North of Tyne and Gateshead Guidelines for Management of Heart Failure
Revised March 2017
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Introduction
This guidance is intended to inform the diagnosis and management of patients with chronic and acute heart failure and updates earlier local guidelines. It has been developed jointly between primary and secondary care and identifies and interprets the recommendations from the NICE Heart Failure guideline\(^1\) published in August 2010, and the NICE TAGs for device therapy (2014)\(^2\) and for treatment with ivabradine (2012)\(^3\) and sacubitril valsartan (2016)\(^4\) for local implementation.

**Underpinning principles**
- The guideline is only intended for patients who are suspected of having heart failure or who have an established diagnosis of heart failure.
- Clinical assessment is fundamental in diagnosing and managing patients and should be performed by a clinician competent to do so.
- Consideration should be given to ensure that diagnostic testing is performed to high quality standards.
- The guideline is intended to guide clinical management, but every patient should be assessed and managed individually, taking into consideration the evidence which underpins the different therapeutic interventions, patient comorbidities and patient wishes.
- In making recommendations for drug treatment it is assumed that clinicians will exclude contra-indications, referring to the BNF and local formulary as necessary, when managing individual patients.
- This local guideline is not a rewrite of national and international guidance, but is a summary of the main points with additional information for local implementation. The NICE and ESC guidelines should be referred to as appropriate.
- There are various sources of patient information, and it is beyond the scope of this guideline to specifically evaluate and endorse any particular ones. Examples include; https://www.bhf.org.uk/publications/heart-conditions/living-with-heart-failure
  https://patient.info/health/heart-failure-leaflet
  http://www.nhs.uk/conditions/Heart-failure/Pages/Introduction.aspx
Patients that the heart failure nurses are seeing, usually have a handheld record.

**Using the guideline**
This guideline is intended to be used by clinicians in Newcastle, North Tyneside, Northumberland and Gateshead who are responsible for diagnosing patients presenting with suspected heart failure or who have an established diagnosis of heart failure. The flow charts (which can be laminated) summarise the diagnostic and management pathways for patients with heart failure and left ventricular systolic dysfunction and heart failure with

\(^{1}\) NICE CG 108 Management of chronic heart failure in adults in primary and secondary care
\(^{2}\) https://www.nice.org.uk/guidance/ta314
\(^{3}\) https://www.nice.org.uk/Guidance/ta267
\(^{4}\) https://www.nice.org.uk/guidance/ta388
preserved left ventricular ejection fraction, as well as a flow chart summarising assessment and management of acute heart failure, with additional notes thereafter.

The BNF and the North of Tyne and Gateshead Formulary should be referred to as appropriate. Information about drug costs (sourced May 2016) is included in the appendix, to help inform prescribing decisions.
Diagnosis of heart failure: recommended for use in patients without an established diagnosis of heart failure or left ventricular dysfunction in whom further diagnostic assessment is being considered

Suspected heart failure?

Assess and investigate for alternative diagnoses as appropriate

Take a detailed clinical history, perform a clinical examination and arrange an ECG

If heart failure still suspected, consider starting appropriate treatment (usually diuretics), and arrange further diagnostic testing

Has the patient had a previous MI (history or definite past MI on the ECG) and/or does the ECG show LBBB?

Take blood for FBC, U&E, eGFR, LFT, TFT, HbA1c, lipids if indicated (see FATS) within 24 working hours

Within 2 weeks

Specialist assessment and Doppler echocardiography

Within 2 weeks

NT-proBNP high (age dependent values)*

Clinical assessment and echo consistent with heart failure?

Yes

Assess precipitating factors, type of cardiac dysfunction, severity and aetiology

No

Consider measuring NT-proBNP if levels unknown

Raised levels (age dependent values)

Consider other diagnoses

Heart failure due to other cardiac abnormality

Heart failure due to left ventricular systolic dysfunction

Heart failure with preserved ejection fraction

Heart failure unlikely, consider other diagnoses

* NT-proBNP age dependent thresholds

<table>
<thead>
<tr>
<th>Age Group</th>
<th>NT-proBNP Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60 years</td>
<td>≥ 50 ng/L</td>
</tr>
<tr>
<td>Age 60-74 years</td>
<td>≥ 100 ng/L</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>≥ 250 ng/L</td>
</tr>
</tbody>
</table>

Hildebrandt et al. EHJ 2010;31:1881-1889
Personal communication. Paul Collinson
Management of patients with chronic heart failure (see main guideline text for more detail)

**Patient education / other interventions throughout the management pathways**
- Informational care (see page 3)
- Lifestyle advice (see page 12)
- Fluid intake
- Self management advice
- Appropriate follow up
- Consider cardiac rehabilitation, or if not available individualised advice (see page 12)
- Social care needs

**Patient with heart failure due to LVSD**
- Review blood results and identify any contra-indications to medications
- Assess fluid status and ensure appropriate diuretic treatment

**Patient with heart failure and preserved LV ejection fraction**
- Assess fluid status and ensure appropriate diuretic treatment
- Manage co-morbid conditions such as diabetes, hypertension and IHD

**Able to tolerate an ACEI**
- Consider sacubitril / valsartan (see appendix)

**Able to tolerate an ACEI or ARB** and no contra-indications to sacubitril / valsartan (see appendix)
- Consider sacubitril / valsartan to replace ACEI (or ARB). See appendix, refer to HF nurse

**Sinus rhythm, resting heart rate ≥ 75 bpm**
- Consider CRT (see table, page 11)

**Consider ivabradine**

**Still symptomatic NYHA IV, in particular if recent / recurrent admissions to hospital**
- Ensure no reversible causes. If may be eligible for heart transplant, ensure been referred to advance heart failure service
- Review goals of therapy and patient preferences for management
- Consider low dose digoxin if sinus rhythm

**Review (all patients with heart failure)**
- All patients require at least a 6 monthly review, some require more frequent follow up (days to weeks), including:
  - Clinical assessment of functional capacity, fluid status, cardiac rhythm (pulse palpation minimum), nutritional status, and cognitive function. Screen for anxiety and depression, and if appropriate falls
  - Consider need for an ECG / cardiology reassessment (eg worsening symptoms, risk of developing arrhythmias/BBB)
  - Drug review - ? Optimised, ? Adverse effects ? Need for changes. Consider risk of developing of AKI and need for individualised advice to the patient in the event of other illness (eg D&V, infections etc)
  - Measure minimum of renal function and electrolytes. Digoxin level (8-12 hours after the last dose) if toxicity or non-adherence is suspected
  - Patient information and education – self management, what to do if condition deteriorates, other informational care
  - Review social care needs
  - If approaching End of Life, review management plan, ensure advanced care planning etc

**Assess response to first line treatment.**
- If still symptomatic (NYHA II-IV) despite optimising diuretics, ACEI and beta blocker treatment, in particular if LVEF ≤ 35%, review renal function and add a mineralocorticoid antagonist (MRA) if no contra-indications
- Consider obtaining specialist advice

**If still symptomatic (NYHA II-IV) and LVEF ≤ 35%**
- Review options for additional treatment (combine if appropriate in a stepwise management plan)
- Consider obtaining specialist advice, if not already done
- If may be eligible for heart transplant, refer to Advanced HF Service (Freeman Hospital)

If LVEF ≤ 35%, on optimal medical management consider indications for ICD (see table, page 11)
Management of patients with acute heart failure in hospital (refer to local trust guidelines as appropriate)

Suspected acute heart failure?
- Yes: Assess and investigate for alternative diagnoses as appropriate
- No: Clinical assessment – history, examination, ECG, chest x ray, blood tests, other ancillary investigations as appropriate,

Consider reversible causes requiring specific early treatment eg arrhythmia, myocardial infarction. Treat as appropriate

Initiate first line treatment for acute heart failure
- Instigate appropriate monitoring – type and frequency
- Assess response within 30 minutes

Is second line treatment required?
- Yes: Review and modify regular treatment, arrange any further investigation required, manage reversible causes
- No: Continue first line treatment for acute heart failure, Instigate appropriate monitoring – type and frequency

Assess response within 30 minutes

Should more intensive interventional treatment be considered?
- Yes: Continue acute management, review and modify regular treatment, review goals of therapy. Arrange any further investigation required, manage reversible causes
- No: Continue acute management, review and modify regular treatment, review goals of therapy. Arrange any further investigation required, manage reversible causes

Initiate second line treatment
- GTN IV infusion, increased as tolerated by BP (managed in at least level 2 care bed)
- Consider repeating first line treatments
- Ensure managed in the most appropriate setting

Assess response within 30 minutes

Should inotropes and or non invasive ventilation be considered (response to initial treatment, ABG)?
- Yes: Initiate appropriate treatment, continue / repeat other treatments
- No: Continue acute management, review and modify regular treatment, review goals of therapy. Arrange any further investigation required, manage reversible causes

Other treatments
- Continue beta blockers if possible, but reduce / stop if heart failure is refractory or hypotension a problem
- Continue ACE inhibitors / ARBs unless hypotension and or renal function are a problem.
- Review any drugs which might exacerbate heart failure

Assess response within 30 minutes

Should more intensive interventional treatment be considered?
- Yes: Arrange further interventional treatment as appropriate
- No: Continue acute management, review and modify regular treatment, review goals of therapy. Arrange any further investigation required, manage reversible causes
**Diagnosis of chronic heart failure**

The diagnostic pathway is summarised in the first flow chart above and is recommended for use in patients without an established diagnosis of heart failure or left ventricular dysfunction. The summary in the quick reference version of the NICE chronic heart failure guideline has been refined to incorporate more explicit recommendations for performing an ECG, and to consider treating patients pending the outcome of specialist assessment and further investigation. The local guideline development group also felt it was appropriate to include recommended timescales within which initial blood tests should be performed. A fasting sample is not required.

Measurement of natriuretic peptides is recommended in patients with no past history of MI to determine if further diagnostic testing is indicated or if heart failure can be ruled out, and it was agreed to use NT-proBNP locally. There is good evidence that levels are influenced by a number of factors, including a powerful influence by age, and in younger patients in particular the thresholds recommended in the NICE guideline were considered to be too conservative. From published evidence and national consensus and personal communication by Dr Neely with Dr Paul Collinson, thresholds for inclusion in the local guideline were agreed, and are included in the flow chart.

**Management of patients with chronic heart failure**

This guideline only includes recommendations for management of patients with left ventricular systolic dysfunction and patients with heart failure with preserved ejection fraction. Patients with other causes of chronic heart failure, including for example valvular heart disease and management of atrial arrhythmias are not included. Management is summarised in the second flow chart above.

**Drug treatment in patients with chronic heart failure and left ventricular systolic dysfunction**

The key components to consider in all patients include:

**First line treatment**
- Diuretics as required to control congestion
- ACE inhibitors and beta blockers in all patients in the absence of contra-indications.

In patients who still have evidence of congestion, ACE inhibitors, such as lisinopril or ramipril, should be started before beta blockers, and beta blockers started once the congestion is controlled. In those without congestion, either ACE inhibitors or beta blockers can be started first. Beta blockers should be started in low dose and up-titrated slowly. In all cases, ACE inhibitors and beta blockers should be up-titrated to target doses if possible. Beta blockers licensed for heart failure should be used (and if necessary other beta blockers should be switched to a licensed preparation). Recommended target doses of commonly prescribed ACE inhibitors and beta blockers are included in the appendix.

The NICE heart failure guideline emphasises that beta blockers should be considered for all patients including in older patients, and those with peripheral arterial disease, erectile dysfunction, diabetes, interstitial lung disease and COPD without reversibility.

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5 Cowie MR et al. Recommendations on the clinical use of B-type natriuretic peptide testing (BNP or NTproBNP) in the UK and Ireland Br J Cardiol 2010;17:76–80
ARBs should only be used in place of ACE inhibitors if patients have been shown to be intolerant of an ACE inhibitor.

Renal function and electrolytes should be measured during titration of ACE inhibitors and ARBs, and periodically when stable. All patients with chronic heart failure should be reviewed at least 6 monthly and more frequently if there are clinical concerns.

The local CKD guideline includes additional recommendations for managing changes in renal function and for managing hyperkalaemia.

If patients are intolerant of both ACE inhibitors and ARBs, hydralazine in combination with nitrates should be considered following advice from specialist care.

The NICE chronic heart failure guideline recommends that mineralocorticoid receptor antagonist (MRAs) are confined to second line treatment in patients with more severe heart failure, and generally to be used with advice from specialist care. However, more recent evidence\(^6\) has shown that eplerenone is also effective in patients with milder symptoms of heart failure if they have other high risk features, including age at least 55 years, and left ventricular ejection fraction no more than 30%, (or if >30% to 35% if the QRS duration is > 130 msecs on ECG). In addition patients had been admitted to hospital for a cardiovascular indication within the last 6 months or the natriuretic peptides were high on other treatment.

It is not recommended for local implementation that natriuretic peptides are measured to determine if patients with mild heart failure should be treated with an aldosterone antagonist, but an MRA (spironolactone or eplerenone) should be considered in all patients with left ventricular systolic dysfunction who remain symptomatic (NYHA II-IV), in particular if left ventricular ejection fraction is ≤ 35%, providing there are no contraindications. If patients are treated with spironolactone and develop oestrogenic side effects (eg gynaecomastia), patients should be considered for a switch to eplerenone.

Renal function and electrolytes (particularly potassium) must be measured at baseline and a week after starting a MRA, after 4 weeks, 3 months and periodically thereafter and as a minimum every 6 months. More frequent measurements may be required in patients with chronic kidney disease and or if there are concerns about developing hyperkalaemia. A recent MHRA\(^7\) alert emphasised the importance of monitoring these patients.

**Second line treatment**

These drugs will generally be used with advice from specialist care.

- Sacubitril valsartan may be substituted for an ACE inhibitor or ARB (and cannot be given in combination with either of those), in line with NICE guidance\(^8\). This should only be initiated from specialist care, with robust arrangements for safe initiation and monitoring. Further information is included in appendix 1.

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\(^8\) https://www.nice.org.uk/guidance/ta388
Hydralazine in combination with a nitrate, in addition to an ACE inhibitor
Might be considered as an option particularly in patients of African or Caribbean origin.

Ivabradine
Beta blockers remain first line and ivabradine is not a substitute when beta blockers are
not contra-indicated, are tolerated and achieve the required therapeutic response.

However, ivabradine is now licensed and has been evaluated by NICE as a single
technology appraisal which states:

1.1 Ivabradine is recommended as an option for treating chronic heart failure for people:
   • with New York Heart Association (NYHA) class II to IV stable chronic heart
     failure with systolic dysfunction and
   • who are in sinus rhythm with a heart rate of 75 beats per minute (bpm) or
     more and
   • who are given ivabradine in combination with standard therapy including
     beta-blocker therapy, angiotensin-converting enzyme (ACE) inhibitors and
     aldosterone antagonists, or when beta-blocker therapy is contra-indicated or
     not tolerated and with a left ventricular ejection fraction of 35% or less
1.2 Ivabradine should only be initiated after a stabilisation period of 4 weeks on optimised
   standard therapy with ACE inhibitors, beta-blockers and aldosterone antagonists.
1.3 Ivabradine should be initiated by a heart failure specialist with access to a
   multidisciplinary heart failure team. Dose titration and monitoring should be carried out by
   a heart failure specialist, or in primary care by either a GP with a special interest in heart
   failure or a heart failure specialist nurse.

**Recommended doses:**
- Initial dose ivabradine 5 mg bd
- After 2 weeks
  - If heart rate > 60 beats per minute, increase to 7.5 mg bd
  - If heart rate 50 to 60 beats per minute, continue 5 mg bd
  - If heart rate < 50 beats per minute and or symptoms and signs of
    bradycardia reduce dose to 2.5 mg bd.

If necessary to manage bradycardia, the dose of ivabradine should be reduced, not the
dose of beta blocker.

Digoxin
May be considered in patients with on-going symptoms of moderate to severe heart failure
despite all other optimal management, particularly those with recent admission(s) to
hospital with worsening heart failure. Lower doses, compared to those for arrhythmia
management, are often sufficient.

**Drug treatment in patients with chronic heart failure and preserved ejection fraction**
- Diuretics as required to control to congestion
- Other drugs should be used as appropriate to manage co-morbid conditions.

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9 NICE single technology appraisal. Ivabradine for treating chronic heart failure.
Other drugs
Other agents should be considered as appropriate for co-morbid conditions, taking into account any contra-indications.

Drugs to try and avoid
Patients with heart failure are usually elderly and may have co-morbid conditions which will lead to polypharmacy. All patients with a new diagnosis of heart failure should have their existing medication reviewed. A number of commonly used drugs may lead to a clinical deterioration of heart failure, in particular:-

- NSAIDs can lead to fluid retention and renal impairment
- ‘Over the counter’ analgesic drugs containing NSAIDS and aspirin
- St John’s Wort, liquorice and some herbal and homeopathic remedies
- Most calcium channel antagonists (except amlodipine and felodipine which should be used only for angina or uncontrolled hypertension)
- Corticosteroids- by causing sodium and water retention
- Tricyclic antidepressant drugs- may depress cardiac function and have pro-arrhythmic effect
- Lithium, as levels can be affected by changes in diuretic doses. Lithium levels should be checked each time U & Es are done.
- Erythromycin and some antifungal agents- prolongation of QT interval; may precipitate ventricular arrhythmias.
- Glitazones may exacerbate fluid retention and should not be used in patients with heart failure or a history of heart failure / left ventricular dysfunction.
- Doxazosin should be used with caution in heart failure as can lead to deterioration of symptoms.
- Flecainide, propafenone and dronedarone are contraindicated.
- Ensure side effects/interactions of any new drugs are checked in BNF prior to commencement.

Device therapy (implantable defibrillators and cardiac resynchronisation therapy)

The NICE TAG\textsuperscript{10} clearly sets out recommendations for considering device therapy in patients with left ventricular systolic dysfunction. Patients with an initial left ventricular ejection fraction \(\leq 35\%\) should have a reassessment of left ventricular function once established taking optimal medical therapy for 3 months. If left ventricular ejection fraction remains \(\leq 35\%\) the table below from the NICE TAG summarises the indications for device therapy.

\textsuperscript{10} https://www.nice.org.uk/guidance/ta314
Management of patients with resistant heart failure, including right heart failure with congestion

These recommendations are for patients being managed in hospital or if as an out-patient, in liaison with a specialist clinician.

- Remember salt and fluid restriction, and bed rest
- DVT prophylaxis
- Increase diuretic dose (furosemide can be increased up to 500 mg od or more, particularly in CKD)
- Consider switching furosemide to bumetanide: experience is that in some patients this leads to a better diuresis
- Consider IV diuretic: intermittent bolus or infusion
- Consider the combination of a loop diuretic with a thiazide eg furosemide 120 mg od / bendroflumethiazide 1.25 – 2.5 mg od initially. Watch U&E
- High dose bendroflumethiazide or intermittent metolazone, in combination with a loop diuretic may be needed.

Some patients with decompensated heart failure respond poorly during community management. In which case whether patients are admitted to hospital, have ambulatory care or continue with community management should be determined on an individual patient basis, taking into account what additional management options there are, patient and carer wishes and social circumstances.

Lifestyle advice

- Physical activity
  Basic physical activity recommendations are:-
  - Walking, cycling/static bike and gentle resistance exercise.
  - Gentle resistance exercise at home using stairs, lifting weights (for example, tins of beans), and squats can be encouraged.
Initially aim for slow gentle progression aiming to achieve initially 15 minutes - once achieved a gradual increase to 30 minutes x 5 weekly.

Current Government guidelines advocate 30 minutes x 5 weekly. (This can be achieved in 5/10/15/20 minute blocks). Patients should be able to exercise but be able to hold a conversation through their exercise. All breathlessness should resolve on resting.

**AVOID**
- Swimming, jogging, heavy lifting, and gymnasium work unless advised by the Cardiac Rehabilitation Team / cardiologist

**Contra-Indications for Exercise**

- MI – previous 3 weeks
- Symptomatic aortic stenosis
- Acute Infection
- Progressive worsening of exercise tolerance, until assessed and management stabilised
- Worsening of symptoms, until managed appropriately
- Complex ventricular arrhythmia at rest or exercise induced, until stabilised
- Decrease in systolic blood pressure during exercise
- Resting Heart Rate ≥100 beats per minute until managed appropriately
- Patients who are NYHA IV should have individualised advice and management

Limited access to heart failure rehabilitation is available via secondary care of the heart failure specialist nurses.

- Smoking cessation
- Alcohol; within safe limits unless patients have an alcohol related cardiomyopathy when complete abstinence should be recommended.
- Diet, including avoiding excess salt and fluid intake
- Make recommendations to address over weight and obesity
- Vaccination

**Patient education and information**

Patients should have information about their condition, including information to allow them to participate in planning their care and in the on-going management of their condition as appropriate.

Other advice should be tailored to the individual, for example with respect to occupational and leisure activities, driving requiring category 2 licence (refer to DVLA website), travel and sexual activity.

Appropriate and accurate information should be provided about prognosis when it is timely to do so.

**Review and monitoring**

There should be secure arrangements for clinical review and monitoring. All patients require at least a 6 monthly review, some require more frequent follow up (days to weeks), including;
• Clinical assessment of functional capacity, fluid status, cardiac rhythm (pulse palpation minimum), nutritional status and cognitive function.
• Assess patients as appropriate, for symptoms of anxiety and depression
• Drug review - ? optimised, ? adverse effects ? need for changes
• Is there an indication for device therapy
• Measure minimum of renal function and electrolytes. Digoxin level (8-12 hours after the last dose) only if toxicity is suspected
• Patient information and education – self management, what to do if condition deteriorates, other informational care
• Review social care needs
• If approaching End of Life, review management plan, ensure advanced care planning and an emergency health care plan is in place if appropriate etc

**Cardiac rehabilitation**

Stable patients should be offered a supervised exercise based programme designed for patients with heart failure as local resources allow. The programme should include psychological and educational components. When a cardiac rehabilitation programme is not available, patients should be offered individualised advice.

**Integration between primary and secondary care, and with social care**

Individual patient management plans and service provision should be integrated between primary, community and secondary care with effective communication between them, and with the patient. Social care needs should also be considered and addressed.

**Other interventions**

• Transplantation and left ventricular assist devices

• There is no good evidence for revascularisation in patients with coronary artery disease for the management of heart failure, and NICE guidelines do not recommend it is done routinely. Studies about this are ongoing and management should be individualised. An opinion from a cardiologist should be obtained if there is uncertainty.

**End of life care**

This should be discussed when it is appropriate to do so, tailored to the wishes of individual patients. Deactivation of ICDs should be done in line with other local guidelines for this [here](http://www.necvn.nhs.uk/content.aspx?id=1972&terms=ICD+deactivation) and the writing of an emergency healthcare care plan considered.
Management of acute heart failure

Initial management is summarised in the third flow chart, and any local Trust guidelines, including for the local diagnostic pathway for suspected heart failure, should also be referred to. All patients should be treated as an emergency and following initial investigation and treatment should be reassessed within a timescale appropriate for the individual, this might be within a few minutes, but as a minimum within 30 minutes. Ongoing monitoring and identification and management of any reversible causes are important, and patients' longer term regular treatment and management plan should always be reviewed. NICE recommend specialist advice about management is obtained for all patients admitted because of heart failure.

If possible treatment with beta blockers should be continued, but may need to be reduced or stopped if heart failure is refractory and or hypotension is a problem. In many patients ACE inhibitors/ ARBs can be continued, but may need to be stopped if renal function and or hypotension is a particular problem.

Discharge should be:

- When stable
- With a management plan and with arrangements for follow up in the community with the GP and a heart failure nurse.

The provision of heart failure nurse follow up and monitoring will be determined by available capacity, but ideally should be available to all patients. Community heart failure nursing should integrate with primary and secondary care.
Appendices

Appendix 1

The following sections provide practical guidance for problem solving with drugs in patients with heart failure and reduced ejection fraction, taking into account the recommendations made in the web appendix to the ESC 2016 heart failure guidelines\textsuperscript{11}. In all cases, management should be individualised taking into account the overall clinical status of the patient. The BNF, individual SPCs and the ESC heart failure guidelines appendix should be referred to as appropriate. There are separate sections for:

- ACE inhibitors / ARBs
- Beta blockers
- Mineralocorticoid antagonists (MRAs)
- Diuretics
- Ivabradine

Sacubitril / valsartan is included in appendix 2.

\textsuperscript{11} doi:10.1093/eurheartj/ehw128
Asymptomatic low blood pressure does not usually require any change in therapy.  

Symptomatic hypotension
- Dizziness / lightheadedness are common and often improve with time – patients should be reassured.
- Consider discontinuing nitrates, calcium channel blockers and other vasodilators before changing dose of ACE inhibitor/ARBs
- If no signs/symptoms of congestion consider reducing diuretic dose.  
  If these measures do not solve problem seek specialist advice.

Cough
- Cough is common in patients with chronic heart failure, many of whom have smoking-related lung disease.
- Cough is also a symptom of pulmonary oedema which should be excluded when a new or worsening cough develops.

Only relates to ACE inhibitors:
- ACE Inhibitor cough is characterised by a tickle starting in the back of the throat and is persistent and dry, it usually starts within 1-6 weeks (but in some patients can start months or up to a year) of starting the ACE inhibitor but rarely requires treatment discontinuation and often improves within 3-6 months of continued treatment.
- If the patient develops a troublesome dry cough which interferes with sleep and is likely to be caused by an ACE inhibitor, consider substituting an ARB e.g. Candesartan for the ACE inhibitor.

Worsening renal function
- These recommendations are drafted with reference to the ESC HF guidelines 2016, and should be considered alongside those in the local CKD guidelines.
- ACEI/ARB therapy should not normally be started if the pre-treatment serum potassium concentration is significantly above the normal reference range (typically >5.0 mmol/l), without first discussing with specialist care.
- Stop ACEI/ARB therapy and other drugs known to promote hyperkalaemia if the serum potassium concentration rises to above 6.0 mmol/l. Consider if referral to hospital for immediate assessment and treatment is required.
- If creatinine is >200µmol/l, seek specialist advice before initiating ACEI/ARB therapy
- Following the introduction or dose increase of ACEI/ARB, do not routinely modify the dose if either the GFR decrease from pre-treatment baseline is <25% or the plasma creatinine increase from baseline is <30%.
- If there is a fall in eGFR or rise in plasma creatinine after starting or increasing the dose of ACEI/ARB, but it is less than 25% (eGFR) or 30% (serum creatinine) of baseline, the test should be repeated in a further 1–2 weeks. Do not routinely modify the ACE/ARB dose if the change in eGFR <25% or change in plasma creatinine is <30%.
- If the eGFR change is ≥25% or change in plasma creatinine is ≥30%:-
  1. Stop NSAID, amiloride, triamterene, non-essential vasodilators (e.g. calcium channel blockers, nitrates) if prescribed and review U and E’s one week
  2. If no improvement in eGFR or above not prescribed and no signs of fluid volume overload, reduce loop diuretic dose and review patient and, eGFR, U and E’s in one week
  3. If no improvement in renal function and or patient is not taking loop diuretics and there are no signs of fluid overload, consider reducing the dose of MRA if taken and or reduce to a lower dose of ACE or ARB and review patient and U and E’s in 2 weeks.
  4. If already on lowest dose ACE or ARB or no improvement in eGFR stop ACE or ARB and refer for specialist opinion if not already done so
- If creatinine is > 350µmol/l, the ACE inhibitor or ARB should be stopped and specialist advice sought.
- Blood electrolytes and renal function should be monitored closely until K+ and creatinine concentrations are stable.

Note:
Management requires regular review of clinical status, and haemodynamics and fluid status, not just a review of blood biochemistry. Patients who are acutely unwell and or have AKI may need referral to hospital for immediate assessment and treatment
It is very rarely necessary to stop ACE inhibitor/ARB and clinical deterioration is likely if treatment is withdrawn; ideally, specialist advice should be sought before treatment discontinuation.
Angiotensin II Receptor Blockers

Angiotensin II Receptor Antagonists can be considered as an alternative to ACE inhibitors in patients who are intolerant to or contra-indicated to an ACE inhibitor. ACE inhibitors and Angiotensin II Receptor Antagonists are not routinely used together and would only be considered after specialist assessment.

Examples of some ACE inhibitors and ARBs are given below.

<table>
<thead>
<tr>
<th>ACE inhibitor and Angiotensin II Receptor Blocker titrations</th>
<th>ACE Inhibitors</th>
<th>Titration</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAMIPRIL</td>
<td>Initiation 1.25mgs od→ 2.5mgs bd→ 5mgs bd or 10mg od (Increase in two week increments)</td>
<td>5mgs BD or 10mg daily</td>
<td></td>
</tr>
<tr>
<td>LISINOPRIL</td>
<td>2.5mgs od→ 5mgs od→ 10mgs od→ 15mgs od→ 20mgs od→ 30mgs od (Increase in two week increments)</td>
<td>20-30mgs daily</td>
<td></td>
</tr>
<tr>
<td>ENALAPRIL</td>
<td>2.5mgs od→ 5mgs od→ 10mgs od→ 5mgs od→ 20mgs od (Increase in two week increments)</td>
<td>20mgs daily or 10 mg bd</td>
<td></td>
</tr>
<tr>
<td>PERINDOPRIL</td>
<td>Initiate at 2mgs od→ 4mgs od (In LVSD post MI uptitrate to 8mgs daily) (Increase in two week increments)</td>
<td>4 – 8 mgs daily</td>
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</table>

If truly intolerant to ACE Inhibitor (due to cough), consider Angiotensin II Receptor Antagonist.

| Candesartan | Initiate 4mgs od→ 8mgsod→ 16mgs od→ 32mgs od (Increase in two week increments) | 32mgs daily |
**Beta Blockers**

Switch stable patients who are currently taking non-licensed beta blockers for another co-morbidity to one which is licensed for heart failure during clinical review.

**Beta Blockers** are well tolerated in heart failure and should be considered for all patients with LVSD, including older patients, who do not have contra indications.

- **Contra-indications**
  - True Bronchial Asthma (unless after specialist assessment and recommendation)
  - Heart Block or heart rate < 55bpm (in absence of a pacemaker)
  - Sick sinus syndrome
  - Liver disease
  - Hypersensitivity to beta blockers
  - Metabolic acidosis
  - Cardiogenic shock
  - Prinzmetal angina
  - Critical limb ischaemia (until treated)
  - Phaeochromocytoma
  - Known allergy / adverse reaction
  - Persistent congestion (seek specialist advice first)

- **Cautions (but beta blockers can still be initiated)**
  - Renal and hepatic impairment
  - Diabetes
  - Peripheral arterial disease
  - Interstitial pulmonary disease
  - COPD without reversibility
  - Erectile Dysfunction
  - Systolic BP < 90mmHg
  - Heart rate < 60bpm
  - Patients taking rate limiting calcium channel blockers (discontinue first)
  - Pregnancy and lactation

- **Pre-initiation checks**
  - Clinically stable
  - ECG: heart rate >55/min
  - Systolic BP >90mmHg
  - No contra-indications

- **Bisoprolol titration**
  - Starting dose 1.25mg once daily
  - Target dose 10mg once daily
  - Start at low dose and increase by increments of 1.25mg until 5mg, **at no less than 2 weekly intervals**
  - When at 5mg, increase by 2.5mg increments at monthly intervals

- **Carvedilol titration**
  - Starting dose 3.125mg twice daily
  - Target dose 25-50mg twice daily*
  - Start at low dose and double dose **at no less than two weekly intervals**
  - *Carvedilol – maximum dose of 25mg twice daily in severe heart failure. In mild to moderate heart failure if weight is > 85kg – maximum dose of 50mg twice daily
  - No monitoring required

- **Other considerations**
  - Verapamil/diltiazem (rate limiting calcium channel blockers) should be discontinued unless absolutely necessary (specialist advice). Diltiazem & verapamil are generally contraindicated in CHF. Verapamil must be avoided in combination with beta-blockers
  - Aim for target dose, failing that, the highest tolerated dose.
  - Titration should be tailored to suit individual needs of patients. This may mean that titration schedules are slightly variable.
  - Check U & E’s 1-2 weeks after initiation and 1-2 weeks after final dose titration
  - Nebivolol can be considered for patients over the age of 70 with mild to moderate heart failure who cannot tolerate Bisoprolol or Carvediolol
  - The local formulary should be taken into account when making drug choices
# Problem solving – Beta Blockers

## Worsening Symptoms/Signs (Increasing dyspnoea, fatigue, peripheral oedema, weight gain)

- If increasing congestion, increase diuretic dose for 3 days, if symptoms resolve revert to lower diuretic dose & continue with beta blocker.
- If symptoms persist consider reducing or stopping beta blocker dose temporarily.
- If any dose other than the lowest dose is being stopped, consider obtaining specialist advice first.
- Do not attempt to up-titrate or re-initiate beta blocker, until the patient has been stable for at least 2 weeks.

## Excessive Bradycardia

Heart rate < 55/min and:
- If symptomatic, consider reducing or stopping beta blocker
- If asymptomatic, revert to the lower beta blocker dose
- Consider stopping or reducing other rate controlling drugs first (e.g. digoxin, amiodarone, diltiazem). Verapamil must not be used in combination with beta blockers.
- Review within 1 week and seek specialist advice if bradycardia persists

Heart rate <45/min
- Obtain 12-lead ECG to exclude heart block and reduce or stop beta blocker

## Asymptomatic low blood pressure does not usually require any change in therapy.

## Symptomatic Hypotension (e.g. Dizziness, light-headedness, confusion)

- If no signs/symptoms of congestion, consider reducing diuretic dose
- If symptoms persist, consider reducing or stopping other drugs which can lower blood pressure and have no value in heart failure.
- Consider temporarily reducing the ACE inhibitor dose
- If symptoms persist, consider reducing or stopping the beta blocker. Ideally, seek specialist advice before stopping beta blocker.
- Do not attempt to up-titratre or re-initiate beta blocker, until the patient has been stable for at least 2 weeks

### Note

Beta Blockers should not be stopped suddenly unless absolutely necessary (risk of a rebound increase in MI and arrhythmias), and patients should be advised to avoid doing so without obtaining advice from a health professional first
Diuretics

Diuretics should be routinely used for the relief of congestion and fluid retention in patients with heart failure, and titrated (up and down) according to need following the initiation of subsequent heart failure therapies. Low to medium dose of loop diuretics should also be offered to patients with a preserved ejection fraction to manage symptoms of volume overload. The following is given for guidance only and each patient requires individual clinical assessment. Treatment decisions should not be made from blood chemistry results alone.

Diuretics Flow Chart

Deteriorating HF Symptoms
- Daily weight ↑ > 1kg above dry weight
- Sustained over 2-3 days
- With/without symptoms of ↑ dyspnoea and/or ↑ peripheral oedema
- Stable blood chemistry

Stable HF Symptoms
- Do not change dose if weight is static and symptoms are stable
- Daily weight ↓ < 1kg below dry weight
- Sustained over 2-3 days
- No symptoms of ↑ dyspnoea or peripheral oedema and/or symptoms of thirst, dizziness or generally feeling washed out

Increase dose of:
- Furosemide:
  - Current Dose
    - 40mg od
    - 80mg od
    - 80mg & 40mg
    - 80mg bd
  - Increased to
    - 80mg od
    - 80mg & 40mg
    - 80mg bd
    - * 120mg & 80mg

- Bumetanide:
  - Current Dose
    - 1mg od
    - 2mg od
    - 2mg & 1mg
    - 2mg bd
  - Increased to
    - 2mg od
    - 2mg & 1mg
    - * Seek specialist advice

Patients symptoms should be reviewed in 3 days and if an increased diuretic dose is sustained, blood chemistry should be checked.

Decrease dose of:
- Furosemide:
  - Current dose
    - 80mg bd
    - 80mg & 40mg
    - 80 mg & 40 mg
    - 80mg od
  - Decreased to
    - 80mg & 40mg
    - 80mg od
    - 80mg od
    - 1mg od

- Bumetanide:
  - Current dose
    - 2mg bd
    - 2mg & 1mg
    - 2mg od
  - Decreased to
    - 2mg & 1mg
    - 2mg od
    - 1mg od

Patient’s symptoms should be reviewed 3 days following a diuretic reduction for signs of deterioration.

- The goal of diuretic treatment should be to achieve a dry weight using the lowest diuretic dose possible.
- A flexible diuretic regime should be encouraged to suit patient needs. Daily timing need not be fixed. Diuretics can be taken up to mid-afternoon, if inconvenient to take in mornings.
- Observe for signs of over treatment: dizziness/light headedness/fatigue (washed out feeling), uraemia and gout.
- Over treatment can occur if the patient develops diarrhoea, vomiting. Hot weather and reduced fluid intake can also exacerbate over treatment.
- Non-specific symptoms may occur in the elderly such as confusion, impaired mobility, falls and urinary incontinence.
Thiazide and thiazide-like diuretics

These diuretics may be used in combination with loop diuretics in patients with severe heart failure. Unlike loop diuretics, thiazide and thiazide-like diuretics are long acting and adjustment of the timing of dosing is not advantageous as for loop diuretics.

Combinations of thiazide/thiazide-like diuretics and loop diuretics must be used with extreme caution with close clinical and biochemical monitoring and will usually be initiated by a member of the heart failure specialist team. It is advisable to seek advice from the team before considering commencing a thiazide in such combinations.

Add Bendroflumethiazide to loop diuretic
- Start at 2.5mg on alternate days
- Review symptoms after 3 days
- If symptoms stable, repeat U & Es weekly for first 4 weeks then monthly thereafter
- If no improvement in symptoms, increase to 2.5mg daily and review after 1 week. Repeat U & Es as above
- If still symptomatic on 2.5mg daily, seek specialist advice.

Problem solving (consider asking for specialist advice / support with management)
- Consider reducing bendroflumethiazide to 2.5mg to alternate days or stopping, if patient shows signs of hypovolaemia, renal impairment or heart failure has stabilised
- Review after 1 week
- Consider stopping bendroflumethiazide if taking, if no sign of decompensation

If no improvement in condition and patient remains symptomatic, contact Heart Failure Specialist team

Please note: Metolazone is currently no longer available as a licensed product in the UK. Unlicensed imports of metolazone are available as a “special” but difficulties in obtaining supplies have been reported. Metolazone should be reserved for treatment following specialist advice.
Mineralocorticoid Antagonists (MRAs) (ie Spironolactone and Eplerenone)

**Spironolactone / eplerenone**
Spironolactone is given to improve symptoms, prevent worsening of heart failure and to increase survival. Symptom improvement occurs within a few weeks to a few months of starting treatment. Where an MRA is indicated in primary care, either can be used (generic eplerenone is now available).

### Assess suitability for treatment
- In all patients with persisting symptoms (NYHA II-IV) and LVEF ≤ 35% (LVEF ≤ 40% if 3 to 14 post acute MI) despite optimal therapy with an ACE inhibitor and/or beta-blocker (unless contra-indicated or not tolerated).
- Dose 12.5mg-25mg daily (50mg may be advised by a specialist if heart failure deteriorates and no problem with hyperkalaemia)

### Pre-initiation checks
- Potassium supplements & potassium sparing diuretics (e.g. Amiloride) should be discontinued prior to spironolactone being commenced.
- Stop NSAIDs and do not start NSAIDs in treated patients. If NSAIDs are being considered, do so with extreme caution and not without careful assessment of renal function and electrolytes, and considering potential risks of treatment
- Check renal function and electrolytes (particularly serum potassium) before initiation
- If serum creatinine > 200 micromol/l, eGFR < 30 ml/min/1.73m², and or serum potassium (K+) > 5 mmol/l, seek specialist advice before initiation
- If considering eplerenone, be aware of an interaction with strong CYP3A4 inhibitors (eg ketoconazole, clarithromycin, ritonavir – see BNF and ESC HF guidelines for full list)

### MRA initiation
- Start Spironolactone / eplerenone 25mg on alternate days for 2 weeks then increase to 25mg once daily, if U & E’s permit. (Target dose 25mg-50mg once daily)
- Check renal function and electrolytes one week after each dose titration, and then at 4, 8 and 12 weeks, then at 6, 9 and 12 months. Continue 6 monthly monitoring of renal function and electrolytes as a minimum long term

### Problem Solving
- If serum potassium rises to 5 – 5.5 mmol/l, consider repeating renal function and electrolytes earlier than routinely planned. Ensure other potassium sparing drugs have been stopped
- If serum potassium rises to > 5.5 mmol/l, but is less than 6 mmol/l, and or creatinine to > 220 micromol/l, halve the MRA dose and monitor renal function and electrolytes closely (within a week). If no improvement in U & E’s after 1 to 2 weeks, consider stopping spironolactone after discussion with heart failure specialist
- If serum potassium rises to ≥ 6 mmol/l, and or creatinine > 310 micromol/l, stop MRA immediately. Consider if immediate admission to hospital is required.
- If patients experience significant gynaecomastia whilst treated with spironolactone, consider switching to eplerenone, repeating the renal function and electrolytes after as week, with ongoing monitoring as above

### Cautions, include
- Elderly
- Hepatic impairment
- Renal impairment
- Acute porphyria
- Be aware of drug interactions (see BNF)

### Contra-indications, include
- Hyperkalaemia
- Hyponatraemia
- Addison’s Disease
- Pregnancy and breast feeding
- Previous adverse reaction
Ivabradine

Ivabradine should be initiated by a heart failure specialist with access to a multidisciplinary heart failure team, as recommended in the NICE TAG. Dose titration and monitoring should be carried out by a heart failure specialist and multidisciplinary team or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse.

Assess suitability for treatment

Consider in symptomatic patients (NYHA class II-IV) with LVEF ≤ 35%, in sinus rhythm and with a resting heart rate ≥ 75 bpm who are already optimally treated with with standard therapy including beta-blocker therapy, ACE inhibitors and MRAs, or when beta-blocker therapy is contraindicated or not tolerated.

Ivabradine should only be initiated in patients who have been stable for at least 4 weeks on optimised standard therapy with ACE inhibitors, beta-blockers and MRAs, as tolerated.

Initiation and Monitoring of Ivabradine

- Start with a dose of 5 mg bd (or if aged ≥ 75 years, consider 2.5 mg bd initially, and titrate as appropriate).
- After two weeks of treatment:
  - If resting heart rate is persistently above 60 bpm, increase to 7.5 mg bd, or
  - If resting heart rate is persistently below 50 bpm or if symptoms related to bradycardia (such as dizziness, fatigue or hypotension), decrease to 2.5 mg bd
  - If resting heart rate is between 50 and 60 bpm, the dose of 5 mg bd should be maintained.
- Monitor heart rate, blood pressure and clinical status.

Problem Solving

- Reduce dose or stop if resting heart rate decreases persistently below 50 bpm at rest or the patient experiences symptoms related to bradycardia (reduce ivabradine, not the beta blocker)
- Arrange an ECG if resting heart rate ≤ 45 bpm to exclude heart block
- Ensure non-essential drugs which may exacerbate bradycardia have been stopped.
- Stop if develops persistent atrial arrhythmias.
- Ivabradine can cause visual disturbances, especially where sudden variations in light intensity may occur. Patient should be advised regarding driving, especially when driving at night and when operating machinery. Visual symptoms are usually transient, and resolve during the first few months of treatment, but in the event of patient discomfort, ivabradine could be stopped.

Drug Interactions, include

- Contra-indicated in combination with strong cytochrome P450 3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone
- Avoid in combination with verapamil or diltiazem, and monitor for bradycardia in combination with digoxin and amiodarone
- Grapefruit juice should be restricted when taking Ivabradine
- Precaution with use in moderate CYP3A4 inhibitors and CYP3A4 inducers (see spc for full details http://www.medicines.org.uk/EMC/medicine/17188/SPC/Procoralan/#INDICATIONS

Contra-indications

- Adverse reaction to ivabradine
- Unstable cardiovascular disease
- Severe renal or liver disease
- Sick sinus syndrome
- Pregnancy and lactation
- Not indicated in atrial arrhythmias

Cautions / seek specialist advice

- Moderate liver / renal disease
- Severe (NYHA IV) heart failure
- Chronic retinal diseases, including retinitis pigmentosa
Appendix 2

Criteria and operational arrangements for the local implementation of sacubitril valsartan in Newcastle, North Tyneside, Northumberland and Gateshead

Patients should meet the following criteria

- The NICE TAG\textsuperscript{12} states that “Sacubitril valsartan is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction, 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 angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBs)”.

- Patients should be optimally treated with ACE inhibitor or ARB, beta blockers and spironolactone as tolerated, and recent left ventricular ejection on treatment ≤ 35%

- Recent (within the last 4 weeks) serum potassium ≤ 5.4 mmol/l

- Recent (within the last 4 weeks) e GFR ≥ 30 ml/min/1.73m\textsuperscript{2}

- Systolic blood pressure ≥ 100 mmHg

- Seen by a consultant cardiologist for a discussion about the advantages of treatment, and also about possible side effects and the uncertainty about potential long term adverse effects

- Access to a specialist heart failure nurse, with capacity to manage and monitor the patient during initiation and stabilisation of treatment

Process for initiation and monitoring treatment

Request to initiate and monitor the sacubitril valsartan to be sent by letter by the cardiologist to the specialist heart failure nurse team in the appropriate locality, with a copy to the GP.

\textbf{The specialist heart failure nurse team will:}

Ensure they have sufficient capacity to initiate and monitor treatment

Discuss and ensure secure arrangements for the patient to stop the ACE inhibitor / ARB for 48 hours before starting sacubitril valsartan.

Ensure baseline renal function and potassium have been measured and are within the acceptable limits and systolic blood pressure is ≥ 100 mmHg

\textsuperscript{12} https://www.nice.org.uk/guidance/ta388
Arrange initiation of treatment with sacubitril valsartan after the ACE inhibitor / ARB has been stopped for a minimum of 48 hours.

Recommended starting dose one tablet of 49 mg/51 mg twice daily, reduced to 24 mg/26 mg twice daily, if systolic blood pressure 100 – 110 mmHg and or in moderate renal impairment, ie eGFR 30-60 ml/min/1.73 m². A lower starting dose may also be considered if there are concerns about tolerability eg lower tolerated dose of ACE inhibitor / ARB before being switched.

Ensure patients have the "Entresto alert card", that they know to carry this with them and show it to any health professional who may be considering them for any additional treatment.

Ensure that patients have appropriate information and education about sacubitril valsartan and in particular that they must not all also take an ACE inhibitor and or ARB.

Ensure that patients have a telephone number to contact the specialist heart failure nurse team and that there are secure arrangements for follow up and monitoring.

Review the patient, check blood pressure and check renal function and serum electrolytes after 1 to 2 weeks (or earlier if clinically indicated).

If repeat renal function and serum potassium on initial treatment are within acceptable limits, and systolic blood pressure ≥ 100 mmHg, uptitrate sacubitril valsartan as tolerated, doubling the dose with a target dose of one tablet of 97 mg/103 mg twice daily, as tolerated.

Continue to review and monitor the patient, including checking blood pressure and renal function and electrolytes, until clinically and biochemically stable, on a stable dose of sacubitril valsartan for at least 3 months, before discharging for ongoing management in primary care (unless the patient remains for an extended period of monitoring with the specialist heart failure nurse team).

Ensure that all changes in medication are communicated to the GP and that the GP is informed when the patient is discharged from regular management by the specialist heart failure nurse team.

Patients will be reviewed 6 monthly in primary care, including with repeat measurement of renal function and electrolytes, (3 monthly if also treated with spironolactone or eplerenone), or more frequently if there are concerns about change in renal function and or electrolytes.
**Troubleshooting / other points**

If patients experience problems such as systolic blood pressure ≤95 mmHg, symptomatic hypotension, hyperkalaemia, renal dysfunction, management should be individualised, and may include adjustment of other drugs dependent on fluid status, and if necessary temporary down–titration or discontinuation of sacubitril valsartan.

The specialist heart failure nurse / GP should obtain additional advice from the consultant cardiologist if necessary.

If a consultant cardiologist chooses to initiate and prescribe sacubitril valsartan themselves, the consultant will ensure there are arrangements for safely initiating this after a wash out period for the ACEI/ ARB and for follow up and monitoring.

The SPC states that “Entresto” be stored in the original package in order to protect from moisture. Further clarification has been asked for from the company regarding a compliance aid being used with “Entresto” who have responded that they cannot recommend the storage of a product other than as detailed in its Summary of Product Characteristics, and that there is no information on the storage of “Entresto” tablets in compliance aids. At the present time, the use of a compliance aid therefore cannot be endorsed, pending further information\(^\text{13}\).

Natriuretic peptide levels are affected by sacubitril / valsartan. The SPC states “BNP is not a suitable biomarker of heart failure in patients treated with Entresto because BNP is a neprilysin substrate. NT-proBNP is not a neprilysin substrate and is therefore a more suitable biomarker.”

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\(^{13}\) Added June 2016: The manufacturer has further responded, stating that the Summary of Product Characteristics (SmPC) provides the following information regarding storage:

**From Section 6.4 Special precautions for storage**

*This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from moisture.*

Any storage of the product other than as stated in the SmPC would be off licence and is therefore not recommended by Novartis. Furthermore, no studies on storing Entresto in dosette boxes have been conducted. With this in mind, please be informed that stability studies have been conducted on Entresto in so called ‘open dish’ conditions, where tablets were exposed to an ambient temperature (25°C) and 60% relative humidity without any packaging. Please note all tablets were found to be stable for at least 3 months under those conditions. Please note, Novartis recommends that the product should only be stored in compliance with its SmPC. If any storage medium other than the original licensed packaging is used, this is under the responsibility of the concerned healthcare professional.
Appendix 3

Examples of recommended target doses of commonly prescribed ACE inhibitors, beta blockers and ARBs

Lisinopril 30-40 mg od

Ramipril 5 mg bd or 10 mg od

Perindopril 8 mg od

Bisoprolol 10 mg od

Carvedilol 25 mg bd (in the absence of severe heart failure, 50 mg bd if weight > 85kg)

Candesartan 32 mg od

Losartan 150 mg od

Costs of heart failure drugs

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Appendix 4

Membership of the group (2017); TBC
Dr Kristian Bailey, Consultant Cardiologist, Newcastle upon Tyne Hospitals NHS Foundation Trust
Dr Rachel Cooper, GP, Newcastle Gateshead CCG
Vivienne Crisp, BHF Heart failure specialist nurse, Newcastle upon Tyne Hospitals NHS Foundation Trust
John Eastland, Heart failure specialist nurse, Northumbria Healthcare NHS Foundation Trust
Matthew Lowery, Formulary Pharmacist, Newcastle upon Tyne Hospitals NHS Foundation Trust
Dr Guy MacGowan, Consultant Cardiologist, Newcastle upon Tyne Hospitals NHS Foundation Trust
Dr Steve Kirk, GP, Newcastle Gateshead CCG
Dr Dave Morris, Consultant Cardiologist, Northumbria Healthcare NHS Foundation Trust
Dr Frances Naylor, GP, Northumberland CCG
Dr Dermot Neely, Consultant in Clinical Biochemistry, Newcastle upon Tyne Hospitals NHS Foundation Trust
Dr Mark Redpath, Consultant in Clinical Biochemistry, Northumbria Healthcare NHS Foundation Trust
Judith Robson, Community heart failure nurse, Northumbria Healthcare NHS Foundation Trust
Dr Craig Runnett, Consultant Cardiologist, Northumbria Healthcare NHS Foundation Trust
Dr Mike Scott, GP, Newburn, Newcastle
Dr David Shovlin, GP, West Northumberland
Dr Jane Skinner, Consultant Community Cardiologist, Newcastle upon Tyne Hospitals NHS Foundation Trust
Dr Caroline Sprake, GP, North Tyneside CCG
Sarah Tulip, Medicines Management, Newcastle and Gateshead CCG
Susan Turner, Medicines Optimisation, North of England Commissioning Support Unit

Date of guideline
May 2011, updated May 2016, further update March 2017

Review date
March 2020