allow longer intervals between dose titrations
  - Aim to maintain treatment with both ACE-I and BB, at a reduced dose if necessary
  - Seek specialist advice if measures do not resolve symptomatic hypotension
- **Worsening renal function:** An increase in serum urea, creatinine and K^+ is to be expected after initiation/titration of ACE-I. If the increase is small and asymptomatic, no action is necessary. See **BOX 4** for recommended actions
- **Persistent dry cough:** If ACE-I cough is significantly affecting the patient's quality of life, an ARB licensed for HF may be considered as an alternative to ACE-I

BOX 3: RECOMMENDATIONS WHEN MONITORING ACE-I therapy in patients with normal renal function (eGFR >60ml/min)

Blood Chemistry	Action
Creatinine ↑ up to 50% above baseline or to 265 micromol/L (whichever is smaller). OR serum K^+ ↑ to ≤5.5 mmol/L	No urgent action required. Repeat blood chemistry (urea, creatinine and serum K^+) within 2-4 weeks
Creatinine ↑ > 50% but < 100% above baseline or between 265 micromol/L and 310 micromol/L (whichever is smaller). OR serum K^+ ↑ to ≥ 5.5 - ≤5.9 mmol/L	Review required - consider: a) Stopping concomitant nephrotoxic drugs e.g. NSAIDs, non essential vasodilators (e.g. calcium antagonists, nitrates) and if no signs of fluid retention, reduce the dose of diuretic. b) Review causes of high serum K^+. Stop other agents that cause hyperkalaemia e.g. potassium sparing diuretics, or dietary intake. Recheck renal function within 2 weeks. If despite adjusting medication the creatinine and serum K^+ remain higher than above the dose of ACE-I should be halved or stopped if at initiation dose and the blood chemistry re-checked in 5-7days. If the response to this is not satisfactory, seek specialist advice. Blood chemistry should be monitored closely until serum K^+ and creatinine concentrations are stable
Creatinine ↑ by >100% (from baseline) or to above 310 micromol/L. OR serum K^+ ≥ 6 mmol/L	Discontinue ACE-I and discuss with cardiologist **Note:** It is very rarely necessary to stop an ACE-I and in patients with HF, clinical deterioration is likely if treatment is withdrawn; in this instance specialist advice should be sought before treatment discontinuation.

- **Additional recommendations for monitoring in patients with chronic kidney disease (CKD) Stage 3 (eGFR <60ml/min) and above can be found here**

Prescribing BETA BLOCKERS (BB) in patients with LVSD/HFrEF (LVEF≤40%)
Read code 585f
See overleaf for more detailed information

BB should be offered to ALL patients with LVSD (LVEF≤40%)
Do NOT start BB if there are signs of fluid overload
SEE **BOX 1** (overleaf) FOR IMPORTANT INFORMATION AND CONTRAINDICATIONS

Baseline

- HR
- BP
- Absence of fluid overload
- ECG if HR<60 bpm

Initiation

- Ensure patient stable
- Caution if other drug changes within past 2 weeks
- Start at LOWEST dose and titrate as tolerated to achieve a HR of 50-60bpm if Sinus Rhythm (SR) or 70-80bpm if AF
  - BISOPROLOL 1.25mg daily
  - CARVEDILOL 3.125mg twice daily

Up titration

- Increase every 2-4 weeks to achieve target or maximum tolerated dose
- Repeat baseline checks before each dose change

IMPORTANT: If a BB has been stopped for more than 2 weeks, re-introduce cautiously. Consider re-starting from the initiation dose.
SEE SUGGESTED UPTITRATION SCHEDULE
SEE **BOX 2** (overleaf) FOR ADVERSE EFFECTS/PROBLEM SOLVING

Monitoring

- Stable dose - 6 monthly review

Patient information

- May take weeks /months to notice benefit
- Expect temporary increased fatigue/shortness of breath
- Self weigh daily and report ≥1.5kg over 3-4 days or increase in symptoms of fluid retention
- DO NOT STOP SUDDENLY without speaking to GP/HF team

SUGGESTED UP TITRATION SCHEDULE
Some BB is better than no BB.

- BB should not be stopped suddenly unless necessary due to possible rebound effects (↑ myocardial ischaemia/risk of infarction and arrhythmias).
- Seek specialist advice before treatment discontinuation.

BB licensed for LVSD:
1st line - preferred agent in South London: BISOPROLOL
2nd line - more effective at reducing blood pressure: CARVEDILOL
3rd line - consider for patients over 70 years: NEBIVOLOL
If already on a BB switch to one licensed for LVSD

DRUG / Week	Week 0-2	Week 2-4	Week 4-6	Week 6-8	Week 8-10	Week 10-12
BISOPROLOL	1.25MG OD	2.5MG OD	3.75MG OD	5MG OD	7.5MG OD	10MG OD
CARVEDILOL	3.125MG BD	6.25MG BD	12.5MG BD	25MG BD*	50MG BD**	
NEBIVOLOL***	1.25MG OD	2.5MG OD	5MG OD	10MG OD		

*maximum dose in patients with severe heart failure or body weight <85kg
**maximum dose for those with body weight ≥85kg
***Nebivolol is only available in 2.5mg (parallel import) and 5mg tablets, which complicates the initiation and dose titration process

Primary care to carry out 6 monthly medical review for all HF patients (please see General Practice Six Month Review template on local prescribing system)
For support with education and management please contact your local community HF team (see appendix for details)

Prescribing BETA BLOCKERS (BB) for patients with LVSD/HFrEF (LVEF≤40%)
Read code 585f
See overleaf for flow chart

BOX 1: FOR IMPORTANT INFORMATION AND CONTRAINDICATIONS

ALL patients with LVSD should be offered a BB licensed for heart failure as per NICE guidance. BBs reduce mortality (by about 30%) and hospital admissions (by about 20%) when included as part of standard heart failure therapy as an adjunct to diuretics and ACE-I.

BB therapy should ***not*** be withheld for any of the following reasons: increasing age, presence of PVD, erectile dysfunction, DM, interstitial pulmonary disease and chronic obstructive pulmonary disease (COPD) without reversibility.

CONTRA-INDICATIONS

•Severe bronchial asthma or COPD with reversibility

•Uncontrolled/acute HF, decompensated HF, symptoms of fluid retention

•Prinzmetal's angina

•Sinus bradycardia (HR <50bpm)

•Sick sinus syndrome including sino-atrial block, second or third degree heart block (without a pacemaker)

•Hypotension (systolic BP <90mmHg) or symptomatic hypotension

•Severe peripheral circulatory disturbances/ peripheral arterial disease

•Phaeochromocytoma

•Hypersensitivity to BB or any of the excipients

•Patients on verapamil

CAUTIONS

•Mild to moderate reversible airways disease - monitor peak flow prior to and following initiation and after dose change

•Renal/hepatic disease (see BNF for further details)

•Monitor diabetics closely especially Insulin Dependent Diabetes Mellitus (IDDM). May mask early signs of hypoglycaemia and worsen blood glucose monitoring (BM) control

• First degree heart block

•Concomitant medication that may increase risk of bradycardia

•Peripheral arterial occlusive disease

•Pregnancy

•Breastfeeding

Box 2: ADVERSE EFFECTS/PROBLEM SOLVING

Worsening symptoms:
- If signs of overload – double dose of diuretic then if still overloaded halve dose of beta blocker
- If marked fatigue/bradycardia – halve dose of BB
- Review in 1-2 weeks
- If no improvement seek advice from community HF team or HF consultant

Asymptomatic hypotension
- Does not usually warrant a change in therapy

Symptomatic hypotension:
- Consider stopping other contributing drugs e.g. CCB, nitrates

Bradycardia (HR<50 bpm):
- Halve dose of BB or stop if severe deterioration (rare)
- Re-consider need for other rate reducing drugs e.g. digoxin, amiodarone and if possible stop
- Arrange ECG to exclude heart block

Second/third degree heart block:
- Stop BB and seek specialist advice
- Repeat ECG after BB stopped

Impotence:
- May resolve as HF improves. Consider erectile dysfunction clinic referral.

Prescribing ANGIOTENSIN-II RECEPTOR BLOCKERS (ARB) for patients with LVSD/HFrEF (LVEF≤40%)
Read code 585f
See overleaf for more detailed information

ARBs should be used 'second line' in patients with LVSD (LVEF≤40%) who are intolerant of ACE-I
SEE **BOX 1** (overleaf) FOR IMPORTANT INFORMATION AND CONTRAINDICATIONS

Baseline

- BLOODS – U&Es (Ur, Cr, K^+, Na^+), eGFR
- BP

Initiation

- Start at LOWEST dose and titrate up
  - **CANDESARTAN*** 2mg daily
  - LOSARTAN 25mg daily
  - VALSARTAN 40mg twice daily

*ARB of choice in LVSD

- Review other medications such as NSAIDs/ nephrotoxic drugs/ diuretics/ K^+ sparing diuretics etc.
- Stop K^+ supplements

Up titration

- Aim for TARGET dose or Maximum Tolerated Dose
- Double dose at 2-4 weekly intervals
  - CANDESARTAN 32mg daily
  - LOSARTAN 150mg daily
  - VALSARTAN 160mg twice daily (max dose 80mg daily if mild/ moderate hepatic impairment without cholestasis)

SEE SUGGESTED UPTITRATION SCHEDULE

- Repeat baseline checks within 1-2 weeks of initiation and before/after any dose changes
- More frequent monitoring may be required if patient is on combined loop and thiazide therapy, or MRA/AA.

SEE **BOX 2** (overleaf) FOR ADVERSE EFFECTS/PROBLEM SOLVING

Monitoring

- Stable dose – 6 monthly review

SEE **BOX 3** (overleaf) FOR RECOMMENDATIONS WHEN MONITORING

Patient information

- ARBs will improve symptoms, prevent HF worsening, reduce risk of hospital admissions and prolong life
- It may take a few weeks for it to start showing an effect
- Hypotension and dizziness are the most common side effects
- Avoid any OTC anti-inflammatories (NSAIDS)

SUGGESTED UPTITRATION SCHEDULE
Some ARB is better than no ARB

ARB licensed for LVSD:
1st line - preferred agent in South London: CANDESARTAN
2nd line - LOSARTAN
3rd line - VALSARTAN
If already on an ARB switch to one licensed for LVSD

DRUG / Week	Week 0-2	Week 2-4	Week 4-6	Week 6-8	Week 8-10
CANDESARTAN	4MG OD	8MG OD	16MG OD	32MG OD	
LOSARTAN*	12.5MG OD	25MG OD	50MG OD	100MG OD	150MG OD
VALSARTAN	40MG BD	80MG BD	160MG BD		

*Losartan has evidence in HF at doses >100mg OD

Primary care to carry out 6 monthly medical review for all HF patients (please see General Practice Six Month Review template on local prescribing system)
For support with education and management please contact your local community HF team (see appendix for details)

Prescribing ANGIOTENSIN-II RECEPTOR BLOCKERS (ARB) for patients with LVSD/HFrEF (LVEF≤40%)

Read code 585f

See overleaf for flow chart

BOX 1: FOR IMPORTANT INFORMATION AND CONTRAINDICATIONS

ARBs have a more limited evidence base than ACE-I and have not shown superiority over ACE-I in any large robust clinical trial. There are currently no compelling indications for the use of ARBs routinely first line in HF. ARBs should only be considered second line in patients intolerant to ACE-I.

CONTRAINDICATIONS

- History of hypersensitivity to ARB or any excipients
- Pregnancy and breastfeeding
- Severe hepatic impairment and/or cholestasis; biliary cirrhosis
- Rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
- Patient on both an ACE-I and MRA/AA
- Baseline serum K^+ > 5.5 mmol/L

CAUTIONS

- Symptomatic or severe asymptomatic hypotension (systolic BP <90 mmHg)
- Moderate to severe renal impairment i.e. serum creatinine >150 micromol/L or eGFR < 50 ml/min. See individual SPCs for dose adjustment requirements
- Patients with volume depletion such as those on high dose diuretics may lead to symptomatic hypotension therefore volume should be restored prior to administration
- Bilateral renal artery stenosis, or renal artery stenosis in a single functioning kidney
- Patients on haemodialysis
- Kidney transplant recipients
- Hepatic impairment
- Haemodynamically relevant aortic or mitral valve stenosis
- Hypertrophic cardiomyopathy
- Primary aldosteronism
- Patients taking potassium supplements or other drugs that may increase potassium
- Baseline serum K^+ between 5 to 5.5 mmol/L
- Drug interactions – see BNF for list

Seek specialist advice prior to initiation:

- Concomitant therapy with an ACE-I – The triple combination of an ACE-I, ARB, and an MRA/AA or other potassium-sparing diuretic is not recommended due to the risk of adverse events, especially renal impairment and hyperkalaemia. Further checks of blood chemistry should be made every 4 weeks for 3 months and then 3 monthly for one year and then at least 6 monthly, but more frequently if clinically indicated.
- Suspected or confirmed aortic or mitral valve disease
- Primary aldosteronism
- Hypertrophic cardiomyopathy
- Hyponatraemia (serum Na^+ <135 mmol/L)
- Symptomatic or severe asymptomatic hypotension (systolic BP<90 mmHg)
- Significant renal dysfunction / renovascular disease e.g. creatinine > 150 micromol/L or eGFR<50 ml/min or hyperkalaemia (serum K^+ >5.0 mmol/L)
- Renovascular disease (diagnosed, undiagnosed and clinically silent disease)
- Kidney transplant recipients

BOX 2: ADVERSE EFFECTS/PROBLEM SOLVING

- **Angioedema:** Rare but life threatening. Discontinue therapy and seek urgent medical advice.
- **Asymptomatic hypotension:** Does not usually warrant a change in therapy. Do not increase dose if systolic BP < 90 mmHg
- **Symptomatic hypotension:**
  - Consider dehydration and address as appropriate - review diuretic dose with a view to decreasing dose if patient free of symptoms suggestive of fluid retention
  - If dizziness, light-headedness and/or confusion occur in the setting of low BP, reduce dose of ARB (back to last tolerated dose), and review use of other vasodilators (e.g. nitrates, CCB). Monitor closely and allow longer intervals between dose titrations
  - Aim to maintain treatment with both ARB and beta-blockers, at a reduced dose if necessary
  - Seek specialist advice if measures do not resolve symptomatic hypotension
- **Worsening renal function:** An increase in serum urea, creatinine and K^+ is to be expected after initiation/titration of ARB. If the increase is small and asymptomatic, no action is necessary. See **BOX 3** for recommended actions.

BOX 3: RECOMMENDATIONS WHEN MONITORING ARB therapy in patients with normal renal function (eGFR >60ml/min)

Blood Chemistry	Action
Creatinine ↑ up to 50% above baseline or to 265 micromol/L (whichever is smaller). OR serum K^+ ↑ to ≤5.5 mmol/L	No urgent action required. Repeat blood chemistry (urea, creatinine and K^+) within 2-4 weeks
Creatinine ↑ > 50% but < 100% above baseline or between 265 micromol/L and 310 micromol/L (whichever is smaller). OR serum K^+ ↑ to ≥ 5.5 - ≤5.9 mmol/L	Review required- consider: a. Stopping concomitant nephrotoxic drugs e.g. NSAIDs, non essential vasodilators (e.g. calcium antagonists, nitrates) and if no signs of fluid retention, reduce the dose of diuretic. b. Review causes of high potassium. Stop other agents that cause hyperkalaemia e.g. potassium sparing diuretics, or dietary intake. Recheck renal function within 2 weeks. If despite adjusting medication the creatinine and K^+ remain higher than above the dose of ARB should be halved or stopped if at initiation dose and the blood chemistry re-checked in 5-7days. If the response to this is not satisfactory, seek specialist advice. Blood chemistry should be monitored closely until K^+ and Creatinine concentrations are stable
Creatinine ↑ by >100% (from baseline) or to above 310 micromol/L OR serum K^+ ≥ 6 mmol/L	Discontinue ARB and discuss with cardiologist Note: It is very rarely necessary to stop an ARB and in patients with heart failure clinical deterioration is likely if treatment is withdrawn; in this instance specialist advice should be sought before treatment discontinuation.

- **Additional recommendations for monitoring in patients with chronic kidney disease (CKD) Stage 3 (eGFR <60ml/min)* and above can be found here**

Prescribing MINERALOCORTICOID RECEPTOR ANTAGONISTS (MRA)/ALDOSTERONE ANTAGONISTS (AA) in patients with LVSD/HFrEF (LVEF≤40%)
Read code 585f
See overleaf for more detailed information
Please seek specialist advice first if you are not confident in initiation

MRA/AAs should be considered in all LVSD patients if still symptomatic (NYHA II-IV) despite maximum tolerated ACE-I, BB and diuretics (2nd line therapy)
(Post-MI – MRA/AA should be prescribed within 3-14 days, preferably after ACE-I, for patients with symptoms of HF and LVEF <40%)
SEE **BOX 1** (overleaf) FOR IMPORTANT AND CONTRAINDICATIONS, INCLUDING A LIST OF COMMON DRUG INTERACTIONS

Baseline

- •BLOODS – U&Es (Ur, Cr, K^+, Na^+), eGFR , Liver Function Tests (LFTs)
- •BP

Initiation

Spironolactone or Eplerenone
25mg once daily

- •Review other medications such as NSAIDs/ nephrotoxic drugs/ diuretics/ K^+ sparing diuretics etc.
- •Stop K^+ supplements

Up titration

Repeat baseline checks within 1 week after initiation
If remain symptomatic at 4 weeks – repeat baseline checks and if within acceptable limits, increase to target dose of 50mg once daily and repeat baseline checks within 1 week.
SEE **BOX 2**(overleaf) FOR ADVERSE EFFECTS/ PROBLEM SOLVING

Monitoring

Routine bloods monthly for the first 3 months, then every 3 months for 1 year
Routine bloods 6 monthly once established and stable
SEE **BOX 3** FOR MONITORING FOR HYPERKALAEMIA

Patient information

- •MRAs/AAs are given to improve symptoms, prevent HF worsening, reduce hospitalisations and prolong life
- •It may take a few weeks for it to start showing an effect
- •Take spironolactone with food
- •Light-headedness/dizziness are the commonest side-effects
- •Avoid any OTC anti-inflammatories (NSAIDS), cystitis remedies or salt substitutes
- •If irritation/diarrhoea/vomiting occurs – stop and seek medical advice

BOX 3: MONITORING FOR HYPERKALAEMIA
There is a higher risk of hyperkalaemia in HF due to concomitant treatment with ACE-I/ARB and MRA/AA.

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	• Not applicable

Primary care to carry out 6 monthly medical review for all HF patients (please see General Practice Six Month Review template on local prescribing system)
For support with education and management please contact your local community HF team (see appendix for details)

Prescribing MINERALOCORTICOID RECEPTOR ANTAGONISTS (MRA)/ALDOSTERONE ANTAGONISTS (AA) in patients with LVSD/HFrEF (LVEF≤40%)
Read code 585f
See overleaf for flow chart

BOX 1: FOR IMPORTANT INFORMATION AND CONTRAINDICATIONS

MRA/AA in addition to optimal ACE-I and BB therapy, have been proven to reduce mortality and hospitalisation in selected patients with heart failure due to LVSD.

CONTRAINDICATIONS
- Anuria
- Acute renal impairment or severe renal impairment (baseline serum creatinine >200 micromol/L or eGFR <30 ml/min)
- Hyperkalaemia (serum K^+ >5.0 mmol/L) at initiation
- Addison's disease
- Hypersensitivity to specific AA/MRA or excipients
- Hyponatraemia (serum Na^+ <135 mmol/L)
- Co-prescription of potassium sparing diuretics, potassium supplements
- Co-prescription of eplerenone with strong CYP3A4 enzyme inhibitors – see BOX 2 for 'common drug interactions'
- Severe hepatic impairment (Childs Pugh Class C)
- In addition to the combination of both an ACE-I and an ARB

CAUTIONS
- Porphyria
- Pregnancy and lactation
- Hepatic impairment (Child Pugh Class A & B, monitor electrolytes closely)
- Moderate to severe renal impairment (Cr>150 micromol/L or eGFR< 50 ml/min)
- Diabetic microalbuminuria
- Elderly - monitor K^+ carefully.
- Drug/Food interactions - see BOX 2 for 'common drug interactions'

Seek specialist advice prior to initiation:
- Hyponatraemia (serum Na^+<135 mmol/L)
- Pregnancy and lactation
- Symptomatic hypotension or severe asymptomatic hypotension (systolic BP<90 mmHg)
- Significant renal dysfunction / renovascular disease e.g. creatinine > 150 micromol/L or eGFR< 50 ml/min or hyperkalaemia

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 MRA/AA 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.
Glucocorticoids, tetracosactide	May precipitate sodium and fluid retention - monitor carefully.
NSAIDs	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 or drinks e.g. spinach, mangos, bananas, coconut water	Increased risk of hyperkalaemia. Monitor serum 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 is not recommended.

BOX 2: ADVERSE EFFECTS/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.
- **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^+ < 135 mmol/L, consider stopping 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 moderate-severe LVSD, where spironolactone is indicated but has not been tolerated usually due to the development of gynaecomastia.

For support with education and management across South London:

CCG	Heart Failure Community Team
Bexley	gst-tr.bexelycardiology@nhs.net 020 7188 8952
Bromley	kch-tr.PRUHheartfailurenurses@nhs.net 01689866097 and Bleep number is 739
Croydon	mhn-tr.cuhintegratedheartfailurenursespecialist@nhs.net 0208 274 6416
Greenwich	oxl-tr.cardiac@nhs.net
Kingston	Khn-tr.HeartFailure@nhs.net
Lambeth and Southwark	**gst-tr.KHPcommunityHF@nhs.net** 020 3049 4652
Lewisham	**LH.commuhfreferrals@nhs.net** 0203 049 3473
Merton	CLCHT.mertonheartfailure@nhs.net
Richmond	Khn-tr.HeartFailure@nhs.net
Sutton	rmh-tr.rmcsreferral@nhs.net 0208 661 3908
Wandsworth	stgh-tr.heartfailureteam@nhs.net

ABBREVIATIONS

ACE-I	Angiotensin Converting Enzyme Inhibitor
AF	Atrial Fibrillation
ARB	Angiotensin II Receptor Blocker
AA	Aldosterone Antagonist
BB	Beta Blocker
BD	Twice Daily
BM	Blood glucose Monitoring
BNF	British National Formulary
BP	Blood Pressure
BPM	Beats Per Minute
CCB	Calcium Channel Blocker
COPD	Chronic Obstructive Pulmonary Disease
Cr	Creatinine
DM	Diabetes Mellitus
ECG	Electrocardiogram
eGFR	estimated Glomerular Filtration Rate
EMIS	Egton Medical Information System
GP	General Practitioner
GPwSI	General Practitioner with a Specialist Interest
HF	Heart Failure
HFNS	Heart Failure Nurse Specialist
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
HTN	Hypertension
HR	Heart Rate
IDDM	Insulin Dependent Diabetes Mellitus
IHD	Ischaemic Heart Disease
IV	Intravenous
K^+	Potassium
Kg	Kilogram
LFT	Liver Function Test
LVEF	Left Ventricular Ejection Fraction
LVSD	Left Ventricular Systolic Dysfunction
Micromol/L	Micromole per Litre
Mg	Milligram
mmHg	Millimeter of mercury
mmol/L	Millimoles per litre
ml/min	Millilitre per minute
MRA	Mineralocorticoid Receptor Blocker
Na^+	Sodium
NICE	National Institute for Clinical Excellence
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OD	Once Daily
OTC	Over The Counter
PND	Paroxysmal Nocturnal Dyspnoea
PVD	Peripheral Vascular Disease
SR	Sinus Rhythm
SPC	Summary of Product Characteristics
Ur	Urea
U&Es	Urea and Electrolytes
UV	Ultraviolet

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