

## SIGN 147 • Management of chronic heart failure

*A national clinical guideline*

*March 2016*

## KEY TO EVIDENCE STATEMENTS AND RECOMMENDATIONS

### LEVELS OF EVIDENCE

1 <sup>++</sup>	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1 <sup>+</sup>	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 <sup>-</sup>	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2 <sup>++</sup>	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2 <sup>+</sup>	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 <sup>-</sup>	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

### RECOMMENDATIONS

Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation).

The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation.

Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence, and the balance of benefits and harms of the options.

**R** For **'strong'** recommendations on interventions that **'should'** be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm. For **'strong'** recommendations on interventions that **'should not'** be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more harm than good.

**R** For **'conditional'** recommendations on interventions that should be 'considered', the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

### GOOD-PRACTICE POINTS

✓ Recommended best practice based on the clinical experience of the guideline development group.



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Scottish Intercollegiate Guidelines Network

# Management of chronic heart failure

A national clinical guideline



March 2016

**Scottish Intercollegiate Guidelines Network  
Gyle Square, 1 South Gyle Crescent  
Edinburgh EH12 9EB**

**[www.sign.ac.uk](http://www.sign.ac.uk)**

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# 1 Introduction

## 1.1 THE NEED FOR A GUIDELINE

It is estimated that around 2.3 million people in the United Kingdom (UK) have coronary heart disease, 500,000 of whom have heart failure.<sup>1</sup> In Scotland in 2013 the estimated prevalence in men of all ages was 1.44%, and 1.22% for the UK. Prevalence in Scotland for men aged over 75 years was 8.72%. In women prevalence in Scotland was 0.82% (0.76 for the UK) and 5.97% for those over 75 years old.<sup>1</sup>

The previous SIGN guideline on heart failure (SIGN 95) was published in early 2007. This was followed by guidelines on heart failure from NICE in 2010 and from the European Society of Cardiology in 2012. Since the publication of SIGN 95, important new evidence has emerged for the management of heart failure. These changes are not only in pharmacological therapy but also in device therapy. There is therefore a need to reflect these changes in evidence and practice in a new guideline on the management of chronic heart failure.

This new guideline should help to reduce variations in evidence-based treatments offered to patients across different clinical settings in Scotland.

### 1.1.1 UPDATING THE EVIDENCE

This guideline updates SIGN 95: Management of chronic heart failure to reflect the most recent evidence. Where evidence was not updated, text and recommendations are reproduced verbatim from SIGN 95. The original supporting evidence was not reappraised by the current guideline development group.

## 1.2 REMIT OF THE GUIDELINE

### 1.2.1 OVERALL OBJECTIVES

The aim of this guideline is to improve the care of patients with heart failure (HF). This guideline provides recommendations, based on current evidence, for best practice in the management of patients with HF. In particular it focuses on the management of patients with stable HF rather than on in-hospital management of an episode of acute decompensation of HF (acute HF). It includes recommendations on diagnosis, lifestyle modification to reduce risk and progression of HF, pharmacological and interventional therapies, organisational planning, palliative care and a checklist of information for patients. The management of specific aetiologies of HF such as inherited (genetic) cardiac conditions, has not been covered in this guideline.

Other relevant SIGN guidelines on the management of acute coronary syndrome, arrhythmias and stable angina, primary prevention of coronary heart disease and cardiac rehabilitation are available from [www.sign.ac.uk](http://www.sign.ac.uk)

### 1.2.2 DEFINITIONS

Heart failure is a clinical syndrome of symptoms (eg breathlessness, fatigue) and signs (eg oedema, crepitations) resulting from structural and/or functional abnormalities of cardiac function which lead to reduced cardiac output or high filling pressures at rest or with stress. A list of potential signs and symptoms is given in section 3.1.1.

Heart failure may arise as a consequence of a myocardial, valvular, pericardial, endocardial or arrhythmic problem (or some combination of these). Heart failure can be defined in a number of different ways. This can be on the basis of ejection fraction (reduced versus preserved), clinical status (stable versus acutely decompensated) and symptom severity (New York Heart Association (NYHA) classification<sup>2</sup> or American College of Cardiology/American Heart Association (ACC/AHA) classification).<sup>3</sup>

Heart failure can be defined on the basis of left ventricular ejection fraction (LVEF) as heart failure with reduced ejection fraction (HF-REF) or heart failure with preserved ejection fraction (HF-PEF).

Heart failure with reduced ejection fraction (also referred to as HF with systolic dysfunction) is defined as the presence of signs and symptoms of HF with a left ventricular ejection fraction of <40% (although the cut-off level varies from  $\leq 35\%$  to  $\leq 40\%$  or  $\leq 45\%$ ).

Heart failure with preserved ejection fraction is defined as the presence of signs and symptoms of HF with a normal or only mildly reduced ejection fraction, with an undilated left ventricle. There should be evidence of other relevant structural heart disease (left atrial enlargement, left ventricular hypertrophy) or raised natriuretic peptides or evidence of left ventricular diastolic dysfunction. This has been previously known as diastolic dysfunction heart failure or diastolic heart failure.

This definition is crucial to the management of HF as the aetiology and management of HF-REF and HF-PEF is different. Currently the only randomised controlled trials (RCTs) that have demonstrated a favourable effect of an intervention on outcome are in patients with HF-REF. No therapies have been conclusively shown to alter morbidity or mortality in patients with HF-PEF.

This guideline will focus on the management of HF-REF. The term HF-REF will be used throughout in preference to other terms such as systolic dysfunction or reduced systolic function to refer to patients with heart failure and an ejection fraction of  $\leq 40\%$ , the upper limit for inclusion into the trials underpinning the guideline.

The natural history of heart failure includes periods of relative stability and periods of worsening of the symptoms and signs of heart failure requiring hospitalisation and treatment.<sup>4</sup> These periods are referred to as acute- or acutely-decompensated heart failure. The treatment of episodes of acute heart failure is outside the remit of this guideline.

Once a diagnosis of HF (HF-REF or HF-PEF) has been established symptoms may be used to classify the severity of heart failure. The NYHA classification is the most widely-used stratification tool for assigning patients with HF to functional classes (see Table 1)<sup>2</sup> although the ACC/AHA stages of HF may be useful to classify those patients in need of specialised interventions for HF (see Table 2).<sup>3</sup>

Table 1: New York Heart Association classification<sup>2</sup>

Class	Symptoms
I	No limitation: ordinary physical exercise does not cause undue fatigue, dyspnoea or palpitations.
II	Slight limitation of physical activity: comfortable at rest but ordinary activity results in fatigue, palpitations or dyspnoea.
III	Marked limitation of physical activity: comfortable at rest but less than ordinary activity results in symptoms.
IV	Unable to carry out any physical activity without discomfort: symptoms of heart failure are present even at rest with increased discomfort with any physical activity.

Table 2: American College of Cardiology/American Heart Association stages of heart failure<sup>3</sup>

Class	Symptoms
A	At high risk of HF but without structural heart disease or symptoms of HF
B	Structural heart disease but without signs or symptoms of HF
C	Structural heart disease with prior or current symptoms of HF
D	Refractory HF requiring specialised interventions

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### 1.2.3 TARGET USERS OF THE GUIDELINE

This guideline will be of interest to healthcare professionals involved in the management of patients with chronic heart failure, including cardiac nurses, cardiac surgeons, cardiologists, general practitioners, pharmacists, psychologists, as well as patients, carers, voluntary organisations and policy makers.

### 1.2.4 SUMMARY OF UPDATES TO THE GUIDELINE, BY SECTION

2	Key recommendations	New
3	Diagnosis and investigations	Updated: 3.1.1 Clinical examination, 3.1.4 Natriuretic peptides, 3.2.1 Imaging techniques Minor updates: 3.1.2 Further Investigations, 3.1.3 Electrocardiography, 3.2 Determining the underlying cause of heart failure
4	Emotional wellbeing and health behaviour change	Updated: 4.1 Depression Minor updates: 4.2.2 Fluid restriction, 4.4.3 Nutritional supplements and fruit juices
5	Pharmacological therapies	Minor updates: 5.7 Diuretics/loop diuretics Updated: 5.3 Angiotensin receptor blockers, 5.4 Mineralocorticoid receptor antagonists, 5.10 Figure 2, 5.11 Antithrombotic therapy, 5.15 Patients with heart failure with preserved ejection fraction New: 5.5 Angiotensin Receptor Neprilysin Inhibitors, 5.6 Ivabradine, 5.9 B-type natriuretic peptide-guided treatment, 5.13 Phosphodiesterase inhibitors, 5.14 Patients with anaemia
6	Interventional procedures	New: 6.1 Cardiac resynchronisation therapy and implantable cardioverter defibrillators, 6.4 Mechanical circulatory support Updated: 6.2 Assisted ventilation, 6.3 Coronary artery bypass grafting
7	Models of care	no update
8	Palliative care	Updated: Introduction, 8.4 Rationalising treatments
9	Provision of information	New: 9.2 Checklist for provision of information
10	Implementing the guideline	Updated

### 1.2.5 PATIENT VERSION

A patient version of this guideline is available from the SIGN website, [www.sign.ac.uk](http://www.sign.ac.uk)

## 1.3 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

### 1.3.1 INFLUENCE OF FINANCIAL AND OTHER INTERESTS

It has been recognised that financial interests in, or close working relationships with, pharmaceutical companies may have an influence on the interpretation of evidence from clinical studies.

It is not possible to completely eliminate any possible bias from this source, nor even to quantify the degree of bias with any certainty. SIGN requires that all those involved in the work of guideline development should declare all financial interests, whether direct or indirect, annually for as long as they are actively working with the organisation. By being explicit about the influences to which contributors are subjected, SIGN acknowledges the risk of bias and makes it possible for guideline users or reviewers to assess for themselves how likely it is that the conclusions and guideline recommendations are based on a biased interpretation of the evidence.

Details of those involved in developing this guideline can be found in section 12.

### 1.3.2 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off-label' use.

Medicines may be prescribed 'off label' in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.

Generally 'off-label' prescribing of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.<sup>5</sup>

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability".<sup>5</sup>

The General Medical Council (GMC) recommends that when prescribing a medicine 'off label', doctors should:

- be satisfied that such use would better serve the patient's needs than an authorised alternative (if one exists)
- be satisfied that there is sufficient evidence/experience of using the medicines to show their safety and efficacy, seeking the necessary information from appropriate sources
- record in the patient's clinical notes the medicine prescribed and, when not following common practice, the reasons for the choice
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to any prescribing, the licensing status of a medication should be checked in the summary of product characteristics (SPC).<sup>6</sup> The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.<sup>7</sup>

### 1.3.3 HEALTH TECHNOLOGY ASSESSMENT ADVICE FOR NHSSCOTLAND

Specialist teams within Healthcare Improvement Scotland issue a range of advice that focuses on the safe and effective use of medicines and technologies in NHSScotland.

The Scottish Medicines Consortium (SMC) provides advice to NHS boards and their Area Drug and Therapeutics Committees about the status of all newly-licensed medicines and new indications for established products. NHSScotland should take account of this advice and ensure that medicines accepted for use are made available to meet clinical need where appropriate.

In addition, Healthcare Improvement Scotland reviews Multiple Technology Assessments (MTAs) produced by the National Institute for Health and Care Excellence (NICE) and provides advice about their applicability in NHSScotland. If Healthcare Improvement Scotland advises that MTA guidance is applicable in Scotland, NHSScotland should take account of this and ensure that recommended medicines and treatment are made available to meet clinical need where appropriate.

On publication NICE MTAs deemed valid for NHSScotland supersede extant SMC advice as they are generally underpinned by a larger and more recent evidence base.

SMC advice and NICE MTA guidance relevant to this guideline are summarised in section 10.4.

## 2 Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation.

### 2.1 DIAGNOSTIC INVESTIGATIONS

- R** Natriuretic peptide (BNP-type natriuretic peptide or NT-proBNP) levels (or an electrocardiogram if BNP testing is not available) **should be measured to decide if echocardiography is needed or not, in patients with suspected heart failure.**
- ✓ Echocardiography is recommended in patients with suspected heart failure who have either a raised BNP or NT-proBNP level or abnormal electrocardiogram to confirm the diagnosis and establish the underlying cause. The investigation should include:
- a description of overall left ventricular systolic function (preferably measured by the LVEF) together with any wall-motion abnormalities
  - Doppler assessment of any significant valve disease
  - estimation of pulmonary artery systolic pressure, where possible.

### 2.2 EMOTIONAL WELLBEING AND HEALTH BEHAVIOUR CHANGE

- ✓ Patients with heart failure should be screened for depression using a validated measure and within the context of a collaborative, stepped-care model which includes a locally-defined clinical care pathway.
- R** Cognitive behaviour therapy **should be considered for patients with heart failure and clinical depression.**

### 2.3 PHARMACOLOGICAL THERAPY

- R** All patients with heart failure with reduced ejection fraction, NYHA class II-IV should be started on beta blocker therapy as soon as their condition is stable.
- R** Patients with heart failure with reduced ejection fraction of all NYHA functional classes, should be given angiotensin-converting enzyme inhibitors.
- R** Patients with heart failure with reduced ejection fraction, NYHA class II-IV, who are intolerant of angiotensin-converting enzyme inhibitors should be given an angiotensin receptor blocker.
- R** Patients with heart failure with reduced ejection fraction who have ongoing symptoms of heart failure, NYHA class II to IV, LVEF  $\leq 35\%$ , despite optimal treatment, should be given mineralocorticoid receptor antagonists unless contraindicated by the presence of renal impairment (chronic kidney disease stage  $>4-5$ ) and/or elevated serum potassium concentration ( $K > 5.0$  meq/l).
- R** Patients with heart failure with reduced ejection fraction who have ongoing symptoms of heart failure, NYHA class II-III, LVEF  $\leq 40\%$  despite optimal treatment should be given sacubitril/valsartan instead of their ACE inhibitor or ARB, unless contraindicated. It may be considered in patients with NYHA class IV symptoms.
- If the patient is already on an ACE inhibitor, the ACE inhibitor should be stopped for 36 hours before initiating sacubitril/valsartan to minimise the risk of angioedema.

**R** Patients with a diagnosis of heart failure with reduced ejection fraction of NYHA class II-IV, LVEF  $\leq 35\%$ , who have had a previous hospital admission for heart failure in the previous 12 months but have stabilised on standard therapy for at least four weeks, should be given ivabradine. Patients must have a sinus rhythm heart rate  $\geq 75$  beats/minute despite maximum tolerated dose of beta blockers.

✓ Specialist advice should be sought before initiating ivabradine.

## 2.4 INTERVENTIONAL PROCEDURES

**R** Implantable cardioverter defibrillators, cardiac resynchronisation therapy with defibrillator or cardiac resynchronisation therapy with pacing are recommended as treatment options for patients with heart failure with reduced ejection fraction, LVEF  $\leq 35\%$ , as specified in the following table:

*Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure.<sup>8</sup>*

QRS interval (ms)	NYHA class			
	I	II	III	IV
<120	ICD if there is a high risk of sudden cardiac death			ICD and CRT not clinically indicated
120-149 without LBBB	ICD	ICD	ICD	CRT-P
120-149 with LBBB	ICD	CRT-D	CRT-P or CRT-D	CRT-P
$\geq 150$ with or without LBBB	CRT-D	CRT-D	CRT-P or CRT-D	CRT-P

ICD = implantable cardioverter defibrillator; CRT-D = cardiac resynchronisation therapy with an implantable cardioverter defibrillator; CRT-P = cardiac resynchronisation therapy with pacing

## 2.5 DISCHARGE AND ANTICIPATORY CARE PLANNING

**R** Comprehensive discharge planning should ensure that links with postdischarge services are in place for all patients with symptomatic heart failure.

✓ Comprehensive planning requires communication between primary and secondary-care teams, including discharge planning following a hospital admission and anticipatory care planning, specialist nurse input and, where appropriate, home-based care.

## 2.6 PALLIATIVE CARE

✓ Patients with advanced heart failure with ongoing symptoms despite optimally-tolerated heart failure treatment should have access to a collaborative cardiology and palliative approach to their care. This includes:

- active heart failure management in collaboration with symptom control
- rationalisation of medical therapy
- anticipatory care planning
- co-ordination of care
- multidisciplinary team working
- communication across primary and secondary care
- good end-of-life care.

This approach to care should be practised by all healthcare professionals involved with the management of patients with advanced disease with access to specialist advice as needed.

### 3 Diagnosis and investigations

Patients with HF often present with symptoms of fatigue and/or shortness of breath and/or ankle swelling. These patients are frequently obese, often smoke and they may have a history of chronic obstructive pulmonary disease, hypertension, coronary heart disease or diabetes. The challenge for healthcare professionals is to differentiate those patients with HF from a myriad of other conditions with similar symptoms and signs and to streamline the patient's journey along the most efficient diagnostic and therapeutic pathway. A successful diagnosis is likely to require both subjective (review of symptoms) and objective (evidence of cardiac dysfunction) components.

#### 3.1 DIAGNOSING HEART FAILURE

##### 3.1.1 CLINICAL EXAMINATION AND INITIAL INVESTIGATIONS

There is no symptom or sign that is both sensitive and specific for the diagnosis of HF and a purely clinical diagnosis is problematic. Table 3 lists some common symptoms and signs associated with HF.<sup>9</sup>

Table 3: Symptoms and signs typical of heart failure

Symptoms	
Typical	Less typical
Breathlessness	Nocturnal cough
Orthopnoea	Wheezing
Paroxysmal nocturnal dyspnoea	Weight gain (>2 kg/week)
Reduced exercise tolerance	Weight loss (in advanced heart failure)
Fatigue, tiredness, increased time to recover after exercise	Bloated feeling
Ankle swelling	Loss of appetite
	Confusion (especially in older people)
	Depression
	Palpitations
	Syncope
Signs	
More specific	Less specific
Elevated jugular venous pressure	Peripheral oedema (ankle, sacral, scrotal)
Hepatojugular reflux	Pulmonary crepitations
Third heart sound (gallop rhythm)	Reduced air entry and dullness to percussion at lung bases (pleural effusion)
Laterally displaced apical impulse	Tachycardia
Cardiac murmur	Irregular pulse
	Tachypnoea (> 16 breaths/min)
	Hepatomegaly
	Ascites
	Tissue wasting (cachexia)

Reproduced from McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;14(8):803-69, with permission from Oxford University Press

In clinical practice it is the combination of symptoms and signs, and the presence or otherwise of a likely cause of heart failure which are most useful rather than any of these in isolation.

Basic early investigations are necessary to differentiate heart failure from other conditions and to provide prognostic information. Urinalysis, serum urea and creatinine tests may help to determine if there is kidney failure, since symptoms of kidney disease are similar to those of HF. Chest X-ray may indicate signs of HF such as cardiomegaly, pulmonary congestion or pleural effusion and also non-cardiac indications such as lung tumours which account for breathlessness. An electrocardiogram is also indicated as it may demonstrate an underlying aetiology such as prior myocardial infarction or identify other important diagnoses such as atrial fibrillation.

A health technology appraisal (HTA) concluded that a scoring system can be used to determine who should be referred directly for echocardiography and who should have a natriuretic peptide test.<sup>10</sup> The scoring system included three items; the presence of any one of which should direct the patient to an echocardiogram instead of a natriuretic peptide testing. The three items in the score were: 1. Being male with ankle oedema, 2. A history of myocardial infarction and 3. Basal crepitations in the lungs. Their findings were based on five relatively small datasets (105–391 patients). The cut off for the clinical decision rule was arbitrary. Prospective clinical trials are needed to determine whether this approach is effective and reduces the number of natriuretic peptide tests required pre-echocardiography.

2<sup>++</sup>

- ✓ Patients with suspected chronic heart failure should receive a range of basic tests. The investigations chosen will vary depending on the presentation but should usually include a full blood count, fasting blood glucose, serum urea and electrolytes, urinalysis, thyroid function, electrocardiogram and chest X-ray.

### 3.1.2 FURTHER INVESTIGATIONS

Following clinical examination and basic investigations, a decision must be made as to whether the patient should undergo an echocardiogram (*see section 3.1.5*). To help make this decision, the patient should undergo either an electrocardiogram (ECG, *see section 3.1.3*) or measurement of B-type natriuretic peptide or N terminal-pro-BNP levels (*see section 3.1.4*), or both depending on local circumstances. If either test is abnormal, there is sufficient likelihood of HF to warrant echocardiography to confirm a diagnosis. If both tests are normal, HF is unlikely and alternative tests for the symptoms should be considered.

If echocardiography suggests a diagnosis of HF, an ECG should be done (if it has not already been done) to help identify the underlying cause of the heart failure.

Pulmonary-function tests should be considered in selected patients, ie in those whom HF is excluded and also in those with HF and comorbid lung disease which may contribute to dyspnoea.

### 3.1.3 ELECTROCARDIOGRAPHY

The ECG can be used firstly as a screening test to assess the likelihood of HF and the need for subsequent echocardiography to confirm or refute a diagnosis. It is unusual for a patient with HF to have a normal ECG, so it is a good tool to rule out HF. The ECG abnormalities reported in HF are all non-specific, and relatively common in older patients. The specificity of an abnormal ECG is relatively poor (around 60% at best).<sup>11</sup>

2<sup>++</sup>

Electrocardiographic abnormalities in patients with HF include:

- pathological Q waves
- left bundle branch block
- left ventricular hypertrophy (LVH)
- atrial fibrillation
- non-specific ST and/or T-wave changes.

Electrocardiography is also useful once HF has been confirmed as it may help to determine the cause (eg Q waves indicate previous myocardial infarction, LVH is seen in patients with hypertension and aortic valve disease) and it is important to exclude atrial fibrillation.

- ✓ An ECG should be carried out once heart failure is diagnosed to assess rhythm and possible underlying causes of heart failure and determine future management such as cardiac resynchronisation therapy, ivabradine and anticoagulation for atrial fibrillation.

### 3.1.4 NATRIURETIC PEPTIDES

B-type natriuretic peptide (BNP) and N terminal-pro-B-type natriuretic peptide (NT-proBNP) are peptide hormones produced in the heart by breakdown of a precursor protein (pre-pro-BNP). BNP causes natriuresis, diuresis and vasodilation; NT-proBNP is inactive.<sup>12</sup>

Plasma BNP and NT-proBNP concentrations are raised in patients with both HF-REF and HF-PEF and the concentrations tend to rise with deteriorating NYHA class.

There is evidence of clinical effectiveness of using measurement of BNP or NT-proBNP as a diagnostic tool for heart failure from a health technology appraisal carried out by NHS Quality Improvement Scotland, which included 19 observational studies (11 using BNP, eight using NT-proBNP).<sup>11</sup> 2<sup>++</sup>

Pooled sensitivity for the diagnosis of HF using BNP testing was 0.91 (95% confidence intervals (CI), 0.90 to 0.93), specificity was 0.73 (0.71 to 0.75). Pooled sensitivity for the diagnosis of HF using NT-proBNP testing was 0.91 (95% CI 0.88 to 0.93) and specificity was 0.76 (95% CI 0.75 to 0.77). Although simple single value cut offs for the diagnosis of HF have been proposed, a more realistic interpretation of BNP and NT-proBNP levels is to suggest that very low values rule out a diagnosis of HF, very high values make the diagnosis of HF likely in the absence of other causes of a raised BNP, whilst intermediate to high values should be regarded as indeterminate necessitating further investigation. The upper limit of normal is also age, sex and race dependent, and must be determined locally depending on the assay used.<sup>11</sup> 2<sup>++</sup>

BNP and NT-proBNP tests are suitable for widespread screening in patients with suspected HF presenting in the community, assuming appropriate quality control of the assay and selection of appropriate cut-off values for the patients tested. BNP levels fall after commencing therapy for HF, for example diuretics, so the sensitivity is lower in patients who have already started treatment.

No evidence was identified on whether early referral of people with suspected HF and high or moderate BNP levels improves outcome. NICE considered that because BNP levels can predict risk of hospitalisation and mortality, people presenting with signs and symptoms of HF in the community setting and who have very high natriuretic peptide levels should be treated more urgently than those with lower, but still abnormal, levels of natriuretic peptides. NICE devised the following thresholds, based on the expert opinion of the guideline development group:<sup>13</sup> 4

- BNP >400 pg/ml (>116 pmol/l) or NT-proBNP >2,000 pg/ml (>236 pmol/l): echocardiogram and specialist clinical assessment no longer than two weeks from the time of presentation.
- BNP 100–400 pg/ml (29–116 pmol/l) or NT-proBNP 400–2,000 pg/ml (47–236 pmol/l): echocardiogram and specialised clinical assessment within six weeks from the time of presentation.
- BNP <100 pg/ml (<29 pmol/l) or NT-proBNP <400 pg/ml (<47 pmol/l), in the absence of HF therapy: HF is an unlikely cause for the presentation.

While this guidance applies to community-based patients, the evidence supporting a role for measuring natriuretic peptides in unselected patients presenting to the emergency department with dyspnoea is less strong. One meta-analysis suggested a modest effect on length of stay and readmissions with no mortality benefit.<sup>14</sup> 1<sup>+</sup>



NICE reported that a systematic review found ECG to be inferior to natriuretic peptide testing as a diagnostic test for HF, and did not increase diagnostic precision if added to a natriuretic peptide test and clinical assessment. They concluded that natriuretic peptides should be used in preference to the ECG to decide at the diagnostic stage whether the patient needed an echocardiogram. If the diagnosis of HF is confirmed after the echocardiogram, however, an ECG is an essential investigation in the general assessment of the patient.<sup>13</sup>

**R** | **Natriuretic peptide** (BNP-type natriuretic peptide or NT-proBNP) **levels** (or an electrocardiogram if BNP testing is not available) **should be measured to decide if echocardiography is indicated or not, in patients with suspected heart failure.**

✓ | In the assessment of suspected heart failure, BNP or NT-proBNP levels should ideally be checked on samples taken prior to commencing therapy.

**R** | **Patients with suspected heart failure and a BNP level above 400 pg/ml (116 pmol/litre) or an NT-proBNP level above 2,000 pg/ml (236 pmol/litre) may be referred for echocardiography and specialist assessment within two weeks.**

**R** | **Patients with suspected heart failure and a BNP level between 100 and 400 pg/ml (29–116 pmol/litre), or an NT-proBNP level between 400 and 2,000 pg/ml (47–236 pmol/litre) may be referred for echocardiography and specialist assessment within six weeks.**

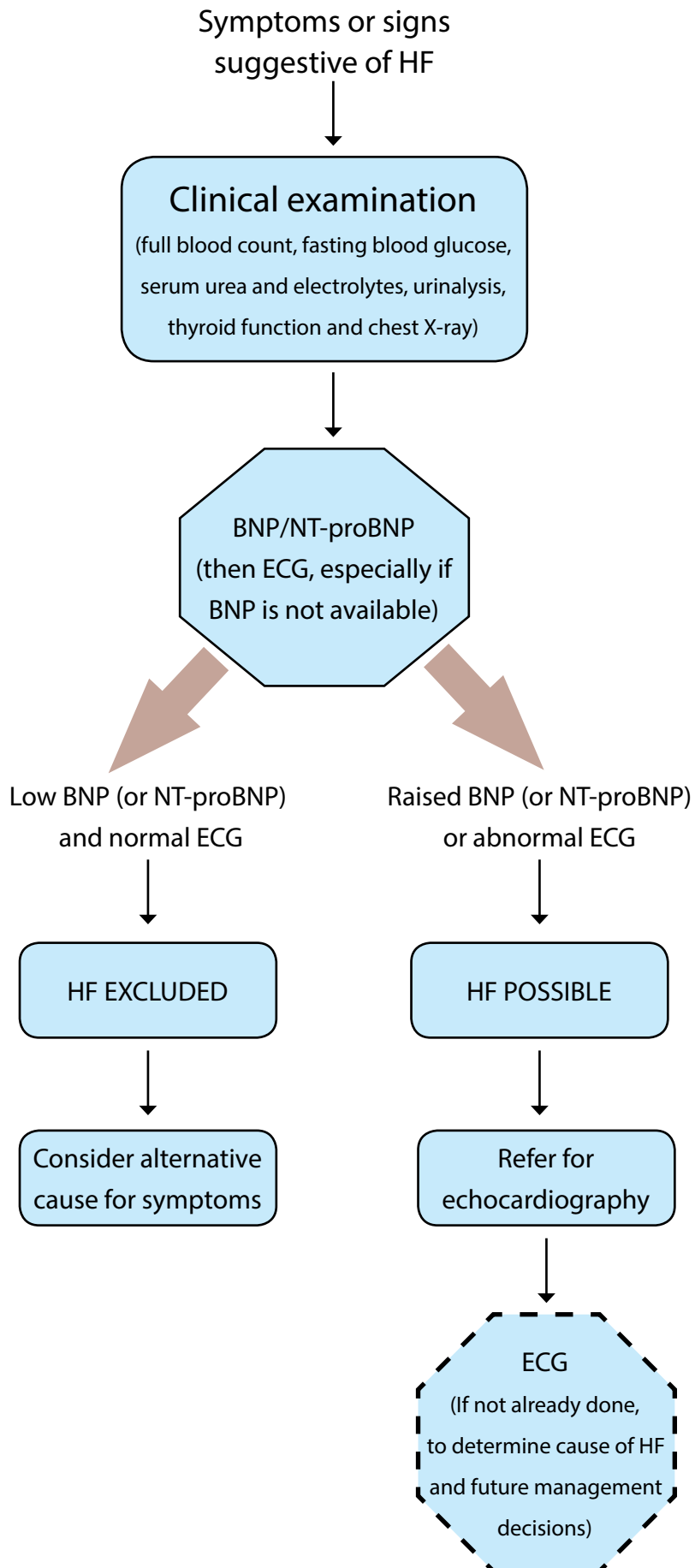
### 3.1.5 ECHOCARDIOGRAPHY

Echocardiography is a safe and relatively inexpensive investigation which is very helpful in diagnosing HF and determining the cause. It provides a quantitative and semiquantitative assessment of left ventricular systolic and diastolic function, valve disorders can usually be accurately delineated, and pulmonary artery systolic pressure can be estimated. The limitation of poor image quality due to obesity or lung disease is minimised by the skilled use of modern imaging equipment and echocardiographic contrast agents.

✓ | Echocardiography is recommended in patients with suspected heart failure who have either a raised BNP or NT-proBNP level or abnormal electrocardiograph result to confirm the diagnosis and establish the underlying cause. The investigation should include:

- a description of overall left ventricular systolic function (preferably measured by the LVEF) together with any wall-motion abnormalities
- Doppler assessment of any significant valve disease
- estimation of pulmonary artery systolic pressure, where possible.

Figure 1: Diagnostic algorithm for patients with suspected chronic heart failure



### 3.1.6 CHEST X-RAY

The chest X-ray (CXR) is important to help exclude other causes of shortness of breath and to look for supportive evidence for a possible diagnosis of HF. On its own it cannot be used to diagnose HF and must be used in combination with other sources of clinical evidence.

In one systematic review pulmonary venous redistribution with upper lobe blood diversion on CXR was shown to have 65% sensitivity (67% specificity) for increased preload in patients with HF. Cardiomegaly on CXR had 51% sensitivity (79% specificity) for decreased ejection fraction in patients with HF. However, neither finding alone can adequately confirm or refute left ventricular dysfunction.<sup>15</sup>

2<sup>++</sup>

**R** | A chest X-ray is recommended early in the diagnostic pathway to look for supportive evidence of heart failure and to investigate other potential causes of breathlessness.

## 3.2 DETERMINING THE UNDERLYING CAUSE OF HEART FAILURE

Much of the evidence base for the management of HF relates to HF-REF. Although this is the most common type of HF in the UK, it should not be overlooked that other causes of the HF, such as valve disease, may be present or the patient may have HF-PEF. This is an important point as HF due to, for example, valve disease, requires different management from other causes of HF such as reduced ejection fraction.<sup>16</sup> Echocardiography can reliably differentiate between these different types of HF.

4

An indication of the presence of coronary disease as the cause of reduced ejection fraction is often apparent from the history, ECG and echocardiogram but in cases of doubt coronary angiography may be required.

✓ | Coronary artery imaging is not recommended as a routine test for patients with heart failure unless the patient has symptoms suggestive of cardiac ischaemia or has had cardiac arrest.

### 3.2.1 IMAGING TECHNIQUES

In addition to echocardiography, a number of other imaging techniques can be used for the assessment of patients with suspected or diagnosed HF.

Cardiac magnetic resonance (CMR) is regarded as the gold standard for assessment of ventricular volumes, ejection fractions and regional wall motion. It enables assessment of valvular function and provides high image quality in most patients.<sup>9</sup> It is useful for assessing ventricular function when echocardiography images are inadequate. It is also indicated for patients with HF with a background of complex congenital heart disease, patients with suspected cardiomyopathy, or where the differential diagnosis includes active myocarditis or infiltrative myocardial disease, for example amyloidosis, scaroidosis, cardiac haemosiderosis.

4

Radionuclide blood pool-multiple gated acquisition (MUGA)-scanning can provide an accurate measure of the left ventricular ejection fraction, but it exposes the patient to ionising radiation, does not allow visualisation of the heart valves and provides less additional information regarding cardiac structure and function than CMR.

Potentially viable myocardium can be detected by single-photon emission computed tomography (SPECT), radionuclide positron emission tomography (PET), magnetic resonance imaging and dobutamine stress echocardiography (DSE). Studies of these imaging modalities have been pooled together in one meta-analysis and one systematic review.<sup>17,18</sup> Each of these techniques appears capable of detecting ischaemic, viable myocardium.

2<sup>+</sup>2<sup>++</sup>

## 4 Emotional wellbeing and health behaviour change

### 4.1 DEPRESSION

Depression is common in patients with HF and is associated with an increased risk of mortality in some,<sup>19-22</sup> but not all, studies<sup>23,24</sup> and may be related to morbidity and rehospitalisation.<sup>20,21</sup> 2+  
3

There is insufficient evidence to guide clinicians as to which screening or assessment measures to use with this population. The 2014/15 British Medical Association Quality Outcome Framework for general practitioners suggests three screening questionnaires to aid clinical judgement in measuring the severity of depression and monitoring treatment (nine-item Patient Health Questionnaire, Hospital Anxiety and Depression Scale and Beck Depression Inventory, 2nd edition).<sup>25</sup> Criteria for depression such as loss of appetite and fatigue must be interpreted with care in patients with HF. 4

The evidence for psychological and pharmacological management of patients with HF and depression is limited. A number of trials were identified but most need further research to substantiate findings.<sup>26</sup> 1++

A nurse-delivered psychological therapy did not improve the primary outcome of depressive symptoms at one week and three months after discharge in a small RCT, but those receiving psychological therapy had improved short-term cardiac event-free survival (80% versus 40% in the control group).<sup>27</sup> 1+

Cognitive behaviour therapy (CBT) has been found to improve depression in patients with HF compared to usual care after six months of treatment (Beck Depression Inventory scores 12.8 v 17.3,  $p=0.008$ ; number needed to treat (NNT) for remission rates 3.76, 95% CI 3.62 to 3.90).<sup>28</sup> The CBT intervention did not lead to a statistically significant improvement in HF self care in this RCT, but there were improvements in secondary outcomes of anxiety, fatigue, mental- and HF-related quality of life (QoL), social functioning and hospitalisations. A systematic review identified a small study that found CBT combined with a home-based walking programme can provide a sustained reduction in depression compared to CBT or exercise alone (effect size Cohen's  $d=1.0$  v  $d=0.4$  and  $d=0.1$ ).<sup>26</sup> 1++

Disease-management programmes, studied in seven RCTs, did not have a significant impact on improving depression.<sup>26</sup> This is in contrast to two studies of a collaborative care model which reported improvements in access and response to treatment for depression.<sup>29,30</sup> These studies were conducted by the same research team, and included patients with a broad range of cardiac diagnoses. 1++  
1+

Two trials on the use of selective serotonin reuptake inhibitors (SSRIs) in patients with HF and depression reported a reduction in depression over 12 weeks compared to placebo, while another two found no difference. The conditions in the control group may have confounded the results in the negative studies, as the controls received psychiatric or nursing support. No serious adverse effects were reported.<sup>26</sup> 1++

If antidepressant medication is felt to be desirable, a tricyclic antidepressant should not be used.<sup>31</sup>

✓ Patients with heart failure should be screened for depression using a validated measure and within the context of a collaborative, stepped-care model which includes a locally-defined clinical care pathway.

R **Cognitive behaviour therapy should be considered for patients with heart failure and clinical depression.**

✓ If antidepressant medication is prescribed, a tricyclic antidepressant should not be used in patients with heart failure.

## 4.2 DIETARY CHANGES

### 4.2.1 SALT INTAKE

The Food Standards Agency has recommended that the total salt intake for adults should not exceed 6 g/day (approximately 1.5 teaspoons). Food labels often include the sodium content rather than salt. To convert the sodium content of food into salt content, the sodium level is multiplied by 2.5.

- ✓ Patients with heart failure should be advised to aim for a salt intake of less than 6 g/day.
- ✓ Patients with heart failure should be advised not to use 'low salt' substitutes due to their high potassium content.

### 4.2.2 FLUID RESTRICTION

- ✓ Healthcare professionals involved in the care of patients with frequent episodes of decompensated heart failure should assess individual patient's fluid intake and use a tailored approach when giving fluid restriction advice.

### 4.2.3 HOME DAILY WEIGHT MONITORING

Although daily weight monitoring is a regular part of management for patients with HF to identify early weight gain and allow rapid intervention to avert serious decompensation, no trials were identified which have examined this in isolation. Daily weight monitoring is included in most multifactorial interventions.

- ✓ Patients with chronic heart failure should be encouraged to weigh themselves at a set time of day, every day (after waking, before dressing, after voiding, before eating). Patients should report to their general practitioner or heart failure specialist any weight gain of more than 1.5–2 kgs (3–4 lbs) in two days.

### 4.2.4 NUTRITIONAL SUPPLEMENTS AND FRUIT JUICES

The evidence for coenzyme Q10 (CoQ10) supplementation is inconsistent. A meta-analysis of nine trials concluded that taking CoQ10 does not improve ejection fraction or mortality.<sup>32</sup> However, in a later RCT in patients with HF awaiting transplant, those randomised to CoQ10 gained improvement in functional status, clinical status and QoL compared to those randomised to placebo.<sup>33</sup>

Healthy eating guidelines from the British Dietetic Association include encouragement to consume five portions of a variety of fruits and vegetables each day. Often fruit juices are seen by patients as a convenient way of increasing their fruit intake. However, the therapeutic effect of certain commonly-prescribed medications in patients with HF is known to be affected by drinking certain fruit juices, for example grapefruit or cranberry juices.

The British National Formulary (BNF) advises that, due to interactions with prescribed medications, certain supplements and fruit juices should be avoided.<sup>5</sup>

- ✓ Patients with heart failure who are taking warfarin should be advised to avoid cranberry juice (which may increase drug potency).
- ✓ Patients with heart failure who are taking simvastatin should be advised to avoid grapefruit juice (which may interfere with liver metabolism of the drug).
- ✓ Patients with heart failure should not take St John's wort supplements due to the interaction with warfarin, digoxin, eplerenone and selective serotonin reuptake inhibitors.

1+

4

### 4.3 ALCOHOL

Long-term heavy alcohol consumption is an important cause of dilated cardiomyopathy. Although the amount and duration of alcohol that results in alcoholic cardiomyopathy (ACM) is not clearly established, men and women who consume alcohol >11 units/day for over five years are at risk.<sup>34</sup> 4

Two prospective studies of patients with severe ACM found that after six months of total abstinence from alcohol, left ventricular function had significantly improved with an accompanying reduction in the cardiothoracic ratio on CXR.<sup>35,36</sup> 3

Another observational study found that among patients with ACM followed for four years, those who continued to drink either 2–3 units or 7–8 units alcohol per day had a similar improvement in cardiac function to those who became total abstainers (0.131 and 0.125 improvement in LVEF respectively), while those who continued to drink >10 units alcohol/day had a further deterioration in LVEF.<sup>37</sup> Non-cardiac harms which may manifest themselves at much lower levels of alcohol consumption were not assessed in this study. 2+

**R** Patients with heart failure should be advised to refrain from excessive alcohol consumption. When the aetiology of heart failure is alcohol related, patients should be strongly encouraged to stop drinking alcohol.

### 4.4 SMOKING

No prospective studies have quantified the effects of a smoking cessation intervention on outcomes in patients with HF. There are observational data supporting the association between continued smoking and increased heart failure mortality and increased rates of hospital admissions due to worsening heart failure compared with never, recent ex- and longer ex-smokers.<sup>38,39</sup> 2+ 3

Because of its many harmful effects, the effect of smoking on HF cannot be viewed in isolation. The effect of smoking on cardiovascular disease is discussed in the SIGN guideline on risk estimation and the prevention of cardiovascular disease.

**R** Patients with heart failure should be strongly advised not to smoke and should be offered smoking cessation advice and support.

### 4.5 EXERCISE TRAINING PROGRAMMES

A large volume of literature is available concerning exercise training for patients with HF although many of the studies have methodological problems. Trials often involved small numbers of patients, were short term and not representative of the population at large.<sup>40</sup> There is some evidence that exercise training improves exercise tolerance and QoL but no single randomised trial has looked at mortality over a sustained period.<sup>41</sup> Studies have looked at different training regimens and diverse outcome measures and generalisation regarding exercise training is difficult. 2++ 4

Two meta-analyses were identified which draw from largely the same trials.<sup>42</sup> One only reported those trials which had survival figures for at least three months and suggested a significant reduction in mortality with exercise training.<sup>43</sup> The second meta-analysis reported no difference in mortality between the two groups despite looking at similar (but not identical) trials.<sup>42</sup> This meta-analysis also reported an improvement in QoL in seven out of nine trials. The trials suggest that moderate-intensity exercise training is safe and progression of exercise should be followed in the order of duration, then frequency, then intensity.<sup>44</sup> Exercise training must be continued to result in sustained benefit.<sup>45</sup> Most of these trials looked at hospital-based supervised training programmes rather than home-based schemes. 1++ 4

**R** Patients with stable heart failure in NYHA class II-III should be offered a moderate-intensity supervised exercise training programme to give improved exercise tolerance and quality of life.

✓ Patients should be encouraged to take aerobic exercise within limits dictated by their symptoms.

## 4.6 UNSUPERVISED PHYSICAL ACTIVITY

Although most lifestyle recommendations are easily understood by patients, the recommendation to become more physically active in the presence of significant known heart disease may be frightening and contradictory to previously suggested management, that is rest and limitation of physical activity in patients with acute heart failure. Supervised exercise programmes are covered in section 4.5.

A 12-week home-based low-intensity walking programme, with a detailed prescription updated weekly, improved the six-minute walking distance of patients with stable HF compared with a control group given a pedometer and advice only. Improvements in quality of life were inconsistent. Walking was well tolerated and appears safe for stable patients. Compliance was lower than in other studies which have supervised group exercise training, despite regular contact and home visits.<sup>46</sup>

1+

Motivational interviewing is a person-centred directive method for enhancing intrinsic motivation to change behaviour by exploring and resolving an individual's ambivalence towards behaviour change. With a motivational interviewing style the healthcare professional avoids adopting an authoritative stance but uses cognitive behaviour strategies to encourage the individual to take active responsibility for the decision to change and goal setting.

In one study, the patients with HF randomised to receive motivational interviewing had better outcomes in terms of level and type of physical activity than those randomised to usual care, such as advice giving.<sup>47</sup>

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**R** | **A motivational interviewing style should be used to promote regular low-intensity physical activity amongst patients with stable heart failure.**

## 4.7 COMPLEMENTARY THERAPIES

No clinical trials were identified on aromatherapy, reflexology or reiki in patients with HF.

A small study of a 12-week programme of tai chi showed enhanced QoL and reduced BNP levels in patients with HF. From the study design, it is uncertain whether the improvement was due to the physical and meditative aspects of tai chi or the benefits of social contact.<sup>48</sup>

1-

There is insufficient evidence to draw conclusions regarding acupuncture. A small placebo-controlled randomised trial showed a single session of acupuncture eliminated surges in sympathetic activation during laboratory-induced mental stress. How this translates to changes in quality of life remains to be evaluated.<sup>49</sup> No trials have examined the effect of a course of acupuncture.

1-

Group relaxation therapy with additional home practice, did not improve physical QoL or exercise capacity but improved the peace-spiritual domains of QoL compared with usual care.<sup>50</sup>

1+

In older patients with optimally-treated HF meditation (an audio tape at home and weekly group sessions) reduced sympathetic activity levels and improved QoL compared to a control group.<sup>51</sup>

1-

## 5 Pharmacological therapies

A large number of high-quality trials of pharmacological therapy have been undertaken in patients with HF-REF. The aims of treatment are to prevent progression of the disease, thereby reducing symptoms, hospital admissions and mortality. Many treatments have been shown to reduce either one or more (often all) of these but each can produce side effects and careful monitoring is essential in order to maximise benefit and minimise adverse effects.

This section lists the main classes of drugs used in the management of patients with HF-REF. Annexes 2-5 list important cautions, contraindications, interactions and recommended starting and target drug doses where possible. Annex 6 lists medicines and herbal preparations which are known to interact with drugs used in the management of HF or which may cause harm. An example of the medicines sick day rules card for patients using ACE inhibitors, angiotensin receptor blockers or diuretics is available in Annex 7.

### 5.1 BETA BLOCKERS

Many RCTs of beta blockers have been undertaken in patients with HF-REF. In the CIBIS II,<sup>67</sup> MERIT-HF,<sup>68</sup> and COPERNICUS<sup>69</sup> trials a consistent, approximately one third reduction in total mortality was seen with each of bisoprolol, extended release metoprolol succinate and carvedilol. In the SENIORS trial, nebivolol significantly reduced a composite outcome of death or cardiovascular hospitalisations in patients with heart failure aged 70 or older.<sup>70</sup>

1++  
1+

There is consistent evidence for positive benefits from beta blockers in patients with HF, NYHA II-IV, LVEF  $\leq 35\%$ , as risk of mortality from cardiovascular causes reduced by 29% (95% CI 14% to 42%); mortality due to pump failure reduced by 36% (95% CI 9% to 55%); and all-cause mortality reduced by 23% (95% CI 8% to 35%).<sup>71</sup> Benefits were seen with beta blockers with different pharmacological properties, whether  $\beta_1$  selective (bisoprolol, metoprolol, nebivolol) or non-selective (carvedilol).

Two formulations of metoprolol were used in clinical trials of patients with HF. Only long-acting metoprolol succinate has been shown to perform better than placebo in reducing mortality (in the MERIT-HF trial).<sup>68</sup> Short-acting metoprolol tartrate, given twice daily, was compared to carvedilol in the COMET trial.<sup>72</sup> Carvedilol reduced mortality over five years by 17% compared with patients treated with metoprolol tartrate (33.8% v 39.5%), hazard ratio (HR) 0.83 (0.74 to 0.93), absolute risk reduction (ARR) 5.7%;  $p=0.0017$ .

1+

Extended-release metoprolol succinate is not available in the UK and no evidence was identified for the effectiveness of metoprolol tartrate, the preparation that is available in the UK.

Beta blockers produce benefit in the medium to long term. In the short term they can produce decompensation with worsening of heart failure and hypotension. For that reason, they should be initiated at low dose and only gradually increased, with monitoring, up to their target doses shown to be effective in RCTs. Beta blockers are contraindicated in patients with asthma, second- or third- degree atrioventricular heart block or symptomatic hypotension and should be used with caution in those with low initial blood pressure (BP) (systolic BP  $<90$  mm Hg). There is some evidence that cardioselective beta blockers can be used safely in patients with chronic obstructive pulmonary disease and HF.<sup>73</sup>

1+

A meta-analysis confirms that beta blockers also reduce mortality in patients with diabetes and HF (relative risk (RR) 0.84, 95% CI 0.73% to 0.96%;  $p=0.011$ ).<sup>74</sup>

1++

**R** All patients with heart failure with reduced ejection fraction, NYHA class II-IV, should be started on beta blocker therapy as soon as their condition is stable.

✓ Bisoprolol, carvedilol or nebivolol should be the first choice of beta blocker for the treatment of patients with heart failure with reduced ejection fraction.

✓ If beta blockers are contraindicated consider using ivabradine (*see section 5.6*).

Annex 4 provides practical guidance on the use of beta blockers



## 5.2 ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Angiotensin-converting enzyme (ACE) inhibitors were first shown to be effective in patients with HF in the 1980s. Since then, many RCTs have confirmed their benefit on mortality and morbidity, not only in HF itself,<sup>52,53</sup> but also in patients with left ventricular systolic dysfunction, HF or both after myocardial infarction (MI)<sup>54-56</sup> and in patients with asymptomatic left ventricular systolic dysfunction.<sup>57</sup> Meta-analysis of these and other major trials (n=7,105 patients) has shown that, in HF, treatment with an ACE inhibitor reduces RR of mortality by 23% (odds ratio (OR) 0.77, 95% CI 67 to 88; ARR 6.1%) and admission for HF is reduced by 35% (95% CI 26 to 43%, ARR 10.2%).<sup>58</sup> In a further meta-analysis in patients with reduced ejection fraction, heart failure or both after MI, and LVEF ≤40%, the relative risk of mortality was reduced by 26% (95% CI 17 to 34%, ARR 5.7%) and hospital admission by 27% (95% CI 15 to 37%, ARR 3.6%).<sup>59</sup>

1++

**R** Patients with heart failure with reduced ejection fraction of all NYHA functional classes, should be given angiotensin-converting enzyme inhibitors.

Important adverse effects are cough, hypotension, renal impairment and hyperkalaemia.<sup>5,60</sup> A key but rare adverse effect, which can be life threatening (due to laryngeal involvement), is angioedema. Any patient who experiences angioedema should have the ACE inhibitor withdrawn immediately and be prescribed an alternative agent. Renal impairment is likely to occur in those with unsuspected (bilateral) renovascular disease. ACE inhibitor-induced renal dysfunction is a possible indicator of renovascular disease and may warrant magnetic resonance imaging (MRI) renal scan.

A systematic review of six RCTs of concomitant ACE inhibitor and aspirin use did not show any significant reduction in efficacy of ACE-inhibitor therapy in patients also taking aspirin.<sup>61</sup> A randomised trial of aspirin versus warfarin in patients with HF-REF did not raise any concerns about a detrimental interaction between aspirin and ACE inhibitors.<sup>62</sup> This combination of drugs can be considered to be safe and effective in reducing cardiovascular disease events in patients with HF.

1++

Annex 2 provides practical guidance on the use of ACE inhibitors.

## 5.3 ANGIOTENSIN RECEPTOR BLOCKERS

Angiotensin II type 1 receptor blockers (ARBs) block the biological effect of angiotensin II. Unlike ACE inhibitors they do not produce cough as a side effect and should be used in patients who cannot tolerate an ACE inhibitor due to cough. In the CHARM-Alternative trial, 2,028 patients, NYHA class II-IV, LVEF ≤40%, intolerant to an ACE inhibitor were randomised to placebo or candesartan, there was a RR reduction of 23% (95% CI 11% to 33%, p=0.0004) in the primary composite outcome of cardiovascular death or hospitalisation for HF in patients receiving candesartan (ARR of seven fewer patients experiencing this outcome per 100 treated).<sup>63</sup>

1++

Angiotensin receptor blockers can also be added to ACE-inhibitor therapy in patients with HF. In the ValHeFT trial, in which 93% of patients were already taking an ACE inhibitor and 35% using a beta blocker, adding the ARB valsartan had no effect on mortality, but it did significantly reduce HF hospitalisation and mortality combined (RR 0.87, 97.5% CI, 0.77 to 0.97, p=0.009).<sup>64</sup> The CHARM-Added trial showed a 15% RR reduction (95% CI 4% to 25%, p=0.01, ARR 4.4%; NNT=27) for cardiovascular death or hospitalisation for HF in patients receiving candesartan in addition to an ACE inhibitor.<sup>65</sup> The overall effect of ARBs on hospitalisations for heart failure was HR 0.81, 95% CI 0.74 to 0.89 in meta-analysis.<sup>66</sup>

1+  
1++

The use of ARB in addition to an ACE inhibitor increased the risk of, and elevation in, serum creatinine (7.8% in the candesartan group versus 4.1% in the placebo group, p=0.0001) in the CHARM-Added trial. In the ValHeFT trial the use of valsartan increased serum creatinine by 7.8 micromol/l more than placebo (p<0.001). Valsartan increased serum potassium by 0.05 mmol/l compared to placebo (p<0.001) in ValHeFT. In CHARM-Added hyperkalaemia was more common in the candesartan group (3.4%) than the placebo group (0.7%), p<0.0001. Rates of hypotension were not increased by the addition of an ARB in ValHeFT or CHARM-Added.<sup>66</sup>

1++

**R** Patients with heart failure with reduced ejection fraction, NYHA class II-IV, who are intolerant of angiotensin-converting enzyme inhibitors should be given an angiotensin receptor blocker.

**R** An angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor should be considered in patients with heart failure with reduced ejection fraction NYHA class II-IV, who are unable to tolerate a mineralocorticoid receptor antagonist.

Annex 3 provides practical guidance on the use of ARBs.

## 5.4 MINERALOCORTICOID RECEPTOR ANTAGONISTS

Aldosterone produces many adverse extrarenal effects, for example on vascular function and myocardial fibrosis. The RALES trial demonstrated that adding the mineralocorticoid receptor antagonist (MRA) spironolactone to an ACE inhibitor reduced all-cause mortality by 30% (RR 0.70, 95% CI 0.60% to 0.82%,  $p < 0.001$ , ARR 11%; NNT=9) and cardiac mortality by 31% (RR 0.69, 95% CI 0.58% to 0.82%,  $p < 0.001$ ) in patients with HF-REF NYHA class II-IV, LVEF  $\leq 35\%$ .<sup>75</sup> The frequency of hospitalisation for worsening HF was 35% lower in the spironolactone group than in the placebo group (RR 0.65; 95% CI 0.54 to 0.77,  $p < 0.001$ ). 1<sup>++</sup>

In the EMPHASIS-HF study, which included patients with less symptomatic but still severe HF (NYHA II and LVEF  $< 30\%$  or  $\leq 35\%$  with a QRS  $> 130$ ) on optimal therapy, who had either been hospitalised in the last six months for a cardiovascular event or had an elevated level of BNP or NT-proBNP, eplerenone reduced the risk of any-cause death by 24% (HR 0.76, 95% CI 0.62 to 0.93) and total hospitalisation by 23% (HR 0.77, 95% CI 0.67 to 0.88) compared to placebo.<sup>76</sup> 1<sup>++</sup>

The EPHEsus study, carried out in patients with LVEF  $\leq 40\%$  following MI and either diabetes or clinical signs of HF, on optimal therapy, found a 13% reduction (95% CI 5% to 21%,  $p = 0.002$ , ARR 3.3%, NNT=30) in the rate of mortality from cardiovascular causes or hospitalisation due to cardiovascular events in patients taking eplerenone.<sup>77</sup> 1<sup>+</sup>

A systematic review comparing eplerenone to other MRAs reported the rate of gynecomastia to be lower in patients taking eplerenone (RR 0.74, 95% CI 0.43 to 1.27) than other MRAs (RR 6.26, 95% CI 3.38 to 11.57).<sup>78</sup> 1<sup>+</sup>

The SMC reported that the use of eplerenone as adjunctive therapy to standard optimal therapy compared to standard optimal therapy alone in patients with NYHA class II HF and left ventricular systolic dysfunction (LVEF  $\leq 30\%$ ) is cost effective. The base case cost-effectiveness ratio was a cost per quality-adjusted life year (QALY) of £3,140 based on a QALY gain of 1.21 and an incremental cost of £3,822.

**R** Patients with heart failure with reduced ejection fraction who have ongoing symptoms of heart failure, NYHA class II-IV, LVEF  $\leq 35\%$ , despite optimal treatment, should be given mineralocorticoid receptor antagonists unless contraindicated by the presence of renal impairment (chronic kidney disease stage  $\geq 4-5$ ) and/or elevated serum potassium concentration ( $K^+ > 5.0$  mmol/l).

✓ Eplerenone can be substituted for spironolactone in patients who develop gynecomastia.

Annex 5 provides practical guidance on the use of MRAs.

## 5.5 ANGIOTENSIN RECEPTOR/NEPRILYSIN INHIBITORS

A large multicentre RCT (PARADIGM) has reported benefit from sacubitril/valsartan in comparison with enalapril. Patients (n=8,399) had HF-REF with NYHA class II, III or IV with an LVEF  $\leq$ 40% (changed to  $\leq$ 35% in a protocol amendment). Patients were required to have a plasma BNP level of at least 150 pg/ml (or NT-pro BNP >600 pg/ml), or, if they had been hospitalised for HF within the previous 12 months, a BNP of at least 100 pg/ml (or NT-pro BNP >400 pg/ml). Excluded patients included those with a history of angioedema, low blood pressure, renal dysfunction or an elevated serum potassium.<sup>79</sup>

A run-in phase involved all patients receiving enalapril 10 mg twice daily for two weeks followed by sacubitril/valsartan for four to six weeks (target dose 200 mg twice daily). Patients with no unacceptable side effects were then randomised to either enalapril (10 mg twice daily) or sacubitril/valsartan (200 mg twice daily). To minimise the risk of angioedema caused by overlapping ACE inhibitor and neprilysin inhibition, patients stopped treatment 36 hours before initiating sacubitril/valsartan.

The primary outcome was a composite of death from cardiovascular causes or a first hospitalisation for HF. The study was terminated early because of overwhelming benefit with a median follow up of 27 months. During the run-in phase, 12% of patients withdrew with a higher rate of withdrawal in the enalapril group.<sup>79</sup>

The primary outcome occurred in 21.8% of sacubitril/valsartan patients versus 26.5% of enalapril patients (HR 0.80, 95% CI 0.73 to 0.87,  $p < 0.001$ ). Cardiovascular deaths were 13.3% versus 16.5% in sacubitril/valsartan versus enalapril (HR 0.80, CI 0.71 to 0.89,  $p < 0.001$ ). Hospitalisations for HF were 12.8% versus 15.6% for sacubitril/valsartan versus enalapril (HR 0.79, 95% CI 0.71 to 0.89,  $p < 0.001$ ). Total deaths were 17% for sacubitril/valsartan versus 19.8% for enalapril (HR 0.84, 95% CI 0.76 to 0.93,  $p < 0.001$ ). Over the trial duration, the NNT was 21 to prevent one death from cardiovascular causes or hospitalisation for HF and 32 to prevent one cardiovascular death.<sup>79</sup>

A subsequent publication showed that the mortality benefit of sacubitril/valsartan compared to enalapril was the same irrespective of the mode of death; there was a similar reduction in both sudden cardiac deaths (20%) and in deaths due to worsening HF (21%).<sup>80</sup>

The benefit of sacubitril/valsartan over enalapril was consistent over all age subgroups and over all categories of risk.<sup>81,82</sup> Only 60 patients in the study had HF-REF class IV, so efficacy in this group is less certain.<sup>79</sup>

Reported adverse events of symptomatic hypotension was more common with sacubitril/valsartan than enalapril (14% v 9.2%) whereas cough, serum potassium >6.0mmol/L, and an elevated creatinine (>2.5 mg/dl) were more common with enalapril. Angioedema was non-significantly more common with sacubitril/valsartan (0.45% v 0.24%).<sup>79</sup>

SMC has accepted sacubitril/valsartan for use in NHSScotland in adult patients for treatment of HF-REF (see section 10.4).

**R** Patients with heart failure with reduced ejection fraction who have ongoing symptoms of heart failure, NYHA class II-III, LVEF  $\leq$ 40% despite optimal treatment should be given sacubitril/valsartan instead of their ACE inhibitor or ARB, unless contraindicated. It may be considered in patients with NYHA class IV symptoms.

**If the patient is already on an ACE inhibitor, the ACE inhibitor should be stopped for 36 hours before initiating sacubitril/valsartan to minimise the risk of angioedema.**

✓ Patients should be seen by a heart failure specialist with access to a multidisciplinary heart failure team before starting treatment with sacubitril/valsartan.

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## 5.6 IVABRADINE

Ivabradine is a new class of drug which targets the sinoatrial node and therefore only acts in patients in sinus rhythm. In a trial of 6,558 participants, when ivabradine was added to usual care for patients with HF-REF, NYHA class II-IV, LVEF  $\leq 35\%$ , heart rate  $\geq 70$  beats per minute and with a previous hospitalisation for HF in the previous 12 months, stabilised on treatment for at least four weeks, the primary end point of cardiovascular death or hospitalisations for HF was reduced (24% in the ivabradine group compared to 29% in the placebo group had an event over 22.9 months; NNT 24). Cardiovascular deaths and all cause mortality were not significantly reduced with ivabradine but there was a reduction in deaths due to HF (3% with ivabradine v 5% with placebo; HR 0.74, 95% CI 0.58 to 0.94).<sup>83</sup>

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Ivabradine had an increased risk of symptomatic and asymptomatic bradycardia compared with placebo (5% v 1% for symptomatic; 6% v 1% for asymptomatic), and an increased risk of phosphenes (3% v 1%).<sup>83</sup>

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An assessment by SMC found that ivabradine, in addition to standard care, was cost effective compared to standard care alone in patients whose resting heart rate remained  $\geq 75$  beats per minute despite optimal standard therapy (see section 10.4). The estimated incremental cost-effectiveness ratio (ICER) was £6,002 per QALY based on an incremental cost of £1,875 and a QALY gain of 0.3. This result was supported by a further cost-utility analysis undertaken in the UK comparing ivabradine added to standard therapy with standard care which found an ICER of £8,498 for patients whose heart rate remained  $\geq 75$  bpm and £13,764 for those whose heart rate remained  $\geq 70$  bpm.<sup>84</sup> Probabilistic sensitivity analysis showed a 95% probability that ivabradine would be considered cost effective at a £20,000 per QALY threshold.<sup>84</sup>

**R** Patients with a diagnosis of heart failure with reduced ejection fraction of NYHA class II-IV, LVEF  $\leq 35\%$ , who have had a previous hospital admission for heart failure in the preceding 12 months but have stabilised on standard therapy for at least four weeks should be given ivabradine. Patients must have a sinus rhythm heart rate  $\geq 75$  beats/minute despite maximum tolerated dose of beta blockers.

✓ Specialist advice should be sought before initiating ivabradine.

## 5.7 DIURETICS/ LOOP DIURETICS

In the majority of patients with heart failure fluid retention occurs, causing ankle oedema, pulmonary oedema or both, contributing to the symptom of dyspnoea. Diuretic treatment relieves oedema and dyspnoea.

A meta-analysis of diuretic therapy found a 75% reduction in mortality (OR 0.25, 95% CI 0.07% to 0.84%,  $p=0.03$ , ARR 8.2%, NNT=12) and a 63% improvement in exercise capacity (OR 0.37, 95% CI 0.1% to 0.64%).<sup>85</sup> Although studies included in this meta-analysis were small and of poor quality they were reasonably consistent. The evidence supports the view that there is benefit in diuretic therapy for patients with dyspnoea or oedema.

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In most cases the agent of choice will be a loop diuretic although a thiazide might suffice where the fluid retention is very mild.

**R** Patients with heart failure and clinical signs or symptoms of fluid overload or congestion should be considered for diuretic therapy.

Care should be taken to select the dose of the loop diuretic on an individual basis, so that the dose chosen or reached should eliminate ankle or pulmonary oedema without dehydrating the patient and placing them at risk of renal dysfunction or hypotension.

The tendency of loop diuretics to cause hypokalaemia is offset by ACE inhibitors, ARBs and spironolactone. Serum potassium should be monitored to maintain its concentration in the range 4–5 mmol/l and adjustments in therapy should be made to prevent both hypokalaemia and hyperkalaemia.

✓ The dose of diuretic should be individualised to reduce fluid retention without overtreatment which may cause dehydration or renal dysfunction.

## 5.8 DIGOXIN

A Cochrane review found a 64% improvement in symptoms (OR 0.31, 95% CI 0.21% to 0.43%, ARR 11.5%, NNT=9) and a 23% reduction in hospitalisation (OR 0.68, 95% CI 0.61% to 0.75%, ARR 5.7%, NNT=18) for patients receiving digoxin (digitalis). Digoxin did not improve survival.<sup>86</sup> This review is dominated by one large trial (the DIG study) which was carried out before the introduction of beta blockers and spironolactone for the treatment of patients with HF, which may have influenced the conclusions.<sup>87</sup> Evidence of benefit must be weighed against the possibility of an increase in sudden deaths associated with digoxin. The risk of digoxin toxicity is increased by hypokalaemia.

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In patients with HF and atrial fibrillation a beta blocker is preferred for control of the ventricular rate, although digoxin may be used initially while the beta blocker is being introduced. If excessive bradycardia occurs with both drugs, digoxin should be stopped (*see the SIGN guideline on cardiac arrhythmias in coronary heart disease*).<sup>88</sup>

In patients with HF and sinus rhythm, digoxin may reduce symptoms and hospital admission for worsening HF although it has not been tested in addition to optimum therapy and is usually only reserved for patients with severe HF who have not responded to other treatments.<sup>86</sup> In two smaller and shorter studies of digoxin withdrawal in patients with stable HF, the PROVED and RADIANCE trials, withdrawal of digoxin was associated with a decline in exercise capacity, deterioration in left ventricular systolic function, and significantly increased risk of hospitalisation for worsening HF.<sup>89,90</sup>

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**R** | **Digoxin should be considered as an add-on therapy for patients with heart failure in sinus rhythm who are still symptomatic after optimum therapy.**

✓ | If excessive bradycardia occurs with concurrent beta blockade and digoxin therapy, digoxin should be stopped.

## 5.9 NATRIURETIC PEPTIDE-GUIDED TREATMENT

It can be difficult, using clinical signs alone, to determine the optimum dose of drugs, such as loop diuretics, in individual patients. Monitoring plasma natriuretic peptide levels can guide such decisions in clinical practice.

Natriuretic peptide-guided treatment was found to reduce all-cause mortality in a meta-analysis of 11 studies, compared to standard care (RR 0.83, 95% CI 0.69 to 0.99).<sup>91</sup> Another meta-analysis reported no significant reduction with natriuretic peptide BNP-guided therapy (OR 0.814, 95% CI 0.518 to 1.279), but all-cause mortality was significantly reduced with NT-proBNP-guided therapy (OR 0.717, 95% CI 0.563 to 0.914).<sup>92</sup> Younger patients responded better to treatment, with combined mortality and heart failure-related hospitalisation significantly reduced in patients under 75 years (OR 0.449, 95% CI 0.207 to 0.973) compared to those over 75 years (OR 0.800, 95% CI 0.423 to 1.513).<sup>92</sup> Heart failure-related rehospitalisation was also significantly reduced with BNP-guided therapy in younger patients (RR 0.45, 95% CI 0.33 to 0.61) or in those with higher baseline BNP (2,114 pg/ml), (RR 0.53, 95% CI 0.39 to 0.72).<sup>91</sup>

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BNP testing is not currently available throughout Scotland and would require training for primary-care providers, as well as placing extra demands on laboratory resources. Three analyses (one UK-based, one North American and one Japanese) found BNP-guided and NT-proBNP-guided treatment to be cost effective, using commonly accepted UK thresholds.<sup>93-95</sup> From an NHSScotland perspective, results showed that a natriuretic peptide monitoring strategy is cost effective in patients with HF-REF, with an ICER of £3,304 compared with clinical assessment.<sup>93</sup> For patients with HF from any cause, natriuretic peptide monitoring was cost effective with an ICER of £14,694 compared with clinical assessment by a specialist, and for patients aged ≤75 years, natriuretic peptide monitoring was cost effective compared with usual care, with an ICER of £2,517. Natriuretic peptide monitoring was not cost effective for patients aged >75 years with HF from any cause.<sup>93</sup>

Natriuretic peptide-guided treatment may not be suitable for patients treated with sacubitril/valsartan. Sacubitril/valsartan increases BNP (though not NT-proBNP levels) through its mechanism of action. How to interpret these changes and their relationship to prognosis is unknown. No prior studies of natriuretic peptide-guided treatment included patients receiving sacubitril/valsartan.

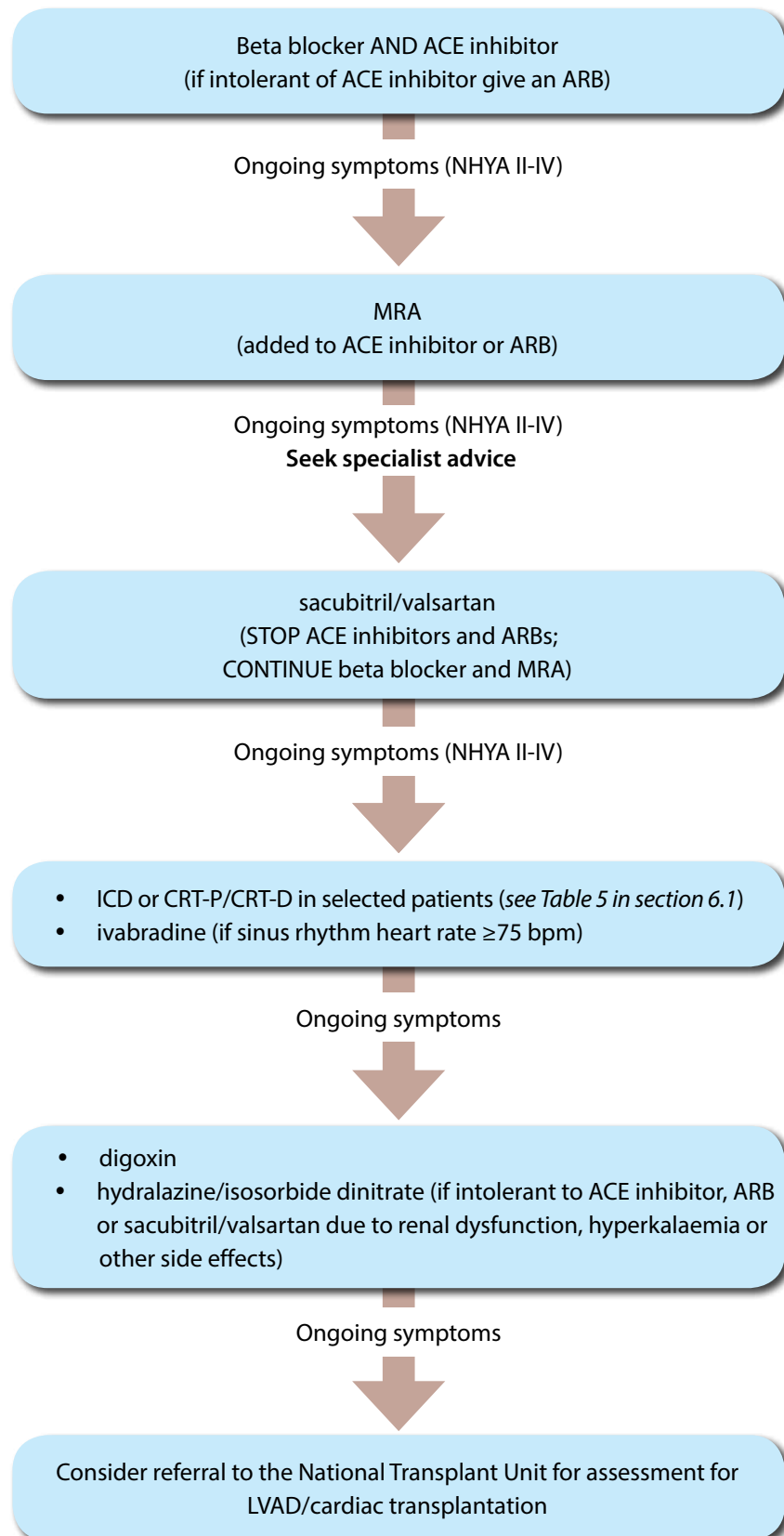
**R** | **NT-proBNP-guided treatment may be considered in patients with heart failure aged less than 75 years, especially in the presence of higher baseline NT-proBNP levels (>2,114 pg/ml).**

## 5.10 SUMMARY OF THE USE OF MAJOR DRUG CLASSES FOR TREATMENT OF HEART FAILURE

Unless contraindicated, all patients with HF-REF should be started on an ACE inhibitor and a beta blocker (and a diuretic, in most cases). For those who remain symptomatic, the addition of an MRA may be considered. No patient should receive three drugs which block the renin-angiotensin-aldosterone system as hyperkalaemia and renal dysfunction will be common. Figure 2 provides a flowchart for sequence of therapy.

**✓** | **The safety and efficacy of combining an ACE inhibitor, an ARB and MRA is uncertain and the use of these three drugs together is not recommended.**

Figure 2: Algorithm for pharmacotherapy and device therapy in patients with HF-REF, NYHA class II-IV



**Other therapies to consider:**

Intravenous iron (ferric carboxymaltose) if haemoglobin 9.5 to 13.5 mg/dl and iron deficiency (defined as ferritin <100 microgram/l or <300 microgram/l if TSAT <20%)

### 5.11 ANTITHROMBOTIC THERAPY

Many patients with HF-REF have had previous cardiovascular events like myocardial infarction (silent or overt) and may need antithrombotic therapy. Meta-analyses have found, in comparison to aspirin, warfarin appears to reduce ischemic strokes by 28–51% while doubling the incidence of major haemorrhage. Overall mortality is similar between aspirin and warfarin.<sup>96–100</sup> Therefore no firm evidence supports the use of any antithrombotic therapy in patients with HF-REF in sinus rhythm.

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### 5.12 HYDRALAZINE AND ISOSORBIDE DINITRATE

The combination of hydralazine and isosorbide dinitrate (H-ISDN) was shown to reduce mortality in patients with HF before ACE inhibitors were introduced.<sup>101</sup> It was found to be less effective than an ACE inhibitor in a subsequent head-to-head comparison with enalapril (28% mortality reduction in favour of enalapril,  $p=0.016$ ).<sup>102</sup> Hydralazine and isosorbide dinitrate has been shown to reduce symptoms and the risk of death and hospital admissions for HF when added to standard treatment (which included ACE inhibitors, ARBs, beta blockers for at least three months before randomisation, digoxin, spironolactone, and diuretics) in African-Americans with NYHA class III or IV HF (absolute survival benefit 4.0%, HR for all-cause mortality 0.57;  $p=0.01$ ).<sup>103</sup> In Caucasian patients the main indication for H-ISDN is intolerance of an ACE inhibitor and ARB due to renal dysfunction or hyperkalaemia. Vasodilator adverse effects are common and, rarely, hydralazine can cause a lupus like syndrome.<sup>104,105</sup>

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**R** Patients who are intolerant of an angiotensin-converting enzyme inhibitor and an angiotensin II receptor blocker due to renal dysfunction or hyperkalaemia should be considered for treatment with a combination of hydralazine and isosorbide dinitrate.

**R** African-American patients with heart failure with reduced ejection fraction, NYHA class III or IV, should be given hydralazine and isosorbide dinitrate in addition to standard therapy.

### 5.13 PHOSPHODIESTERASE INHIBITORS

Two meta-analyses reported improved exercise capacity with use of sildenafil compared to placebo (peak volume of oxygen ( $VO_2$ ) improved by a weighted mean difference (WMD) of 3.2, CI 2.7 to 3.6, and ventilatory equivalent for oxygen ( $VE/VO_2$ ) slope by 5.89, CI 7.1 to 3.6;  $106 VO_2$  at aerobic threshold by 3.47, CI 1.7 to 5.3, and  $VE/VO_2$  slope by 7.1, CI 8.9 to 5.2).<sup>107</sup> Sildenafil also reduced hospitalisation (risk ratio 0.29, CI 0.11 to 0.77).<sup>106</sup> The studies within the meta-analyses, however, were not of sufficient size or quality to support a recommendation.

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### 5.14 PATIENTS WITH ANAEMIA

Two meta-analyses report benefit from intravenous iron in patients with LVEF  $\leq 40\%$  (if NYHA class II) or LVEF  $\leq 45\%$  (if NYHA class III), haemoglobin 9.5 to 13.5 units and iron deficiency (serum ferritin  $< 100$  microg/l or ferritin 100–300 microg/l if transferrin saturation (TSAT) 20%). Intravenous iron improved quality of life according to the Minnesota Living with Heart Failure questionnaire (MLHFQ) with a WMD of -18 ( $I^2 = 0\%$ ). Of the included patients 81% were NYHA class III.<sup>108</sup> Iron also resulted in fewer hospitalisations (WMD 0.51,  $I^2 = 10\%$ ).<sup>108</sup> In the second meta-analysis of 543 patients, iron improved exercise tolerance, quality of life and cardiovascular events.<sup>109</sup> Both meta-analyses are dominated by one large study, the FAIR-HF trial, where ferric carboxymaltose improved patient's symptoms according to the patient global assessment score (OR 2.51, 95% CI 1.75 to 3.61) and the NYHA class (OR for improvement by one class 2.4, 95% CI 1.55 to 3.71).<sup>110</sup> A subanalysis of the FAIR-HF trial showed intravenous ferric carboxymaltose increased quality of life as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ).<sup>111</sup>

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The CONFIRM-HF trial studied 304 patients similar to those in the meta-analyses over a longer time period (52 weeks). Intravenous iron significantly prolonged the six-minute walk distance by  $33 \pm 11$  metres ( $p=0.002$ ). Significant improvements were also seen in NYHA class, patients' global assessment, quality of life and fatigue scores. Heart failure hospitalisations also fell significantly (HR 0.39, 95% CI 0.19 to 0.82,  $p=0.009$ ).<sup>112</sup>

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Intravenous iron has to be administered at intervals and patients are required to attend hospital or their GP so they can be monitored, due to the risk of hypersensitivity reactions.<sup>113</sup> This may incur additional costs to services. Two cost-utility analyses of the FAIR-HF data found that intravenous iron is cost effective over 24 weeks.<sup>114,115</sup> The UK-based analysis showed that ferric carboxymaltose ranged from being more effective and lower cost to costing £12,482 per QALY gained.<sup>114</sup>

Meta-analysis of trials on the use of erythropoietin found no beneficial effects on mortality rates, cardiovascular events or hospitalisations.<sup>109</sup> Quality of life and exercise tolerance did not improve either. There was an increased risk of possible harms, such as venous thromboembolism (RR, 1.36, 95% CI 1.17 to 1.58).<sup>109</sup>

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**R** Patients with heart failure with reduced ejection fraction, NYHA class III with an LVEF  $\leq$ 45%, or NYHA class II, LVEF  $\leq$ 40%, who have a haemoglobin level of 9.5 to 13.5 and iron deficiency (defined as ferritin <100 microgm/l or <300 microgm/l if TSAT <20%) should be considered for therapy with intravenous iron.

**R** Erythropoietin is not recommended for patients with heart failure with reduced ejection fraction and iron deficiency.

## 5.15 PATIENTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION

Not all patients with heart failure have reduced ejection fraction. Patients with clinical heart failure but normal or slightly reduced ejection fraction are described as having heart failure with preserved ejection fraction (*see section 1.2.2*). The proportion of patients with HF-PEF may be as high as 35–50%.<sup>116</sup>

HF-PEF might occur along with myocardial ischaemia, hypertension, myocardial hypertrophy or even myocardial/pericardial constriction. Consideration should be given as to whether these may be present and contribute to the clinical picture in patients with HF-PEF. If present, they should be identified and treated in their own right. An additional contributory factor could be tachyarrhythmias: if so, rate control is likely to be beneficial.

Meta-analysis of two placebo-controlled studies of 7,151 patients with HF and LVEF >40% found no reduction in mortality (RR 1.02, 95% CI 0.93 to 1.12) or total morbidity as measured by total hospitalisations (RR 1.00, 95% CI 0.97 to 1.05) with ARBs compared with placebo.<sup>66</sup> A further systematic review found no significant reduction in total mortality, cardiovascular mortality or hospitalisation with ARBs.<sup>117</sup>

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Meta-analysis of four RCTs of patients with HF and LVEF >40% showed no significant reduction in hospitalisation rates (RR 0.85, 95% CI 0.63 to 1.13), all-cause mortality (1.03, 95% CI 0.73 to 1.46) and cardiovascular mortality (0.57, 95% CI 0.27 to 1.2) with ACE inhibitors versus placebo.<sup>117</sup>

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Beta blockers were found to cause a 9% reduction in relative risk for all-cause mortality, based mainly on heterogenic observational studies, but no reduction in hospitalisations or exercise capacity.<sup>118,119</sup>

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No benefit was found from the use of spironolactone in the single identified RCT in patients with HF and LVEF  $\geq$ 45%.<sup>120</sup>

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## 5.16 HEART FAILURE AND GOUT

Loop diuretics can cause an elevated urate level and may precipitate gout.<sup>121</sup>

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No evidence was identified on how best to treat gout in patients with HF. Current practice in the management of acute gout is to use colchicine to suppress the inflammation and pain.<sup>122</sup> Further advice on the management of gout is available from the British Society of Rheumatology ([www.rheumatology.org.uk](http://www.rheumatology.org.uk)).

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Once the pain is under control, consideration should be given to starting prophylactic antagonist therapy and stopping colchicine.

## 5.17 HEART FAILURE AND RENAL IMPAIRMENT

Renal dysfunction is common in heart failure and the underlying cause of the renal dysfunction should be assessed in each individual patient.

Possible causes include dehydration;<sup>123</sup> ACE inhibitor,<sup>124</sup> ARB and/or spironolactone use; coincidental renal disease, eg diabetic nephropathy or renovascular disease.

- ✓ Renal dysfunction in patients with heart failure caused by:
- dehydration may require a reduction in dose or temporary cessation of the diuretic
  - ACE inhibitor, ARB and/or spironolactone use requires a cessation or a reduction in dose
  - coincidental renal disease requires renal investigations (24 hour urine protein collection, kidney ultrasound and/or MRI of the renal arteries).

## 5.18 HEART FAILURE AND ANGINA

Beta blockers are the drug of choice in patients with HF and angina (*see the SIGN guideline on the management of stable angina*).<sup>125</sup> Sublingual and oral nitrate preparations may also be used safely for the treatment of anginal symptoms where blood pressure permits. Calcium channel blockers (with the exception of amlodipine)<sup>126</sup> have been found to exacerbate symptoms of heart failure or increase mortality after myocardial infarction in people who also have pulmonary congestion or left ventricular dysfunction.<sup>127</sup> Other treatment options are discussed in the SIGN guideline on the management of stable angina.<sup>125</sup>

Some patients with angina will require revascularisation for symptomatic relief (*see section 6.3, and the SIGN guideline on the management of stable angina*).<sup>125</sup>

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## 5.19 HEART FAILURE IN FRAIL OLDER PEOPLE

Many patients with HF are older and many diagnostic and treatment trials did not include frailer, older patients, especially those with multiple comorbidities. Trials that have done so suggest that the benefits of drug treatment do extend to the older population.<sup>70,128</sup> The general approach to the investigation and management of HF in frail, older people should follow the principles outlined in this guideline. The following factors should also be considered.

### 5.19.1 COMORBIDITY

The possible presence of coexistent cognitive impairment, renal dysfunction, urinary incontinence, postural hypotension, falls, chronic obstructive pulmonary disease and depression should be considered as it might influence an individual's treatment.

### 5.19.2 GOAL OF TREATMENT

In older patients with HF significant multimorbidity, functional impairment or other life-limiting systemic disease such as neoplasia, the goal of treatment may be the improvement of symptoms and function alone, rather than the improvement of prognosis. Target-dose titration and multiple drug regimens as utilised in treatment trials may be undesirable or problematic. An effort should always be made to engage older patients or their carers in discussion regarding the goals of HF treatment.

### 5.19.3 MODEL OF CARE

Older patients with heart failure and multimorbidity and functional impairment should be managed within an integrated care model that provides multidisciplinary functional and medical assessment and rehabilitation in both primary- and secondary-care settings.

## 5.20 VACCINATIONS

A large cohort study of older individuals in the general population demonstrated a 37% reduction in hospital admissions for HF among those immunised against influenza during an outbreak of influenza A.<sup>129</sup> A case series also found that, in a group of patients with moderate to severe HF, 23% of episodes of decompensation were associated with infection.<sup>130</sup> A third of these infections were pulmonary. Similarly, a further case series showed that 12% of hospitalisations in patients with HF were due to pulmonary infection.<sup>131</sup>

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The Joint Committee on Vaccination and Immunisations recommends immunisation, for those with chronic conditions, with pneumococcal vaccine. This immunisation is required once only, not annually as with influenza immunisation.

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- ✓ Patients with chronic heart failure should receive one pneumococcal vaccination and an annual influenza vaccination.

## 6 Interventional procedures

### 6.1 CARDIAC RESYNCHRONISATION THERAPY AND IMPLANTABLE CARDIOVERTER DEFIBRILLATORS

HF-REF is a significant predictor of sudden cardiac death and prolonged QRS duration and the presence of left bundle branch block (LBBB) further increases this risk. There is evidence showing the benefits of treatment with an implantable cardioverter defibrillator (ICD), cardiac resynchronisation therapy with pacing (CRT-P) or cardiac resynchronisation therapy with an implantable cardioverter defibrillator (CRT-D) compared to medical therapy. In patients with HF-REF and with prolonged QRS and LBBB, cardiac resynchronisation therapy in addition to optimal medical therapy improved exercise capacity and quality of life and reduced NYHA class and hospitalisations for worsening heart failure,<sup>132,133</sup> and significantly reduced mortality in patients with reduced ejection fraction (HR 0.64, CI 0.48 to 0.85,  $p < 0.002$ ).<sup>134</sup> Most of the evidence for CRT applies to patients with HF who are in sinus rhythm.

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An MTA considered the benefit of ICD and CRT in three populations of patients: with HF at risk of sudden cardiac death from ventricular arrhythmia (13 trials comparing ICD and medical therapy of which nine were primary and four were secondary prevention trials); with HF-REF and cardiac dys-synchrony (four trials comparing CRT-P and medical therapy); and with HF-REF and cardiac dys-synchrony also at risk of sudden cardiac death from ventricular arrhythmia (nine trials comparing CRT-D versus ICDs).<sup>8</sup> Individual data from approximately 12,500 patients (covering 95% of enrolled patients from the identified studies) were utilised to inform the economic modelling.

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Twenty subgroups of patients covering all combinations of NYHA class, QRS duration and presence of LBBB were examined. Incremental cost-effectiveness ratios for the devices were taken into consideration along with modifying factors such as the severity of the condition and the risk of harm. It was concluded that, based on current standard practice in the UK, severity of symptoms (NYHA class), duration of QRS by ECG and the presence or absence of LBBB are important clinical characteristics for identifying patients who are likely to benefit from CRT devices.<sup>8</sup> A meta-analysis demonstrated that the clinical benefit of CRT in patients with QRS durations between 120 and 140 milliseconds was smaller than those with a longer QRS duration, and it could have a potentially harmful effect in patients with a QRS duration of less than 126 milliseconds. In the absence of robust data for this particular patient group (QRS of 120–149 milliseconds) and the risk of harm, a more cautious approach to the use of CRT was suggested for these patients.<sup>8</sup>

1++

Shocks from the devices are associated with poor psychological outcomes, although the reassurance patients experience from having the device may outweigh the anxiety over shocks. Implantation is also associated with adverse events and equipment malfunction. Improvements in the technology and implanter skills and experience may result in a decline in these adverse outcomes.<sup>8</sup>

1++

Assessment of the cost effectiveness of either CRT-P or CRT-D in addition to optimal pharmacological therapy found the therapy to be considered cost effective with a £30,000 threshold.<sup>8</sup>

Treatment options with ICD or CRT are shown in Table 5.

Table 5: Treatment options with ICD or CRT for people with heart failure with an ejection fraction of 35% or less (according to NYHA class, QRS duration and presence of LBBB) (from NICE Multiple Technology Appraisal: Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure)<sup>8</sup>

QRS interval (ms)	NYHA class			
	I	II	III	IV
<120	ICD if there is a high risk of sudden cardiac death			ICD and CRT not clinically indicated
120–149 (without LBBB)	ICD	ICD	ICD	CRT-P
120–149 (with LBBB)	ICD	CRT-D	CRT-P or CRT-D	CRT-P
≥150 (with or without LBBB)	CRT-D	CRT-D	CRT-P or CRT-D	CRT-P

ICD = implantable cardioverter defibrillator; CRT-D = cardiac resynchronisation therapy with an implantable cardioverter defibrillator; CRT-P = cardiac resynchronisation therapy with pacing

- R** Implantable cardioverter defibrillators, cardiac resynchronisation therapy with defibrillator or cardiac resynchronisation therapy with pacing are recommended as treatment options for patients with heart failure with reduced ejection fraction, LVEF ≤35%, as specified in Table 5.
- ✓ Patients receiving cardiac resynchronisation therapy and/or an implantable cardioverter defibrillator should be offered pre- and postplacement counselling, including discussion of potential shocks from the device, and device deactivation (see section 8.4).

## 6.2 ASSISTED VENTILATION

Heart failure is often associated with sleep apnoea. There are at least two forms of sleep apnoea, obstructive sleep apnoea (OSA) and central sleep apnoea (CSA), which can coexist in the same patient. This makes assessment of the literature difficult as not all papers fully characterise the participants into OSA, CSA or both.

Several trials have looked at the impact of continuous positive airway pressure (CPAP) in patients with HF-REF and OSA. Although CPAP does not appear to reduce mortality, CPAP does appear to improve LVEF (mean increase 5.1%, CI 3.7 to 6.4).<sup>135</sup>

With regard to CSA, one large randomised controlled trial (n=1,325 patients) reported an increase in all-cause mortality and cardiovascular mortality with adaptive servoventilation in patients with CSA and HF-REF (HR 1.28, CI 1.06 to 1.55, p=0.01 and HR 1.34, CI 1.09 to 1.65, p=0.006).<sup>136</sup> Therefore, adaptive servoventilation should be avoided in patients with HF-REF and CSA.

- R** Patients with central sleep apnoea and heart failure due to reduced ejection fraction should not be treated with adaptive servoventilation.

## 6.3 CORONARY ARTERY BYPASS GRAFTING SURGERY

An RCT of coronary artery bypass grafting (CABG) surgery and optimal medical management versus optimal medical management alone in patients with heart failure and angina did not find a significant difference between the two trial groups with respect to the primary outcome, rate of death from any cause (244/602 (41%) treated by medical therapy only and 218/610 (36%) assigned to CABG; HR with CABG 0.86, 95% CI 0.72 to 1.04; p=0.12). CABG did reduce the occurrence of the prespecified secondary outcome of cardiovascular death (HR 0.81, 95% CI 0.66 to 1.00; p=0.05) and death from any cause or cardiovascular hospitalisation (HR 0.74, 95% CI 0.64 to 0.85; p<0.001).<sup>137</sup>

- R** Patients with heart failure and angina who require revascularisation can be considered for coronary artery bypass grafting. This can be considered after assessment of their operative risk.

## 6.4 MECHANICAL CIRCULATORY SUPPORT

Mechanical circulatory support (MCS) may be used as a destination therapy or a bridge to transplantation (BTT).

Two studies have shown that MCS with a left ventricular assist device (LVAD) as a destination therapy is superior to medical therapy alone.<sup>138</sup> Interventional procedure guidance from NICE supports its use as a destination therapy for patients ineligible for cardiac transplantation, after selection by a specialist multidisciplinary team.<sup>139</sup> 2++

No RCTs examining MCS as a BTT were identified. Mechanical circulatory support using the HeartWare LVAD improved survival compared to a historical set of controls at six months (90% versus 73%), 12 months (85% versus 58%) and 24 months (79% versus 40%).<sup>138</sup> Implantation of MCS as a BTT incurs risks of infection (16%), neurological dysfunction (4.3%), device malfunction (3%) and right heart failure (4%). 2++

Observational studies have reported significant improvements in quality of life for patients before and after receiving MCS or ventricular assist devices.<sup>140-144</sup> There were also significant improvements in mean depression and anxiety scores in a sample of 19 patients after MCS implantation.<sup>145</sup> 3

The results of two cost-utility analyses of MCS undertaken in the UK found LVADs as a BTT not to be cost effective, with ICERs ranging from £55,173 per QALY in one study to £258,922 in another.<sup>146,147</sup> A further UK HTA showed treatment with ventricular assist devices was not cost effective compared with non-VAD treatment since patients without LVADs had lower costs and higher QALYs than patients with the device.<sup>148</sup>

Mechanical circulatory support is offered in special circumstances, on a case-by-case basis, to appropriately selected patients after specialist assessment in the National Heart Transplant Unit. The UK guidelines for referral and assessment of adults for heart transplantation provide further advice on selection of patients.<sup>149</sup>

## 6.5 CARDIAC TRANSPLANTATION

Cardiac transplantation offers patients good outcomes in both quality of life and survival. There are no randomised trials but registry data both in the UK and internationally demonstrate a one year survival of 80% and a ten year survival of 50%.<sup>150</sup> Few patients with HF optimally managed with medical and complex pacemaker therapies now warrant cardiac transplantation. 2+

- ✓ Patients with drug refractory severe heart failure should be referred to an advanced heart failure centre where they can be assessed with regard to suitability for transplantation.

## 7 Postdischarge care

One high-quality meta-analysis investigated comprehensive discharge planning and postdischarge multidisciplinary support using a variety of interventions.<sup>151</sup>

A reduction in mortality was shown for home/clinic-based specialist team intervention<sup>152,153</sup> but not for comprehensive discharge planning and multidisciplinary follow up, more frequent clinic attendances or telephone follow up or enhanced self care.<sup>154</sup> Tele/video monitoring was also associated with a reduction in mortality. Most successful interventions had an element of home visits.<sup>152</sup>

All-cause admissions were reduced by specialist team interventions in clinics or in a patient's home,<sup>152,153</sup> and by comprehensive discharge planning and multidisciplinary follow up (home visits but not increased clinic visits or frequent telephone contact). Heart failure admissions were reduced by attendance at multidisciplinary heart failure clinics, by specialised follow up by multidisciplinary teams, telephone follow up,<sup>152,153</sup> enhanced self care,<sup>153</sup> and telephone/video monitoring,<sup>152</sup> but not by GP and non-specialist clinic follow up.<sup>152</sup>

Quality of life improved more in patients receiving postdischarge planning and postdischarge support.<sup>151</sup>

None of the trials conducted formal cost-effectiveness analyses but many did record the medical costs of each comparator. Three meta-analyses consistently reported that implementing a discharge-management plan reduced costs compared to usual care.<sup>151,153,155</sup> The resultant savings exceeded the cost of implementation by an average of over six times (range two to 14 times). The savings arose primarily from the lower rate of readmissions. The only study where the intervention costs exceeded savings provided follow-up support in a day hospital.

Tele/video monitoring has not been considered in this guideline.

**R** | **Comprehensive discharge planning should ensure that links with postdischarge services are in place for all those with symptomatic heart failure.**

✓ | Comprehensive planning requires communication between primary and secondary-care teams, including discharge planning following a hospital admission, anticipatory care planning, specialist nurse input and, where appropriate, home-based care.

Palliative care is covered in section 8.

### 7.1 NURSE-LED FOLLOW UP

A small RCT of nurse-led follow up of patients after discharge (which included home visits supplemented by telephone contact) compared to usual care showed that 37% of patients in the intervention group died or were readmitted with HF compared with 53% in the usual care group (HR 0.61, 95% CI 0.33 to 0.96). Compared with usual care, patients in the intervention group had fewer readmissions for any reason (86 v 114, p=0.018), fewer admissions for HF (19 v 45, p<0.001) and spent fewer days in hospital for HF (mean 3.43 v 7.46 days, p=0.0051).<sup>156</sup>

One RCT of a structured telephone service delivered by specially-trained nurses for patients with stable HF (no hospital admission or change in therapy within previous two months and patients on optimal pharmacological treatment) showed a reduction from 31% to 26.3% in the intervention group in the composite primary end point of all-cause mortality or hospital admission for worsening heart failure compared to the group receiving usual care (RR reduction 20%, 95% CI 3% to 34%, p=0.026, ARR 4.7%, NNT =21).<sup>157</sup> This was mainly due to reduction in admission for worsening HF over a mean of 16 months. The nurses could change diuretic therapy and recommend non-scheduled/emergency room visits. Patients in the intervention group were more likely to be compliant with prescribed beta blockers, spironolactone and digoxin at the end of the study.

1++  
1+

1+

1+

Patients in the intervention group had better quality of life than the control patients at the end of the study (mean total score in intervention group 30.6 versus 35.0 in the control group; mean difference =4.4, 95% CI 1.8 to 6.9; p=0.001). 1+

**R** Patients who have been hospitalised with heart failure should be followed up after discharge by a specialist nurse who has the resource to initiate and adjust medication.

## 7.2 ROLE OF PHARMACISTS

Three good-quality RCTs were identified which looked at the contribution of pharmacists to follow up of patients with HF. One trial showed that monthly contact with specially-trained community pharmacists in addition to standard patient care reduced the number of days, and two-day periods of missed diuretic dose.<sup>158</sup> There was no effect on hospital admission or death but there was already high compliance in the control arm. A further RCT found that including a pharmacist intervention at a multidisciplinary heart function clinic improved patient recollection of instruction about drug taking, helped with goal setting and ongoing prompting, although over the three-month follow up there was no measurement of admission or mortality.<sup>159</sup> The third trial found a significant improvement in all-cause mortality, non-fatal HF events (emergency room visits or HF admissions) and ACE inhibitor or other vasodilator therapy for the ACE inhibitor intolerant, for those who had a structured pharmacist intervention about compliance and knowledge of drugs with telephone follow up as well as feedback to physicians about optimisation of therapy, compared to those who had usual care.<sup>160</sup> The result may have been due to optimisation of ACE inhibition or ARB use or to deterioration being noted and acted on sooner. 1+

**R** Patients with heart failure should be offered multidisciplinary follow up, which includes pharmacy input addressing knowledge of drugs and compliance. Follow up should include feedback to clinicians about possibilities for optimising pharmacological interventions.

## 7.3 SELF MANAGEMENT

One small before and after study of a self-care management programme for low-literacy individuals gives an indication that programmes tailored to literacy levels can lead to improved HF knowledge, improved self weighing, increased accuracy of dose adjustment over time, and improved symptoms.<sup>161</sup> 3

✓ Self-management programmes should be tailored to individual patient requirements, paying particular attention to those with low literacy.



## 8 Palliative care

In Scotland, despite progressive HF therapeutic strategies the prognosis remains poor compared to many cancers. After first hospitalisation with HF 50% of men and women have died by 2.3 years and 1.7 years respectively.<sup>162</sup>

There is inequity of access to palliative care compared to patients with cancer. Primary-care data from England showed that 7% of patients with HF were on the palliative care register, compared to 48% of patients with cancer.<sup>163</sup> This is comparable to the national heart failure audit figure of 4% of patients with HF on the specialist palliative care register.<sup>164</sup>

At present there is a lack of robust RCT evidence to support the best means of identifying patients with palliative care needs, what those needs are, how to deliver care, the impact of interventions such as anticipatory care planning, and the clinical and health economic impact of a collaborative cardiology and palliative care approach to care.

Extrapolating from cancer care, general palliative care should be delivered by the patient's usual healthcare professional team appropriately trained to provide it, with access to specialist teams as needed or when the complexity of care increases.<sup>165</sup> This care should be available and have equal priority alongside diagnosis and therapeutic strategies. Of particular priority are those patients who, despite optimally-tolerated heart failure treatments, continue to have troublesome symptoms and hospitalisations.

The studies which exist in this area demonstrate high rates of unmet needs in the areas of symptom management, communication, decision making, emotional support, co-ordination of care and quality end-of-life care.<sup>166-168</sup>

Given that patients with HF are already in a poor prognostic category those who continue to have ongoing symptoms and hospitalisations despite HF treatments merit a collaborative cardiology and palliative care approach to their care.<sup>169</sup>

✓ Patients with advanced heart failure with ongoing symptoms despite optimally-tolerated heart failure treatment should have access to a collaborative cardiology and palliative approach to their care. This includes:

- active heart failure management in conjunction with symptom control
- rationalisation of medical therapy
- anticipatory care planning
- co-ordination of care
- multidisciplinary team working
- communication across primary and secondary care
- good end-of-life care.

This approach to care should be practised by all healthcare professionals involved in the management of patients with advanced disease with access to specialist advice as needed.

### 8.1 PROGNOSIS AND IDENTIFYING PATIENTS WITH PALLIATIVE CARE NEEDS

Because of the complexity of HF with its uncertain trajectory making a prognosis is challenging. One of the main barriers to providing palliative care for patients with advanced HF is the expectation that palliative care is only appropriate when it is known when a patient is going to die. Given the difficulties with making a prognosis this may result in patients and their carers missing out on the opportunity of a collaborative cardiology and palliative care approach to their care.

✓ Issues of sudden death and living with uncertainty are pertinent to all patients with heart failure. The opportunity to discuss these issues should be available to patients at all stages of their care.

## 8.2 QUALITY OF LIFE

In patients with HF, quality of life decreases as NYHA functional class worsens. Although NYHA functional class is the most dominant predictor among somatic variables in studies, the major determinants of reduced quality of life are unknown.<sup>170-172</sup> | 2+  
3  
4

Patients may exhibit psychological distress due to increasing dependence on others, the need for assistance with activities of daily living, and consequent disruption of social life, personal goals, income, faith and daily function.<sup>172,173</sup>

## 8.3 SYMPTOM MANAGEMENT

Healthcare professionals should take a careful history of symptoms. Attention to therapeutic detail, individualised care, open communication and compliance with patients' wishes regarding treatment strategies are all necessary elements of a patient-centred approach to end-of-life care. Little evidence exists on palliative symptom management in patients with HF. Management strategies might be extrapolated and adapted from those used in cancer care, although the use of non-steroidal anti-inflammatory drugs (NSAIDs) and tricyclic antidepressants should be avoided.

### 8.3.1 DYSPNOEA

Dyspnoea is a common debilitating symptom in patients with heart failure. Opioids may ameliorate the sensation of breathlessness by reducing hypercapnic chemosensitivity.<sup>174</sup> Carefully prescribed opioids can reduce the demand for ventilation without significant respiratory depression. In older people, altered pharmacokinetics and diminished renal clearance may necessitate starting with smaller doses and titrating slowly to minimise adverse effects.

No RCTs were identified looking specifically at the use of benzodiazepines in patients with heart failure. A Cochrane review of seven studies of patients with chronic obstructive pulmonary disease or cancer with breathlessness due to advanced disease may be relevant to the management of patients with advanced HF, and showed no significant benefit.<sup>175</sup> | 1++

Three small RCTs identified in a narrative review found improvement with opioids, although the results were not statistically significant.<sup>176</sup> | 4

✓ | After optimising diet, fluid intake and standard management for chronic heart failure, prescription of low-dose opioids, titrated against effect, should be considered in patients with dyspnoea.

### 8.3.2 OXYGEN

No evidence was identified that oxygen at rest or when ambulatory is beneficial in patients with HF.<sup>177</sup> | 4

### 8.3.3 PAIN

The precise prevalence of pain in patients with HF remains uncertain. Retrospective studies indicate a prevalence of 24–35%.<sup>166,168,172</sup> Management strategies used in other chronic pain states might be adapted and applied in individual cases (*see the SIGN guideline on the management of chronic pain*).<sup>178</sup>

### 8.3.4 MOOD DISORDERS

Screening and management of depression are covered in section 4.1.

## 8.4 RATIONALISING TREATMENTS

A collaborative cardiology and palliative care approach does not mean that medical therapies should be stopped automatically. Treatments should be rationalised on the basis of normal practice by weighing up the risks and benefits. If the risk of adverse effects for the patient outweighs the benefit then consideration should be given to stopping or altering that treatment. This approach to all treatments should be carried out on a regular basis by all healthcare professionals involved in the patient's care and rationalising treatment should be discussed within the team providing the care and with the patient and their family/carers.

- ✓ Medications should be reviewed regularly and decisions to adjust or stop drugs should be taken actively rather than in response to adverse effects, in conjunction with the patient and their family. Consideration should be given to the difference between treatments prescribed for symptomatic relief and prognostic benefit.

No robust evidence was identified on the deactivation of implantable cardioverter defibrillators towards end of life in patients with advanced HF, but multidisciplinary, consensus-based guidance on "Cardiovascular Implanted Electronic Devices in people towards the End of Life, during Cardiopulmonary Resuscitation and after Death" is available from the Resuscitation Council (UK).<sup>179</sup> The following recommendations are based on expert opinion from the Resuscitation Council (UK) guidelines:

- The possibility of device deactivation at some time in the future should routinely be discussed with the patient at the time of consent for implantation.
- Routine review should allow the patient the opportunity to discuss deactivation if they wish and all healthcare professionals should always consider on review if the clinical situation has changed and if an active device is still appropriate.
- Patients and their families should be made aware that deactivation decisions can be reversed if their clinical situation changes.
- It must not be assumed that a Do Not Attempt Cardiopulmonary Resuscitation (DNACPR) decision means that a patient's device should be deactivated and a decision to deactivate a patient's device does not mean that a DNACPR decision needs to be taken.

Ideally device deactivation should be done electively by the cardiac physiology team following a multidisciplinary team decision and the consent and outcome clearly documented in the patient's notes. However a patient's device can be deactivated in the event of an emergency with formal deactivation carried out at the earliest opportunity thereafter. Each unit should have elective and emergency deactivation protocols.

- R **Healthcare professionals should follow the advice from the Resuscitation Council (UK) on device deactivation in patients with advanced heart failure who are near the end of life.**

## 9 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by healthcare professionals when discussing heart failure with patients and carers and in guiding the development of locally produced information materials.

### 9.1 COMMUNICATION

Patients with chronic heart failure report high levels of frustration with progressive loss of function, social isolation and the stresses of monitoring a complex medical regimen. In one study, their reported understanding of their condition and involvement in the regimen was lower than that in a comparison group of patients with cancer.<sup>180</sup> Among the same cohort, patients identified unmet needs in psychosocial care, education and co-ordination between primary and secondary care.<sup>181</sup>

3

In a small qualitative study patients listed the following as inhibiting communication with doctors:<sup>182</sup>

- factors intrinsic to heart failure, eg confusion, uncertainty of prognosis
- patient characteristics, eg misconceptions about causes/treatment of symptoms
- structure of the system, eg difficulty attending hospital
- factors in the doctor-patient relationship, eg their belief that doctors found it hard to share some information about heart failure.

#### 9.1.1 COGNITIVE DEFICITS AS BARRIERS TO COMMUNICATION

One systematic review found that HF is associated with a pattern of generalised cognitive impairment which includes memory and attention deficits.<sup>183</sup> There were few good quality studies and heterogeneity of populations. Two studies were identified which looked at general cognitive functioning in 203 patients with HF and 704 controls. Poorer cognitive outcomes were measured on the Mini Mental State Examination and Wechsler Adult Intelligence Scale in the patients with HF (standardised mean difference -0.40, 95% CI -0.56 to -0.24,  $p < 0.00001$ ). The causal mechanisms for the deficits are unclear.

2+

- ✓ Clinicians involved with educating or helping patients with heart failure to manage their condition should be aware of the possibility of cognitive deficits and tailor interventions accordingly.

#### 9.1.2 IMPROVING EDUCATION AND COMMUNICATION

One approach to improving patient education has been structured interventions by a dedicated professional, such as a nurse. Several small studies have shown structured interventions to be better than usual care in improving self management and adherence.<sup>184,185</sup>

One RCT compared two intervention strategies, a nurse facilitator and a combination of patient and provider notification including computer reminders and patient letters aimed at improving the use of beta blockers in 169 patients with HF.<sup>186</sup> The primary outcome, the proportion of patients who were initiated or uptitrated and maintained on beta blockers, was achieved in 67% (36 of 54) of patients in the nurse-facilitator group compared with 16% (10 of 64) in the provider/patient notification and 27% (14 of 51) in the control groups ( $p < 0.001$  for the comparisons between the nurse-facilitator group and both of the other groups). There were no differences in hospital readmission or mortality between groups.

1+

Another approach focused on tackling communication barriers in health consultations. A Cochrane review of three trials involving 347 health professionals caring for patients with cancer concluded that there is some evidence on how to improve behaviours which can be reliably measured, such as responding to patients' cues and asking fewer leading questions. The authors concluded that further work is needed to compare different training methods and to look at patients' awareness of, and satisfaction with, change.<sup>187</sup> No evidence was identified on improving education and communication in HF services.

2+

## 9.2 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients and carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

Following every consultation, the health professional should check the patient's understanding of what they have been told. The health professional should avoid asking questions such as "Is that clear?" and "Have you understood everything?" and instead they should use questions such as: "To be sure that I have explained everything correctly, could you explain to me how you will take your medication?" or "We discussed a lot today. Can you tell me what you found most important?". The patient should be able to explain or demonstrate, using their own words, what has just been discussed with them.<sup>188</sup>

Initial presentation
<ul style="list-style-type: none"> <li>• Explain to patients that their symptoms may be caused by HF or another condition.</li> <li>• Advise patients of the need for referral for further assessment and investigation.</li> <li>• Explain to patients that HF is diagnosed by a comprehensive assessment, including a detailed history and clinical examination, and one or more diagnostic tests including:               <ul style="list-style-type: none"> <li>○ routine bloods and thyroid function tests</li> <li>○ echocardiogram</li> <li>○ ECG</li> <li>○ BNP/NT-proBNP (not available in all areas of Scotland)</li> <li>○ CXR.</li> </ul> </li> <li>• If the patient is a smoker discuss the benefits of stopping smoking.</li> </ul>
Diagnosis
<ul style="list-style-type: none"> <li>• Explain what HF is and check the patient's understanding.</li> <li>• Explain to patients that further tests may be done to assess if any further interventions are required.</li> <li>• Discuss treatment options and offer written and verbal information outlining a clear pathway of how they will be cared for throughout the course of their treatment.</li> <li>• Allow sufficient time to discuss the following issues and ensure patients are involved in the discussions and supported to make informed decisions:               <ul style="list-style-type: none"> <li>○ aims of treatments</li> <li>○ treatment choices</li> <li>○ treatment outcomes</li> <li>○ side effects of treatment and management of these</li> <li>○ prognosis (include Advanced Care Planning if appropriate)</li> <li>○ managing distress (including depression and anxiety)</li> <li>○ referral to other specialists as required.</li> </ul> </li> <li>• If available, refer patients to a clinical nurse specialist for support, advice and information. Provide information on further sources of support (<i>see section 9.3</i>).</li> </ul>

**Treatment**

- See Annexes 2–5 for specific advice on drug therapies.
- Inform patients of treatment plans and advise them that they will need to take their medications on a permanent basis and also advise that some medications, eg diuretics, may require the dose to be adjusted and in some instances stopped.
- If appropriate discuss interventions such as surgery, angiography and insertion of a cardiac device.
- Discuss participation in a clinical trial when available and appropriate.
- Discuss with patients how they are coping and managing distress (including depression and anxiety).
- Explain the importance of attending ongoing follow-up appointments after discharge and inform them of how they are likely to be followed up, ie by whom, where and when.
- Advise patients of where they can receive information about financial issues.

**Follow up**

- Inform patients of the follow up to manage and monitor their condition.
- Give patients the opportunity to ask questions or discuss any concerns they may have.
- Allow discussion of the following issues with patients:
  - self-management strategies
  - how they are coping and managing their symptoms (including depression and anxiety)
  - returning to work
  - how they would like to be managed if their condition deteriorates.
- Advise the patient to report on specific symptoms.
- Reiterate information on sources of support (*see section 9.3*).
- Highlight the benefits of being as active as possible and a healthy diet, including a reduction of dietary salt.
- Discuss the following issues with patients who remain symptomatic despite being on maximum-tolerated therapy:
  - treatment choices and outcomes
  - side effects of treatment and management of these
  - prognosis (include Advanced Care Planning if appropriate)
  - managing distress (including depression and anxiety).

**Palliative care**

- Offer to discuss end-of-life care with the patient when appropriate.
- The following should be discussed with patients:
  - reason for and aim of palliative care
  - who is likely to be involved in their care
  - symptom management
  - Advance Care Planning if appropriate
  - preferred place of care.

### 9.3 SOURCES OF FURTHER INFORMATION

#### **NHS inform**

[www.nhsinform.co.uk](http://www.nhsinform.co.uk)

#### **Heart zone**

[www.nhsinform.co.uk/heart](http://www.nhsinform.co.uk/heart)

Caledonia House , Fifty Pitches Road, Cardonald Park, Glasgow G51 4EB

Tel: 0800 22 44 88

Email: [nhs.inform@nhs24.scot.nhs.uk](mailto:nhs.inform@nhs24.scot.nhs.uk)

The national health and care information service for Scotland which includes conditions such as heart failure, high blood pressure, depression and diabetes. The heart zone provides information and advice on heart conditions.

#### **NHS inform A-Z articles**

- heart failure: [www.nhsinform.co.uk/health-library/articles/h/heart-failure/introduction](http://www.nhsinform.co.uk/health-library/articles/h/heart-failure/introduction)
- high blood pressure: [www.nhsinform.co.uk/health-library/articles/b/blood-pressure-high](http://www.nhsinform.co.uk/health-library/articles/b/blood-pressure-high)
- heart attack: [www.nhsinform.co.uk/health-library/articles/h/heart-attack](http://www.nhsinform.co.uk/health-library/articles/h/heart-attack)

#### **Heart Failure Matters**

[www.heartfailurematters.org](http://www.heartfailurematters.org)

A website produced by the European Society of Cardiology which provides information and monitoring tools for patients, families and caregivers.

#### 9.3.1 LOCAL SUPPORT GROUPS AND TELEPHONE HELPLINES

[www.nhsinform.co.uk/support-services](http://www.nhsinform.co.uk/support-services)

Tel: 0800 22 44 88 (8am -10pm)

The Support Service Directory on the NHS inform website provides information on local groups and telephone helplines.

#### **British Heart Foundation**

Ocean Point 1, 94 Ocean Drive, Edinburgh, EH6 6JH

Tel: 020 7554 0000 • Heart Helpline: 0300 330 3311

[www.bhf.org.uk](http://www.bhf.org.uk) • Email: [bhfh@bhf.org.uk](mailto:bhfh@bhf.org.uk)

The nation's heart charity and the largest independent funder of cardiovascular research. The BHF provides information for patients and carers.

#### **Chest Heart & Stroke Scotland**

Third Floor, Rosebery House, 9 Haymarket Terrace, Edinburgh EH12 5EZ

Tel: 0131 225 6963 • Advice Line Nurses: 0808 801 0899

[www.chss.org.uk](http://www.chss.org.uk) • Email: [admin@chss.org.uk](mailto:admin@chss.org.uk)

The Scottish health charity set up to improve the quality of life for people in Scotland affected by chest, heart and stroke illness, through medical research, influencing public policy, advice and information and support in the community.

### 9.3.2 ADDITIONAL WEBSITES

#### **Action on Depression**

21-23 Hill Street, Edinburgh EH2 3JP

[www.actionondepression.org](http://www.actionondepression.org) • Email: [admin@actionondepression.org](mailto:admin@actionondepression.org)

This website highlights local support and raises awareness about low mood and depression.

#### **Active Scotland**

[www.activescotland.org.uk](http://www.activescotland.org.uk)

This website provides information and ideas on a range of indoor and outdoor activities in Scotland.

#### **Anxiety UK**

[www.anxietyuk.org.uk](http://www.anxietyuk.org.uk)

Anxiety UK provides information, support and therapy for people with anxiety.

#### **Blood Pressure UK**

Wolfson Institute of Preventive Medicine, Charterhouse Square, London EC1M 6BQ

Tel: 020 7882 6218

[www.bloodpressureuk.org](http://www.bloodpressureuk.org) • Email: [help@bloodpressureuk.org](mailto:help@bloodpressureuk.org)

A UK charity dedicated to lowering the nation's blood pressure to prevent disability and death from stroke and heart disease.

#### **Breathing Space**

[www.breathingspace.scot](http://www.breathingspace.scot)

Tel: 0800 83 85 87

A free, confidential telephone and web-based service for any individual who is experiencing low mood or depression, or who is unusually worried and in need of someone to talk to.

#### **Diabetes UK**

Careline Scotland, The Venlaw, 349 Bath Street, Glasgow G2 4AA

[www.diabetes.org.uk](http://www.diabetes.org.uk) • Tel: (Careline Scotland) 0141 212 8710

Email: [careline.scotland@diabetes.org.uk](mailto:careline.scotland@diabetes.org.uk)

Diabetes UK provides information, advice and support to help people with diabetes manage the condition well, and bring people together for support.

#### **Drink Smarter**

[www.drinksmarter.org](http://www.drinksmarter.org)

A national charity working to reduce the harm caused by alcohol, with information on easy ways to cut back and sensible drinking.

#### **Eat Better Feel Better**

[www.eatbetterfeelbetter.co.uk](http://www.eatbetterfeelbetter.co.uk)

This website provides recipes for healthier and cheaper meals and information on improving cooking skills.

#### **GOV.UK**

[www.gov.uk/heart-failure-and-driving](http://www.gov.uk/heart-failure-and-driving)

Government services and information.

#### **Kidney Research UK**

Nene Hall, Lynch Wood Park, Peterborough PE2 6FZ

Tel: 0845 070 7601

[www.kidneyresearchuk.org](http://www.kidneyresearchuk.org) • Email: [enquiries@kidneyresearchuk.org](mailto:enquiries@kidneyresearchuk.org)

An organisation providing kidney health information and support for kidney patients, their families and carers, as well as medical professionals and researchers.



**Living life cognitive behavioural therapy telephone service**

NHS Living Life, 5th Floor, Golden Jubilee National Hospital, Beardmore Street, Clydebank G81 4HX

Tel: 0800 328 9655 (Mon-Fri 1pm to 9pm)

[www.nhs24.com/usefulresources/livinglife](http://www.nhs24.com/usefulresources/livinglife)

Living Life is a free telephone service available to anyone over the age of 16 who is suffering from low mood, mild to moderate depression and/or anxiety.

**Moodjuice**

[www.moodjuice.scot.nhs.uk](http://www.moodjuice.scot.nhs.uk)

A website for patients and professionals which provides self-help resources for emotional problems.

**Smokeline**

Caledonia House, Fifty Pitches Road, Cardonald Park, Glasgow G51 4EB

Tel: 0800 84 84 84

[www.canstopsmoking.com](http://www.canstopsmoking.com) • Email: [smokeline@nhs24.scot.nhs.uk](mailto:smokeline@nhs24.scot.nhs.uk)

Scotland's national stop smoking helpline.

# 10 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

## 10.1 IMPLEMENTATION STRATEGY

Implementation of national clinical guidelines is the responsibility of each NHS board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

Implementation of this guideline will be encouraged and supported by SIGN. The implementation strategy for this guideline encompasses the following tools and activities.

## 10.2 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

No recommendations are considered likely to reach the £5 million threshold which warrants full cost-impact analysis.

## 10.3 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The guideline development group has identified the following as key points to audit to assist with the implementation of this guideline:

The percentage of:

- patients with a diagnosis of HF which has been confirmed by BNP or NT pro-BNP levels and/or an echocardiogram
- patients with HF-REF treated with an ACE inhibitor
- patients with HF-REF treated with a beta blocker
- patients with HF-REF treated with an MRA
- patients fitted with a CRT
- patients with symptomatic HF who receive a home visit from a specialist nurse.

#### 10.4 ADDITIONAL ADVICE FOR NHSSCOTLAND FROM THE SCOTTISH MEDICINES CONSORTIUM

Eplerenone was accepted for use for use within NHSScotland in May 2005, in addition to standard therapy including beta blockers, to reduce the risk of cardiovascular mortality and morbidity between 3–14 days after MI in stable patients with left ventricular dysfunction (LVEF 40%) and clinical evidence of heart failure.

In July 2012 eplerenone was accepted for use in addition to standard optimal therapy, to reduce the risk of cardiovascular mortality and morbidity in adult patients with NYHA class II (chronic) heart failure and left ventricular systolic dysfunction (LVEF  $\leq$ 30%).

In March 2016 sacubitril/valsartan was accepted for use in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

In September 2012 the SMC advised that ivabradine is accepted for use in patients with chronic heart failure NYHA II to IV with systolic dysfunction, in patients in sinus rhythm and whose heart rate is  $\geq$ 75 beats per minute in combination with standard therapy including beta blocker therapy or when beta blocker is contraindicated or not tolerated.

# 11 The evidence base

## 11.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2006–2014. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

### 11.1.1 LITERATURE SEARCH FOR PATIENT ISSUES

At the start of the guideline development process, a SIGN Evidence and Information Scientist conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to patients with HF. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised by the SIGN Patient Involvement Officer and presented to the guideline development group.

### 11.1.2 LITERATURE SEARCH FOR COST EFFECTIVENESS

The guideline development group identified key questions with potential cost-effectiveness implications where it was judged particularly important to gain an understanding of the additional costs and benefits of different treatment strategies, based on the following criteria:

- treatments which may have a significant resource impact
- opportunities for significant disinvestment or resource release
- the potential need for significant service redesign
- cost-effectiveness evidence could aid implementation of a recommendation.

A systematic literature search for economic evidence for these questions was conducted using Medline, Embase, NHS Economic Evaluation Database (NEED) and Health Economics Evaluation Database (HEED), covering the years 2010–2014. Each of the selected papers was evaluated by a Health Economist, and considered for clinical relevance by guideline group members.

Interventions are considered to be cost effective if they fall below the commonly-accepted UK threshold of £20,000 per Quality-Adjusted Life Year (QALY).

## 11.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline (*see Annex 1*). The following areas for further research have been identified:

- Prospective trials to establish whether the use of the male, infarction, crepitations, oedema (MICE) clinical scoring system is effective in diagnosing people with HF in need of echocardiography without a natriuretic peptide test.
- Studies into the role of percutaneous coronary intervention versus optimal medical management or CABG for patients with HF.
- Large, multisite trials investigating the efficacy of psychological and pharmacological therapies for people with HF who are depressed.
- Large, multisite trials investigating the efficacy of psychological and pharmacological therapies for people with HF who have anxiety.
- Comparative studies of SSRIs and non-pharmacological interventions for patients with HF who are depressed.

- An RCT to determine the efficacy of ivabradine in patients with no previous hospitalisation for HF in the preceding 12 months.
- Surveillance to monitor the frequency of angioedema in patients treated with sacubitril/valsartan
- An RCT to compare sacubitril-valsartan with higher doses of enalapril (40 mg).
- A large RCT to study the effect of phosphodiesterase inhibitors on hospitalisation rates, mortality rates and quality of life in patients with HF.
- Larger, longer RCTs to confirm the benefits of iron therapy in patients with HF, with mortality as the main outcome.
- Trials to compare the benefits of oral iron supplements with intravenous iron.
- An evaluation of the benefit of upgrading to CRT-D from CRT-P in patients with NYHA class IV who improve functional class after CRT-P implantation.
- Cost effectiveness of primary CRT-P/D implantation in patients with impaired LVSF requiring pacing for atrioventricular node disease.
- Robust studies to identify which patients would benefit most from anticipatory planning, how to co-ordinate care, and the benefits of palliative care interventions in terms of quality of life, health-related outcomes, and reduction in hospital admissions.
- RCTs into the use of benzodiazepines and opioids to alleviate dyspnoea in patients with advanced heart disease.

### 11.3 REVIEW AND UPDATING

This guideline was issued in 2016 and will be considered for review in three years. The review history, and any updates to the guideline in the interim period, will be noted in the review report, which is available in the supporting material section for this guideline on the SIGN website: [www.sign.ac.uk](http://www.sign.ac.uk)

Comments on new evidence that would update this guideline are welcomed and should be sent to the SIGN Executive, Gyle Square, 1 South Gyle Crescent, Edinburgh, EH12 9EB (email: [sign@sign.ac.uk](mailto:sign@sign.ac.uk)).

## 12 Development of the guideline

### 12.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising healthcare professionals using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in 'SIGN 50: A Guideline Developer's Handbook', available at [www.sign.ac.uk](http://www.sign.ac.uk)

This guideline was developed according to the 2015 edition of SIGN 50.

### 12.2 THE GUIDELINE DEVELOPMENT GROUP

Professor Allan Struthers (Chair)	<i>Professor of Cardiovascular Medicine and Therapeutics, Ninewells Hospital, Dundee</i>
Ms Lynda Blue	<i>Healthcare Innovation Programme Manager, British Heart Foundation, Glasgow</i>
Ms Julie Calvert	<i>Health Services Researcher, Healthcare Improvement Scotland</i>
Dr Anna Maria Choy	<i>Consultant Cardiologist, Ninewells Hospital, Dundee</i>
Dr Jane Church	<i>General Practitioner, Blackfriars Medical Practice, St Andrews</i>
Dr Martin Denvir	<i>Reader and Honorary Consultant Cardiologist, The Queen's Medical Research Institute, University of Edinburgh</i>
Ms Sarah Fraser	<i>Lay Representative, Dingwall</i>
Mr Kenneth Halliday	<i>Locality Principal Pharmacist, Crieff Medical Centre</i>
Dr Karen Hogg	<i>Consultant Cardiologist, Glasgow Royal Infirmary</i>
Dr Pardeep Jhund	<i>Clinical Lecturer in Cardiology, University of Glasgow</i>
Ms Jill Nicholls	<i>Heart Failure Specialist Nurse, Ninewells Hospital, Dundee</i>
Dr John Sharp	<i>Consultant Clinical Psychologist, Scottish National Advanced Heart Failure Service, Golden Jubilee National Hospital, Clydebank</i>
Ms Amanda Smith	<i>Lead Heart Failure Nurse, Raigmore Hospital, Inverness</i>
Mrs Lynne Smith	<i>Evidence and Information Scientist, Healthcare Improvement Scotland</i>
Ms Ailsa Stein	<i>Programme Manager, SIGN</i>
Miss Lisa Wilson	<i>Health Economist, Healthcare Improvement Scotland</i>

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest. A register of interests is available in the supporting material section for this guideline at [www.sign.ac.uk](http://www.sign.ac.uk)

Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive. All members of the SIGN Executive make yearly declarations of interest. A register of interests is available on the contacts page of the SIGN website [www.sign.ac.uk](http://www.sign.ac.uk)

Euan Bremner	<i>Project Officer</i>
Lesley Forsyth	<i>Events Co-ordinator</i>
Karen Graham	<i>Patient Involvement Officer</i>
Karen King	<i>Distribution and Office Co-ordinator</i>
Stuart Neville	<i>Publications Designer</i>
Gaynor Rattray	<i>Guideline Co-ordinator</i>

### 12.2.1 ACKNOWLEDGEMENTS

SIGN would like to acknowledge the guideline development group responsible for the development of SIGN 95: Management of chronic heart failure, on which this guideline is based.

SIGN is also grateful to the following former members of the guideline development group and others who have contributed to the development of the guideline.

Dr Allan Bridges	<i>Consultant Cardiologist, Forth Valley Royal Hospital, Larbert</i>
Dr Marc Dweck	<i>British Heart Foundation Senior Lecturer and Consultant Cardiologist, University of Edinburgh</i>
Dr Alan Japp	<i>Consultant Cardiologist, Royal Infirmary of Edinburgh</i>
Professor Frances Mair	<i>Professor of Primary Care Research, University of Glasgow</i>
Dr Fiona Shearer	<i>Specialty Registrar Cardiology, Victoria Hospital, Kirkcaldy</i>

### 12.3 THE STEERING GROUP

A steering group comprising the chairs of the six SIGN heart disease guidelines and other invited experts was established to oversee the progress of guideline development. This group met regularly throughout the development of the guidelines.

Professor Sir Lewis Ritchie, OBE	<i>Mackenzie Professor and Head of Department, Department of General (Chair) Practice and Primary Care, University of Aberdeen</i>
Mrs Corinne Booth	<i>Senior Health Economist, Healthcare Improvement Scotland</i>
Mr James Cant	<i>Director, British Heart Foundation Scotland</i>
Dr Derek Connelly	<i>Consultant Cardiologist, Golden Jubilee Hospital, Glasgow</i>
Dr Nick Cruden	<i>Interventional Cardiologist, Royal Infirmary of Edinburgh</i>
Mr Steve McGlynn	<i>Principal Pharmacist, Department of Pharmaceutical Sciences, Strathclyde Institute for Biomedical Sciences, Glasgow</i>
Dr Susan Myles	<i>Lead Health Economist, Healthcare Improvement Scotland</i>
Professor David Newby	<i>British Heart Foundation Professor of Cardiology, University of Edinburgh</i>
Dr Morag Osborne	<i>Consultant Clinical Psychologist, Southern General Hospital, Glasgow</i>
Professor Naveed Sattar	<i>Professor of Metabolic Medicine, Institute of Cardiovascular and Medical Sciences, University of Glasgow</i>
Mr Gordon Snedden	<i>Lay representative, Forfar</i>
Professor Allan Struthers	<i>Professor of Cardiovascular Medicine and Therapeutics, Ninewells Hospital and Medical School, Dundee</i>
Dr Iain Todd	<i>Consultant in Cardiovascular Rehabilitation, Astley Ainslie Hospital, Edinburgh</i>

### 12.4 CONSULTATION AND PEER REVIEW

#### 12.4.1 PUBLIC CONSULTATION

The draft guideline was available on the SIGN website for a month to allow all interested parties to comment. All contributors made declarations of interest and further details of these are available on request from the SIGN Executive.

#### 12.4.2 SPECIALIST REVIEWERS INVITED TO COMMENT ON THIS DRAFT

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline.

SIGN is very grateful to all of these experts for their contribution to the guideline.

Dr Sally Cox	<i>Clinical Psychologist, Cardiac Psychology Service, Aberdeen Royal Infirmary</i>
Professor Frank Dunn	<i>President, on behalf of the Royal College of Physicians and Surgeons of Glasgow</i>
Mr Paul Forsyth	<i>Heart Failure Pharmacist, Victoria Infirmary, Glasgow</i>
Dr Mark Francis	<i>Consultant Cardiologist, Victoria Hospital, Kirkcaldy</i>
Dr Roy Gardner	<i>Consultant Cardiologist, Scottish National Advanced Heart Failure Service, Golden Jubilee National Hospital, Clydebank</i>
Mr Robin Lattimore	<i>Patient Representative, Banchory</i>
Mrs Elaine Lee	<i>Heart Failure Nursing Team Leader, NHS Grampian</i>
Mr Steve McGlynn	<i>Specialist Principal Pharmacist (Cardiology), NHS Greater Glasgow and Clyde</i>
Professor John McMurray	<i>Professor of Medical Cardiology, University of Glasgow and Queen Elizabeth University Hospital, Glasgow</i>
Mrs Yvonne Millerick	<i>Lead Nurse Lecturer, NHS Glasgow &amp; Clyde and Glasgow Caledonian University</i>
Professor Scott Murray	<i>Professor of Primary Palliative Care, University of Edinburgh</i>
Dr Mark Petrie	<i>Consultant Cardiologist, Golden Jubilee National Hospital, Glasgow</i>
Dr Graham Scotland	<i>Senior Research Fellow, Health Economics Research Unit/ Health Services Research Unit, University of Aberdeen</i>

The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments. A report of the peer review comments and responses is available in the supporting material section for this guideline on the SIGN website. All expert referees made declarations of interest and further details of these are available on request from the SIGN Executive.

#### 12.4.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows:

Dr Roberta James	<i>SIGN Programme Lead; Co-Editor</i>
Professor John Kinsella	<i>Chair of SIGN; Co-Editor</i>
Dr Rajan Madhok	<i>Royal College of Physicians and Surgeons of Glasgow</i>
Dr Susan Myles	<i>Lead Health Economist, Healthcare Improvement Scotland</i>
Mr Alan Timmins	<i>Royal Pharmaceutical Society</i>

All members of SIGN Council make yearly declarations of interest. A register of interests is available on the SIGN Council Membership page of the SIGN website [www.sign.ac.uk](http://www.sign.ac.uk)



# Abbreviations

<b>ACC/AHA</b>	American College of Cardiology/American Heart Association
<b>ACE</b>	angiotensin-converting enzyme
<b>ACM</b>	alcoholic cardiomyopathy
<b>ADTC</b>	Area Drug and Therapeutics Committees Collaborative
<b>ARB</b>	angiotensin receptor blocker
<b>ARR</b>	absolute risk reduction
<b>BNF</b>	British National Formulary
<b>BNP</b>	B-type natriuretic peptide
<b>BP</b>	blood pressure
<b>BTT</b>	bridge to transplantation
<b>CABG</b>	coronary artery bypass grafting
<b>CBT</b>	cognitive behaviour therapy
<b>CHARM</b>	Candesartan in Heart failure: Assessment of Reduction in Mortality trial
<b>CI</b>	confidence interval
<b>CIBIS II</b>	the Cardiac Insufficiency Bisoprolol Study II trial
<b>CKD</b>	chronic kidney disease
<b>COMET</b>	Carvedilol Or Metoprolol European Trial
<b>CMR</b>	cardiac magnetic resonance
<b>CONFIRM</b>	A study to Compare the use of Ferric Carboxymaltose with placebo in patients with chronic heart failure and iron deficiency
<b>COPERNICUS</b>	Carvedilol Prospective Randomized Cumulative Survival trial
<b>CoQ10</b>	coenzyme Q10
<b>CPAP</b>	continuous positive airway pressure
<b>CRT</b>	cardiac resynchronisation therapy
<b>CRT-D</b>	cardiac resynchronisation therapy with defibrillator
<b>CRT-P</b>	cardiac resynchronisation therapy with pacing
<b>CSA</b>	central sleep apnoea
<b>CXR</b>	chest X-ray
<b><i>d</i></b>	Cohen's <i>d</i> effect size; small ( $d=0.2$ ), medium ( $d=0.5$ ), and large ( $d\geq 0.8$ )
<b>DIG</b>	Digitalis Investigation Group trial
<b>DNACPR</b>	Do Not Attempt Cardiopulmonary Resuscitation
<b>DSE</b>	dobutamine stress echocardiography
<b>ECG</b>	electrocardiogram
<b>EF</b>	ejection fraction
<b>EMPHASIS</b>	Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure trial

<b>EPHESUS</b>	Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study trial
<b>FAIR</b>	Ferric carboxymaltose Assessment in patients with IRon deficiency and chronic Heart Failure trial
<b>GMC</b>	General Medical Council
<b>GP</b>	general practitioner
<b>HEED</b>	health economics evaluation database
<b>HF</b>	heart failure
<b>HF-PEF</b>	heart failure with preserved ejection fraction
<b>HF-REF</b>	heart failure with reduced ejection fraction
<b>H-ISDN</b>	hydralazine and isosorbide dinitrate
<b>HR</b>	hazard ratio
<b>HTA</b>	health technology appraisal
<b>ICD</b>	implantable cardioverter defibrillator
<b>ICER</b>	incremental cost-effectiveness ratio
<b>KCCQ</b>	Kansas City Cardiomyopathy Questionnaire
<b>LBBB</b>	left bundle branch block
<b>LVAD</b>	left ventricular assist device
<b>LVEF</b>	left ventricular ejection fraction
<b>LVH</b>	left ventricular hypertrophy
<b>MA</b>	marketing authorisation
<b>MCS</b>	mechanical circulatory support
<b>MERIT</b>	Metoprolol CR/XL Randomized Intervention trial
<b>MI</b>	myocardial infarction
<b>MICE</b>	male, infarction, crepitations, oedema
<b>MLHFQ</b>	Minnesota Living with Heart Failure Questionnaire
<b>MRA</b>	mineralocorticoid receptor antagonist
<b>MRI</b>	magnetic resonance imaging
<b>MTA</b>	multiple technology assessment
<b>MUGA</b>	multiple gated acquisition
<b>NEED</b>	NHS economic evaluation database
<b>NICE</b>	National Institute for Health and Care Excellence
<b>NNT</b>	number needed to treat
<b>NSAID</b>	non-steroidal anti-inflammatory drug
<b>NT-proBNP</b>	N terminal-pro-B-type natriuretic peptide
<b>NYHA</b>	New York Heart Association
<b>OSA</b>	obstructive sleep apnoea
<b>OR</b>	odds ratio

<b>OSA</b>	obstructive sleep apnoea
<b>PARADIGM</b>	Prospective comparison of Angiotensin Receptor–neprilysin inhibitor with ACE inhibitor to Determine Impact on Global Mortality and Morbidity trial
<b>PCI</b>	percutaneous coronary intervention
<b>PET</b>	positron emission tomography
<b>PROVED</b>	Prospective Randomized study Of Ventricular failure and the Efficacy of Digoxin trial
<b>QALY</b>	quality-adjusted life year
<b>QoL</b>	quality of life
<b>RADIANCE</b>	Randomized Assessment of Digoxin on Inhibitors of the Angiotensin-Converting Enzyme trial
<b>RALES</b>	Randomised Aldactone Evaluation Study trial
<b>REF</b>	reduced ejection fraction
<b>RCT</b>	randomised controlled trial
<b>RR</b>	relative risk
<b>SENIORS</b>	Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure
<b>SIGN</b>	Scottish Intercollegiate Guidelines Network
<b>SMC</b>	Scottish Medicines Consortium
<b>SPC</b>	summary of product characteristics
<b>SPECT</b>	single-photon emission computed tomography
<b>SSRIs</b>	selective serotonin reuptake inhibitors
<b>TSAT</b>	transferrin saturation
<b>UK</b>	United Kingdom
<b>VAD</b>	ventricular assist device
<b>ValHeft</b>	Valsartan Heart failure trial
<b>VE/VO<sub>2</sub></b>	ventilatory equivalent for oxygen
<b>VO<sub>2</sub></b>	volume of oxygen
<b>WMD</b>	weighted mean difference

# Annex 1

## Key questions addressed in this update

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

Guideline section	Key question	
3.1.1	1	<p>Is there any evidence that clinical scoring systems, eg MICE, help to identify people with suspected heart failure for further investigations?</p> <p>Population: adults with suspected heart failure</p> <p>Intervention: clinical scoring systems based on combinations of individual signs and symptoms (breathlessness, effort intolerance, raised jugular venous pressure, third heart sound, displaced apex beat, heart murmurs, fluid retention, fatigue) or other factors (age, gender, previous MI)</p> <p>Comparison: no scoring system</p> <p>Outcome: sensitivity, specificity, likelihood ratio.</p>
3.1.4	2	<p>For adults with suspected heart failure with high or moderate BNP levels does early referral for echocardiography improve outcome?</p> <p>Population: (a) adults with suspected heart failure and BNP level above 400 pg/ml (116 pmol/litre) or an NTproBNP level above 2,000 pg/ml (236 pmol/litre)</p> <p>(b) adults with suspected heart failure and a BNP level between 100 and 400 pg/ml (29–116 pmol/litre), or an NTproBNP level between 400 and 2,000 pg/ml (47–236 pmol/litre)</p> <p>Intervention: referral for echocardiography within two weeks</p> <p>Comparison: referral for echocardiography within six weeks</p> <p>Outcomes: CV mortality, HF hospitalisation, disease-specific QoL, change in symptoms.</p>
3.2.1	18	<p>In patients with suspected heart failure, is cardiac resonance imaging effective in diagnosing heart failure?</p>
4.1	13	<p>Outcomes: sensitivity and specificity. In people with heart failure and depression what evidence is there for:</p> <p>a) pharmacological therapies b) psychological therapies?</p> <p>Consider cost effectiveness</p> <p>Population: adults with chronic heart failure and depression</p> <p>Interventions: pharmacological therapies: antidepressants – tricyclics, SSRIs psychological therapies: CBT, mindfulness, interpersonal therapy</p> <p>Comparisons: optimal treatment for heart failure</p> <p>Outcomes: total mortality, CV mortality, total hospitalisation, CV hospitalisation, QoL, reduction in depressive symptoms, adverse events, exercise capacity.</p>

5.2	5	<p>What are the benefits and harms of adding angiotensin receptor blockers (ARBs) in patients with HF-REF?</p> <p>Population: adults with chronic heart failure with reduced ejection fraction</p> <p>Interventions: ARB added to usual optimal treatment which includes ACEi</p> <p>Comparison: usual optimal treatment including ACEi</p> <p>Outcomes: total mortality, CV mortality, total hospitalisation, HF hospitalisation, exercise capacity, disease-specific QoL, change in symptoms, adverse events.</p>
5.4	4	<p>What are the benefits and harms of mineralocorticoid receptor antagonists (MRAs) in patients with HF-REF? Consider cost effectiveness.</p> <p>Population: adults with chronic heart failure with reduced ejection fraction</p> <p>Interventions: MRAs (eplerenone, spironolactone) added to usual optimal treatment</p> <p>Comparison: usual optimal treatment</p> <p>Outcomes: Total mortality, CV mortality, total hospitalisation, HF hospitalisation, exercise capacity, disease-specific, QoL, change in symptoms, adverse events.</p>
5.5	17	<p>What are the benefits and harms of the angiotensin receptor/neprilysin inhibitor for people with heart failure?</p> <p>Population: adults with chronic heart failure with reduced ejection fraction</p> <p>Interventions: sabutricil/valsartan</p> <p>Comparisons: usual optimal treatment</p> <p>Outcomes: total mortality, CV mortality, total hospitalisation, HF hospitalisation, exercise capacity, disease-specific QoL, change in symptoms, adverse events.</p>
5.6	6	<p>What are the benefits and harms of ivabradine in patients with heart failure? Consider cost effectiveness</p> <p>Population: adults with chronic heart failure with reduced ejection fraction who are in sinus rhythm</p> <p>Interventions: ivabradine added to usual optimal treatment</p> <p>Comparison: usual optimal treatment</p> <p>Outcomes: total mortality, CV mortality, total hospitalisation, HF hospitalisation, exercise capacity, disease-specific QoL, change in symptoms, adverse events</p>
5.9	9	<p>Does BNP-guided treatment improve outcomes compared to standard clinically-guided care in patients with heart failure?</p> <p>Consider cost effectiveness</p> <p>Population: adults with chronic heart failure</p> <p>Interventions: BNP-guided treatment</p> <p>Comparison: non-BNP-guided treatment; clinically-guided treatment</p> <p>Outcomes: total mortality, CV mortality, total hospitalisation, HF hospitalisation, exercise capacity, disease-specific QoL, change in symptoms, adverse events.</p>

5.11	19	<p>For patients with systolic dysfunction heart failure, which pharmacological treatments have been shown to be effective?</p> <p>Interventions: antiplatelets, anticoagulants</p> <p>Outcomes: mortality, morbidity, QoL, symptom management, NYHA functional classification, prevention of acute decompensation, hospitalisation, adverse events.</p>
5.13	3	<p>What are the benefits and harms of phosphodiesterase inhibitors for patients with heart failure?</p> <p>Population: adults with chronic heart failure with reduced ejection fraction</p> <p>Interventions: phosphodiesterase inhibitors added to usual optimal treatment</p> <p>Comparison: usual optimal treatment</p> <p>Outcomes: total mortality, CV mortality, total hospitalisation, HF hospitalisation, exercise capacity, disease-specific QoL, change in symptoms, adverse events.</p>
5.14	8	<p>In patients with HF-REF and iron deficiency what are the benefits of treatment with Fe or Fe with erythropoietin?</p> <p>Population: adults with chronic heart failure with reduced ejection fraction, and iron deficiency</p> <p>Interventions: oral iron salts (iron sulphate, iron fumarate, iron succinate, iron gluconate), IV iron (iron dextran, iron gluconate, iron sucrose, or ferric carboxymaltose)</p> <p>Comparison: placebo</p> <p>Outcomes: total mortality, CV mortality, total hospitalisation, HF hospitalisation, exercise capacity, disease-specific QoL, change in symptoms, adverse events, CV events.</p>
5.15	7	<p>In patients with heart failure and preserved left ventricular function is there any evidence of effectiveness for: a) ACE inhibitors b) beta blockers c) ARBs d) MRAs?</p> <p>Population: adults with chronic heart failure, NYHA class II–IV and left ventricular ejection fraction <math>\geq 40\%</math></p> <p>Interventions: a) ACE inhibitors: captopril, cilazapril, enalapril, fosinopril, imidapril, lisinopril, perindopril, quinapril, ramipril, trandolapril</p> <p>b) beta blockers: bisoprolol, carvedilol, nebivolol, metoprolol</p> <p>c) ARBs: candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan</p> <p>d) MRAs: eplerenone, spironolactone</p> <p>Comparison: placebo</p> <p>Outcomes: total mortality, CV mortality, total hospitalisation, HF hospitalisation, exercise capacity, disease-specific QoL, change in symptoms, adverse events</p>

6.1	10	<p>What are the benefits/harms/cost effectiveness of ICD/CRT for patients with heart failure?</p> <p>Consider cost effectiveness</p> <p>(a) Population: adults with chronic heart failure with reduced ejection fraction, and cardiac dyssynchrony despite optimal pharmacological treatment</p> <p>Interventions: cardiac resynchronisation therapy with pacing (CRT-P), Cardiac resynchronisation therapy with an implantable cardioverter defibrillator (CRT-D)</p> <p>Comparisons: CRT-P, CRT-D and standard care (optimal pharmacological treatment without CRT)</p> <p>Outcomes: sudden cardiac death, total mortality, CV mortality, change in symptoms, total hospitalisation, HF hospitalisation, change in NYHA class, change in ejection fraction, adverse events, incremental cost-effectiveness ratio, QoL, psychological impact, exercise capacity.</p> <p>(b) Population: adults with chronic heart failure with reduced ejection fraction who are at risk of (or have already survived) life-threatening arrhythmias (ventricular fibrillation or ventricular tachycardia) despite optimal pharmacological treatment.</p> <p>Interventions: CRT-D</p> <p>Comparisons: ICD, CRT-P, and standard care (optimal pharmacological treatment without CRT)</p> <p>Outcomes: sudden cardiac death, total mortality, CV mortality, change in symptoms, total hospitalisation, HF hospitalisation, change in NYHA class, change in ejection fraction, adverse events, incremental cost-effectiveness ratio, QoL, psychological impact, exercise capacity.</p>
6.2	20	<p>In patients with sleep apnoea and heart failure, is adaptive servoventilation more effective than non-invasive ventilation/continuous positive airway pressure?</p> <p>Outcomes: CV mortality, HF hospitalisation, adverse events.</p>
6.3	11	<p>What are the benefits/harms of revascularisation for patients with heart failure?</p> <p>Patients: adults with chronic heart failure with reduced ejection fraction</p> <p>Interventions: coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), angioplasty</p> <p>Comparisons: standard care (optimal pharmacological treatment without CABG or PCI or angioplasty)</p> <p>Outcomes: total mortality, CV mortality, total hospitalisation, readmission for heart failure, stroke, MI and repeat revascularisation, adverse events, QoL, psychological impact, cognitive impairment, exercise capacity.</p>
6.4	12	<p>What are the benefits/harms of mechanical circulatory support in patients with heart failure?</p> <p>Consider cost effectiveness</p> <p>Patients: adults with chronic heart failure with reduced ejection fraction</p> <p>Interventions: mechanical circulatory support (MCS), Implantable ventricular assist devices (VADs)</p> <p>Comparisons: standard care (optimal pharmacological treatment without MCS/VADs)</p> <p>Outcomes: total mortality, CV mortality, total readmission, HF hospitalisation, readmission for device repair, stroke, myocardial infarction, adverse events, QoL, psychological impact, cognitive impairment, exercise capacity.</p>

8	16	<p>In patients with heart failure is there evidence that anticipatory care planning can improve end-of-life/palliative care?</p> <p>Population: adults with chronic heart failure</p> <p>Interventions: anticipatory care planning</p> <p>Outcomes: improved end-of life outcomes.</p>
8.3.1	15	<p>In patients with heart failure is there evidence to support the use of opioids and benzodiazapines in managing breathlessness?</p> <p>Population: adults with chronic heart failure and breathlessness</p> <p>Interventions: opioids and/or benzodiazapines</p> <p>Comparisons: no opioid or benzodiazepine</p> <p>Outcomes: reduction in breathlessness, QoL.</p>
8.4	14	<p>In patients with heart failure who have CRT/CRT-D devices what approaches should be taken regarding deactivation of these devices?</p> <p>Population: adults with heart failure who have CRT/CRT-D devices</p> <p>Interventions: clinician-patient/carer discussion</p> <p>Outcomes: care plan for deactivation of device.</p>



## Annex 2

### Practical guidance: use of angiotensin-converting enzyme inhibitors in patients with heart failure with reduced ejection fraction<sup>60</sup>

#### **Indications**

- First line treatment, along with beta blockers.

#### **Contraindications**

- history of angioneurotic oedema
- known bilateral renal artery stenosis.

#### **Cautions/seek specialist advice**

- significant hyperkalaemia ( $K^+ > 5.0$  mmol/l)
- significant renal dysfunction (creatinine  $> 221$  micromol/l)
- symptomatic or severe asymptomatic hypotension (systolic BP  $< 90$  mm Hg).

#### **Drug interactions to look out for:**

- $K^+$  supplements /  $K^+$  sparing diuretics
- 'low salt' substitutes with a high  $K^+$  content.

#### **Starting and target doses**

ACE inhibitor	Starting dose	Target dose
captopril	6.25 mg three times daily	50 mg three times daily
enalapril	2.5 mg twice daily	10–20 mg twice daily
lisinopril	2.5 mg once daily	20 mg once daily (up to 35mg in BNF) <sup>5</sup>
ramipril	2.5 mg once daily	5 mg twice daily

#### **How to use ACE Inhibitors**

- Start with a low dose (*see starting and target doses*) and double the dose at not less than two-weekly intervals. Healthcare professionals with experience in the use of ACE inhibitors may wish to uptitrate the dose of ACE inhibitor more rapidly, taking account of the risk of adverse effects and the need for close monitoring of toleration and blood chemistry.
- Aim for the target dose or, failing that, the highest-tolerated dose.
- Monitor blood pressure and blood chemistry (urea, creatinine, and electrolytes).
- Check blood chemistry one to two weeks after initiation and one to two weeks after each dose titration.
- When to stop uptitration/reduce dose/stop treatment (*see problem solving*).
- A specialist HF nurse may assist with patient education, follow up (in person/by telephone), biochemical monitoring and dose uptitration.

#### **Advice to the patient**

- Give written advice and explain the expected benefits, ie treatment is given to improve symptoms, to prevent worsening of HF thereby avoiding hospital admission and to increase survival.
- Symptoms improve within a few weeks to a few months of starting treatment.
- Advise patients to report principal adverse effects, ie dizziness/symptomatic hypotension, cough (*see problem solving*).
- Advise patients to avoid NSAIDs not prescribed by a physician (self purchased over the counter) and salt substitutes high in  $K^+$ .

**Problem Solving***Asymptomatic low blood pressure*

- Does not usually require any change in therapy.

*Symptomatic hypotension*

- If the patient has dizziness, light headedness and/or confusion and low blood pressure reconsider need for nitrates, calcium channel blockers and other vasodilators. Calcium channel blockers should be discontinued unless absolutely essential (eg, for angina or hypertension).
- If no signs/symptoms of congestion consider reducing diuretic dose.
- If these measures do not solve the problem seek specialist advice.

*Cough*

- Cough is common in patients with heart failure, many of whom have smoking-related lung disease, including cancer.
- Cough is also a symptom of pulmonary oedema which should be excluded when a new or worsening cough develops.
- ACE inhibitor-induced cough rarely requires treatment discontinuation.
- When a very troublesome cough does develop (eg one stopping the patient sleeping) and can be proven to be due to ACE inhibition (ie recurs after ACE inhibitor withdrawal and rechallenge) substitution with an angiotensin receptor blocker should be made.

*Worsening renal function*

- Some rise in urea, creatinine and potassium is to be expected after initiation of an ACE inhibitor; if an increase is small and asymptomatic no action is necessary.
- An increase in creatinine of up to 50% above baseline or 266 micromol/l, whichever is smaller, is acceptable.
- An increase in potassium to <5.5 mmol/l is acceptable.
- If urea, creatinine or potassium do rise excessively consider stopping concomitant nephrotoxic drugs (eg NSAIDs), other potassium supplements/retaining agents (triamterene, amiloride, spironolactone/ eplerenone) and, if there are no signs of congestion, reducing the dose of diuretic. The safety and efficacy of an ACE inhibitor used with an ARB and spironolactone (as well as beta blocker) is uncertain and the use of all three inhibitors of the renin-angiotensin-aldosterone system together is not recommended.
- If greater rises in creatinine or potassium than those outlined above persist despite adjustment of concomitant medications, the dose of the ACE inhibitor should be halved and blood urea, creatinine and electrolytes rechecked within one to two weeks; if there is still an unsatisfactory response specialist advice should be sought.
- If potassium rises to >5.5 mmol/l or creatinine increases by >100% or to above 310 micromol/l the ACE inhibitor should be stopped and specialist advice sought.
- Blood urea, creatinine and electrolytes should be monitored frequently and serially until potassium and creatinine have plateaued.

*Reproduced from: McMurray J, Cohen-Solal A, Dietz R, Eichhorn E, Erhardt L, Hobbs FD, et al. Practical recommendations for the use of ACE inhibitors, beta blockers, aldosterone antagonists and angiotensin receptor blockers in heart failure: putting guidelines into practice. Eur J Heart Fail. 2005;7(5):710-21, with permission from John Wiley and Sons.<sup>60</sup>*

## Annex 3

### Practical guidance: Use of angiotensin receptor blockers in patients with heart failure with reduced ejection fraction<sup>60</sup>

#### **Indications**

- First-line treatment (along with beta blockers) in patients with NYHA Class II-IV HF intolerant of an ACE inhibitor.
- Second-line treatment (after optimisation of ACE inhibitor and beta blocker) in patients with NYHA Class II-III HF who cannot take a mineralocorticoid receptor antagonist. The safety and efficacy of spironolactone used with an ACE inhibitor and an ARB (as well as beta blocker) is uncertain and the use of all three inhibitors of the renin–angiotensin–aldosterone system together is not recommended.

#### **Contraindications**

- known bilateral renal artery stenosis.

#### **Cautions/seek specialist advice**

- significant hyperkalaemia ( $K^+$  >5.0 mmol/l)
- significant renal dysfunction (creatinine >221 micromol/l)
- symptomatic or severe asymptomatic hypotension (systolic BP <90 mm Hg).

#### **Drug interactions to look out for**

- $K^+$  supplements/ $K^+$  sparing diuretics
- 'low salt' substitutes with a high  $K^+$  content.

#### **Starting and target doses**

ARB	Starting dose	Target dose
candesartan	4 or 8 mg once daily	32 mg once daily
valsartan	40 mg twice daily	160 mg twice daily

Candesartan is the only ARB which is licensed for use in patients with HF. Valsartan is the only ARB which is licensed for use in patients following MI with HF or LVSD or both.

#### **How to use angiotensin receptor blockers**

- Start with a low dose (*see starting and target doses*) and double the dose at not less than two-weekly intervals.
- Aim for the target dose or, failing that, the highest-tolerated dose.
- Monitor blood pressure and blood chemistry (urea, creatinine, and electrolytes).
- Check blood chemistry one to two weeks after initiation and one to two weeks after each dose titration.
- When to stop uptitration/reduce dose/stop treatment (*see problem solving*).
- A specialist HF nurse may assist with patient education, follow up (in person/by telephone), biochemical monitoring and dose uptitration.

#### **Advice to the patient**

- Explain the expected benefits, ie treatment is given to improve symptoms, to prevent worsening of HF thereby avoiding hospital admission and to increase survival.
- Symptoms should improve within a few weeks to a few months of starting treatment.
- Advise patients to report principal adverse effects, ie dizziness/symptomatic hypotension.
- Advise patients to avoid NSAIDs not prescribed by a physician (self purchased 'over the counter') and salt substitutes high in  $K^+$ .

**Problem Solving***Asymptomatic low blood pressure*

- Does not usually require any change in therapy.

*Symptomatic hypotension*

- If the patient has dizziness, light headedness and/or confusion and low blood pressure reconsider the need for nitrates, calcium channel blockers and other vasodilators. Calcium channel blockers should be discontinued unless absolutely essential (eg, for angina or hypertension).
- If no signs/symptoms of congestion consider reducing diuretic dose.
- If these measures do not solve problem seek specialist advice.

*Worsening renal function*

- Some rise in urea, creatinine and potassium is to be expected after initiation of an ACE inhibitor; if an increase is small and asymptomatic no action is necessary.
- An increase in creatinine of up to 50% above baseline, or 266 micromol/l whichever is the smaller, is acceptable.
- An increase in potassium to  $\leq 5.5$  mmol/l is acceptable.
- If urea, creatinine or potassium do rise excessively consider stopping concomitant nephrotoxic drugs (eg NSAIDs), other potassium supplements/retaining agents (triamterene, amiloride, spironolactone/ eplerenone) and, if there are no signs of congestion, reducing the dose of diuretic. The safety and efficacy of an ACE inhibitor used with an ARB and spironolactone (as well as beta blocker) is uncertain and the use of all three inhibitors of the renin-angiotensin-aldosterone system together is not recommended.
- If greater rises in creatinine or potassium than those outlined above persist despite adjustment of concomitant medications, the dose of the ARB should be halved and blood urea, creatinine and electrolytes rechecked within one to two weeks; if there is still an unsatisfactory response specialist advice should be sought.
- If potassium rises to  $>5.5$  mmol/l or creatinine increases by  $>100\%$  or to above 310 micromol/l the ARB should be stopped and specialist advice sought.
- Blood urea, creatinine and electrolytes should be monitored frequently and serially until potassium and creatinine have plateaued.

*Reproduced from McMurray J, Cohen-Solal A, Dietz R, Eichhorn E, Erhardt L, Hobbs FD, et al. Practical recommendations for the use of ACE inhibitors, beta blockers, aldosterone antagonists and angiotensin receptor blockers in heart failure: putting guidelines into practice. Eur J Heart Fail. 2005;7(5):710-21, with permission from John Wiley and Sons<sup>60</sup>*

## Annex 4

### Practical guidance: Use of beta blockers in patients with heart failure with reduced ejection fraction<sup>60</sup>

#### **Indications**

- First line treatment, along with ACE inhibitors.

#### **Contraindications**

- asthma
- heart block or heart rate <60/min
- persisting signs of congestion, hypotension/low blood pressure (systolic <90 mm Hg), raised jugular venous pressure, ascites, marked peripheral oedema.

When there is no suitable alternative, it may be necessary to use a beta blocker for a patient with HF who has well-controlled asthma or chronic obstructive pulmonary disease (without significant reversible airways obstruction). The beta blocker should be initiated at a low dose by a specialist and the patient should be closely monitored for adverse effects.<sup>5</sup>

#### **Cautions/seek specialist advice**

- severe (NYHA Class IV) HF
- current or recent (<4 days) exacerbation of HF, eg hospital admission with worsening HF.

#### **Drug interactions to look out for**

- verapamil/diltiazem (calcium channel blockers should be discontinued unless absolutely necessary and diltiazem and verapamil are generally contraindicated in HF.
- digoxin, amiodarone.

#### **Starting and target doses**

Beta blocker	Starting dose	Target dose
bisoprolol	1.25 mg once daily	10 mg once daily
carvedilol	3.125 mg twice daily	25–50 mg twice daily
nebivolol	1.25 mg once daily	10 mg once daily

Only the drugs listed above have UK formulations shown to reduce mortality or morbidity.

#### **How to use beta blockers**

- Start with a low dose (*see starting and target doses*) and double the dose at not less than two-weekly intervals.
- Aim for the target dose or, failing that, the highest tolerated dose.
- Monitor heart rate, BP and clinical status (symptoms, signs, especially of congestion, body weight).
- Check blood urea, creatinine and electrolytes one to two weeks after initiation and one to two weeks after final dose titration.
- When to stop uptitration/reduce dose/stop treatment (*see problem solving*).
- A specialist HF nurse may assist with patient education, follow up (in person/by telephone), biochemical monitoring and dose uptitration.

#### **Advice to the patient**

- Explain the expected benefits, ie treatment is given to improve symptoms, to prevent worsening of HF thereby avoiding hospital admission and to increase survival.
- Symptomatic improvement may develop slowly after starting treatment, taking three to six months or longer.
- Temporary symptomatic deterioration may occur during the initiation/uptitration phase.
- Advise patients to report deterioration and that deterioration (tiredness, fatigue, breathlessness) can

usually be easily managed by adjustment of other medication; patients should be advised not to stop beta blocker therapy without consulting their physician.

- To detect and treat deterioration early, patients should be encouraged to weigh themselves daily (after waking, before dressing, after voiding, before eating) and to increase their diuretic dose should their weight increase, persistently (for longer than two days), by >1 kg over three days.

### **Problem solving**

#### *Worsening symptoms/signs (eg increasing dyspnoea, fatigue, oedema, weight gain)*

- If there is increasing congestion, increase the dose of diuretic and/or halve the dose of beta blocker (if increasing diuretic doesn't work).
- If marked fatigue (and/or bradycardia - see *low heart rate*) halve dose of beta blocker (rarely necessary).
- Review patient in one to two weeks; if not improved seek specialist advice.
- If there is serious deterioration halve the dose of beta blocker or stop this treatment (rarely necessary); seek specialist advice.

#### *Low heart rate*

- If the heart rate is <50 beats/min with worsening symptoms halve the dose of beta blocker or, if there is severe deterioration, stop beta blocker (rarely necessary).
- Review the need for other heart rate slowing drugs, eg digoxin, amiodarone, diltiazem/verapamil (diltiazem and verapamil are generally contraindicated in HF).
- Arrange an ECG to exclude heart block.
- Seek specialist advice.

#### *Asymptomatic low blood pressure*

- does not usually require any change in therapy.

#### *Symptomatic hypotension*

- If the patient has dizziness, light headedness and/or confusion and low BP reconsider need for nitrates, calcium channel blockers and other vasodilators. Calcium channel blockers should be discontinued unless absolutely essential (eg for angina or hypertension).
- If there are no signs/symptoms of congestion consider reducing diuretic or ACE inhibitor dose.
- If these measures do not solve the problem seek specialist advice.

*Reproduced from McMurray J, Cohen-Solal A, Dietz R, Eichhorn E, Erhardt L, Hobbs FD, et al. Practical recommendations for the use of ACE inhibitors, beta blockers, aldosterone antagonists and angiotensin receptor blockers in heart failure: putting guidelines into practice. Eur J Heart Fail. 2005;7(5):710-2, with permission from John Wiley and Sons<sup>60</sup>*

## Annex 5

### Practical guidance: Use of mineralocorticoid receptor antagonist in patients with heart failure reduced ejection fraction<sup>60</sup>

#### **Indications**

- Second-line treatment (after optimisation of ACE inhibitor and beta blocker) in patients with NYHA class II-IV HF. The safety and efficacy of spironolactone used with an ACE inhibitor and an ARB (as well as beta blocker) is uncertain and the use of all three inhibitors of the renin-angiotensin-aldosterone system together is not recommended.

#### **Cautions/seek specialist advice**

- significant hyperkalaemia ( $K^+ >5.0$  mmol/l).
- significant renal dysfunction (creatinine  $>220$  micromol/l or CKD stage  $>3$ ).

#### **Drug interactions to look out for**

$K^+$  supplements/ $K^+$  sparing diuretics

ACE inhibitors, ARBs, NSAIDs (avoid unless essential)

- 'low salt' substitutes with a high  $K^+$  content.

#### **Starting and target doses**

Mineralocorticoid receptor antagonist	Starting dose	Target dose
spironolactone	25 mg once daily or on alternate days	25–50 mg once daily
eplerenone	25 mg once daily	50 mg once daily

#### **How to use mineralocorticoid receptor antagonists**

- Start with a low dose (see starting and target doses).
- Check urea, creatinine and electrolytes at one, four, eight and 12 weeks; six, nine and 12 months; six monthly thereafter.
- If  $K^+$  rises above 5.5 mmol/l or creatinine rises to  $>220$  micromol/l reduce the dose to 25 mg on alternate days and monitor blood chemistry closely.
- If  $K^+$  rises  $\geq 6.0$  mmol/l or creatinine to 310 micromol/l stop spironolactone immediately and seek specialist advice.
- A specialist HF nurse may assist with patient education, follow up (in person/by telephone), biochemical monitoring and dose uptitration.

#### **Advice to the patient**

- Explain the expected benefits, ie treatment is given to improve symptoms, to prevent worsening of HF thereby avoiding hospital admission and to increase survival.
- Symptoms should improve within a few weeks to a few months of starting treatment.
- Advise patients to report principal adverse effects, ie dizziness/symptomatic hypotension.
- Advise patients to avoid NSAIDs not prescribed by a physician (self purchased 'over the counter') and salt substitutes high in  $K^+$ .
- If diarrhoea and/or vomiting occurs, patients should stop the MRA and contact their physician.

**Problem solving**

*Worsening renal function/hyperkalaemia*

- See the *how to use mineralocorticoid receptor antagonists* section.
- The major concern is hyperkalaemia ( $\geq 6.0$  mmol/l); conversely, a high normal potassium may be desirable in patients with HF, especially if they are taking digoxin.
- It is important to avoid other  $K^+$  retaining drugs (eg  $K^+$  sparing diuretics such as amiloride and triamterene) and nephrotoxic agents (eg NSAIDs).
- The safety and efficacy of an MRA used with an ACE inhibitor and an ARB (as well as a beta blocker) is uncertain and the use of all three inhibitors of the renin-angiotensin-aldosterone system together is not recommended.
- Be aware that some 'low salt' substitutes have a high  $K^+$  content.
- Male patients treated with spironolactone may develop breast discomfort and/or gynaecomastia. These problems are significantly less common with eplerenone.

*Reproduced from McMurray J, Cohen-Solal A, Dietz R, Eichhorn E, Erhardt L, Hobbs FD, et al. Practical recommendations for the use of ACE inhibitors, beta blockers, aldosterone antagonists and angiotensin receptor blockers in heart failure: putting guidelines into practice. Eur J Heart Fail. 2005;7(5):710-21, with permission from John Wiley and Sons.<sup>60</sup>*



## Annex 6

### Drugs to avoid in patients with chronic heart failure

The following tables list some of the more commonly prescribed medicines and herbal remedies and their effect on the myocardium.

#### *Cardiac medications affecting ventricular function*

Drug or class	Effect(s)
Class I and III antiarrhythmics (excluding amiodarone)	reduced contractility, proarrhythmia
Rate-limiting calcium channel blockers (eg verapamil and diltiazem)	reduced contractility and/or neurohormonal activation
Minoxidil	activation of the renin-angiotensin-aldosterone system
Moxonidine	increases mortality

#### *Non-cardiac medications affecting ventricular function*

Drug or class	Effect(s)
Corticosteroids	sodium and water retention
Non-steroidal anti-inflammatory drugs	sodium and water retention, antagonism of diuretic therapy, increased systemic vascular resistance
Thiazolidinediones (glitazones)	fluid retention
Tricyclic antidepressants	reduced contractility, proarrhythmia
Itraconazole	reduced contractility
Carbenoxolone	fluid retention
Macrolide antibiotics and some antifungal agents	proarrhythmia mediated by QT prolongation
Terfenadine, and some other antihistamines	proarrhythmia mediated by QT prolongation, especially when used with macrolide antibiotics or some antifungal agents

#### *Selected herbal medicines with cardiac effects*


Drug or class	Effect(s)
Liquorice	fluid retention
Ma huang Yohimbe bark	sympathomimetic
Dong quai Aescin	anticoagulant: increased risk of bleeding
Gingko Garlic Dan shen	antiplatelet: increased risk of bleeding
Gossypol	hypokalaemia
Dandelion	sodium retention

A number of other herbs contain constituents with cardiac glycoside effects and enhance the effects of digoxin or interfere with assays.

## Annex 7

### Medicine Sick Day Rules card

The Medicine Sick Day Rules card is a resource for patients, carers and healthcare professionals to raise awareness of potential harms if patients continue to take certain prescribed medicines whilst experiencing a dehydrating illness. Further information and order forms for cards are available from the Scottish Patient Safety Programme website: [www.scottishpatientsafetyprogramme.scot.nhs.uk/programmes/primary-care/medicine-sick-day-rules-card](http://www.scottishpatientsafetyprogramme.scot.nhs.uk/programmes/primary-care/medicine-sick-day-rules-card)



**NHS SCOTLAND**

### Medicine Sick Day Rules

When you are unwell with any of the following:

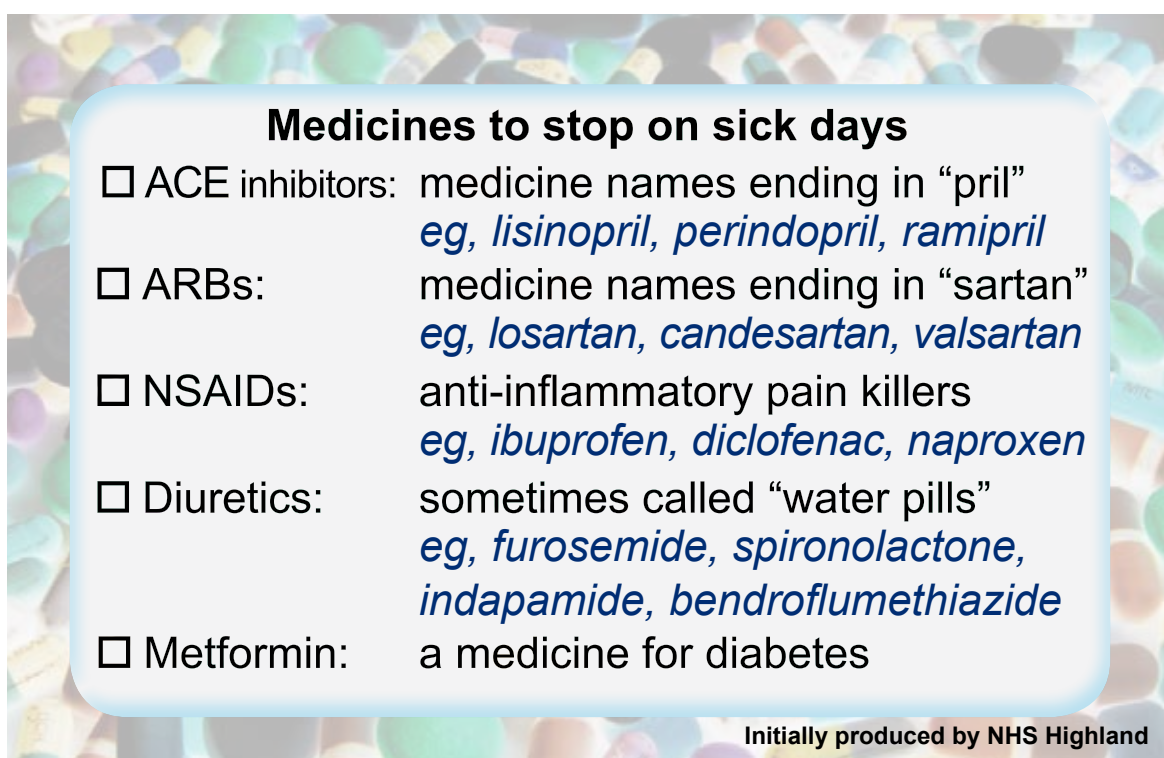
- Vomiting or diarrhoea (unless only minor)
- Fevers, sweats and shaking

Then **STOP** taking the medicines listed overleaf

Restart when you are well (after 24-48 hours of eating and drinking normally)

If you are in any doubt, contact your pharmacist, GP or nurse

**EVERY PERSON EVERY TIME** SCOTTISH PATIENT SAFETY PROGRAMME



### Medicines to stop on sick days

- ACE inhibitors: medicine names ending in “pril”  
*eg, lisinopril, perindopril, ramipril*
- ARBs: medicine names ending in “sartan”  
*eg, losartan, candesartan, valsartan*
- NSAIDs: anti-inflammatory pain killers  
*eg, ibuprofen, diclofenac, naproxen*
- Diuretics: sometimes called “water pills”  
*eg, furosemide, spironolactone, indapamide, bendroflumethiazide*
- Metformin: a medicine for diabetes

Initially produced by NHS Highland

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Edinburgh Office | Gyle Square | 1 South Gyle Crescent | Edinburgh | EH12 9EB  
Telephone 0131 623 4300 Fax 0131 623 4299

Glasgow Office | Delta House | 50 West Nile Street | Glasgow | G1 2NP  
Telephone 0141 225 6999 Fax 0141 248 3776

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