South East London guidance on the pharmacological management of Heart Failure in adults

Developed by the South London Cardiovascular Disease Medicines Working Group on behalf of the SEL Area Prescribing Committee (SEL APC)

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If you have any queries or comments on this guideline please contact: LAMCCG.medicinesoptimisation@nhs.net

South East London Area Prescribing Committee. A partnership between NHS organisations in South East London: South East London Clinical Commissioning Group (covering the boroughs of Bexley/ Bromley/ Greenwich/ Lambeth/ Lewisham /Southwark) and GSTFT/KCH/SLaM/Oxleas NHS Foundation Trusts and Lewisham & Greenwich NHS Trust

Pharmacological management of Heart Failure

Approved and Developed By

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Please also refer to the primary care guidance and template developed by NHS Southwark Borough:

http://www.clinicaleffectivenesssouthwark.co.uk/wp-content/uploads/2018/12/CES-Heart-Failure-Guide_e-version_V9.pdf

This includes the management and referral pathway for a new diagnosis of heart failure (local pathways may differ) and recognition of palliative care requirements.

All patients must be coded correctly in primary care: SNOMED codes now replace previous READ codes.

ALL patients are to included in the **QOF heart failure register** using read code G58 or SNOMED code 84114007.
For Clinical and QOF purposes, patients with reduced ejection fraction heart failure (HFrEF) need to be differentiated from those with preserved ejection fraction HFpEF). To be classed as HFrEF patients need one of the following codes for left ventricular systolic dysfunction (LVSD):
Read code 585f SNOMED 407596008; G5yy9 SNOMED 134401001; EMISNQSE142 no SNOMED code.

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 Oral 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 (e.g. @home team) 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?

No → Continue to reduce dose and monitor for signs of fluid overload

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)

Please note that subcutaneous furosemide may be administered in end of life by palliative care teams (refer to local guidance- off label use)

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%)
Use SNOMED code 84114007 for QOF HF register
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

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 **BOX 2** 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

Monitoring

- Stable dose – 6 monthly review

SEE **BOX 4** (overleaf) FOR RECOMMENDATIONS WHEN MONITORING

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
- **Discontinue sacubitril valsartan (Entresto) at least 36 hours prior to starting an ACE-I**

BOX 2: 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

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%)

Use SNOMED code 84114007 for QOF HF register

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

•In combination with aliskiren in patients with moderate to severe renal impairment (eGFR<60ml/min) and/or diabetes mellitus

•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 & Breastfeeding – seek specialist advice

•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 or perindopril)

•Haemodynamically relevant left ventricular inflow or outflow obstruction (e.g. symptomatic aortic or mitral valve stenosis)

•Unilateral renal artery stenosis with two functioning kidneys.

•Patients on high dose diuretics (i.e. furosemide > 80mg daily) – increased risk of hypotension, renal dysfunction and SIADH

•Liver cirrhosis and or ascites

•Moderate to severe renal impairment (eGFR < 60 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. eGFR <60 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 3: 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 4: RECOMMENDATIONS WHEN MONITORING ACE-I therapy

eGFR > 60ml/min at initiation	eGFR < 60ml/min at initiation	Action
	Creatinine ↑: **≤ 30%** (from baseline) or **eGFR ≤ 25%**	Recheck renal function within 1-2 weeks. If stable, continue treatment/dose adjustments.
Creatinine ↑: **≤ 50%** (from baseline) or **≤ 265µmol/**L **OR** **K+ ↑ to ≥ 5.5 - ≤5.9mmol/**L	**Creatinine ↑ :** **>30%** (from baseline) or **eGFR > 25%** **OR** **K+ ↑ to ≥ 5.5 - ≤5.9mmol/**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. Recheck renal function within 2 weeks. If despite adjusting medication the creatinine and K+ remain high, the dose of ACE-I should be reduced to the previous dose/halved and the blood chemistry re-checked within 7 days. 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 ↑ : >50% (from baseline) or **>265µmol/L** **OR** **K+ ≥ 6mmol/l**	**K+ ≥ 6mmol/l**	**Discontinue ACE-I and discuss with cardiologist** **Note: It is very rarely necessary to stop an ACE-I and in patients with heart failure clinical deterioration is likely if treatment is withdrawn; specialist advice should be sought before treatment discontinuation.**

Prescribing BETA BLOCKERS (BB) in patients with LVSD/HFrEF (LVEF≤40%)
Use SNOMED code 84114007 for QOF HF register
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
- Electrocardiogram (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 **BOX 2** FOR SUGGESTED UPTITRATION SCHEDULE
SEE **BOX 3** (overleaf) FOR 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%)
Use SNOMED code 84114007 for QOF HF register
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

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

•Sinus bradycardia (HR <50bpm)

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

•Metabolic acidosis

•Phaeochromocytoma (unless with α-blockers)

•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

•First degree heart block

•Prinzmetal's angina

•Severe peripheral arterial/circulatory diseases – may worsen symptoms

•Severe renal/hepatic impairment (see BNF for further details)

•Diabetes mellitus (esp. with insulin) - beta-blockers may mask early warning signs of hypoglycaemia, and worsen control of blood glucose. Additional monitoring may be required.

•Concomitant medication that may increase risk of bradycardia

•Pregnancy & Breastfeeding – seek specialist advice

BOX 3: 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 (ARBs) for patients with LVSD/HFrEF (LVEF≤40%)
Use SNOMED code 84114007 for **QOF HF register**
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 12.5mg 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
- Ensure sacubitril valsartan (Entresto) is not prescribed concomitantly

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 **BOX 2** 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 3** (overleaf) FOR ADVERSE EFFECTS/PROBLEM SOLVING

Monitoring

- Stable dose – 6 monthly review

SEE **BOX 4** (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)

BOX 2: 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	2MG OD	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 (ARBs) for patients with LVSD/HFrEF (LVEF≤40%)

Use SNOMED code 84114007 for QOF HF register

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

- In combination with aliskiren in patients with moderate to severe renal impairment (eGFR<60ml/min) and/or diabetes mellitus
- History of hypersensitivity to ARB or any excipients
- Rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
- Pregnancy and breastfeeding – seek specialist advice
- Severe hepatic impairment and/or cholestasis; biliary cirrhosis
- 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 (eGFR < 60 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. eGFR<60 ml/min or hyperkalaemia (serum K^+ >5.0 mmol/L)
- Renovascular disease (diagnosed, undiagnosed and clinically silent disease)
- Kidney transplant recipients

BOX 3: 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 4** for recommended actions.

BOX 4: RECOMMENDATIONS WHEN MONITORING ARB therapy

eGFR > 60ml/min at initiation	eGFR < 60ml/min at initiation	Action
	Creatinine ↑: **≤ 30%** (from baseline) or **eGFR ≤ 25%**	Recheck renal function within 1-2 weeks. If stable, continue treatment/dose adjustments.
Creatinine ↑: **≤ 50%** (from baseline) or **≤ 265µmol/**L **OR** **K+** ↑ to **≥ 5.5 - ≤5.9mmol/**L	**Creatinine ↑ :** **>30%** (from baseline) or **eGFR > 25%** **OR** **K+** ↑ to **≥ 5.5 - ≤5.9mmol/**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. Recheck renal function within 2 weeks. If despite adjusting medication the creatinine and K+ remain high, the dose of ACE-I should be reduced to the previous dose/halved and the blood chemistry re-checked within 7 days. 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 ↑ : >50% (from baseline) or **>265µmol/L** **OR** **K+ ≥ 6mmol/l**	**K+ ≥ 6mmol/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; specialist advice should be sought before treatment discontinuation.**

Prescribing MINERALOCORTICOID RECEPTOR ANTAGONISTS (MRA)/ALDOSTERONE ANTAGONISTS (AA) in patients with LVSD/HFrEF (LVEF≤40%)

Use SNOMED code 84114007 for QOF HF register

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, **AND BOX 2** (overleaf) FOR COMMON DRUG INTERACTIONS

Baseline

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

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

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 3** FOR MANAGEMENT OF HYPERKALAEMIA
SEE **BOX 4** (overleaf) FOR 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 4** FOR MONITORING FOR HYPERKALAEMIA

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%)
Use SNOMED code 84114007 for QOF HF register
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 (eGFR< 60 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. eGFR< 60 ml/min or hyperkalaemia

BOX 2: 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 4: 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.

Prescribing SACUBITRIL VALSARTAN in patients with LVSD/HFrEF (LVEF≤40%)
Use SNOMED code 84114007 **for QOF HF register**
See overleaf for more detailed information

Sacubitril valsartan (Entresto®) is a combination drug, including both a neprilysin inhibitor (sacubitril) and an angiotensin II receptor blocker (ARB; valsartan).
In South London, sacubitril valsartan may be considered for initiation by Heart Failure (HF) specialists, working in community or hospital settings, for treating chronic HF in patients meeting all of the following criteria, and in line with NICE guidance https://www.nice.org.uk/Guidance/TA388**:**

- New York Heart Association (NYHA) class II to IV symptoms
- On a stable dose of angiotensin-converting enzyme inhibitors (ACE-I) or an ARB
- Left ventricular ejection fraction of 35% or less

Initiation of sacubitril valsartan should be undertaken by a **heart failure specialist working in community or hospital settings** with access to a multidisciplinary HF team. The initiating clinician is responsible for ensuring the patient is stabilised on sacubitril valsartan and providing any necessary follow up. Prescribing responsibility to patient's own GP may be considered following **at least 3 months of treatment and when the patient has been stable on the maximum tolerated dose for at least one month**. If sacubitril valsartan is prescribed for non-approved or unlicensed indications, prescribing responsibility will remain with the initiating clinician/organisation.

Additional Resources

- Screening checklist and Notification of initiation of sacubitril valsartan used in the treatment of symptomatic chronic HF with reduced ejection fraction. This document **must be completed and sent to the General Practitioner (GP) on initiation.** It can be found on EPR under "orders" – called "Sacubitril Valsartan Initiation Form"
- Transfer of prescribing responsibility to primary care for sacubitril valsartan. This document **must be completed and sent to the GP when transferring the prescribing responsibility** in accordance to South London guidelines. It can be found on EPR under "orders" – called "Sacubitril Valsartan Transfer of Care Form"

The recommended starting dose is one tablet of **49mg/51mg TWICE daily**

The dose should be doubled at 2 to 4 week intervals to a maximum target dose of 97mg/103mg TWICE daily, or highest tolerated dose by the patient.

A **reduced** starting dose of **24mg/26mg TWICE daily** with a slow dose titration (doubling every 3 to 4 weeks) should be considered for patients with:

- Systolic blood pressure between 100 to 110mmHg.
- Moderate renal impairment (eGFR 30-60ml/min/1.73m^2).
- Moderate liver impairment (Child-Pugh B classification or with AST/ALT greater than twice the upper limit of normal range)

ON INITIATION OF SACUBITRIL VALSARTAN, ACEI or ARB therapy MUST BE DISCONTINUED

ACE-I therapy must be discontinued at least 36 hours before initiation of sacubitril valsartan

Sacubitril valsartan should be prescribed using the generic name to avoid concomitant prescribing of ACE-I or additional ARB therapy

Monitoring
Should be undertaken prior to initiation and before and after each dose titration.

- BLOODS – U&Es, K^+, Na^+, eGFR
- BP
- Clinical status
- Adherence

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 SACUBITRIL VALSARTAN in patients with LVSD/HFrEF (LVEF≤40%)
Use SNOMED code 84114007 for QOF HF register
See overleaf for flow chart

BOX 1: CONTRAINDICATIONS AND CAUTIONS

CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients
- **Concomitant use with an ACE-I**. Sacubitril valsartan must not be administered until 36 hours after discontinuing ACE-I therapy and if sacubitril valsartan is to be stopped, an ACE-I must not be initiated until 36 hours after discontinuation of sacubitril valsartan therapy.
- **Concomitant use with another ARB**, as the combination drug contains valsartan
- Known history of angioedema related to previous ACE-I or ARB therapy
- Hereditary or idiopathic angioedema
- Systolic blood pressure (SBP) <100mmHg
- End-stage renal disease
- Serum potassium >5.4 mmol/L
- Severe hepatic impairment, biliary cirrhosis and cholestasis (Child-Pugh C)
- Concomitant use with aliskiren in patients with diabetes mellitus. Also avoid concomitant use with aliskiren in patients with renal impairment (eGFR <60ml/min)
- Pregnancy and/ or breastfeeding

CAUTIONS

- Serum potassium levels >5mmol/l. Note: contraindicated if >5.4mmol/l
- Renal artery stenosis
- Renal impairment - eGFR 15-60ml/min. NB: Patients with eGFR <30ml/min are at greater risk of hypotension
- Moderate hepatic impairment (Child-Pugh B) or with alanine transaminase (ALT) / aspartate aminotransferase (AST) values more than twice the upper limit of the normal range
- Dehydration
- NYHA class IV – limited evidence of use
- Drug interactions – see box 2

BOX 2: Drug Interactions

ACE-inhibitors:

- Avoid concurrent use and allow a washout period of 36 hours when switching between ACE-I and sacubitril valsartan treatment due to the risk of angioedema

ARBs

- Avoid prescribing any additional ARBs as sacubitril valsartan already contains the ARB valsartan

Aliskiren

- Avoid concurrent use due to a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function

Medicines that increases potassium

- Monitoring of serum potassium is recommended

Statins

- Sacubitril valsartan can increase the plasma concentration of atorvastatin and its metabolites. Caution should be exercised when co-administering statins

Phosphodiesterase type 5 (PDE5) inhibitors

- Concomitant use can result in a significant reduction in blood pressure after a single dose. Caution should be exercised if a PDE5 inhibitor is initiated

BOX 3: Side-effects

Most common reported adverse reactions for sacubitril valsartan were:

Hypotension: It is recommended to review and correct volume and/ or salt depletion prior to starting treatment, if hypotension occurs during treatment, review patients' medication and consider adjusting those that are contributing to low blood pressure or review the dose of sacubitril valsartan which may need to be reduced or discontinued.

Hyperkalaemia: Serum potassium should be monitored periodically especially in high risk patients (e.g. renal impairment, diabetes, hypoaldosteronism or patients receiving medicines that increase potassium). Dose reduction should be considered where the potassium level is 5.0mmol/L or greater. If potassium level is >5.4mmol/L then discontinue therapy and seek further advice from the HF team.

Renal impairment: Renal function should be closely monitored and may need to dose adjust or discontinue sacubitril valsartan as indicated.

Other common side effects include: anaemia, hypokalaemia, cough, nausea, diarrhoea and gastritis. Angioedema (reported in 0.5% of patients in PARADIGM-HF). Sacubitril valsartan should be discontinued if angioedema occurs and patient given the appropriate therapy and monitored for airway compromise.

Prescribing IVABRADINE in patients with LVSD/HFrEF (LVEF≤40%)
Use SNOMED code 84114007 for QOF HF register
See overleaf for more detailed information

In South London, **Ivabradine** should be considered as an option in line with its licensed indication and supporting NICE guidance (TA267, 2012). Use is only recommended if all the following criteria are met:

- ✓ Left ventricular systolic dysfunction with an ejection fraction of ≤35% and NYHA class II-IV
- ✓ On maximum tolerated dose of both ACE inhibitor (or ARB) and beta-blocker (unless contraindicated); and a mineralocorticoid receptor antagonist
- ✓ In sinus rhythm, with a resting heart rate ≥ 75 beats per minute (bpm)

SEE **BOX 1** (overleaf) FOR IMPORTANT INFORMATION AND CONTRAINDICATIONS, INCLUDING A LIST OF COMMON DRUG INTERACTIONS

Baseline

- •BP
- •HR
- •ECG or ambulatory 24-hour monitoring should be considered when determining resting heart rate

Patient information

- •Visual symptoms, headache & dizziness are the commonest side-effects
- •Report visual changes to GP/ HF team
- •Avoid grapefruit juice during treatment with ivabradine
- •If irritation/diarrhoea/vomiting occurs – stop and seek medical advice

Initiation

- ➢ **Initiation Dose: 5mg twice daily**

Ivabradine should **only** be initiated:

- ✓ after a stabilisation period of 4 weeks on optimised standard therapy with ACE inhibitors, beta-blockers and mineralocorticoid receptor antagonist.
- ✓ by a **heart failure specialist** with access to a multidisciplinary team.

Up titration

- •Repeat baseline checks before each dose change
- •After 3 to 4 weeks the dose may be increased to **7.5mg twice daily** if the heart rate remains >60bpm and greater symptom control is required.

SEE **BOX 3**(overleaf) FOR ADVERSE EFFECTS/ PROBLEM SOLVING

SUGGESTED DOSE ADJUSTMENTS/DOWN-TITRATIONS

Dose titration and monitoring should be carried out by a heart failure specialist in primary or secondary care, such as a GP with a special interest in heart failure or a heart failure specialist nurse.

- If the patient is elderly (>75 years) or 5mg twice daily is not tolerated, the dose can be reduced to 2.5mg twice daily.
- If the heart rate falls persistently below 50 beats per minute (at rest) and / or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension - reduce the dose:
  - from 7.5mg twice daily to 5mg twice daily; or
  - from 5mg twice daily to 2.5mg twice daily (half a 5 mg tablet twice daily)
- Discontinue treatment if heart rate remains below 50bpm or symptoms of bradycardia persist after dose reduction

Monitoring

- •Stable dose - 6 monthly review
- •Regularly monitor for atrial fibrillation

TRANSFER OF CARE TO PRIMARY CARE SETTING

- ✓ Responsibility for the prescribing of ivabradine may be transferred to the GP when the dose of ivabradine is optimised (i.e. heart rate controlled to between 50-60bpm or on maximum ivabradine dose) and the patient is considered stable.

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 HF community nurse specialist or HF Consultant (see appendix for details)

Prescribing IVABRADINE in patients with LVSD/HFrEF (LVEF≤40%)
Use SNOMED code 84114007 for QOF HF register
See overleaf for flow chart

BOX 1: FOR IMPORTANT INFORMATION AND CONTRAINDICATIONS

Ivabradine is not recommended in patients with atrial fibrillation (AF) or other cardiac arrhythmias that interfere with sinus node function; as it is **unlikely to be effective in this circumstance.** It is recommended that all patients prescribed ivabradine are regularly monitored for the occurrence of AF (sustained or paroxysmal), including in patients with a history of AF who are currently in sinus rhythm. If AF occurs during treatment, ivabradine should be **stopped**.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients
- Resting heart rate <70bpm at initiation
- Sick sinus syndrome
- Sino-atrial block & 3rd degree AV-block
- Congenital QT syndrome
- Pacemaker dependent patients* (i.e. where heart rate is maintained exclusively by the pacemaker)
- Severe Hypotension (BP < 90/50mmHg)
- Cardiogenic shock and acute MI
- Unstable or acute heart failure
- Severe hepatic impairment
- Unstable angina
- Pregnancy and lactation
- Note: Drug Interactions – see interaction table

**Ivabradine is suitable for use in patients with specialist pacing devices under cardiology supervision*

BOX 2: CAUTIONS and DRUG INTERACTIONS

- Pre-existing cardiac arrhythmias
- Concurrent heart rate lowering agents
- Mild to moderate hypotension
- Severe heart failure (NYHA IV)
- Post-CVA (use not recommended immediately after a stroke)
- Retinitis pigmentosa
- Moderate hepatic impairment
- Established renal failure (CrCl <15ml/min)

COMMON DRUG INTERACTIONS (for full list of interacting drugs see BNF/SPC)

Interacting drug	Mechanism of action/significance and action to be taken
Strong CYP3A4 inhibitors. E.g. • Azoles antifungals e.g. ketoconazole, itraconazole, posaconazole, voriconazole; • HIV protease inhibitors e.g. ritonavir; • Macrolide antibiotics e.g. clarithromycin	Concomitant use is contraindicated – risk of increased plasma concentration of ivabradine.
Mild to moderate CYP3A4 inhibitors (e.g. amiodarone, diltiazem, verapamil)	Concomitant use is contraindicated – risk of increased plasma concentration of ivabradine.
CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin, St John's Wort)	Use with caution as may decrease ivabradine exposure. May require closer monitoring and dose adjustment. Concomitant use with St John's Wort is not recommended.
Drugs which prolong QTc (e.g. amiodarone, sotalol, disopyramide, mefloquine)	Concomitant use is contra-indicated – increased risk of ventricular arrhythmias.

BOX 3: ADVERSE EFFECTS/PROBLEM SOLVING - Side effects (for full details see BNF or SPC)

- **Ivabradine is a black triangle drug - any adverse effect must be reported to the MHRA and via the local incident reporting system.**
- Visual symptoms are the most common adverse effect reported. Luminous phenomena were reported in 14.5% of patients and therefore new patients should be warned about this potential side effect. Phosphenes generally begin to occur within the first two months of treatment after which they may occur repeatedly. Phosphenes were generally reported to be of mild to moderate intensity. All phosphenes resolved during or after treatment. Blurred vision also occurs commonly. Cessation of treatment should be considered if any unexpected deterioration in visual function occurs.
- Other common side effects (occurring in between 1 in 10 and 1 in 100 patients) include headache and dizziness, bradycardia, 1st degree AV block and ventricular extrasystoles and uncontrolled blood pressure.

Prescribing HYDRALAZINE AND NITRATES in patients with LVSD/HFrEF (LVEF≤40%)
Use SNOMED code 84114007 for QOF HF register
See overleaf for more detailed information

There is no clear evidence to suggest that the combination of hydralazine and a nitrate should be used in all patients with heart failure with a reduced ejection fraction (HFrEF) but it should be considered in patients:

- Who are symptomatic with heart failure with a reduced ejection fraction (≤ 40%) who cannot tolerate an ACE-I nor an ARB (or they are contraindicated)
- In self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated left ventricle in NYHA class III-IV despite treatment with an ACE-I/ARB, beta-blocker and an MRA.

Baseline

- BLOODS – U&Es, K^+, Na^+, eGFR
- BP
- HR

Initiation

Isosorbide dinitrate: 20mg three times a day
OR
Isosorbide mononitrate (immediate release):
20 mg twice daily

In combination with
Hydralazine: 25mg 3-4 times daily

Up titration

Aim to titrate to maximum tolerated dose:

- **Isosorbide dinitrate**: 240mg daily in divided doses
- **Isosorbide mononitrate (immediate release):** 120 mg daily in divided doses
- **Hydralazine:** 50–75 mg 3-4 times a day

Double dose at 2-4 weekly intervals
Repeat baseline checks within 1-2 weeks of initiation and before/after any dose changes

Patient information

- It may take a few weeks to start showing an effect
- Hypotension and dizziness are the most common side effects
- Avoid any over the counter (OTC) anti-inflammatories (NSAIDs)
- Nitrate induced headache should diminish and resolve after continued treatment.

Renal Function

Hydralazine: Active metabolites are excreted mainly in the urine. For patients with impaired renal function, start with a low dose and titrate to response.

Nitrates: Dose as in normal renal function.

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 HYDRALAZINE AND NITRATES in patients with LVSD/HFrEF (LVEF≤40%)
Use SNOMED code 84114007 for QOF HF register
See overleaf for flow chart

BOX 1: CONTRAINDICATIONS AND CAUTIONS

CONTRAINDICATIONS

- Hypersensitivity to nitrates and or hydralazine (and any excipients)
- Acute circulatory failure (shock, vascular collapse)
- Severe tachycardia and heart failure with a high cardiac output (e.g. in thyrotoxicosis).
- Conditions with fixed cardiac output: Hypertrophic (obstructive) cardiomyopathy, severe aortic stenosis, cardiac tamponade, constrictive pericarditis, mitral stenosis (unless under specialist supervision)
- Raised intracranial pressure due to cerebral haemorrhage or head trauma
- Idiopathic systemic lupus erythematosus and related diseases (hydralazine)
- Cor pulmonale
- Dissecting aortic aneurysm
- Acute porphyria (hydralazine)

CAUTIONS

- Symptomatic or severe asymptomatic hypotension
- Avoid starting hydralazine in the setting of an acute coronary event (unless under specialist supervision)
- Caution with symptomatic angina
- Patients with severe hepatic impairment – reduce dose of hydralazine
- Manufacturers advise use with caution in severe renal impairment - reduce dose of
- Hydralazine if eGFR < 30 mL/minute/1.73 m2
- Pregnancy:
  - **Isosorbide Dinitrate -** may cross placenta; manufacturers advise avoid unless potential benefit outweighs risk
  - **Hydralazine** - manufacturer advises avoid before third trimester
  - Breast-feeding - no information available for **Isosorbide Dinitrate** – manufacturers advise use only if potential benefit outweighs risk. **Hydralazine** - present in milk but not known to be harmful; monitor infant.

BOX 2: Common Side-effects

- Tachycardia/palpitations:
  - All nitrates are subject to tachyphylaxis, a rapid decrease in drug efficacy, due to rapidly developing tolerance. For this reason there must be at least one 12-hour window between doses of short-acting preparations (e.g. overnight), and long-acting preparations must only be taken once daily.
  - Hydralazine: Administration causes a reduction in peripheral resistance producing a reflex in crease in heart rate. Concomitant use of a beta-blocker will reduce this reflex effect.
- Flushing
- Hypotension
- Fluid retention
- Gastro-intestinal disturbances
- Headache/dizziness

Hydralazine: If the dose is kept below 100mg daily, then the likelihood of side-effects is lower. However systemic lupus erythematosus should be suspected if there is unexplained weight loss, arthritis, or any other unexplained ill health.

Box 3: Special information

Isosorbide mononitrate (ISMN) is the active metabolite of isosorbide dinitrate (ISDN). ISMN has a longer half-life (4-6 hours) than ISDN. ISDN and immediate release ISMN are licensed for use in heart failure. Whilst the modified release preparation of ISMN is not licensed in heart failure, it can be used due to "concomitant" conditions e.g. ischaemic heart disease in heart failure.

Hydralazine is subject to polymorphic acetylation; slow acetylators generally have higher plasma levels of hydralazine and require lower doses to maintain control of blood pressure. The dose of hydralazine should not be increased above 100mg daily without first checking the patient's acetylator status.

Prescribing THIAZIDE/THIAZIDE-LIKE DIURETICS in patients with heart failure

See overleaf for more detailed information

Thiazide/thiazide like diuretics (bendroflumethiazide and metolazone) can be used in combination with a loop diuretic in cases of severe fluid overload. This will result in a powerful diuresis and should be initiated only on **advice from the specialist heart failure (HF) service**.

SEE **BOX 1** (overleaf) FOR IMPORTANT INFORMATION AND CONTRAINDICATIONS, INCLUDING A LIST OF COMMON DRUG INTERACTIONS

HF patient on doses ≥ 180mg/day of oral furosemide OR 4mg/day of oral bumetanide with inadequate response:

- Discuss with HF consultant on duty (GPs refer to community HF team)
- Prescribe/recommend: **Metolazone 2.5mg** OR **Bendroflumethiazide 2.5mg as a once only dose*** (bendroflumethiazide first line as licensed product and metolazone if the eGFR<30ml/min).
- U&Es to be checked within 7 days and patient re-booked for review in 1/2 weeks

Review 1-2 weeks later

Good response

- Improvement in symptoms and weight reduction of 0.5kg/day
- No further thiazide dose required

Suboptimal response:

- Prescribe/recommend an additional dose of metolazone 2.5mg OR bendroflumethiazide 2.5mg as a once only dose.
- U&Es to be checked after 7 days and rebook to see in 1-2 weeks

No Improvement:

- Increase dosing to twice weekly for 2 weeks.
- U&Es to be checked after 7 days
- Schedule a review for 2 weeks

No Improvement:

- Discuss with HF team to agree an ongoing management plan
- Some patients are prescribed metolazone long term and primary care may be asked to prescribe in exceptional cases under HF team guidance- please follow monitoring and review guidance above

Monitoring (at baseline and each subsequent review):

BLOODS: U&Es, K^+, Na^+, eGFR
Blood Pressure (BP)
Heart Rate (HR)
Jugular Venous Pressure (JVP)
Weight and Fluid status

Discuss with HF consultant if

- K^+: If < 4mmol/l
- Na^+: If <130mmol/l
- eGFR: Change from baseline of >30% or >265µmol/L
- Blood Pressure (BP): Symptomatic hypotension (SBP < 90mmHg)

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

Prescribing THIAZIDE/THIAZIDE-LIKE DIURETICS in patients with heart failure

See overleaf for flow chart

BOX 1: FOR IMPORTANT INFORMATION AND CONTRAINDICATIONS

CONTRAINDICATIONS

- Hypersensitivity to thiazides or to any of the excipients
- Severe renal or hepatic insufficiency
- Addison's disease
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia and symptomatic hyperuricaemia

CAUTIONS

- Diabetes
- Gout
- Hyperaldosteronism
- Malnourishment
- Nephrotic syndrome
- Systemic lupus erythematosus

Box 3: SPECIAL INSTRUCTIONS

Metolazone is only available as an unlicensed product in the UK. The product recommended to purchase is Zaroxolyn tablets, imported and supplied by Idis Ltd. Community pharmacies will not have this readily available and will need advance warning to order metolazone.

**Research has demonstrated that bendroflumethiazide and metolazone were equally effective in establishing diuresis in patients with severe congestive cardiac failure resistant to loop diuretics.*Channer KS, McLean KA, Lawson-Matthew P, Richardson M. Combination diuretic treatment in severe heart failure: a randomised controlled trial. *Br Heart J* 1994;71:146-150

BOX 2: ADVERSE EFFECTS of thiazide/thiazide-like diuretics

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.

Hypokalaemia (<3.5mmol/L):

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

Hyponatraemia (<135mmol/L):

•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 (eGFR: Change from baseline of >30% or >265µmol/L):

•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 .

For support with education and management across South London:

Borough	Heart Failure Community Team
Bexley	oxl-tr.cardiac@nhs.net 020 7188 8952 or 02083197060
Bromley	kch-tr.PRUHheartfailurenurses@nhs.net 01689866097 and Bleep number is 739 kch-tr.br-bromleyintegratedheartfailurenurses@nhs.net 0797 1484 508
Croydon	mhn-tr.cuhintegratedheartfailurenursespecialist@nhs.net 0208 274 6416
Greenwich	oxl-tr.cardiac@nhs.net 02083197060
Kingston	Khn-tr.HeartFailure@nhs.net 020 8934 6453
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	hounslowandrichmond.spa@nhs.net 0208 321 5332
Sutton	esth.shc-hf@nhs.net 0208 661 3908
Wandsworth	clcht.wandsworthspa@nhs.net 0333 300 0950

Patient information leaflet: “Your medicines for heart failure” is available from GSTT and can also be accessed at: https://www.guysandstthomas.nhs.uk/resources/patient-information/pharmacy/your-medicines-for-heart-failure.pdf

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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