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Pharmacological Management of Chronic Heart Failure with Reduced Left Ventricular Ejection Fraction (HFrEF) in adults in primary care

These are prescribing guidelines that are to be used in primary care. These are not produced on a commissioning arrangement

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Glossary

Acronym/Term

ACE inhibitors	Angiotensin converting enzyme inhibitors
AIIRA	Angiotensin II receptor antagonist also known as ARB - angiotensin receptor blocker
BB	Beta-blocker
bpm	beats per minute
CKD	Chronic kidney disease
eGFR	Estimated Glomerular Filtration Rate
HFrEF	Heart failure with reduced left ventricular ejection fraction
LVSD	Left Ventricular Systolic Dysfunction
MRA	Mineralocorticoid Receptor Antagonist (MRA), previously referred to as aldosterone antagonist
MHRA	Medicines & Healthcare products Regulatory Agency
NYHA	New York Heart Association
SBP	Systolic blood pressure
SPC	Summary of product characteristics

Appendices

A. Algorithm of the Pharmacological Management of Chronic Heart Failure With Reduced Left Ventricular Ejection Fraction (HFrEF) in adults in primary.

Notes

- Heart failure with reduced ejection fraction (HFrEF) is used in this document in preference to chronic heart failure with left ventricular systolic dysfunction (LVSD). Earlier versions of this guideline used the description chronic heart failure with LVSD.

- Where patients have been seen in the diagnostic clinic and diagnosed as having 'heart failure due to LVSD' GPs are advised to record a read code of **heart failure and LVSD**. Management and monitoring of heart failure due to LVSD, regardless of severity, is in accordance with these guidelines.

- The doses in this guideline are locally recommended and may differ from those in the SPC.

Summary of guidance

The pharmacological management of HFrEF is covered in this guideline. The guideline is targeted at health care professionals in primary care but is also applicable to secondary care clinicians.

NICE have reviewed their guidance and this can be found here NICE NG106.

The guideline also takes into account, ESC guidelines 2016, NICE technology appraisal on ivabradine TA267 November 2012, and NICE technology appraisal on sacubitril valsartan TA388 April 2016.

Diagnosis

The basis for historical diagnosis of HFrEF should be reviewed and only patients whose diagnosis is confirmed via an echocardiogram or specialist assessment should be managed in accordance with this guidance.

See NICE NG106 for more detailed information on diagnosis.

Pharmacological Management of HFrEF

The management of HFrEF can be divided into separate stages [1,]

1st line - ACE inhibitor/AIIRA*, BB and an MRA

(Offer an MRA, in addition to an ACE inhibitor (or AIIRA) and BB, to people who have HFrEF if they continue to have symptoms of heart failure)

2nd line Refer to specialist for the following:
- Entresto® (sacubitril valsartan) replacing ACE inhibitor / AIIRA
- Ivabradine
- Hydralazine in combination with nitrate

Further steps in management:

- Addition of digoxin

Diuretics should be routinely used for the relief of congestive symptoms and fluid retention at all stages. (See below)

*AIIRAs may be used in patients who are intolerant to ACE inhibitors

Angiotensin Converting Enzyme (ACE) inhibitors 1st Line

- ACE inhibitors are offered to all patients with HFrEF

- They reduce heart failure symptoms, improve exercise tolerance, and significantly reduce hospitalisation rate and mortality rate.
- ACE inhibitor therapy is usually, but not necessarily initiated before beta-blocker is introduced.

- Start at a low dose and up titrate it to the maximum tolerated dose (see Table 1).

Table 1 Sheffield Formulary licensed ACE inhibitors for HFrEF [2, 4]

Drug	Initial Dose	Increment titrations	Maximum Dose	Monitoring (see below)
Ramipril	1.25mg OD/BD	1.25 mg OD/BD up to the dose of 5 mg/day and then at 2.5 mg OD/BD at 1 to 2 week intervals	10mg OD	U &Es, eGFR
Lisinopril	2.5mg OD	2.5-5 mg increments at intervals of at least 2 weeks	*20mg OD	U & Es, eGFR
Enalapril	2.5mg OD	Increased gradually over 2-4 weeks	10- 20 mg BD	U & Es, eGFR

*Locally recommended maximum dose

- The up titration should be done 1-2 weekly in the community.

- The up titration should be continued unless systolic pressure falls below 100 mmHg. Sometimes, the physician may decide to go beyond that limit.

- The creatinine can rise whilst up titrating. A rise in the creatinine following a single up titration step of over 30% is a sign that further up titration is not advisable. Consider potential reasons for this change; further U&Es after 2 weeks is advisable as a minimum.

- Monitor U&Es and assess renal function before initiation and 1 to 2 weeks after initiation and at each dose increment.

- Measure blood pressure before and after each dose increment. Follow the recommendations on measuring blood pressure, including measurement in people with symptoms of postural hypotension, in the NICE guideline on hypertension in adults[18].

- Once the target or maximum tolerated dose of an ACE inhibitor is reached, monitor treatment at least every 6 months, unless the patient is also on MRA then monitor monthly for the first three months and then 3 monthly, or at any time the person becomes acutely unwell.

- If the patient is intolerant to ACE inhibitor then use an AIIRA (see below).

Angiotensin II receptor antagonists (AIIRAs) if intolerant to ACE inhibitor

- AIIRAs are usually indicated as an alternative to ACE inhibitors for patients with intolerable side effects to ACE inhibitors.

- The AIIRAs with the best evidence base in the treatment of heart failure are candesartan and valsartan.

- Unlike ACE inhibitor, AIIRA treatment **does not** reduce the mortality of patients with HFrEF. They do however improve patient's symptoms and reduce the risk of hospitalisation.

- The combined use of ACE inhibitors and AIIRAs is **not** routinely recommended [5 17].

Table 2 Licensed AIIRAs in HFrEF [2]

Drug	Initial Dose	Dose titration	Maximum Dose	Monitoring (see below)
Candesartan	2-4 mg OD	Increased gradually at least 2 weekly intervals	32 mg OD	U & Es, eGFR
Valsartan	20-40 mg OD	Increased gradually at least 2 weekly intervals	160 mg BD	U & Es, eGFR
Losartan	12.5mg OD	12.5mg OD weekly increments	*150mg	U & Es, eGFR

*The dose of losartan beyond 100 mg per day is usually associated with excess hyperkalaemia and renal impairment

- Monitor U&Es and assess renal function, before and after initiating an AIIRA and after each dose increment.
- Measure blood pressure after each dose increment. Follow the recommendations on measuring blood pressure, including measurement in people with symptoms of postural hypotension in the NICE guideline on hypertension in adults[18].
- Once the target or maximum tolerated dose of an AIIRA is reached, monitor treatment at least every 6 months, unless the patient is also on MRA then monitor monthly for the first three months and then at 3 monthly intervals or at any time the person becomes acutely unwell.

Beta-blockers (BB) 1st Line

- BB are proven to reduce morbidity and mortality in HFrEF
- BB should be given to all patients with HFrEF, including older adults and to patients with:
  - Peripheral vascular disease (PVD),
  - Erectile dysfunction,
  - Diabetes mellitus,
  - Interstitial pulmonary disease
  - Chronic obstructive pulmonary disease (COPD) with no reversibility.
- BB licensed for use in HFrEF should be initiated in patients with symptomatic HFrEF, usually after ACE inhibitor therapy (even if rendered asymptomatic with diuretic and ACE inhibitor).
- Start at a low dose and up titrate the BB to the maximum tolerated dose.
- Measure blood pressure before and after each dose increment. Follow the recommendations on measuring blood pressure, including measurement in people with symptoms of postural hypotension, in the NICE guideline on hypertension in adults[18].
- Each increment of a BB could be associated with a transient increase in pulmonary congestion. This may be overcome by pre-warning the patient, and at times by a transient increase in the dose of the loop diuretic for 2-3 days.
- It is ideal if the heart rate is kept at 55-60 bpm in those who are in sinus rhythm. Please, do not continue to up titrate when the heart rate reaches 60 bpm or below. Similarly, while the physician may exceed this limit, it is customary not to persevere with the up titration if the systolic BP is at 100 mmHg or below.

- Patients with HFrEF associated with AF do not derive mortality benefit from BB. However, a BB needs to be used even in these patients for the reduction in morbidity and the control of the ventricular response to AF. In these patients the aim of therapy should be to reduce the heart rate to no less than 75 bpm.

- Patients should have a 12 lead ECG at the outset of the BB therapy; if there is left bundle branch block, bi-fascicular block or 1st degree AV block, it will then be favourable to get an ECG performed after each up titration.
- If a patient with HFrEF is already taking a BB for a concomitant condition, then the BB should be switched to one of the BB licensed in heart failure.

Table 3 Beta-blockers licensed for the treatment of heart failure in the UK [2]

Drug	Initial Dose	Increment titrations	Maximum Dose	Monitoring
Bisoprolol	1.25 mg OD	Weekly by 1.25 mg up to 5mg OD then every 4 weeks by 2.5 mg OD	10 mg OD	Pulse, BP, U & Es, eGFR (after up titration)
Carvedilol (Avoid in COPD & PVD)	3.125 mg BD	Weekly to 6.25 mg BD, 12.5 mg BD, then 25 mg BD	< 85kg: 25 mg BD > 85kg: 50 mg BD	Pulse, BP, U & Es, eGFR (after up titration)
Nebivolol (licensed in patients 70 years and over)	1.25 mg OD	Increased at intervals of 1-2 weeks to 2.5mg OD, then 5mg OD	10 mg OD	Pulse, BP, U & Es, eGFR (after up titration)

Titration of BB and ACE inhibitors

Clinical judgement is used by the clinician when initiating either a BB first or an ACE inhibitor. Both can be up titrated simultaneously. However, it does not usually matter which one to up titrate first; unless the patient has tachy-arrhythmias when preference should be given to BB; or is hypertensive when preference is given to ACE inhibitor. Otherwise it would be appropriate to alternate between the two agents during the up titration process. Patients should be reviewed within 2 weeks of any change in their dose or type of heart failure medication [14].

It is important that both ACE inhibitors and BB are given at the highest possible doses for patients with HFrEF [9]. However, if the patient is intolerant of these high doses then lower doses need to be accepted. Moreover, having a high

dose of one without the other at all is inferior to having both agents at lower than the maximum doses.

It is important to ensure that we document and code in the patient's notes that higher doses have been trialled and were not tolerated, and document that the patient had reached the maximum tolerated dose.

Mineralocorticoid Receptor Antagonists (MRA) 1st Line

Offer an MRA, in addition to an ACE inhibitor (or AIIRA) and beta-blocker, to people who have HFrEF if they continue to have symptoms of heart failure, as the third agent in first line therapy.

The introduction of an MRA results in significant reduction of both morbidity and mortality.

There is a risk of hyperkalaemia when spironolactone is used in combination with ACE inhibitors, AIIRAs or with sacubitril-valsartan [12].

- **DO NOT USE:**
  - in patients on ACE inhibitor who have a serum creatinine of 200 micromol/L;
  - if serum creatinine rises to 220 micromol/L and on both ACE inhibitor & MRA - seek timely specialist cardiology advice and withdraw one of the two agents or reduce dose.

- See table 4 for dose and titration. Spironolactone should be used in preference to eplerenone unless the patient cannot tolerate due to gynaecomastia.

- Monitor U&Es and assess renal function before initiation.

- The monitoring of the renal biochemical profile during the first 3 months of adding MRA to ACE inhibitor or AIIRA is at the following frequency 1, 4, 8 and 12 weeks.

- Measure blood pressure before and after each dose increment. Follow the recommendations on measuring blood pressure, including measurement in people with symptoms of postural hypotension, in the NICE guideline on hypertension in adults.[18]

- Once the target or maximum tolerated dose is reached, monitor the renal function monthly for 3 months and then every 3 months, or at any time the person becomes acutely unwell.

- Patients with heart failure taking an MRA should have blood potassium and creatinine levels monitored for signs of hyperkalaemia and/or deteriorating renal function.

- If hyperkalaemia is a problem then the dose of the MRA should be halved and biochemistry rechecked. (For doses less than 25mg please advise patient to use a tablet cutter).

Table 4 MRA licensed for the treatment of HFrEF [2]

Drug	**Initial Dose**	**Doses for impaired renal function or low BP**	**Maximum Dose**	**Monitoring** (see above)
Spironolactone	25mg OD	12.5mg OD / alternate days	50mg OD	U & Es, eGFR
Eplerenone (preferred if there is painful gynaecomastia)	25 mg OD	12.5mg OD / alternate days	50mg OD	U & Es, eGFR

Entresto® (sacubitril valsartan) 2nd line

Sacubitril valsartan is an angiotensin receptor-neprilysin inhibitor, including both a neprilysin inhibitor (sacubitril) and an AIIRA (valsartan). It is licensed for use in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

NICE TA388 states that sacubitril valsartan is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction, only in people with:

- NYHA class II to IV symptoms **and**
- a left ventricular ejection fraction of 35% or less **and**
- who are already taking a stable dose of ACE inhibitors or AIIRA

The initiation is restricted to the cardiologists who monitor the patient's response and up-titration along with the heart failure specialist nurses. Once the patient has reached their optimal dose and is stable, further prescribing and monitoring of the renal function is passed to the general practitioner. This is likely to be within 6-12 weeks from initiation.

- Sacubitril-valsartan (Entresto®) should **not be** co-administered with an ACE inhibitor or an AIIRA.

- Due to the potential risk of angioedema when used concomitantly with an ACE inhibitor, it must not be started for at least **36 hours** after discontinuing ACE inhibitor therapy.

- Should not be used in patients with a known history of angioedema related to previous ACE inhibitor or AIIRA therapy or hereditary or idiopathic angioedema.

- Treatment should **not** be initiated in patients with serum potassium level >5.4 mmol/l or with SBP <100 mmHg.

Table 5 Sacubitril-Valsartan (Entresto®) Dosage and Monitoring

Drug	Initial Dose	Increment titrations	Maximum Dose	Monitoring Once stable: monitor U&Es 6 monthly or 3 monthly if co-prescribed with MRA; BP routinely
Entresto® (sacubitril valsartan)	49 mg/51 mg BD	2-4 week increments	97 mg/103 mg BD	BP, U & Es, eGFR (after up titration)
Entresto® (sacubitril valsartan) If not previously taking or on a low dose of ACEI/AIIRA **or** eGFR 30-60 ml/min **or** SBP ≥100 to 110 mmHg.	24 mg/26 mg BD	3-4 week increments	97 mg/103 mg BD	BP, U & Es, eGFR (after up titration)

- If patients experience tolerability issues (SBP ≤95 mmHg, symptomatic hypotension, hyperkalaemia, renal dysfunction), adjustment of concomitant medicinal products, temporary down–titration or discontinuation of sacubitril-valsartan (Entresto®) is recommended.

- For full details of adverse reactions, drug interactions and contraindications, see the SPC.

Hydralazine with Nitrate

This combination is started under specialist supervision as second line therapy in patients of Afro-Caribbean origin with NYHA class III-IV.

The combination has been shown to reduce mortality in patients with heart failure, improve survival and improve exercise tolerance when added to other evidence-based

treatments (to ACE inhibitor / AIIRA, BB and MRA) in African-Americans with NYHA class III or IV HF [6].

Generally, this combination should be reserved for those with systolic BP above 110 mmHg, and, once commenced; it is preferable that the systolic BP is not allowed to be below 100 mmHg.

The combination is suitable in patients who are intolerant of both ACE inhibitors and AIIRA or with advanced CKD without renal replacement therapy.

Table 6 Hydralazine with nitrate licensed for HFrEF [2]

Drug	Initial Dose	Maximum Dose	Monitoring
Hydralazine (Must have systolic BP>110mgHg)	25mg TDS	Commonly 50mg TDS Rarely up to 75mg TDS	BP
Isosorbide mononitrate (ISMN)	10-20 mg BD given asymmetrically	120mg daily in divided doses	BP

Ivabradine

Ivabradine is recommended as a treatment option for treating chronic heart failure for people with:

- NYHA class II to IV stable chronic heart failure with systolic dysfunction **and**
- who are in sinus rhythm with a heart rate of 75 bpm or more **and**
- who are given standard therapy including BB therapy, ACE inhibitors and MRA, or when BB therapy is contraindicated or not tolerated **and**
- with a left ventricular ejection fraction of 35% or less.

Ivabradine is started under specialist supervision.

Ivabradine should only be initiated by secondary care after a stabilisation period of 4 weeks on optimised standard therapy with ACE inhibitors, BB and MRA[8].

- The starting dose of ivabradine is **2.5 mg twice daily**.
- The maintenance dose should not exceed **7.5 mg twice daily**.
- Carefully monitor patients for bradycardia or its symptoms (e.g. dizziness, fatigue, hypotension) MHRA June 2014.

- Only increase the dose to 7.5 mg twice daily after 3 to 4 weeks of treatment and if the 5 mg dose is well tolerated but insufficient. Carefully monitor the effect of a dose increase on heart rate.

- Down-titrate the dose if resting heart rate decreases persistently below 60 bpm or if the patient experiences symptoms of bradycardia. The dose can be down-titrated to 2.5 mg twice daily if necessary.

- Stop ivabradine treatment if the resting heart rate remains below 55 bpm or symptoms of bradycardia persist.

Treating HFrEF in people with Chronic Kidney Disease (CKD)[1]

For people who have HFrEF and CKD with an eGFR of 30 ml/min/1.73 m^2 or above:

- offer the treatment outlined above **and**
- if the person's eGFR is 45 ml/min/1.73 m^2 or below, consider lower possible doses and/or slower titration of dose of ACE inhibitors or AIIRAs, MRAs and digoxin.

Patients who have HFrEF and CKD with an eGFR below 30 ml/min/1.73 m^2, the specialist heart failure MDT should consider liaising with a renal physician.

Monitor the response to titration of medicines closely in people who have HFrEF and CKD, taking into account the increased risk of hyperkalaemia.

Digoxin

- Started under specialist supervision

Digoxin is recommended for:

- Worsening or severe HFrEF despite ACE inhibitor, beta-blocker and diuretic therapy. Digoxin improves symptoms and reduces the risk of hospitalisation.
- Patients with atrial fibrillation and any degree of heart failure [7].

Diuretics

In patients with HFrEF in the presence of congestion, a loop diuretic should be added to the above treatment:

- furosemide 40 mg od or bd, OR
- bumetanide 1 mg od or bd

In severe congestion a combination with a thiazide could be considered.

The diuretics should be titrated according to need. Dose reduction should be considered once the patient is stable, free from fluid overload and when the other HFrEF treatments are maximised.

The diuretic must not be stopped.

The diuretic dose may need to be increased according to the patients' needs. If not responding, seek specialist opinion with regards to admission for intravenous therapy or for sequential diuretics therapy.

Calcium-channel blockers

Avoid verapamil, diltiazem and short-acting dihydropyridine agents (e.g. nifedipine immediate release) in people who have HFrEF.[1]

ECG monitoring

Please note the ECG is part of the monitoring tasks that the GP should undertake in primary care. Whilst it is not a specific recommendation in NICE NG106, it is required in order to detect whether the patient meets the criteria in NICE TA314 Implantable cardioverter defibrillators (ICF) and cardiac resynchronisation therapy (CRT) for arrhythmias and heart failure.

Patients, who have left bundle branch block, should have an ECG **every 6 months** to detect prolongation of the QRS complex beyond 130 m sec. The latter is one of the criteria for considering patients for the lifesaving cardiac resynchronisation therapy (CRT) [13].

Those who have heart failure and do not have left bundle branch block and who are stable, should have an **annual ECG** to detect the development of prolonged QRS complexes (above 120 m sec) and thus the development of left bundle branch block.

The GP should state on the request form that the ECG is to detect left bundle branch block. If this is found, the patient should be referred to the specialist.

Antiplatelet and statin

Antiplatelet and statins are not routinely indicated for HFrEF; however, they should be prescribed for patients with the combination of heart failure and symptomatic atherosclerotic arterial disease (including coronary heart disease). See local guidelines for further information [10,11].

Salt and fluid restriction

Do not routinely advise patients with heart failure to restrict their sodium or fluid consumption. Ask about salt and fluid consumption and, if needed, advise as follows:

- restricting fluids for people with dilutional hyponatraemia
- reducing intake for people with high levels of salt and/or fluid consumption
- continue to review the need to restrict salt or fluid
- advise patients with heart failure to avoid salt substitutes that contain potassium.

Referral for Heart Failure Rehabilitation

Patients with heart failure benefit from exercise-based cardiac rehabilitation programme[1].

Patients can be referred to the cardiac rehabilitation via 0114 3078260.

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Appendix A

Algorithm of the Pharmacological Management of Chronic Heart Failure With Reduced Left Ventricular Ejection Fraction (HFrEF) in adults in primary care

Patients with confirmed diagnosis of LVSD from echo and specialist assessment

First Line

ACEI or AIIRA
Titrate to target doses or maximum tolerated doses

Titrate SBP >100mmHg
&/or
If creatinine has not risen by > 30%

And

Beta Blocker
Titrate to target doses or maximum tolerated doses

Titrate if HR is >60 bpm
&/or
SBP is > 100mmHg

Add in MRA if patient still symptomatic with the above agents:
- If creatinine is < 200 micromol/L

Refer to specialist for initiation for the following:

Second Line

Entresto ® (sacubatril valsartan)

Recommended as an option for treating symptomatic chronic HFrEF only in people:

-with New York Heart Association (NYHA) class II to IV symptoms **and**
-with a left ventricular ejection fraction of 35% or less **and**
-who are already taking a stable dose of ACE inhibitors or AIIRA.

Replaces ACE inhibitor/AIIRA

Add ivabradine

NYHA class II to IV stable chronic heart failure with systolic dysfunction **and**

-who are in sinus rhythm with a heart rate of 75 bpm or more **and**

-who are given standard therapy including BB therapy, ACE inhibitors and MRA, or when BB therapy is contraindicated or not tolerated **and**

-with a left ventricular ejection fraction of < 35%

Hydralazine and nitrate
As second line therapy in patients of Afro-Caribbean origin with NYHA class III-IV.

Suitable in patients intolerant of both ACE inhibitors and AIIRA or with advanced chronic kidney disease without renal replacement therapy

Combination reserved for those with systolic BP > 110 mmHg, and once commenced, it is preferable that the systolic BP is not allowed to be < 100 mmHg.

Additional Therapies to consider

Digoxin
Initiated in patients with
- AF
-Or worsening heart failure

Specialist initiation

Diuretics
Start furosemide 40 mg od/ bd, **OR** bumetanide 1 mg od/ bd
Titrate to fluid overload but do not stop

Antiplatelet & Statins
Suitable in combination of heart failure and symptomatic atherosclerotic arterial disease See local guidelines [10,11].