Guy's and St Thomas' NHS Foundation Trust

Clinical Guideline

Diagnosis and Management of Heart Failure

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Guy's and St Thomas' NHS Foundation Trust

Guidelines for Diagnosis and Management of Heart Failure

THESE GUIDELINES ARE AIMED AT JUNIOR DOCTORS AT THIS TRUST AND **INPATIENTS** UNDER THEIR CARE.

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Diagnosis of Heart Failure

Heart failure is a *clinical syndrome* characterised by the inability of the heart to maintain adequate tissue perfusion. Common symptoms and signs include dyspnoea, fatigue, pulmonary and peripheral oedema, liver congestion and ascites. Other associated features may include arrhythmia, hypotension and syncope.

Heart failure is commonly secondary to left ventricular dysfunction function with *reduced ejection fraction* (**HFrEF**), but *up to half* of cases presenting with fluid overload may have *preserved ejection fraction* (**HFpEF**). Other causes of heart failure include "right sided" pathology (right ventricular failure and/or pulmonary hypertension, e.g. secondary to chronic lung disease) or valvular disease (commonly aortic stenosis, mitral or tricuspid regurgitation).

Treatment may differ significantly depending on the underlying pathology; differential diagnosis relies on echocardiography. Timing of echocardiography depends on clinical history (in particular previous myocardial infarction) or level of natriuretic peptides (BNP (pg/ml) in the A&E setting or NT-proBNP (ng/L) in the ward setting), which is helpful in both diagnosis and risk-stratification.

Echocardiography is helpful in establishing:

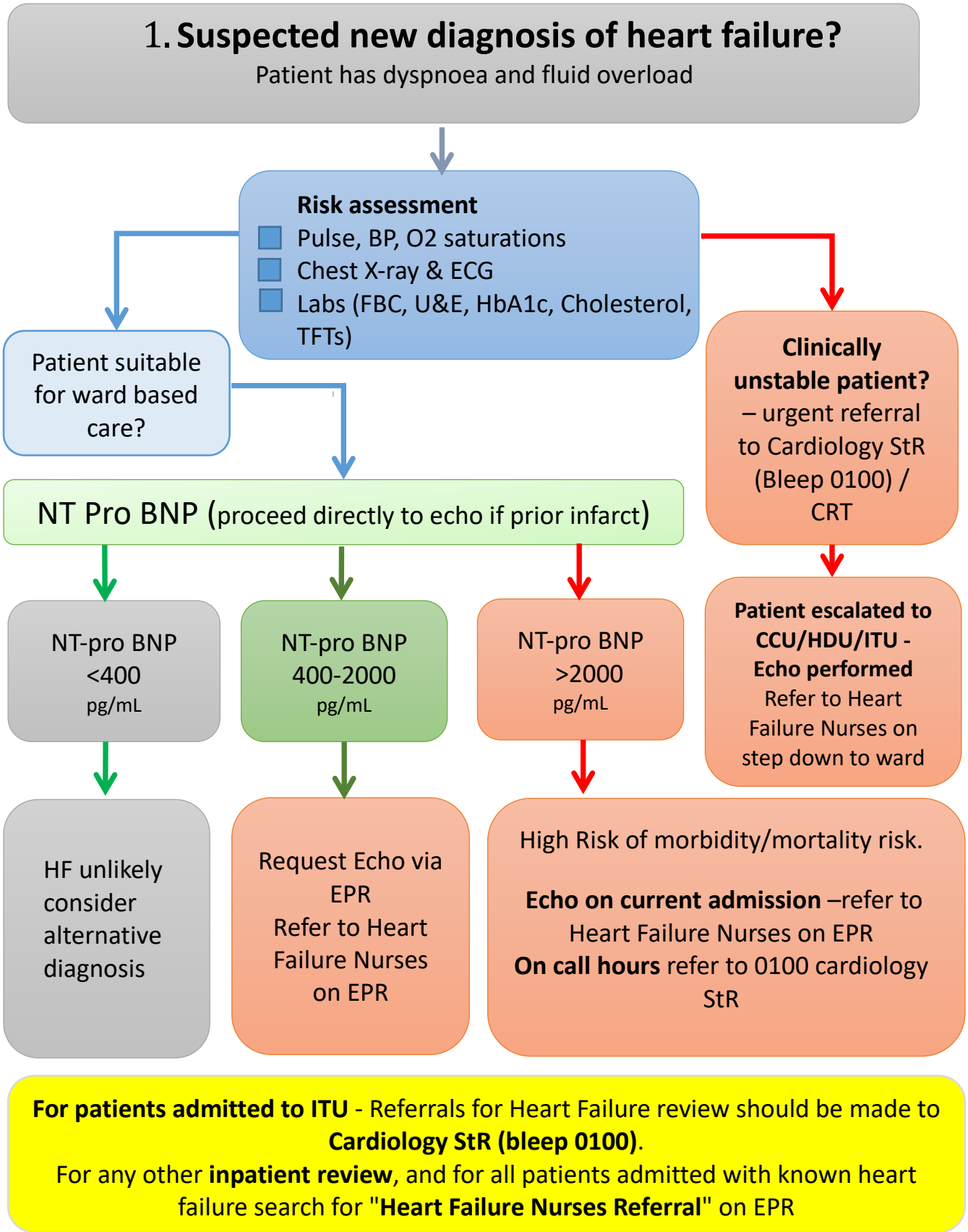
1. Severity of LV dysfunction
2. Presence of 'diastolic dysfunction' where LV function appears preserved
3. Severity of valvular disease
4. Right ventricular function and rough assessment of Pulmonary Artery Systolic Pressure (PASP)
5. Presence of constrictive pericarditis or restrictive cardiomyopathy where patients present with peripheral oedema and raised JVP but no other cause found on echo

Natriuretic peptides have a very high negative predictive value (≥95%) for presence of heart failure (i.e. if normal then HF is not the cause of the patient's symptoms), but poor specificity with high false-positive rates; they are therefore used as a **rule-out test**, not a rule-in test.

Cut-offs for peptides:

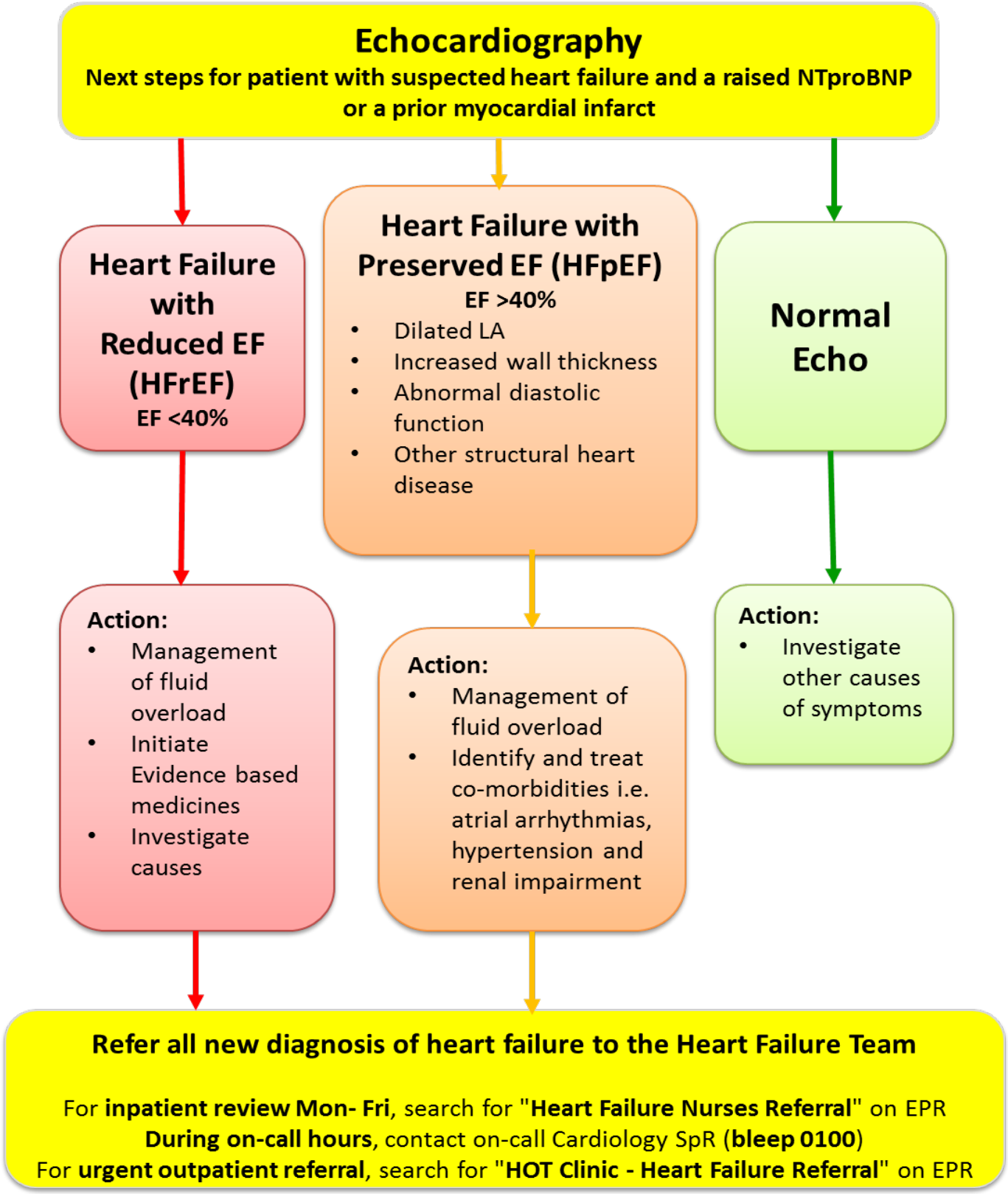
Severity	NT-pro BNP (ng/L)	BNP (pg/ml)
Normal	<400 ng/L	< 100 pg/ml
Intermediate	400 – 2000 ng/L	100 – 400 pg/ml
Clearly elevated	≥ 2000 ng/L	≥ 400 pg/ml

Algorithm for initial inpatient diagnosis



For patients admitted to ITU - Referrals for Heart Failure review should be made to **Cardiology StR (bleep 0100)**.
For any other **inpatient review**, and for all patients admitted with known heart failure search for "**Heart Failure Nurses Referral**" on EPR

Algorithm for further inpatient investigation & referral for specialist input



Guidelines for Treatment of Heart Failure (HF)

Treatment of HF includes non-pharmacological interventions and medical therapy *appropriate to the type of Heart Failure*. Treatment is directed towards both symptomatic relief and where applicable improving long-term prognosis.

Initial therapy for acute heart failure

1. Supportive therapy (Give O_2 if sats <95% (<92% in COPD), sit upright)
2. Urine output, blood pressure, mixed (central) venous saturations, Lactate, base excess, electrolytes, Hb
3. Treat acute myocardial infarction if present
4. Consider opiates if distressed (2.5-5mg morphine i.v.)
5. **If Normotensive** (SBP ≥ 90 mmHg)
    a. Consider CPAP if pulmonary oedema and continued hypoxaemia.
    b. i.v. GTN for pulmonary oedema (2-10 ml/h of a 1mg/ml preparation), monitor BP closely
    c. i.v. Furosemide 40-80mg (caution - hypotension)
    d. Possible role for Dobutamine, particularly with low mixed venous saturations (< 65%) and metabolic acidosis
6. **If hypotensive / cardiogenic shock** please call Cardiology StR (0100) or Met Team (0610)
7. Be aware that low cardiac output failure may present **with no fluid overload** and symptoms may be vague, secondary to poor tissue perfusion (typically hypotension, agitation, malaise).

Non-Pharmacological interventions – All types of Heart Failure

1. Fluid balance should be routine in all patients:
    a. Daily weights
    b. Fluid restriction – 1-1.5 L/day, if overloaded. 2-2.5L/day if at dry weight.
    c. Awareness of salt intake – avoid 'LoSalt' (high potassium) alternatives
2. Education via the Heart Failure Nurse Specialist:
    a. BHF Living with Heart Failure booklet
    b. Heart Failure: Self-management tool
    c. Heart Failure: Managing fluid balance
    d. Your medicines for heart failure
    e. Your heart failure team leaflet
    f. Contact details for heart failure nursing team
    g. Contact details for 'Pumping Marvellous' heart failure charity
    h. Cardiac Rehab groups
        i. Education
        ii. Physical exercise/mobilisation
    i. Immunisations, including yearly flu vaccinations
3. Specialist Input from HF team:
    a. Family screening where appropriate
    b. Pregnancy counselling
    c. Anxiety / Depression

Pharmacological Treatment – Systolic Heart Failure

The cornerstone of therapy is directed at initiation and up-titration of prognostic therapies. Other treatments, e.g. loop diuretics, thiazides and digoxin, are used as appropriate for symptomatic relief.

Prognostic Therapy *(please refer to diagram on page 8)*

1. **ACE inhibitors**[1] – *Ramipril* is preferred [**Appendix A**]. Where possible should always be initiated and up-titrated to target dose of 10 mg daily. May be limited by renal function and BP
    a. Cut-offs for initiation
        i. Creatinine > 200µmol/l (Use with caution when creatinine 150-200µmol/l)
        ii. Potassium > 5.0mmol/l
        Although ACE inhibitors are contraindicated in patients with a baseline potassium of over 5.5 mmol/l, in practice ACE inhibitors would not usually be prescribed for patients with a baseline potassium over 5 mmol/l. Please seek specialist advice from the Heart Failure Team for patients with a baseline potassium over 5mmol/l.
        iii. Systolic BP < 90 mmHg

2. **Angiotensin Receptor Blockers (ARB)**[2] – *Candesartan* is preferred [**Appendix B**]. Use where ACEi not tolerated – e.g intractable cough, angioedema (use with caution). Target dose is 32 mg daily; same limitations as for ACEi.

3. **Beta-blockers**[3] – *Bisoprolol* is preferred [**Appendix C**]. Should be started in all patients with heart rates >50bpm: COPD without significant obstruction and peripheral vascular disease are not contraindications. Target dose is 10 mg daily. May be limited by bradycardia <50bpm, 2nd or 3rd degree AV block, hypotension, fatigue, night terrors. Carvedilol is a good alternative depending on side effect profile (target dose 25 mg bd). Nebivolol is an alternative in hypertensive patients as it has effect on endothelial NO mechanism as well. Caution is advised when considering use in those with significant bronchial asthma.

4. **Mineralocorticoid Receptor Antagonists (MRA)**[4] [**Appendix D**]
    a. **Spironolactone** – NYHA class III-IV HF with no recent history of myocardial infarction. Target dose is 25-50mg od.
    b. **Eplerenone** – NYHA class II with left ventricular systolic dysfunction (LVEF ≤30%) or in stable patients with left ventricular dysfunction (LVEF ≤ 40 %) and clinical evidence of heart failure after recent myocardial infarction. Should also be used if hormonal side effects from Spironolactone (gynaecomastia, reduced libido, erectile dysfunction). Target dose is 25-50mg od.

5. **Ivabradine [Appendix E]**[5] – In patients with LVEF <35% and resting heart rates ≥ 75 bpm in sinus rhythm despite maximal tolerated beta blocker dose. Target dose is 5 mg bd or 7.5 mg bd for rate control.

6. **Sacubitril/Valsartan [Appendix F]**[8]- In South London, Sacubitril valsartan may be considered for initiation by Heart Failure (HF) specialists for treating chronic HF in patients meeting all of the following criteria:
    a. New York Heart Association (NYHA) class II to IV symptoms
    b. On a stable dose of angiotensin-converting enzyme inhibitors (ACE-I) or an ARB
    c. Left ventricular ejection fraction of 35% or less

Additional resources have been developed to support implementation including:

- 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.**
- 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.

7. **Hydralazine+Nitrates [Appendix G]** – alternative to ACEi/ARB in renal failure or hyperkalaemia. Can be used *in addition to ACEi/ARB* in African / Caribbean patients that remain symptomatic, blood pressure permitting. Reduce dose of hydralazine in severe renal dysfunction (eGFR <30ml/min).

Medication for symptom management

1. **Loop diuretics [Appendix H]**. Treatment of pulmonary or peripheral oedema.
2. **Thiazide diuretics [Appendix H]**. May be added to loop diuretic ± MRA for treatment of oedema.
3. **Digoxin[6]** – rate control in atrial fibrillation. Possible role for symptomatic relief in sinus rhythm.
4. ***i.v.* Iron** – Treating Fe^{2+} deficiency even in absence of anaemia should always be considered in symptomatic patients.

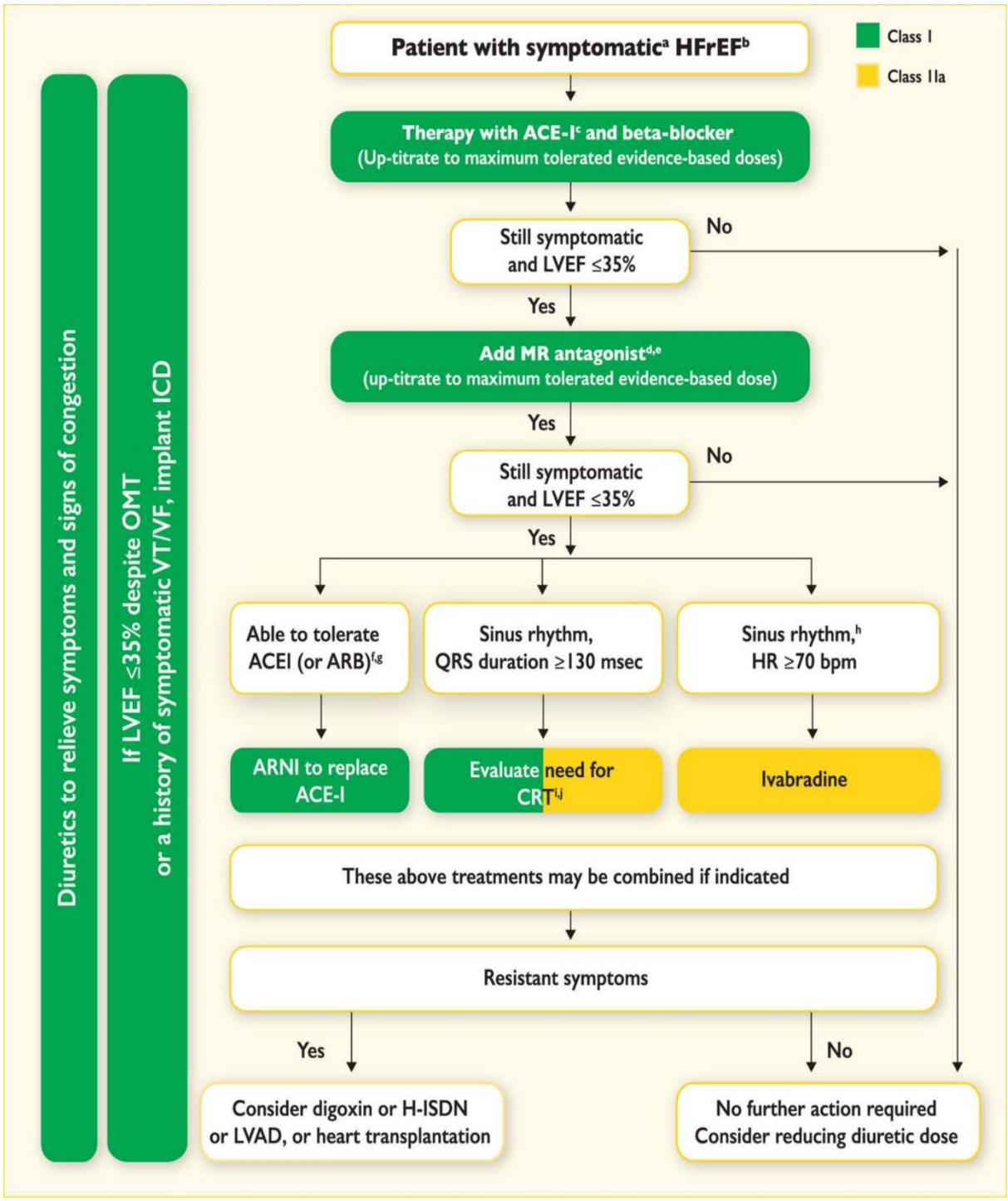
Device Therapy – Systolic Heart Failure

Implantable Defibrillators (ICD) are indicated as *secondary prophylaxis* in patients with pulseless VT/VF, or for *primary prophylaxis* in patients with LVEF ≤ 35%. For detailed guidance see Appendix I.

Biventricular Pacing (Cardiac Resynchronisation Therapy, or CRT) with or without an implantable defibrillator is indicated if:

1. Symptomatic on maximum achievable medical therapy and
    a. LVEF ≤ 35% and LBBB on ECG (QRS > 130msec or RBBB with QRS > 150msec) or
    b. Chronically RV paced if LVEF < 50%

Flow chart for pharmacotherapy in LV systolic dysfunction



Flow diagram taken from ESC guidance showing heart failure medication pathway[7].

Pharmacological Therapy – Heart Failure with preserved Ejection Fraction (HFpEF)

There is no proven prognostic therapy in HFpEF, hence treatment revolves around management of fluid overload and treatment of conditions associated with this.

1. The cornerstone of treatment is management of fluid balance and diuretic therapy as needed.
2. Hypertension should be aggressively treated.
3. Atrial arrhythmias should be treated with either rate control, or rhythm control. Patients may need to be anticoagulated.
4. COPD and renal dysfunction should be managed as per guidelines
5. Possible coronary disease should be ruled out and treated

End of Life Care – decision made by Specialist team

Heart failure carries a high mortality and it is important to recognise when patients should be for Advance Care Planning (ACP). ACP should include the following steps:

1. Discussion of case at Heart Failure Multidisciplinary Meeting to ensure consensus that there the patient is on optimal heart failure therapy and no further interventions are available/appropriate given the patients' condition.
2. Discuss with patient and others the patient identifies as important to them:
    a. Prognosis
    b. Clarify patients' wishes, preferences or fears in relation to their future treatment and care
    c. Establish any religious/spiritual care needs and any support required
    d. Establish which interventions may be considered/undertaken in an emergency i.e. resuscitation
    e. Clarify preferred place of care and preferred place of death highlighting care and management options available in each place i.e. home, hospice, hospital
    f. If symptom burden significant or further support needed refer to Palliative care (via EPR)
    g. Document the above within the patients record

    https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/treatment and-care-towards-the-end-of-life/working-with-the-principles-and-decision-making-models---cont

Indicators that the patient is approaching end of life:

1. Intractable signs of heart failure in spite of medical/non-medical interventions.
2. Increasingly frequent readmissions with decompensated heart failure.
3. Increasingly intolerant of medication because of hypotension, hyperkalaemia, worsening renal function, leading to multiple dose reductions.

Ensure that once end-of life care has been considered the patient is referred to palliative care services for specialist input. The following documents have been included for further information on end of life care:

- Deactivating Implantable Cardioverter Defibrillators

If the patient has implantable defibrillator, shock therapies should be switched off.

Please Note: Furosemide can be administered subcutaneously and may be preferred for some patients.

APPENDICES

Appendix A - ACE Inhibitors (ACEi) in patients with heart failure due to left ventricular dysfunction

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. Please note that the cautions, contraindications, interactions and side effects listed for each drug are not exhaustive; please refer to the BNF for full list. Unless otherwise stated, doses assume normal renal and hepatic function.

Evidence from clinical trials demonstrates that patients with heart failure, due to left ventricular dysfunction, show an improvement in symptom control and a reduction in morbidity and mortality when treated with an ACE inhibitor (ACEi). Therefore, all patients diagnosed with heart failure due to left ventricular systolic dysfunction (ejection fraction ≤ 40%) should be considered for an ACEi.

Contraindications

- 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 ACEi or excipients or to any other ACEi
- History of angioedema of any cause
- Pregnancy
- Baseline potassium > 5.5 mmol/L

Cautions

- Symptomatic or severe asymptomatic hypotension (systolic blood pressure (BP)< 90mmHg)
- Patients with a documented intolerance of ACEi due to symptomatic hypotension - consider re-challenging with a longer acting ACEi (such as Ramipril)
- Patients on high dose diuretics (i.e. furosemide > 80mg daily) – increased risk of hypotension and renal dysfunction
- Breastfeeding – seek specialist advice
- Moderate to severe renal impairment: creatinine > 150µmol/L or eGFR < 50ml / min. See individual SPCs for dose adjustment requirements.
- Baseline potassium > 5 to 5.5mmol/L

Seek specialist advice prior to initiation

- Hypertrophic cardiomyopathy
- Hyponatraemia (serum Na <135mmol/L)
- Symptomatic or severe asymptomatic hypotension (SBP<90mmHg)
- Significant renal dysfunction/renovascular disease e.g. creatinine > 150 µmol/L or eGFR < 50ml/min or hyperkalaemia (serum K+ 5-5.5mmol/L)
- Renovascular disease (diagnosed as well as undiagnosed and clinically silent disease) e.g. PAD or severe generalised atherosclerosis
- Patients undergoing dialysis/extracorporeal treatments or having desensitisation with wasp or bee venom

Initiation and monitoring

- Check baseline blood chemistry. (e.g. serum creatinine, potassium, sodium and eGFR) and blood pressure (BP)
- Discontinue potassium supplements/potassium sparing diuretics (with the exception of aldosterone antagonists) and review need for concomitant nephrotoxic drugs e.g. NSAIDs
- Review dose of diuretic therapy to the minimum necessary to control oedema
- Start with the lowest recommended dose of ACEi and titrate as suggested below. Aim for the target dose, failing that, the maximum tolerated dose. **Some ACEi is better than no ACEi**

Dose titration

- BP and blood chemistry (e.g. serum Creatinine, potassium, sodium and eGFR) **should be checked daily** during inpatient up-titration.
- Cautious monitoring may be required especially if patients are on combined loop and thiazide diuretic therapy, or are taking aldosterone antagonists. Reduce dose/stop according to *"worsening renal function"* and *"symptomatic hypotension"* in "*problem solving"* below.
- ACEi dose can be doubled **every 1-2 days**. If appropriate smaller dose increments may be more clinically suitable for certain patients

Licensed ACEi	Starting Dose (mg)	Target Dose (mg)
Ramipril	1.25mg once daily	5mg twice daily or 10mg once daily

Ramipril is the ACEi of choice for heart failure; however some patients will require titration of existing ACEi therapy.

Problem Solving

1. **Angioedema:** Rare but life threatening. Discontinue therapy and seek advice immediately.
2. **Worsening renal function:** An increase in creatinine and K^+ is to be expected after initiation/titration of ACEi. If the increase is small and asymptomatic, no action is necessary. Please see the table below for recommended actions.

GFR ≥ 60ml/min at initiation	GFR < 60ml/min at initiation	Action
	Creatinine ↑: **≤ 30% (from baseline)** **or** **eGFR ≤ 25%** **OR** **K+ ↑ to ≥ 5.0 - ≤5.4mmol/L**	**Recheck renal function within 24 hrs. 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 24 hrs. 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. 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.**

3. **Asymptomatic hypotension:** Does not usually warrant a change in therapy.

4. **Symptomatic hypotension:**
   a. Consider dehydration and address as appropriate
   b. Review diuretic dose with a view to decreasing dose if patient free of symptoms suggestive of fluid retention.
   c. If dizziness, light-headedness and/or confusion occur in the setting of low blood pressure, consider stopping nitrates, calcium channel blockers and other vasodilators.
   d. Monitor closely and allow longer intervals between dose titrations.
   e. Aim to maintain treatment with both ACEi and beta-blockers, at a reduced dose if necessary
   f. Seek specialist advice if measures do not resolve symptomatic hypotension

5. **Persistent dry cough:**
   a. Review aetiology of cough e.g. due to smoking, worsening heart failure/pulmonary oedema, respiratory disease, respiratory tract infection or ACEi therapy.
   b. Review cough tolerability against benefits of an ACEi in chronic heart failure. Some patients may tolerate re-institution of the ACEi after a drug free period.
   c. ACEi cough is harmless and every effort should be made to maintain treatment. If ACEi cough is significantly affecting the patient's quality of life, an Angiotensin Receptor Blocker (ARB) licensed for heart failure may be considered as an alternative to ACEi (see separate ARB guideline).

Appendix B - **Angiotensin Receptor Blockers (ARBs)** in patients with heart failure due to left ventricular systolic dysfunction

Angiotensin Receptor Blockers (ARBs) have a more limited evidence base than ACE inhibitors (ACEi) and have not shown superiority over ACEi in any large robust clinical trial. There are currently no compelling indications for the use of ARBs routinely first line in heart failure. ARBs should only be considered second line in patients intolerant to ACEi.

Indication
Candesartan is the ARB of choice for use in heart failure and impaired left ventricular systolic function (ejection fraction ≤ 40%), and should be considered for the following patients:

- Patients intolerant of ACEi or
- Symptomatic CHF patients already on maximum tolerated dose of ACEi and beta-blocker, unless also taking an aldosterone antagonist (under specialist advice)

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, lactase deficiency or glucose-galactose malabsorption
- Patient on both an ACEi and aldosterone antagonist
- Baseline potassium > 5.5 mmol/L

Caution

- Symptomatic or severe asymptomatic hypotension (systolic blood pressure (BP) <90mmHg).
- Moderate to severe renal impairment i.e. serum creatinine >150μmol/L or eGFR < 50ml/min.
- 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 potassium > 5 to 5.5mmol/l

Initiation and Monitoring

- Check baseline blood chemistry (e.g. serum creatinine, potassium, sodium and eGFR) and blood pressure (BP).
- Discontinue potassium supplements/potassium sparing diuretics (with the exception of aldosterone antagonists) and review need for concomitant nephrotoxic drugs e.g. NSAIDs.
- Consider reducing diuretic dose.
- Start with the lowest recommended dose of ARB and titrate as suggested below. Aim for the target dose, failing that, the maximum tolerated dose. **Some ARB is better than no ARB.**

Dose Titration

- BP and renal function monitoring daily during up-titration.
- Reduce dose/stop according to *"worsening renal function"* and *"symptomatic hypotension"* in "*problem solving"* below.
- ARB dose can be doubled every 2 days. Smaller increments may be more clinically suitable for certain patients.

ARB	Starting Dose (mg)	Target Dose (mg)
Candesartan	2 mg once daily	32 mg daily

Problem Solving

a. **Angioedema:** Rare but life threatening. Discontinue therapy and seek immediate specialist advice.

b. **Worsening renal function:** An increase in creatinine and K^+ is to be expected after initiation/titration of ARB. If the increase is small and asymptomatic, no action is necessary. Please see the table below for recommended actions:

GFR ≥ 60ml/min at initiation	GFR < 60ml/min at initiation	Action
	Creatinine ↑: **≤ 30% (from baseline) or** **eGFR ≤ 25%** **OR** **K+ ↑ to ≥ 5.0 - ≤5.4mmol/L**	**Recheck renal function within 24 hrs. 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 24 hrs. 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. 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.**

Appendix C - **Beta-blockers** in patients with heart failure due to left ventricular systolic dysfunction

Beta-blockers reduce mortality (by about 30%) and hospital admissions (by about 20%) when included as part of standard heart failure therapy, including ACE inhibitor treatment. In line with NICE guidance, beta-blockers licensed for heart failure should be offered to all patients with heart failure due to left ventricular systolic dysfunction (ejection fraction (EF) ≤ 40%).

UK Licensed beta blockers for heart failure:

- **Bisoprolol** – adjunct in stable moderate to severe heart failure with reduced systolic ventricular function (EF≤35% on echo). Bisoprolol is cardioselective and therefore should be the preferred agent if beta-blockers are used in patients with respiratory problems.
- **Carvedilol** – used as an adjunct to diuretics, digoxin or ACE inhibitors in symptomatic chronic heart failure. Carvedilol may be more effective at reducing hypertension however crosses the blood-brain barrier and has a higher incidence of night terrors. Note: Carvedilol should be prescribed twice daily for heart failure.
- **Nebivolol** – adjunct in stable mild to moderate heart failure in patients over 70 years. Nebivolol has vasodilating properties, which may be useful in treating hypertension.

NICE recommends that patients who are already taking a beta-blocker for a comorbidity (for example, angina or hypertension), and who develop heart failure due to left ventricular systolic dysfunction, should be switched to a beta-blocker licensed for heart failure.

Contraindications

- Severe bronchial asthma or COPD with reversibility
- Uncontrolled/acute heart failure / decompensated heart failure / symptoms of fluid retention in the past 6 weeks
- Prinzmetal's angina
- Sinus bradycardia <50bpm
- Sick sinus syndrome including sino-atrial block, second or third degree heart block (without a pacemaker)
- Hypotension – (systolic blood pressure <90mmHg) or symptomatic hypotension)
- Cardiogenic shock
- Metabolic acidosis
- Severe peripheral circulatory disturbances/peripheral arterial disease
- Phaeochromocytoma (apart from specific use with αblockers)
- Hypersensitivity to beta-blockers or any of the excipients
- Patients treated with verapamil

Caution

- Mild to moderate reversible airways disease – monitor peak flow prior to and following initiation and after any dose change. If concerned, seek specialist advice prior to initiation
- Renal or hepatic disease (see BNF for further details)
- Beta-blockers may mask early signs of hypoglycaemia, Worsening control of blood glucose may occur. Additional monitoring is therefore necessary in patients with diabetes when beta-blockers are initiated and during dose titration phase, especially in unstable diabetes and in patients on insulin
- First degree heart block
- Use of concomitant medication that may increase the risk of bradycardia

Beta-blocker therapy should not be withheld for any of the following reasons: increasing age, presence of peripheral vascular disease, erectile dysfunction, diabetes

mellitus, interstitial pulmonary disease and chronic obstructive pulmonary disease with no reversibility.

Initiation and dose titration
Treatment should be initiated and titrated by those experienced in the management of heart failure. Introduce beta-blockers at lowest dose and uptitrate every 2-3 days.

Drug	Starting dose	Target dose
Bisoprolol	1.25 mg od	10 mg od
Carvedilol	3.125 mg **bd**	25 mg **bd**
Nebivolol	1.25 mg od	10 mg od

- Aim for the target dose as detailed above. Failing that, aim for the maximum tolerated dose. **Some beta-blocker is better than no beta-blocker.**
- Monitor heart rate, blood pressure, clinical status, symptoms and signs of congestion e.g. body weight, breathlessness and oedema daily. An ECG should always be performed prior to initiation.

IMPORTANT: If a beta-blocker has been stopped for more than 5 days, re-introduce cautiously. Consider re-starting from the initiation dose.
Patients switching from another beta-blocker to one licensed for use in heart failure do not usually require re-starting from the initiation dose. Start at an equivalent point within the dose range depending on clinical status and monitor closely**.**

IMPORTANT: Beta-blockers should not be stopped suddenly unless absolutely necessary due to the rebound effects (increased myocardial ischaemia / risk of infarction and arrhythmias). Specialist advice should be sought before treatment discontinuation.

Problem solving

1. **Worsening symptoms/signs** (e.g. increasing dyspnoea, fatigue, oedema, weight gain >1.5kg over 3days)
    a. If increased congestion, double dose of diuretic and/or halve dose of beta-blocker (if increasing diuretic does not work).
    b. If marked fatigue (and/or bradycardia, see below) halve dose of beta blocker (rarely necessary).
    c. If serious deterioration, halve the dose of beta-blocker or stop treatment (rarely necessary) and seek specialist advice.
    d. If there are worsening symptoms of airways disease, stop the beta-blocker and seek specialist advice.

2. **Asymptomatic hypotension** does not usually warrant a change in therapy.

3. **Symptomatic hypotension**
    a. If combined with dizziness, light-headedness or confusion, consider discontinuing drugs such as nitrates, calcium channel blockers and other vasodilators.
    b. If no signs/symptoms of congestion, consider reducing dose of diuretic.
    c. If these measures do not solve problem, seek specialist advice.

4. **Bradycardia (HR<55)**
    a. If bradycardia and worsening symptoms, halve the dose of beta-blocker or if severe deterioration, stop beta-blocker (rarely necessary).

b. Consider need to continue treatment with other drugs used to slow the heart (digoxin, amiodarone, diltiazem) and discontinue if co-morbidities allow. Consider referral if in doubt.
c. Arrange ECG to exclude heart block.
d. Seek specialist advice.
e. 2nd or 3rd degree heart block: Stop beta-blocker and consult immediate specialist advice. Undertake a further ECG after beta-blocker stopped.

5. **Impotence -** This may resolve as heart failure improves although a referral to the Male Cardiovascular Health clinic should be offered.

Appendix D - **Mineralcorticoid Receptor Antagonists (MRAs)** in patients with heart failure due to left ventricular systolic dysfunction

Evidence from clinical trials has shown that the use of a mineralcorticoid receptor antagonist (MRA) in addition to optimal ACE inhibitor and beta-blocker therapy can reduce mortality and hospitalisations in selected patients with heart failure due to left ventricular systolic dysfunction (LVSD).

Indications

- All patients with LVSD (ejection fraction ≤ 35%) who remain symptomatic despite optimal therapy with an ACE inhibitor and a beta-blocker (both at maximum tolerated doses).
- An MRA should be prescribed within 3–14 days of myocardial infarction, preferably after initiation of ACE inhibitor therapy, for patients with symptoms and/or signs of heart failure and left ventricular systolic dysfunction (LVSD) and an ejection fraction (EF) ≤40%.
- *Spironolactone* is licensed for use in patients with severe heart failure (NYHA Class III-IV)
- *Eplerenone* is licensed for use in adult patients with NYHA class II (chronic) heart failure and left ventricular systolic dysfunction (LVEF ≤30%); and also in stable patients with left ventricular dysfunction (LVEF ≤ 40 %) and clinical evidence of heart failure after recent myocardial infarction.
- *Eplerenone* may be used as an alternative to spironolactone in moderate to severe heart failure if the patient experiences intolerable side effects with spironolactone (painful gynaecomastia, loss of libido).

Contraindications

- Anuria
- Acute renal insufficiency
- Rapidly deteriorating or severe impairment of renal function (baseline Serum Cr >200µmol/L or eGFR <30mls/min)
- Hyperkalaemia defined as K+ >5.0mmol/L at initiation
- Addison's disease
- Hypersensitivity to specific aldosterone antagonist or excipients
- Hyponatraemia defined as Na+<135mmol/L
- Co-prescription of potassium sparing diuretics, potassium supplements.
- Co-prescription of Eplerenone with strong CYP3A4 enzyme inhibitors – see 'interactions' below.
- Severe hepatic impairment Child-Pugh Class C
- In addition to the combination of both an ACEi and an ARB

Caution

- Porphyria
- Pregnancy and lactation
- Hepatic impairment (Child Pugh Class A & B, monitor electrolytes closely)
- Moderate to severe renal impairment Serum Creatinine >150 µmol/L or eGFR< 50mls/min
- Diabetic microalbuminuria
- Elderly: initial spironolactone dose of 12.5mg daily recommended; no adjustment of Eplerenone dose required; monitor potassium carefully.
- Drug/Food interactions

Initiation and Monitoring
Check baseline blood chemistry. (e.g. serum creatinine, sodium and eGFR and liver function tests): aldosterone antagonists should not be started in patients with a serum K+ > 5.0mmol/L.

For both Spironolactone and Eplerenone, start at 25mg daily (consider using 12.5 mg in the elderly if using Spironolactone). If needed, the dose can be up-titrated (usually by increments of 25 mg) providing renal function and Potassium levels are satisfactory to a maximum of 50mg (both Spironolactone and Eplerenone – please liaise with Heart Failure Specialist).

Managing Hyperkalaemia	
Serum potassium (mmol/L)	Action
5.0 - 5.4	No dose adjustment
5.5 – 5.9	Withhold for 24-48 hours and restart at half dose
≥ 6.0	Withhold drug and seek specialist advice

Other 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 aldosterone antagonist
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 daily. If symptoms persist or are severe, reduce or discontinue therapy.
GI upset	Reduce dose or discontinue therapy.
Hyponatraemia	Serum Na< 130 mmol/L, stop aldosterone antagonist and manage Hyponatraemia.
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 severe LVSD, where spironolactone is indicated but has not been tolerated usually due to the development of gynaecomastia. This is an unlicensed use.

Interacting Drug	**Mechanism of action/Significance and Action to be taken**
ACEi / ARB	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 and ARB and an aldosterone antagonist is only to be used under specialist supervision.
Aliskiren	This is contraindicated with ACEi/ARB.
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.

Drosperinone	Increased risk of hyperkalaemia. Monitor serum K+ during first cycle
Lithium	• May affect lithium levels • No additional monitoring required with spironolactone but ensure the patient is aware to report symptoms of lithium toxicity • Co-administration of eplerenone and lithium should be avoided. If this combination appears necessary, lithium plasma concentrations should be monitored
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 as hazardous as potassium supplements.
Potassium rich foods e.g. spinach, mangos bananas	Increased risk of hyperkalaemia. Monitor 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, Co-trimoxazole	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, nefazadone, Grapefruit juice.	Risk of increased plasma concentration of eplerenone - concomitant use is contra-indicated.

Appendix E – **Ivabradine** in patients with heart failure due to left ventricular systolic dysfunction

Ivabradine, a sinoatrial I_f channel inhibitor, is a pure heart-rate lowering agent with no AV node blockade. Recent data from the SHIFT study has demonstrated that heart rate reduction using Ivabradine, in selected patients with chronic heart failure, can significantly reduce hospitalisations due to worsening heart failure and prevent heart failure related death.

Selection of Patients
Ivabradine should **ONLY** be considered for patients that meet all the following criteria:

- 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 antagonist if tolerated.
- In sinus rhythm, with a resting heart rate ≥ 75 bpm
- Network guidance states that patients should be on Ivabradine for 3 months before GPs can continue repeat prescriptions.

Contraindications

- Atrial fibrillation
- Sick sinus syndrome
- Bradycardia (resting heart rate <60bpm)
- Cardiogenic shock and acute MI
- Within 4 weeks of CVA
- Sino-atrial block & 3rd degree AV-block
- Congenital QT syndrome
- Unstable angina
- Pregnancy and lactation

Caution

- Pre-existing cardiac arrhythmias
- Concurrent HR lowering agents
- Post-CVA
- Retinitis pigmentosa
- Hypotension
- Hepatic insufficiency (avoid if severe)
- Severe renal insufficiency (eGFR<15ml/min)

Commonly Used Interacting Drugs

- Amiodarone or disopyramide – increased risk of ventricular arrhythmias
- Macrolide antibiotics, particularly clarithromycin and erythromycin – avoid concomitant use
- Imidazole antifungals, particularly ketoconazole and itraconazole – avoid concomitant use
- Nelfinavir and ritonavir – avoid concomitant use
- Sotalol – increased risk of ventricular arrhythmias
- Calcium channel blockers, specifically diltiazem and verapamil – avoid concomitant use
- Mefloquine – avoid concomitant use

Initiation and Dose Titration

- **Ivabradine should be initiated at a dose of 5mg twice daily.** If the patient is elderly or 5mg twice daily is not tolerated, the dose can be reduced to 2.5mg twice daily.

- **Once initiated the dose of Ivabradine should be adjusted to achieve a heart rate ≤ 60bpm.**
- If the heart rate remains ≥ 60bpm, the dose should be increased to 7.5mg twice daily
- If the heart rate is less than 50bpm consider dose reduction or cessation of therapy.

Adverse Effects
Asymptomatic bradycardia is the most common adverse effect when using Ivabradine in chronic heart failure; a small proportion of patients will experience symptomatic bradycardia, for which dose reduction or cessation of therapy should be considered.
Visual symptoms are also reported.

Appendix F – **Sacubitril Valsartan** in patients with heart failure

Initiation of sacubitril valsartan should be undertaken by **Heart Failure specialists** 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. During this time, efforts should be made to reinforce adherence and address any adverse effects.

Appendix G – **Isosorbide Mononitrate/Dinitrate and Hydralazine** in patients with heart failure due to left ventricular systolic dysfunction

Evidence from clinical trials has shown that patients with LV systolic dysfunction who are intolerant of an ACE inhibitor or an angiotensin-II receptor antagonist, or in whom they are contra-indicated, may be given a nitrate in combination with hydralazine. Furthermore, the combination may be considered in addition to standard therapy (including the addition of sacubitril/valsartan) when the patient remains symptomatic (particularly in patients of African or Caribbean origin who have moderate to severe heart failure).

In practice in the UK isosorbide mononitrate rather than dinitrate is used.

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.

Indications

- Patients who are symptomatic with heart failure with a reduced ejection fraction (≤ 40%) who cannot tolerate an ACEi 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.

Contraindications

- Hypersensitivity to nitrates or hydralazine or excipients
- Acute circulatory failure (shock, vascular collapse)
- Severe tachycardia and heart failure with a high cardiac output (e.g. in thyrotoxicosis).
- Symptomatic or severe asymptomatic hypotension
- 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 (hydralazine)
- Cor pulmonale
- Dissecting aortic aneurysm
- Acute porphyria (hydralazine)

Caution

- 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 m^2
- Pregnancy:
    - *Isosorbide mononitrate* **-** Data on the use of isosorbide mononitrate during pregnancy are insufficient to be able to assess the possible harmful effect; manufacturers advise avoid unless potential benefit outweighs risk
    - *Hydralazine* - manufacturer advises avoid before third trimester

- Breast-feeding - There is data that nitrates are excreted in breast milk and may cause methemoglobinemia in infants. The effects of this exposure on a nursing infant are unknown. As precautionary measure, breast-feeding should be discontinued during treatment with *isosorbide mononitrate*.
  Hydralazine - present in milk but not known to be harmful; monitor infant.

Adverse 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 increase in heart rate. Concomitant use of a beta-blocker will reduce this reflex effect.

Other side effects:

- •Flushing
- •Hypotension
- •Fluid retention
- •Gastro-intestinal disturbances
- •Headache/dizziness – patients should be informed that the nitrate induced headache should diminish and resolve with continued treatment

Initiation and Dose Titration

Initiation: Isosorbide mononitrate (immediate release) 20mg BD in combination with hydralazine 25mg 3-4 times daily.

Up-titration: Isosorbide mononitrate (immediate release): 120 mg daily in divided doses and hydralazine: 50–75 mg 3-4 times a day

Appendix H - **Diuretics** in patients with heart failure

Diuretics are used for the relief of congestive symptoms and fluid retention in patients with heart failure, and titrated (up and down) according to need following the initiation *of subsequent heart failure therapies.*

UK Licensed diuretics for heart failure:
Loop Diuretics - preferred in heart failure, because of their more potent diuretic action.

- ***Furosemide***
  - *Oral or i.v. preparations (bolus or continuous infusion)*
- ***Bumetanide***
  - *Preferred where intestinal oedema limits bioavailability of oral Furosemide*
  - *1 mg Bumetanide is equivalent to 40 mg of Furosemide*

Both act within 1 hour of oral administration and diuresis is complete within 6 hours so that, if necessary, they can be given twice in one day without interfering with sleep. Following intravenous administration they have a peak effect within 30 minutes. The diuresis associated with these drugs is dose related.

Thiazide diuretics – used in resistant oedema in addition to loop diuretics.

- ***Bendroflumethiazide*** *is effective in mild or moderate heart failure but requires preserved renal function (eGFR ≥ 40 ml/min) as it depends on being excreted into the distal tubules.*
- ***Metolazone (unlicensed product in the UK)*** *is particularly effective when combined with a loop should therefore be monitored carefully. This is the only thiazide effective in significant renal dysfunction (eGFR ≤ 40 ml/min) as its action doesn't depend on excretion into the distal convoluted tubules. Prolonged use only under specialist supervision.*

Thiazides are moderately potent diuretics. They act within 1 to 2 hours of oral administration and most have duration of action of 12 to 24 hours; they are usually administered early in the day so that the diuresis does not interfere with sleep.

Potassium-sparing diuretics (e.g. Amiloride) – not recommended in the management of heart failure, because most patients will be taking an ACE inhibitor or ARB and MRA, all of which counteract the potassium-losing effect of loop and thiazide diuretics, increasing the risk of hyperkalaemia.

Cautions

- ***Elderly:*** *Lower initial doses of diuretics should be used in the elderly because they are particularly* susceptible to the side effects. The dose should then be adjusted according to renal function. Diuretics should not be used continuously on a long-term basis to treat simple gravitational oedema (which will usually respond to increased movement, raising the legs, and support stockings).

- Hypovolaemia and hypotension should be corrected before initiation of treatment with loop diuretics

- Exacerbation of diabetes, gout, and SLE.

- **Potassium loss:** Hypokalaemia can occur with both thiazide and loop diuretics. The risk of hypokalaemia depends on the duration of action as well as the potency and is thus greater with thiazides than with an equipotent dose of a loop diuretic

- **Renal impairment:** Diuretics are less effective if the eGFR is less than 30 mL/minute/1.73 m^2 Metolazone remains effective but should only be used under specialist supervision. Electrolytes should be monitored, particularly with high doses, long-term use, or in renal impairment.

- **Hepatic Impairment:** Diuretics should be used with caution in mild to moderate impairment and avoided in severe liver disease.

- **Pregnancy:** Thiazide diuretics may cause neonatal thrombocytopenia, bone marrow suppression, jaundice, electrolyte disturbances, and hypoglycaemia; placental perfusion may also be reduced. Stimulation of labour, uterine inertia, and meconium staining have also been reported. Loop diuretics may be used under specialist supervision.

- **Breast-feeding:** The amount of diuretics present in milk is too small to be harmful; large doses may suppress lactation.

Contraindications

- All diuretics should be avoided in severe hypokalaemia, severe hyponatraemia or hypercalcaemia
- Anuria
- Do not use in comatose and pre-comatose states associated with liver cirrhosis
- Avoid in symptomatic hyperuricaemia
- Thiazide diuretics should be avoided in Addison's disease.

Common adverse effects

- Electrolyte disturbances (including hypokalaemia, hyponatraemia, hypomagnesaemia, hypercalcaemia) often manifest by weakness, dizziness, mental confusion, anorexia, lethargy, vomiting, and cramps.
- Renal impairment – allow up to 30% increase in Creatinine after initiation/up-titration of diuretics
- Hypotension – may manifest as orthostatic dizziness. See Problem Solving below.

Initiation and dose titration

Treatment should be initiated and titrated by those experienced in the management of heart failure. Patients in hospital should be reviewed daily, including assessment of fluid balance and electrolyte levels, and doses changed accordingly.

Drug	Starting dose	Usual daily dose
Bendroflumethiazide	2.5 mg od	2.5-10 mg od
Furosemide	20-40 mg od	40-240 mg (divided doses)
Bumetanide	0.5-1 mg od	1-5 mg (divided doses)
Metolazone	2.5 mg od (alt days)	2.5-5 mg od

Monitor blood pressure, clinical status, symptoms and signs of congestion e.g. *body weight*, breathlessness and oedema daily. Fluid restrict as necessary.

Problem solving

1. **Worsening symptoms/signs** (e.g. increasing dyspnoea, fatigue, oedema, weight gain >1.5kg over 3days):

a) If increased congestion, double dose of diuretic and/or halve dose of beta-blocker (if increasing diuretic does not work).
a. Contact a member of the heart failure team for further review & advice.

2. **Asymptomatic hypotension** does not usually warrant a change in therapy.

3. **Symptomatic hypotension**
   a. If combined with dizziness, light-headedness or confusion, consider discontinuing drugs such as nitrates and other vasodilators.
   b. If no signs/symptoms of congestion, consider reducing dose of diuretic.
   c. If these measures do not solve problem, seek specialist advice.

Appendix I – NICE guidance on **device therapy** in heart failure

When to offer implantable cardioverter defibrillators and cardiac resynchronisation therapy

The following recommendations are an extract from NICE technology appraisal guidance on implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure.

Implantable cardioverter defibrillators (ICDs), cardiac resynchronisation therapy (CRT) with defibrillator (CRT-D) or CRT with pacing (CRT-P) are recommended as treatment options for people with heart failure who have left ventricular dysfunction with a left ventricular ejection fraction of 35% or less as specified below.

	New York Heart Association class			
QRS interval	**I**	**II**	**III**	**IV**
<120 milliseconds	ICD if there is a high risk of sudden cardiac death			ICD and CRT not clinically indicated
120–149 milliseconds without left bundle branch block	ICD	ICD	ICD	CRT-P
120–149 milliseconds with left bundle branch block	ICD	CRT-D	CRT-P or CRT-D	CRT-P
≥150 milliseconds with or without left bundle branch block	CRT-D	CRT-D	CRT-P or CRT-D	CRT-P

NICE has written information for the public on implantable cardioverter defibrillators and cardiac resynchronisation therapy.

Discussing and reviewing treatment

When discussing implantation of a cardioverter defibrillator:

- Explain the risks, benefits and consequences of cardioverter defibrillator implantation, following the principles on shared decision making in the NICE guidance on patient experience in adult NHS services
- Ensure the person knows that the defibrillator function can be deactivated without affecting any cardiac resynchronisation or pacing, and reactivated later
- Explain the circumstances in which deactivation might be offered
- Discuss and dispel common misconceptions about the function of the device and the consequences of deactivation
- Provide the person and, if they wish, their family or carers with written information covering the information discussed.

- Review the benefits and potential harms of a cardioverter defibrillator remaining active in a person with heart failure:
    - At each 6-monthly review of their heart failure care
    - Whenever their care goals change
    - As part of advance care planning if it is thought they are nearing the end of life.

References

[1] **ACEi Trials:**

- CONSENSUS (1987):
  - Enalapril vs placebo – RR of 40% in all cause mortality at 6 months and 27% over entire study period in NYHA IV
- SOLVD (1991):
  - Enalapril vs placebo – RR 16% of death with LVEF <35% in ANY NYHA class.

[2] **ARB Trials**

- Val-HeFT (2001):
  - Valsartan vs placebo – NO mortality benefit.
- CHARM – Alternative (2003):
  - Candesartan vs placebo in those *intolerant of ACEi* – 23% RRR of CV mortality with LVSD
- CHARM – Added (2003)
  - Addition of Candesartan to standard therapy for those with LVSD and persistent symptoms. RR 23.7% vs 27.3%, HR 0.84)
  -

[3] **Beta-Blocker Trials:**

- US Carvedilol Heart Failure Study (1996):
  - First study to show mortality benefit of β blockers in reduced LVEF.
- CIBIS-II (1999); CAPRICORN (2001); COPERNICUS (2001); COMET (2003):
  - Superiority of Bisoprolol and Carvedilol vs placebo and metoprolol with ~35% reduction in mortality.
  -

[4] **Aldosterone Blocker Trial:**

- RALES (1999):
  - Spironolactone vs placebo – 30% reduction in mortality with NYHA III-IV and LVSD.
- EPHESUS (2003)
  - Eplerenone vs placebo after AMI with LVSD – 15% RRR.
- EMPHASIS – HF (2010)
  - Eplerenone vs placebo in NYHA II symptoms and LVSD. 34% reduction in risk of death.
  -

[5] **Ivabradine Trial:**

- SHIFT (2010):
  - Ivabradine vs placebo – 18% reduction in RR for CV death and readmission in LVSD in those on β blockers.
  -

[6] **Digoxin Trial:**

- DIG (1997):
  - Digoxin vs placebo – no mortality benefit, but significant reduction in re-hospitalisations from HF exacerbations.
  -

[7] *European Heart Journal*, Volume 37, Issue 27, 14 July 2016, Pages 2129–2200, https://doi.org/10.1093/eurheartj/ehw128

[8] **Sacubitril/Valsartan Trial**:

- PARADIGM HF (2014):
  - Angiotensin-neprilysin inhibition with LCZ696 (Sacubitril/Valsartan) was superior to enalapril in reducing the risks of death and of hospitalization for heart failure.

NICE Guidelines for management of Chronic Heart Failure
http://guidance.nice.org.uk/CG108/NICEGuidance/pdf/English

NICE Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure https://www.nice.org.uk/Guidance/TA314