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

Authors/Task Force Members: John J.V. McMurray (Chairperson) (UK)*, Stamatis Adamopoulos (Greece), Stefan D. Anker (Germany), Angelo Auricchio (Switzerland), Michael Böhm (Germany), Kenneth Dickstein (Norway), Volkmar Falk (Switzerland), Gerasimos Filippatos (Greece), Cândida Fonseca (Portugal), Miguel Angel Gomez-Sanchez (Spain), Tiny Jaarsma (Sweden), Lars Køber (Denmark), Gregory Y.H. Lip (UK), Aldo Pietro Maggioni (Italy), Alexander Parkhomenko (Ukraine), Burkert M. Pieske (Austria), Bogdan A. Popescu (Romania), Per K. Rønnevik (Norway), Frans H. Rutten (The Netherlands), Juerg Schwitter (Switzerland), Petar Seferovic (Serbia), Janina Stepinska (Poland), Pedro T. Trindade (Switzerland), Adriaan A. Voors (The Netherlands), Faiez Zannad (France), Andreas Zeiher (Germany).

ESC Committee for Practice Guidelines (CPG): Jeroen J. Bax (CPG Chairperson) (The Netherlands), Helmut Baumgartner (Germany), Claudio Ceconi (Italy), Veronica Dean (France), Christi Deaton (UK), Robert Fagard (Belgium), Christian Funck-Brentano (France), David Hasdai (Israel), Arno Hoes (The Netherlands), Paulus Kirchhof (Germany/UK), Juhani Knuuti (Finland), Philippe Kolh (Belgium), Theresa McDonagh (UK), Cyril Moulin (France), Bogdan A. Popescu (Romania), Željko Reiner (Croatia), Udo Sechtem (Germany), Per Anton Sirnes (Norway), Michal Tendera (Poland), Adam Torbicki (Poland), Alec Vahanian (France), Stephan Windecker (Switzerland).

Document Reviewers: Theresa McDonagh (CPG Co-Review Coordinator) (UK), Udo Sechtem (CPG Co-Review Coordinator) (Germany), Luis Almenar Bonet (Spain), Panayiotis Avraamides (Cyprus), Hisham A. Ben Lamin (Libya), Michele Brignole (Italy), Antonio Coca (Spain), Peter Cowburn (UK), Henry Dargie (UK), Perry Elliott (UK), Frank Arnold Flachskampf (Sweden), Guido Francesco Guida (Italy), Suzanna Hardman (UK), Bernard lung
Table of Contents

Abbreviations and acronyms ............................ 805
1. Preamble ........................................... 807
2. Introduction ...................................... 808
3. Definition and diagnosis ............................ 808
   3.1 Definition of heart failure .................... 808
   3.2 Terminology related to left ventricular ejection fraction .... 808
   3.3 Terminology related to the time-course of heart failure .... 809
   3.4 Terminology related to the symptomatic severity of heart failure .................. 809
   3.5 Epidemiology, aetiology, pathophysiology, and natural history of heart failure .... 810
   3.6 Diagnosis of heart failure ..................... 810
      3.6.1 Symptoms and signs ...................... 810
      3.6.2 General diagnostic tests in patients with suspected heart failure .............. 811
      3.6.3 Essential initial investigations: echocardiogram, electrocardiogram, and laboratory tests ...... 811
      3.6.4 Natriuretic peptides ..................... 811
      3.6.5 Chest X-ray ................................ 813
      3.6.6 Routine laboratory tests .................. 813
      3.6.7 Algorithm for the diagnosis of heart failure .............. 815
4. The role of cardiac imaging in the evaluation of patients with suspected or confirmed heart failure .......... 816
   4.1 Echocardiography ................................ 816
      4.1.1 Assessment of left ventricular systolic dysfunction ........... 816
      4.1.2 Assessment of left ventricular diastolic dysfunction .......... 816
      4.2 Transoesophageal echocardiography .......... 816
      4.3 Stress echocardiography .................... 818
      4.4 Cardiac magnetic resonance .................. 818
      4.5 Single-photon emission computed tomography and radionuclide ventriculography .......... 819
      4.6 Positron emission tomography imaging .......... 819
      4.7 Coronary angiography ....................... 819
      4.8 Cardiac computed tomography ............... 819
5. Other investigations ................................ 819
   5.1 Cardiac catheterization and endomyocardial biopsy ........... 819
   5.2 Exercise testing ................................ 820
   5.3 Genetic testing ................................ 820
   5.4 Ambulatory electrocardiographic monitoring ........... 820
6. Prognosis ......................................... 820
7. Pharmacological treatment of heart failure with reduced ejection fraction (systolic heart failure) ............ 820
   7.1 Objectives in the management of heart failure ............ 820
   7.2 Treatments recommended in potentially all patients with systolic heart failure ............... 820
      7.2.1 Angiotensin-converting enzyme inhibitors and beta-blockers ............... 820
      7.2.2 Mineralocorticoid/aldosterone receptor antagonists ............... 823
      7.2.3 Other treatments recommended in selected patients with systolic heart failure ........ 825
      7.2.4 Angiotensin receptor blockers ................ 825
      7.2.5 Ibuprofen ................................ 825
      7.2.6 Digoxin and other digitalis glycosides ................ 826
      7.2.7 Combination of hydralazine and isosorbide dinitrate ................ 826
      7.2.8 Omega-3 polyunsaturated fatty acids ............... 826
      7.3 Treatments not recommended (unproven benefit) ........ 827
      7.3.1 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (‘statins’) .......... 827
      7.3.2 Renin inhibitors ................................ 827
      7.3.3 Oral anticoagulants .......................... 827
      7.4 Treatments not recommended (believed to cause harm) .... 827
      7.5 Diuretics ...................................... 828
8. Pharmacological treatment of heart failure with ‘preserved’ ejection fraction (diastolic heart failure) .......... 828
9. Non-surgical device treatment of heart failure with reduced ejection fraction (systolic heart failure) .......... 829
   9.1 Implantable cardioverter-defibrillator ............... 829
      9.1.1 Secondary prevention of sudden cardiac death .......... 829
      9.1.2 Primary prevention of sudden cardiac death .......... 829
      9.2 Cardiac resynchronization therapy ............... 830
         9.2.1 Recommendations for cardiac resynchronization therapy where the evidence is certain .......... 831
         9.2.2 Recommendations for cardiac resynchronization therapy where the evidence is uncertain .......... 831
10. Arrhythmias, bradycardia, and atrioventricular block in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction .......... 832
   10.1 Atrial fibrillation .............................. 832
      10.1.1 Rate control ................................ 832
      10.1.2 Rhythm control ................................ 833
      10.1.3 Thrombo-embolism prophylaxis ............... 834
      10.2 Ventricular arrhythmias ....................... 834
      10.3 Symptomatic bradycardia and atrioventricular block .......... 835

Keywords
Heart failure • Natriuretic peptides • Ejection fraction • Renin–angiotensin system • Beta-blockers • Digitalis • Transplantation
11. Importance and management of other co-morbidity in heart failure with reduced ejection fraction and heart failure with preserved ejection fraction

12. Acute heart failure

12.1 Initial assessment and monitoring of patients
12.2 Treatment of acute heart failure
12.2.1 Pharmacological therapy
12.2.2 Non-pharmacological/non-device therapy
12.3 Invasive monitoring
12.3.1 Intravascular line
12.3.2 Pulmonary artery catheterization
12.4 Monitoring after stabilization
12.5 Other in-patient assessments
12.6 Readiness for discharge
12.7 Special patient populations
12.7.1 Patients with a concomitant acute coronary syndrome
12.7.2 Isolated right ventricular failure
12.7.3 Acute heart failure with ‘cardiorenal syndrome’
12.7.4 Perioperative acute heart failure
12.7.5 Peripartum cardiomyopathy
12.7.6 Adult congenital heart disease

13. Coronary revascularization and surgery, including valve surgery, ventricular assist devices, and transplantation

13.1 Coronary revascularization
13.2 Ventricular reconstruction
13.3 Valvular surgery
13.3.1 Aortic stenosis
13.3.2 Aortic regurgitation
13.3.3 Mitral regurgitation
13.4 Heart transplantation
13.5 Mechanical circulatory support
13.5.1 End-stage heart failure

13.5.2 Acute heart failure

14. Holistic management, including exercise training and multidisciplinary management programmes, patient monitoring, and palliative care

14.1 Exercise training
14.2 Organization of care and multidisciplinary management programmes
14.3 Serial natriuretic peptide measurement
14.4 Remote monitoring (using an implanted device)
14.5 Remote monitoring (no implanted device)
14.6 Structured telephone support
14.7 Palliative/supportive/end-of-life care

15. Gaps in evidence

15.1 Diagnosis
15.2 Co-morbidity
15.3 Non-pharmacological, non-interventional therapy
15.4 Pharmacological therapy
15.5 Devices
15.6 Acute heart failure
15.7 End-of-life care

References

Abbreviations and acronyms

ACE: angiotensin-converting enzyme
ACHD: adult congenital heart disease
AF: atrial fibrillation
AF-CHF: Atrial Fibrillation and Congestive Heart Failure
AHF: acute heart failure
AIRE: Acute Infarction Ramipril Efficacy
ARR: absolute risk reduction
ATLAS: Assessment of Treatment with Lisinopril And Survival
AV: atrioventricular
AVP: arginine vasopressin
BEAUTIFUL: MorBidity-mortality EvAlUaTion of the I7 inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction
BEST: Beta-Blocker Evaluation of Survival Trial
BIVAD: bi-ventricular assist device
BNP: B-type natriuretic peptide
B.P.M.: beats per minute
BRC: bridge to candidacy
BT: bridge to decision
BTR: bridge to recovery
BTT: bridge to transplantation
CABG: coronary artery bypass graft
CAD: coronary artery disease
CARE-HF: Cardiac Resynchronization in Heart Failure Study
CCB: calcium-channel blocker
1. Preamble

Guidelines summarize and evaluate all available evidence at the time of the writing process, on a particular issue with the aim of assisting physicians in selecting the best management strategies for an individual patient, with a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines are no substitutes, but are complements, for textbooks and cover the European Society of Cardiology (ESC) Core Curriculum topics. Guidelines and recommendations should help physicians to make decisions in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible physician(s).

A large number of Guidelines have been issued in recent years by the ESC as well as by other societies and organizations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (http://www.escardio.org/guidelines-surveys/esc-guidelines/about/Pages/rules-writing.aspx). ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

Members of this Task Force were selected by the ESC to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for diagnosis, management, and/or prevention of a given condition according to ESC Committee for Practice Guidelines (CPG) policy. A critical evaluation of diagnostic and therapeutic procedures was performed including assessment of the risk–benefit ratio. Estimates of expected health outcomes for larger populations were included, where data exist. The level of evidence and the strength of recommendation of particular treatment options were weighed and graded according to pre-defined scales, as outlined in Tables A and B.

The experts of the writing and reviewing panels filled in declarations of interest forms of all relationships which might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC website (http://www.escardio.org/guidelines). Any changes in declarations of interest that arise during the writing period must be notified to the ESC and updated. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new Guidelines produced by Task Forces, expert groups, or consensus panels. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts. After appropriate revisions, it is approved by all the experts involved in the Task

<table>
<thead>
<tr>
<th>Table A Classes of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classes of recommendations</td>
</tr>
<tr>
<td>Class I</td>
</tr>
<tr>
<td>Class II</td>
</tr>
<tr>
<td>Class IIa</td>
</tr>
<tr>
<td>Class IIb</td>
</tr>
<tr>
<td>Class III</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table B Levels of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of evidence A</td>
</tr>
<tr>
<td>Level of evidence B</td>
</tr>
<tr>
<td>Level of evidence C</td>
</tr>
</tbody>
</table>
3. Definition and diagnosis

3.1 Definition of heart failure

Heart failure can be defined as an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues, despite normal filling pressures (or only at the expense of increased filling pressures).1 For the purposes of these guidelines, HF is defined, clinically, as a syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) resulting from an abnormality of cardiac structure or function. The diagnosis of HF can be difficult (see Section 3.6). Many of the symptoms of HF are nondiscriminating and, therefore, of limited diagnostic value.2–6 Many of the signs of HF result from sodium and water retention and resolve quickly with diuretic therapy, i.e. may be absent in patients receiving such treatment. Demonstration of an underlying cardiac cause is therefore central to the diagnosis of HF (see Section 3.6). This is usually myocardial disease causing systolic ventricular dysfunction. However, abnormalities of ventricular diastolic function or of the valves, pericardium, endocardium, heart rhythm, and conduction can also cause HF (and more than one abnormality can be present) (see Section 3.5). Identification of the underlying cardiac problem is also crucial for therapeutic reasons, as the precise pathology determines the specific treatment used (e.g. valve surgery for valvular disease, specific pharmacological therapy for LV systolic dysfunction, etc.).

3.2 Terminology related to left ventricular ejection fraction

The main terminology used to describe HF is historical and is based on measurement of LV ejection fraction (EF). Mathematically, EF is the stroke volume (which is the end-diastolic volume minus the end-systolic volume) divided by the end-diastolic volume. In patients with reduced contraction and emptying of the left ventricle (i.e. systolic dysfunction), stroke volume is maintained by an increase in end-diastolic volume (because the left ventricle dilates), i.e. the heart ejects a smaller fraction of a larger volume. The more severe the systolic dysfunction, the more the EF is reduced from normal and, generally, the greater the end-diastolic and end-systolic volumes.

The EF is considered important in HF, not only because of its prognostic importance (the lower the EF the poorer the survival) but also because most clinical trials selected patients based upon EF (usually measured using a radionuclide technique or echocardiography). The major trials in patients with HF and a reduced EF (HF-REF), or ‘systolic HF’, mainly enrolled patients with an EF ≤35%, and it is only in these patients that effective therapies have been demonstrated to date.

Other, more recent, trials enrolled patients with HF and an EF >40–45% and no other causal cardiac abnormality (such as valvular or pericardial disease). Some of these patients did not have an entirely normal EF (generally considered to be >50%)

2. Introduction

The aim of this document is to provide practical, evidence-based guidelines for the diagnosis and treatment of heart failure (HF). The principal changes from the 2008 guidelines1 relate to:

(i) an expansion of the indication for mineralocorticoid (aldosterone) receptor antagonists (MRAs);
(ii) a new indication for the sinus node inhibitor ivabradine;
(iii) an expanded indication for cardiac resynchronization therapy (CRT);
(iv) new information on the role of coronary revascularization in HF;
(v) recognition of the growing use of ventricular assist devices; and
(vi) the emergence of transcatheter valve interventions.

There are also changes to the structure and format of the guidelines. Therapeutic recommendations now state the treatment effect supported by the class and level of recommendation in tabular format; in the case of chronic heart failure due to left ventricular (LV) systolic dysfunction, the recommendations focus on mortality and morbidity outcomes. Detailed summaries of the key evidence supporting generally recommended treatments have been provided. Practical guidance is provided for the use of the more important disease-modifying drugs and diuretics. When possible, other relevant guidelines, consensus statements, and position papers have been cited to avoid unduly lengthy text. All tables should be read in conjunction with their accompanying text and not read in isolation.

The principal changes from the 2008 guidelines1 relate to:

(i) an expansion of the indication for mineralocorticoid (aldosterone) receptor antagonists (MRAs);
(ii) a new indication for the sinus node inhibitor ivabradine;
(iii) an expanded indication for cardiac resynchronization therapy (CRT);
(iv) new information on the role of coronary revascularization in HF;
(v) recognition of the growing use of ventricular assist devices; and
(vi) the emergence of transcatheter valve interventions.

There are also changes to the structure and format of the guidelines. Therapeutic recommendations now state the treatment effect supported by the class and level of recommendation in tabular format; in the case of chronic heart failure due to left ventricular (LV) systolic dysfunction, the recommendations focus on mortality and morbidity outcomes. Detailed summaries of the key evidence supporting generally recommended treatments have been provided. Practical guidance is provided for the use of the more important disease-modifying drugs and diuretics. When possible, other relevant guidelines, consensus statements, and position papers have been cited to avoid unduly lengthy text. All tables should be read in conjunction with their accompanying text and not read in isolation.

The task of developing ESC Guidelines covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. To implement the guidelines, condensed pocket guidelines versions, summary slides, booklets with essential messages, and an electronic version for digital applications (smartphones, etc.) are produced. These versions are abridged and, thus, if needed, one should refer to the full text version which is freely available on the ESC website. The National Societies of the ESC are encouraged to endorse, translate, and implement the ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Surveys and registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines, thus completing the loop between clinical research, writing of guidelines, and implementing them into clinical practice.

The guidelines do not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patients, in consultation with that patient, and, where appropriate and necessary, the patient’s guardian or carer. It is also the health professional’s responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.
but also did not have a major reduction in systolic function either. Because of this, the term HF with ‘preserved’ EF (HF-PEF) was created to describe these patients. Patients with an EF in the range 35–50% therefore represent a ‘grey area’ and most probably have primarily mild systolic dysfunction. The diagnosis of HF-PEF is more difficult than the diagnosis of HF-REF because it is largely one of exclusion, i.e. potential non-cardiac causes of the patient’s symptoms (such as anaemia or chronic lung disease) must first be discounted (Table 1).7,8 Usually these patients do not have a dilated heart and many have an increase in LV wall thickness and increased left atrial (LA) size. Most have evidence of diastolic dysfunction (see Section 4.1.2), which is generally accepted as the likely cause of HF in these patients (hence the term ‘diastolic HF’).7,8

It is important to note that EF values and normal ranges are dependent on the imaging technique employed, method of analysis, and operator. Other, more sensitive measures of systolic function may show abnormalities in patients with a preserved or even normal EF (see Section 4.1.1), hence the preference for stating preserved or reduced EF over preserved or reduced ‘systolic function’.9,10

### 3.3 Terminology related to the time-course of heart failure

The terms used to describe different types of HF can be confusing. As described above, in these guidelines the term HF is used to describe the symptomatic syndrome, graded according to the New York Heart Association (NYHA) functional classification (see Section 3.4 and Table 2), although a patient can be rendered asymptomatic by treatment. In these guidelines, a patient who has never exhibited the typical signs or symptoms of HF is described as having asymptomatic LV systolic dysfunction (or whatever the underlying cardiac abnormality is). Patients who have had HF for some time are often said to have ‘chronic HF’. A treated patient with symptoms and signs, which have remained generally unchanged for at least a month, is said to be ‘stable’. If chronic stable HF deteriorates, the patient may be described as ‘decompensated’ and this may happen suddenly, i.e. ‘acutely’, usually leading to hospital admission, an event of considerable prognostic importance. New (‘de novo’) HF may present acutely, for example as a consequence of acute myocardial infarction or in a subacute (gradual) fashion, for example in a patient who has had asymptomatic cardiac dysfunction, often for an indeterminate period, and may persist or resolve (patients may become ‘compensated’). Although symptoms and signs may resolve in the latter patients, their underlying cardiac dysfunction may not, and they remain at risk of recurrent ‘decompensation’. Occasionally, however, a patient may have HF due to a problem that resolves completely (e.g. acute viral myopericarditis). Some other patients, particularly those with ‘idiopathic’ dilated cardiomyopathy, may also show substantial or even complete recovery of LV systolic function with modern disease-modifying therapy [including an angiotensin-converting enzyme (ACE) inhibitor, beta-blocker, and mineralocorticoid receptor antagonist (MRA)]. ‘Congestive HF’ is a term that is sometimes still used, particularly in the USA, and may describe acute or chronic HF with evidence of congestion (i.e. sodium and water retention). Congestion, though not other symptoms of HF (e.g. fatigue), may resolve with diuretic treatment. Many or all of these terms may be accurately applied to the same patient at different times, depending upon their stage of illness.

### 3.4 Terminology related to the symptomatic severity of heart failure

The NYHA functional classification (Table 2) has been used to select patients in almost all randomized treatment trials in HF and, therefore, to describe which patients benefit from effective therapies. Patients in NYHA class I have no symptoms attributable to heart disease; those in NYHA classes II, III or IV are sometimes said to have mild, moderate or severe symptoms, respectively.

It is important to note, however, that symptom severity correlates poorly with ventricular function, and that although there is a clear relationship between severity of symptoms and survival, patients with mild symptoms may still have a relatively high absolute risk of hospitalization and death.11–13 Symptoms can also change rapidly; for example, a stable patient with mild symptoms can become suddenly breathless at rest with the onset of arrhythmia, and an acutely unwell patient with pulmonary oedema and NYHA class IV symptoms may improve rapidly with the administration of a diuretic. Deterioration in symptoms indicates heightened risk of hospitalization and death, and is an indication to seek prompt medical attention and treatment. Obviously, improvement in symptoms (preferably to the point of the patient becoming asymptomatic) is one of the two major goals of treatment of HF (the other being to reduce morbidity, including hospital admissions, and mortality).

The Killip classification may be used to describe the severity of the patient’s condition in the acute setting after myocardial infarction.14

---

**Table 1** Diagnosis of heart failure

<table>
<thead>
<tr>
<th>The diagnosis of HF-REF requires three conditions to be satisfied:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Symptoms typical of HF</td>
</tr>
<tr>
<td>2. Signs typical of HF</td>
</tr>
<tr>
<td>3. Reduced LVEF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The diagnosis of HF-PEF requires four conditions to be satisfied:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Symptoms typical of HF</td>
</tr>
<tr>
<td>2. Signs typical of HF</td>
</tr>
<tr>
<td>3. Normal or only mildly reduced LVEF and LV not dilated</td>
</tr>
<tr>
<td>4. Relevant structural heart disease (LV hypertrophy/LA enlargement) and/or diastolic dysfunction (see Section 4.1.2)</td>
</tr>
</tbody>
</table>

HF = heart failure; HF-PEF = heart failure with ‘preserved’ ejection fraction; HF-REF = heart failure and a reduced ejection fraction; LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction.

*Signs may not be present in the early stages of HF (especially in HF-PEF) and in patients treated with diuretics (see Section 3.6)."
3.5 Epidemiology, aetiology, pathophysiology, and natural history of heart failure

Approximately 1%–2% of the adult population in developed countries has HF, with the prevalence rising to ≥10% among persons 70 years of age or older. There are many causes of HF, and these vary in different parts of the world (Appendix A). At least half of patients with HF have a low EF (i.e. HF-REF). HF-REF is the best understood type of HF in terms of pathophysiology and treatment, and is the focus of these guidelines. Coronary artery disease (CAD) is the cause of approximately two-thirds of cases of systolic HF, although hypertension and diabetes are probable contributing factors in many cases. There are many other causes of systolic HF (Appendix A), which include previous viral infection (recognized or unrecognized), alcohol abuse, chemotherapy (e.g. doxorubicin or trastuzumab), and ‘idiopathic’ dilated cardiomyopathy (recognized or unrecognized), alcohol abuse, chemotherapy (e.g. doxorubicin or trastuzumab), and ‘idiopathic’ dilated cardiomyopathy (Appendix A). Syndromes, such as coronary artery disease and hypertension, are particularly non-specific. Signs resulting from cardiac damage, whereas certain features, particularly previous myocardial infarction, greatly increase the likelihood of HF in a

Two key neurohumoral systems activated in HF are the renin–angiotensin–aldosterone system and sympathetic nervous system. In addition to causing further myocardial injury, these systemic responses have detrimental effects on the blood vessels, kidneys, muscles, bone marrow, lungs, and liver, and create a pathophysiological ‘vicious cycle’, accounting for many of the clinical features of the HF syndrome, including myocardial electrical instability. Interruption of these two key processes is the basis of much of the effective treatment of HF.11,20

Clinically, the aforementioned changes are associated with the development of symptoms and worsening of these over time, leading to diminished quality of life, declining functional capacity, episodes of frank decompensation leading to hospital admission (which is often recurrent and costly to health services), and premature death, usually due to pump failure or a ventricular arrhythmia. The limited cardiac reserve of such patients is also dependent on atrial fibrillation, synchronized contraction of the left ventricle, and a normal interaction between the right and left ventricles. Recurrent events affecting any of these [e.g. the development of AF or conduction abnormalities, such as left bundle branch block (LBBB)] or imposing an additional haemodynamic load on the failing heart (e.g. anemia) can lead to acute decompensation.

Before 1990, the modern era of treatment, 60%–70% of patients died within 5 years of diagnosis, and admission to hospital with worsening symptoms was frequent and recurrent, leading to an epidemic of hospitalization for HF in many countries. Effective treatment has improved both of these outcomes, with a relative reduction in hospitalization in recent years of 30%–50% and smaller but significant decreases in mortality.21–23

3.6 Diagnosis of heart failure

3.6.1 Symptoms and signs

The diagnosis of HF can be difficult, especially in the early stages. Although symptoms bring patients to medical attention, many of the symptoms of HF (Table 4) are non-specific and do not, therefore, help discriminate between HF and other problems. Symptoms that are more specific (i.e. orthopnoea and paroxysmal nocturnal dyspnea) are less common, especially in patients with milder symptoms, and are, therefore, insensitive.2–6

Many of the signs of HF result from sodium and water retention, and are, therefore, also not specific. Peripheral oedema has other causes as well, and is particularly non-specific. Signs resulting from sodium and water retention (e.g. peripheral oedema) resolve quickly with diuretic therapy (i.e. may be absent in patients receiving such treatment, making it more difficult to assess patients already treated in this way). More specific signs, such as elevated jugular venous pressure and displacement of the apical impulse, are harder to detect and, therefore, less reproducible (i.e. agreement between different doctors examining the same patient may be poor).2–6

Symptoms and signs may be particularly difficult to identify and interpret in obese individuals, in the elderly, and in patients with chronic lung disease.24–26

The patient’s medical history is also important. HF is unusual in an individual with no relevant medical history (e.g. a potential cause of cardiac damage), whereas certain features, particularly previous myocardial infarction, greatly increase the likelihood of HF in a

---

Table 2  New York Heart Association functional classification based on severity of symptoms and physical activity

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations.</td>
</tr>
<tr>
<td>Class II</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations.</td>
</tr>
<tr>
<td>Class III</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations.</td>
</tr>
<tr>
<td>Class IV</td>
<td>Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.</td>
</tr>
</tbody>
</table>

---

ESC Guidelines
patient with appropriate symptoms and signs.2–5 These points highlight the need to obtain objective evidence of a structural or functional cardiac abnormality that is thought to account for the patient’s symptoms and signs, to secure the diagnosis of HF (see below).

Once the diagnosis of HF has been made, it is important to establish the cause, particularly specific correctable causes (Appendix A). Symptoms and signs are important in monitoring a patient at risk of urgent hospital admission and death and merits prompt medical attention.

### 3.6.2 General diagnostic tests in patients with suspected heart failure

In view of the difficulty in grading the evidence for diagnostic tests, all diagnostic recommendations have been given an arbitrary evidence level of C.

### 3.6.3 Essential initial investigations: echocardiogram, electrocardiogram, and laboratory tests

The echocardiogram and electrocardiogram (ECG) are the most useful tests in patients with suspected HF. The echocardiogram provides immediate information on chamber volumes, ventricular systolic and diastolic function, wall thickness, and valve function.7–10,27–34 This information is crucial in determining appropriate treatment (e.g. an ACE inhibitor and beta-blocker for systolic dysfunction or surgery for aortic stenosis). Echocardiography is discussed in detail later (see Section 4). The ECG shows the heart rhythm and electrical conduction, i.e. whether there is sinoatrial disease, atrioventricular (AV) block, or abnormal intraventricular conduction (see Section 5). These findings are also important for decisions about treatment (e.g. rate control and anticoagulation for AF, pacing for bradycardia, or CRT if the patient has LBBB) (see Section 9.2 on treatment). The ECG may also show evidence of LV hypertrophy or Q waves (indicating loss of viable myocardium), giving a possible clue to the aetiology of HF. HF is very unlikely (likelihood <2%) in patients presenting acutely and with a completely normal ECG.2,3,35–38 In patients with a non-acute presentation, a normal ECG has a somewhat lower negative predictive value (likelihood <10–14%).

The information provided by these two tests will permit an initial working diagnosis and treatment plan in the majority of patients. Routine biochemical and haematological investigations are also important, partly to determine whether renin–angiotensin–aldosterone blockade can be initiated safely (renal function and potassium) and to exclude anaemia (which can mimic or aggravate HF) and because they provide other, useful information (see Section 3.6.6).

Other tests are generally only required if the diagnosis remains unclear (e.g. if echocardiographic images are suboptimal or if an unusual cardiac cause, or a non-cardiac cause, of the patient’s condition is suspected) or if further evaluation of the underlying cause of the patient’s cardiac problem is indicated (e.g. perfusion imaging or angiography in suspected CAD or endomyocardial biopsy in certain infiltrating diseases of the myocardium). Special tests are discussed in more detail in Sections 4 and 5.

### 3.6.4 Natriuretic peptides

Because the signs and symptoms of HF are so non-specific, many patients with suspected HF referred for echocardiography are not found to have an important cardiac abnormality. Where the availability of echocardiography is limited, an alternative approach to diagnosis is to measure the blood concentration of a natriuretic peptide, a family of hormones secreted in increased amounts when the heart is diseased or the load on any chamber is increased (e.g. by AF, pulmonary embolism, and some non-cardiovascular conditions, including renal failure).39–42 Natriuretic peptide levels also increase with age, but may be reduced in obese patients.26 A normal natriuretic peptide level in an untreated patient virtually excludes significant cardiac disease, making an echocardiogram unnecessary (investigation for a non-cardiac cause of the patient’s problems is likely to be more productive in such patients).39–42 The use of natriuretic peptides as a ‘rule-out’ test in the diagnosis of HF is discussed in detail elsewhere.39–50 Multiple studies have examined the threshold concentration that excludes HF for the
two most commonly used natriuretic peptides, B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP). The exclusion threshold differs for patients presenting with acute onset or worsening of symptoms (e.g. to a hospital emergency department) and those presenting with a more gradual onset of symptoms.

For patients presenting with acute onset or worsening of symptoms, the optimal exclusion cut-off point is 300 pg/mL.

### Recommendations for the diagnostic investigations in ambulatory patients suspected of having heart failure

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Classa</th>
<th>Levelb</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigations to consider in all patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transthoracic echocardiography is recommended to evaluate cardiac structure and function, including diastolic function (Section 4.1.2), and to measure LVEF to make the diagnosis of HF, assist in planning and monitoring of treatment, and to obtain prognostic information.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>A 12-lead ECG is recommended to determine heart rhythm, heart rate, QRS morphology, and QRS duration, and to detect other relevant abnormalities (Table 5). This information also assists in planning treatment and is of prognostic importance. A completely normal ECG makes systolic HF unlikely.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Measurement of blood chemistry (including sodium, potassium, calcium, urea/blood urea nitrogen, creatinine/estimated glomerular filtration rate, liver enzymes and bilirubin, ferritin/TIBC) and thyroid function is recommended to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) Evaluate patient suitability for diuretic, renin–angiotensin–aldosterone antagonist, and anticoagulant therapy (and monitor treatment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ii) Detect reversible/treatable causes of HF (e.g. hypocalcaemia, thyroid dysfunction) and co-morbidities (e.g. iron deficiency)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(iii) Obtain prognostic information.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>A complete blood count is recommended to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) Detect anaemia, which may be an alternative cause of the patient’s symptoms and signs and may cause worsening of HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ii) Obtain prognostic information.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Measurement of natriuretic peptide (BNP, NT-proBNP, or MR-proANP) should be considered to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) Exclude alternative causes of dyspnoea (if the level is below the exclusion cut-point– see Figure 1–HF is very unlikely)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ii) Obtain prognostic information.</td>
<td>IIA</td>
<td>C</td>
</tr>
<tr>
<td>A chest radiograph (X-ray) should be considered to detect/exclude certain types of lung disease, e.g. cancer (does not exclude asthma/COPD). It may also identify pulmonary congestion/oedema and is more useful in patients with suspected HF in the acute setting.</td>
<td>IIA</td>
<td>C</td>
</tr>
<tr>
<td><strong>Investigations to consider in selected patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMR imaging is recommended to evaluate cardiac structure and function, to measure LVEF, and to characterize cardiac tissue, especially in subjects with inadequate echocardiographic images or where the echocardiographic findings are inconclusive or incomplete (but taking account of cautions/contraindications to CMR).</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Coronary angiography is recommended in patients with angina pectoris, who are considered suitable for coronary revascularization, to evaluate the coronary anatomy.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Myocardial perfusion/ischaemia imaging (echocardiography, CMR, SPECT, or PET) should be considered in patients thought to have CAD, and who are considered suitable for coronary revascularization, to determine whether there is reversible myocardial ischaemia and viable myocardium.</td>
<td>IIA</td>
<td>C</td>
</tr>
<tr>
<td>Left and right heart catheterization is recommended in patients being evaluated for heart transplantation or mechanical circulatory support, to evaluate right and left heart function and pulmonary arterial resistance.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Exercise testing should be considered:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) To detect reversible myocardial ischaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ii) As part of the evaluation of patients for heart transplantation and mechanical circulatory support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(iii) To aid in the prescription of exercise training</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(iv) To obtain prognostic information.</td>
<td>IIA</td>
<td>C</td>
</tr>
</tbody>
</table>

BNP = B-type natriuretic peptide; CAD = coronary artery disease; CMR = cardiac magnetic resonance; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; HF = heart failure; LV = left ventricular; LVEF = left ventricular ejection fraction; MR-proANP = mid-regional pro atrial natriuretic peptide; NT-proBNP = N-terminal pro B-type natriuretic peptide; PET = positron emission tomography; SPECT = single photon emission computed tomography; TIBC = total iron-binding capacity.

aClass of recommendation.

bLevel of evidence.

This list is not exhaustive and other investigations are discussed in the text. Additional investigations may be indicated in patients with suspected acute HF in the emergency department/hospital, including troponins and D-dimer measurement and right heart catheterization.
for NT-proBNP and 100 pg/mL for BNP. In one other study, mid-regional atrial (or A-type) natriuretic peptide (MR-proANP), at a cut-off point of 120 pmol/L, was shown to be non-inferior to these thresholds for BNP and NT-proBNP in the acute setting.51

For patients presenting in a non-acute way, the optimum exclusion cut-off point is 125 pg/mL for NT-proBNP and 35 pg/mL for BNP. The sensitivity and specificity of BNP and NT-proBNP for the diagnosis of HF are lower in non-acute patients. 43–50

### 3.6.5 Chest X-ray

A chest X-ray is of limited use in the diagnostic work-up of patients with suspected HF. It is probably most useful in identifying an alternative, pulmonary explanation for a patient’s symptoms and signs. It may, however, show pulmonary venous congestion or oedema in a patient with HF. It is important to note that significant LV systolic dysfunction may be present without cardiomegaly on the chest X-ray.

### 3.6.6 Routine laboratory tests

In addition to standard biochemical [sodium, potassium, creatinine/estimated glomerular filtration rate (eGFR)] and haematological tests (haemoglobin, haematocrit, ferritin, leucocytes, and platelets), it is useful to measure thyroid-stimulating hormone (thyrotropin) as thyroid disease can mimic or aggravate HF (Table 6). Blood glucose is also worth measuring as undiagnosed diabetes is common in patients with HF. Liver enzymes may also be abnormal in HF (important if considering amiodarone or warfarin).

As well as a pre-treatment check, biochemical monitoring is important after the initiation of renin—angiotensin system blockers, while the dose is being up-titrated (see Section 7.2) and during longer term follow-up, especially if an intercurrent illness leading to sodium and water loss occurs (e.g. diarrhoea and vomiting) or another drug that affects sodium and water homeostasis or renal function is started or the dose altered [e.g. non-steroidal anti-inflammatory drugs (NSAIDs) or diuretics]. Many

### Table 5 Most common abnormalities on the electrocardiogram in heart failure

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Causes</th>
<th>Clinical implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus tachycardia</td>
<td>Decompensated HF, anaemia, fever, hyperthyroidism</td>
<td>Clinical assessment</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>Beta-blockade, digoxin, ivabradine, verapamil, diltiazem Antiarrhythmics</td>
<td>Review drug therapy</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
<td>LABORATORY INVESTIGATION</td>
</tr>
<tr>
<td></td>
<td>Sick sinus syndrome</td>
<td>LABORATORY INVESTIGATION</td>
</tr>
<tr>
<td>Atrial tachycardia/flutter/</td>
<td>Hyperthyroidism, infection, mitral valve disease</td>
<td>Slow AV conduction, anticoagulation, pharmacological cardioversion, electrical cardioversion, catheter ablation</td>
</tr>
<tr>
<td>fibrillation</td>
<td>Decompenated HF, infarction</td>
<td>LABORATORY INVESTIGATION</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>Ischaemia, infarction, cardiomyopathy, myocarditis hypokalaemia, hypomagnesaemia Digitalis overdose</td>
<td>LABORATORY INVESTIGATION</td>
</tr>
<tr>
<td>Myocardial ischaemia/infarction</td>
<td>Coronary artery disease</td>
<td>Echocardiography, troponins, perfusion/viability studies, coronary angiography, electrophysiology testing, ICD</td>
</tr>
<tr>
<td>Q waves</td>
<td>Infarction, hypertrophic cardiomyopathy</td>
<td>Echocardiography, perfusion/viability studies, coronary angiography</td>
</tr>
<tr>
<td>LV hypertrophy</td>
<td>Hypertension, aortic valve disease, hypertrophic cardiomyopathy</td>
<td>Echocardiography/CMR</td>
</tr>
<tr>
<td>AV block</td>
<td>Infarction, drug toxicity, myocarditis, sarcoidosis, genetic cardiomyopathy (laminopathy, desminopathy), Lyme disease</td>
<td>Review drug therapy, evaluate for systemic disease, family history/ genetic testing indicated. Pacemaker or ICD may be indicated.</td>
</tr>
<tr>
<td>Low QRS voltage</td>
<td>Obesity, emphysema, pericardial effusion, amyloidosis</td>
<td>Echocardiography/CMR, chest X-ray; for amyloidosis consider further imaging (CMR, 99mTc-DPD scan) and endomyocardial biopsy</td>
</tr>
<tr>
<td>QRS duration ≥120 ms and</td>
<td>Electrical and mechanical dyssynchrony</td>
<td>Echocardiography, CRT-P, CRT-D</td>
</tr>
<tr>
<td>LBBB morphology</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AV = atrioventricular; CMR = cardiac magnetic resonance; CRT-P = cardiac resynchronization therapy pacemaker; CRT-D = cardiac resynchronization therapy defibrillator; ECG = electrocardiogram; HF = heart failure; ICD = implanta ble cardioverter-defibrillator; LBBB = left bundle branch block; LV = left ventricular. 99mTc-DPD = technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid.
<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Causes</th>
<th>Clinical implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal/kidney impairment</td>
<td>Renal disease</td>
<td>Calculate eGFR</td>
</tr>
<tr>
<td>(creatinine &gt;150 µmol/L/1.7 mg/dL, eGFR &lt;60 mL/mim/1.73 m²)</td>
<td>Renal congestion</td>
<td>Consider reducing ACE inhibitor/ARB or MRA dose (or postpone dose up-titration)</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitor/ARB, MRA</td>
<td>Check potassium and BUN</td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
<td>Consider reducing diuretic dose if dehydrated but if renal congestion, more diuresis may help</td>
</tr>
<tr>
<td></td>
<td>NSAIDs and other nephrotoxic drugs</td>
<td>Review drug therapy</td>
</tr>
<tr>
<td>Anaemia (&lt;13 g/dL/8.0 mmol/L in men, &lt;12 g/dL/7.4 mmol/L in women)</td>
<td>Chronic HF, haemodilution, iron loss or poor utilization, renal failure, chronic disease, malignancy</td>
<td>Diagnostic work-up</td>
</tr>
<tr>
<td></td>
<td>Diuretics and other nephrotoxic drugs</td>
<td>Consider treatment</td>
</tr>
<tr>
<td>Hyponatraemia (&lt;135 mmol/L)</td>
<td>Chronic HF, haemodilution, AVP release, diuretics (especially thiazides) and other drugs</td>
<td>Consider water restriction, adjusting diuretic dosage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ultrafiltration, vasopressin antagonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Review drug therapy</td>
</tr>
<tr>
<td>Hypernatraemia (&gt;150 mmol/L)</td>
<td>Water loss/inadequate water intake</td>
<td>Assess water intake</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diagnostic work-up</td>
</tr>
<tr>
<td>Hypokalaemia (&lt;3.5 mmol/L)</td>
<td>Diuretics, secondary hyperaldosteronism</td>
<td>Risk of arrhythmia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider ACE inhibitor/ARB, MRA, potassium supplements</td>
</tr>
<tr>
<td>Hyperkalaemia (&gt;5.5 mmol/L)</td>
<td>Renal failure, potassium supplement, renin–angiotensin–aldosterone system blockers</td>
<td>Stop potassium supplements/potassium sparing diuretic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduce dose of stop ACE inhibitor/ARB, MRA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Assess renal function and urine pH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk of bradycardia and serious arrhythmias</td>
</tr>
<tr>
<td>Hyperglycaemia (&gt;6.5 mmol/L/117 mg/dL)</td>
<td>Diabetes, insulin resistance</td>
<td>Evaluate hydration, treat glucose intolerance</td>
</tr>
<tr>
<td>Hyperuricaemia (&gt;500 µmol/L/8.4 mg/dL)</td>
<td>Diuretic treatment, gout, malignancy</td>
<td>Allopurinol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduce diuretic dose</td>
</tr>
<tr>
<td>Albumin high (&gt;45 g/L)</td>
<td>Dehydration</td>
<td>Rehydrate</td>
</tr>
<tr>
<td>Albumin low (&lt;30 g/L)</td>
<td>Poor nutrition, renal loss</td>
<td>Diagnostic work-up</td>
</tr>
<tr>
<td>Transaminase increase</td>
<td>Liver dysfunction</td>
<td>Diagnostic work-up</td>
</tr>
<tr>
<td></td>
<td>Liver congestion</td>
<td>Liver congestion</td>
</tr>
<tr>
<td></td>
<td>Drug toxicity</td>
<td>Review drug therapy</td>
</tr>
<tr>
<td>Elevated troponins</td>
<td>Myocyte necrosis</td>
<td>Evaluate pattern of increase (mild increases common in severe HF)</td>
</tr>
<tr>
<td></td>
<td>Prolonged ischemia, severe HF, myocarditis, sepsis, renal failure</td>
<td>Perfusion/ viability studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coronary angiography</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Evaluation for revascularization</td>
</tr>
<tr>
<td>Elevated creatine kinase</td>
<td>Inherited and acquired myopathies (including myositis)</td>
<td>Consider genetic cardiomyopathy ( laminopathy, desminopathy, dystrophinopathy), muscular dystrophies Statin use</td>
</tr>
<tr>
<td>Abnormal thyroid tests</td>
<td>Hyper-/hypothyroidism</td>
<td>Treat thyroid abnormality</td>
</tr>
<tr>
<td></td>
<td>Amiodarone</td>
<td>Reconsider amiodarone use</td>
</tr>
<tr>
<td>Urine analysis</td>
<td>Proteinuria, glycosuria, bacteria</td>
<td>Diagnostic work-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rule out infection, diabetes</td>
</tr>
<tr>
<td>International normalized ratio &gt;3.5</td>
<td>Anticoagulant overdose</td>
<td>Review anticoagulant dose</td>
</tr>
<tr>
<td></td>
<td>Liver congestion/disease</td>
<td>Assess liver function</td>
</tr>
<tr>
<td></td>
<td>Drug interactions</td>
<td>Review drug therapy</td>
</tr>
<tr>
<td>CRP &gt;10 mg/L, neutrophilic leukocytosis</td>
<td>Infection, inflammation</td>
<td>Diagnostic work-up</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; AVP = arginine vasopressin; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; HF = heart failure; MRA = mineralocorticoid receptor antagonist; NSAID = non-steroidal anti-inflammatory drug.
routine laboratory tests provide valuable prognostic information (see Section 6).

3.6.7 Algorithm for the diagnosis of heart failure
An algorithm for the diagnosis of HF or LV dysfunction is shown in Figure 1.

In patients presenting to hospital as an emergency with suspected HF and acute onset of symptoms, early echocardiography is recommended (and immediate echocardiography in shocked or severely haemodynamically compromised patients). If a natriuretic peptide is measured, a high exclusion cut-off point should be used.39–50 In patients presenting non-emergently in primary care, or to a hospital outpatient

Figure 1 Diagnostic flowchart for patients with suspected heart failure—showing alternative 'echocardiography first' (blue) or 'natriuretic peptide first' (red) approaches.
4. The role of cardiac imaging in the evaluation of patients with suspected or confirmed heart failure

Imaging plays a central role in the diagnosis of HF and in guiding treatment. Of the several imaging modalities available, echocardiography is the method of choice in patients with suspected HF for reasons of accuracy, availability (including portability), safety, and cost.\(^{27–34}\) It may be complemented by other modalities, chosen according to their ability to answer specific clinical questions and taking account of contraindications to, and risks of, specific tests (see Table 7).\(^{9,10,52–60}\) All imaging examinations, regardless of type, should be performed only by individuals competent and experienced in the specific technique.\(^{32}\)

4.1 Echocardiography

Echocardiography is a term used here to refer to all cardiac ultrasound imaging techniques, including two-dimensional/three-dimensional echocardiography, pulsed and continuous wave Doppler, colour flow Doppler, and tissue Doppler imaging (TDI).\(^{8,27–34,61–64}\) Echocardiography provides information about cardiac anatomy (e.g. volumes, geometry, mass) and function (e.g. LV function and wall motion, valvular function, right ventricular function, pulmonary artery pressure, pericardium).

4.1.1 Assessment of left ventricular systolic dysfunction

LVEF is not an index of contractility as it depends on volumes, preload, afterload, heart rate, and valvular function, and is not the same as stroke volume. Stroke volume may be maintained by LV dilation in a patient with HF-REF, whereas it may be reduced in patients with HF-PEF and concentric LV hypertrophy. EF may also be preserved (and stroke volume reduced) in patients with significant mitral regurgitation. Thus EF must be interpreted in its clinical context.

The recommended echocardiographic method for measurement of EF is the apical biplane method of discs (the modified Simpson’s rule).\(^{8,27–34,61}\) However, because this method relies on accurate tracing of the endocardial border, use of a contrast agent to better delineate the endocardial border is recommended when image quality is suboptimal (i.e. where <80% of the endocardial border is adequately visualized).\(^{61}\) The Teichholz and Quinones methods of calculating EF from linear dimensions may result in inaccuracies, particularly in patients with regional LV dysfunction; the same is true for another technique for assessing LV systolic function—fractional shortening. These and visual assessment of EF (‘eye-balling’) are not recommended.\(^{61}\) Three-dimensional echocardiography of adequate quality further improves the quantification of ventricular volumes and EF calculation.\(^{62}\) The LV wall motion score index may be an acceptable alternative to EF but is not widely used. Other indices of LV systolic function include AV plane systolic excursion, systolic tissue Doppler velocities, and measurements of deformation (strain and strain rate). Deformation imaging is more sensitive than EF in detecting minor changes in LV systolic function. However, issues of reproducibility and standardization currently limit the routine clinical use of deformation imaging. Stroke volume and cardiac output can also be calculated by measuring the velocity time integral at the LV outflow tract area.

The most common echocardiographic abnormalities seen in patients with HF and their clinical significance are presented in Table 8.

4.1.2 Assessment of left ventricular diastolic dysfunction

LV diastolic dysfunction is thought to be the underlying pathophysiological abnormality in patients with HF-PEF, and thus its identification is fundamental to the diagnosis of this type of HF (Table 9).\(^{7,8,27–34,63,64}\) The Doppler echocardiographic diastolic indices commonly measured in patients with HF are shown in Table 9. Of note, normal values for functional echocardiographic indices of LV diastolic dysfunction may also depend on age, heart rate, and body size.\(^{63,64}\) Importantly, no single echocardiographic parameter is sufficiently accurate and reproducible to be used in isolation to make a diagnosis of LV diastolic dysfunction. Therefore, a comprehensive echocardiographic examination incorporating all relevant two-dimensional and Doppler data is recommended.\(^{8,63,64}\) This should include the evaluation of both structural (LV hypertrophy, LA dilation) and functional abnormalities (Table 1). Tissue Doppler imaging-derived early diastolic myocardial velocities (‘e’), measured at the mitral annulus, allow the assessment of myocardial relaxation. A normal e’ (>8 cm/s septal, >10 cm/s lateral, or >9 cm/s average, measured using real-time pulsed TDI) is very unusual in a patient with HF. The E/e’ ratio correlates with LV filling pressure.\(^{63,64}\) (Table 9).

Thus, echocardiographic evidence of LV diastolic dysfunction may consist of a reduced e’ (e’ average <9 cm/s) or an increased E/e’ ratio (>15), or a combination of these parameters (Table 9). The presence of at least two abnormal measurements and/or AF increases the likelihood of the diagnosis.

4.2 Transoesophageal echocardiography

Transoesophageal echocardiography (TOE) is not needed in routine diagnostic assessment unless the transthoracic ultrasound window is inadequate (e.g. because of obesity, chronic lung disease, ventilated patients) and an alternative modality (e.g. cardiac magnetic resonance (CMR) imaging) is not available or applicable.

TOE is, however, valuable in patients with complex valvular disease (especially mitral disease and prosthetic valves), suspected endocarditis, and in selected patients with congenital heart disease.
### Table 7  Possible applications of various imaging techniques in the diagnosis of HF

<table>
<thead>
<tr>
<th>Remodelling/dysfunction</th>
<th>Echo</th>
<th>CMR</th>
<th>Cath</th>
<th>SPECT</th>
<th>MDCT</th>
<th>PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV: EDV</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>LV: ESV</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>LV: EF</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>LV: Mass</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>RV: EDV</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>RV: ESV</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>RV: EF</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>RV: Mass</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>LV diastolic dysfunction</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dyssynchrony</td>
<td>++</td>
<td>+</td>
<td></td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Aetiology**

| CAD: Ischaemia           | ++++ | +++ | ++++ | ++++ | .    | +++ |
| CAD: Hibernation         | ++++ | ++++ | .    | ++++ | .    | +++ |
| CAD: Scar                | ++   | +++ | .    | ++   | .    | ++  |
| CAD: Coronary anatomy    | .    | .   | +++  | .    | +++  | .   |
| Aortic stenosis          | ++++ | +   | ++++ | .    | .    | -   |
| Regurgitation            | ++++ | ++  | ++   | .    | .    | -   |
| Myocarditis              | ++++ | ++++ | ++++ | .    | .    | -   |
| Sarcoidosis              | ++++ | ++++ | ++++ | .    | .    | -   |
| Hypertrophic CMP: HCM    | ++++ | ++  | ++   | .    | .    | -   |
| Hypertrophic CMP: Amyloidosis | +++ | +++ | ++++ | .    | .    | -   |
| Dilated CMP: Myocarditis | ++++ | ++++ | ++++ | .    | .    | -   |
| Dilated CMP: Eosinophilic syndromes | ++++ | ++++ | ++++ | .    | .    | -   |
| Dilated CMP: Iron: haemochromatosis | ++++ | ++++ | ++++ | .    | .    | -   |
| Dilated CMP: Iron: thalassaemia | ++++ | ++++ | ++++ | .    | .    | -   |
| ARVC                    | ++++ | ++++ | ++++ | .    | +    | -   |
| Restrictive CMP: Pericarditis | ++++ | ++++ | ++++ | .    | .    | -   |
| Restrictive CMP: Amyloidosis | ++++ | ++++ | ++++ | .    | .    | -   |
| Restrictive CMP: Endomyocardial fibrosis | ++++ | ++++ | ++++ | .    | .    | -   |
| Restrictive CMP: Anderson–Fabry | ++++ | ++++ | ++++ | .    | .    | -   |
| Unclassified CMP         | Takotsubo-CMP | ++++ | ++++ | .    | .    | -   |

**Main advantages**

<table>
<thead>
<tr>
<th>Wide availability</th>
<th>Portability</th>
<th>No radiation</th>
<th>Relatively low cost</th>
<th>Good quality images</th>
<th>No radiation</th>
<th>Good availability</th>
<th>Good quality images</th>
<th>Reasonable availability</th>
<th>High quality images</th>
<th>Limited availability</th>
<th>Good quality images</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echo</td>
<td>Limited availability</td>
<td>Contraindications: Family history, obesity, claustrophobia</td>
<td>Radiation invasive</td>
<td>Radiation</td>
<td>Radiation</td>
<td>Image quality limited if arrhythmia</td>
<td>Radiation</td>
<td>Limited availability</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Main disadvantages**

| Echo window needed | Limited availability | Contraindications: Family history, obesity, claustrophobia | Radiation invasive | Radiation | Radiation | Image quality limited if arrhythmia | Radiation | Limited availability |

Selection of a test in daily practice should consider availability, local expertise, advantages/disadvantages, and, in the case of several questions to address, which test could best answer several of them.

ARVC = arrhythmogenic right ventricular cardiomyopathy; CAD = coronary artery disease; Cath = cardiac catheterization; CMP = cardiomyopathy; CMR = cardiac magnetic resonance; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; HCM = hypertrophic cardiomyopathy; LV = left ventricular; MDCT = multidetector computed tomography; PET = positron emission tomography; RV = right ventricular; SPECT = single photon emission computed tomography.

aStress (dobutamine) imaging.

bFractional flow reserve or ‘Doppler’ flow reserve measurements.

bIncluding measurements of aortic annulus for transcatheter aortic valve implantation.

cEndomyocardial biopsy.

dHemodynamic evaluation (constriction).

eDescribes disease activity by contrast-enhanced CMR.

fCalcifications.

gGood quality irrespective of patient habitus.

hExcellent attenuation correction.

iForeign metallic bodies in specific locations (e.g. in the eye) and electronic devices (some pacemakers are MR-compatible); relative contra-indication: claustrophobia.
TOE is also used to check for thrombus in the left atrial appendage of patients with AF.

4.3 Stress echocardiography

Exercise or pharmacological stress echocardiography may be used to identify the presence and extent of inducible ischaemia and to determine whether non-contracting myocardium is viable (see Section 13).34 This technique may also be useful in evaluating patients with suspected severe aortic stenosis, reduced EF, and a low transvalvular gradient (see Section 13.3.1). Diastolic stress testing is an emerging procedure to identify HF-PEF in patients with HF symptoms during physical activity, normal EF, and inconclusive diastolic function parameters at rest.63

4.4 Cardiac magnetic resonance

CMR is a non-invasive technique that provides most of the anatomical and functional information available from echocardiography, including evaluation of ischaemia and viability, as well as additional assessments.32,57,65 CMR is regarded as the gold standard with respect to accuracy and reproducibility of volumes, mass, and wall motion. Because CMR yields good image quality in most patients, it is the best alternative imaging modality in patients with non-diagnostic echocardiographic studies.

CMR is particularly valuable in identifying inflammatory and infiltrative conditions, and in predicting prognosis in patients with these (Table 7).65 CMR is also useful in the work-up of patients with suspected cardiomyopathy, arrhythmias, suspected cardiac tumours (or cardiac involvement by tumour), or pericardial diseases, and is the imaging method of choice in patients with complex congenital heart disease.66

Limitations include lack of availability, inability to image patients with certain metallic implants (including many, but not all, cardiac devices), and cost. Also, the accuracy of functional analysis is limited in patients with atrial arrhythmias. Some patients cannot tolerate the procedure, often because of claustrophobia. Linear gadolinium chelates are contraindicated in individuals with a GFR < 30 mL/min/m² because they cause the rare condition known as nephrogenic systemic fibrosis.

| Table 8 Common echocardiographic abnormalities in patients with heart failure |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| **Measurement** | **Abnormality** | **Clinical implications** |
| Parameters related to systolic function |
| LV ejection fraction | Reduced (<50%) | LV global systolic dysfunction |
| LV fractional shortening | Reduced (<25%) | LV radial systolic dysfunction |
| LV regional function | Hypokinesia, akinesia, dyskinesis | Myocardial infarction/ischaemia Cardiomyopathy, myocarditis |
| LV end-diastolic size | Increased (diameter ≥60 mm, >32 mm²/m², volume >97 mL/m²) | Volume overload HF likely |
| LV end-systolic size | Increased (diameter >45 mm/25 mm²/m², volume >43 mL/m²) | Volume overload HF likely |
| LV outflow tract velocity time integral | Reduced (<15 cm) | Reduced LV stroke volume |
| Parameters related to diastolic function |
| LV diastolic dysfunction parameters | Abnormalities of the mitral inflow pattern, tissue velocities (e’) or the E/e’ ratio | Indicate LV diastolic dysfunction degree and suggest level of filling pressure |
| Left atrial volume index | Increased (volume >34 mL/m²) | Increased LV filling pressure (past or present) Mitral valve disease |
| LV mass index | Increased; >95 g/m² in women and >115 g/m² in men | Hypertension, aortic stenosis, hypertrophic cardiomyopathy |
| Parameters related to valvular function |
| Valvular structure and function | Valvular stenosis or regurgitation (especially aortic stenosis and mitral regurgitation) | May be the cause of HF or a complicating factor or the result of HF (secondary mitral regurgitation) Assess dysfunction severity and haemodynamic consequences Consider surgery |
| Other parameters |
| RV function (e.g. TAPSE) | Reduced (TAPSE <16 mm) | RV systolic dysfunction |
| Tricuspid regurgitation peak velocity | Increased (>3.4 m/s) | Increased RV systolic pressure |
| Systolic pulmonary artery pressure | Increased (>50 mmHg) | Pulmonary hypertension likely |
| Inferior vena cava | Dilated, with no respiratory collapse | Increased right atrial pressure RV dysfunction, volume overload Pulmonary hypertension possible |
| Pericardium | Effusion, haemopericardium, calcification | Consider tamponade, malignancy, systemic diseases, acute or chronic pericarditis, constrictive pericarditis |

E/e’ = ratio of the mitral inflow E wave to the tissue Doppler e’ wave; HF = heart failure; LV = left ventricular; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion.
4.5 Single-photon emission computed tomography and radionuclide ventriculography

Single-photon emission computed tomography (SPECT) may be useful in assessing ischaemia and viability if CAD is suspected, and provides prognostic as well as diagnostic information (Table 7). Gated SPECT can also yield information on ventricular volumes and function, but exposes the patient to ionizing radiation.

4.6 Positron emission tomography imaging

Positron emission tomography (PET) [alone or with computed tomography (CT)] may be used to assess ischaemia and viability, but the flow tracers (N-13 ammonia or O-15 water) require an on-site cyclotron. Rubidium is an alternative tracer for ischaemia testing with PET, which can be produced locally at relatively low cost (Table 7). Lack of availability, radiation exposure, and cost are the main limitations.

4.7 Coronary angiography

Coronary angiography should be considered in patients with angina pectoris or a history of cardiac arrest if the patient is otherwise suitable for coronary revascularization. Angiography should also be considered in patients with evidence of reversible myocardial ischaemia on non-invasive testing, especially if the EF is reduced (because coronary artery bypass surgery may be beneficial) (Section 13). Non-invasive assessment of myocardial viability may also be carried out before angiography as some observational data show that coronary angiography may be of little, if any, benefit and may confer considerable risk, in the absence of significant viability. In cases where ischaemia information is lacking, fractional flow reserve gives information about the haemodynamic relevance of lesions. Coronary angiography may be required, urgently, in selected patients with acute HF (AHF) (shock or acute pulmonary oedema), particularly those with an associated acute coronary syndrome (see Section 12.7.1 and revascularization guidelines). Coronary angiography may also be indicated in patients with valve disease when surgical correction is planned.

5. Other investigations

5.1 Cardiac catheterization and endomyocardial biopsy

In patients with suspected constrictive or restrictive cardiomyopathy, cardiac catheterization used in combination with other non-invasive imaging techniques may help to establish the correct diagnosis (see Table 7). In patients with suspected myocarditis and infiltrative diseases (e.g. amyloidosis, see Table 7), endomyocardial biopsy may be needed to confirm the diagnosis. The use of this procedure is described in detail in other guidelines.
5.2 Exercise testing

Exercise testing allows objective evaluation of exercise capacity and exertional symptoms, such as dyspnoea and fatigue. The 6-min walk test and a variety of treadmill and bicycle protocols are available. Gas exchange analysis helps differentiate between cardiac and respiratory causes of dyspnoea, shows whether the anaerobic threshold has been reached, and provides prognostic information (peak oxygen consumption is often measured as part of the assessment of candidates for heart transplantation). A normal exercise capacity in a patient not receiving treatment effectively excludes the diagnosis of symptomatic HF, although it must be remembered that there is a poor correlation between exercise capacity and resting haemodynamic measures, including EF.

5.3 Genetic testing

The emerging role of genetic testing in ‘idiopathic’ dilated and hypertrophic cardiomyopathy is described in detail elsewhere. Currently this is recommended in patients with dilated cardiomyopathy and AV block or a family history of premature unexpected sudden death, as a prophylactic implantable cardioverter-defibrillator (ICD) may be indicated.

5.4 Ambulatory electrocardiographic monitoring

Ambulatory ECG monitoring is valuable in the assessment of patients with symptoms suggestive of an arrhythmia or bradycardia (e.g. palpitations or syncope) and in monitoring ventricular rate control in patients with AF. It is useful for identifying the type, frequency, and duration of atrial and ventricular arrhythmias, silent episodes of ischaemia and bradycardia, and conduction disturbances, which may cause or exacerbate HF.

6. Prognosis

Many variables provide prognostic information (Appendix B), although most of this can be obtained from readily available data such as age, aetiology, NYHA class, EF, key co-morbidities (renal dysfunction, diabetes, anaemia, hyperuricaemia), and plasma natriuretic peptide concentration. Clearly these variables change over time, as does prognosis. Assessment of prognosis is particularly important when counselling patients about devices and surgery (including transplantation) and in planning end-of-life care with patients, their family, and caregivers.

7. Pharmacological treatment of heart failure with reduced ejection fraction (systolic heart failure)

7.1 Objectives in the management of heart failure

The goals of treatment in patients with established HF are to relieve symptoms and signs (e.g. oedema), prevent hospital admission, and improve survival. Although the focus of clinical trials was previously mortality, it is now recognized that preventing HF hospitalization is important for patients and healthcare systems. Reductions in mortality and hospital admission rates both reflect the ability of effective treatments to slow or prevent progressive worsening of HF. This is often accompanied by reverse LV remodelling and a reduction in circulating natriuretic peptide concentrations.

The relief of symptoms, improvement in quality of life, and increase in functional capacity are also of the utmost importance to patients, but they have not been the primary outcome in most trials. This is in part because they are difficult to measure and partly because some treatments previously shown to improve these outcomes also decreased survival. However, effective pharmacological therapies and CRT improve these outcomes, as well as mortality and hospitalization.

Figure 2 shows a treatment strategy for the use of drugs (and devices) in patients with HF-REF; the recommendations for each treatment are summarized below. Three neurohumoral antagonists—an ACE inhibitor [or angiotensin receptor blocker (ARB)], a beta-blocker, and an MRA—are fundamentally important in modifying the course of systolic HF and should at least be considered in every patient. They are commonly used in conjunction with a diuretic given to relieve the symptoms and signs of congestion. The following text summarizes the evidence supporting the recommendations in this section, in Appendices C–E and in Figure 2. The recommended doses of these disease-modifying medications are given in Table 14. The recommendations given in Section 7.4 summarize drugs that should be avoided in patients with HF-REF.

7.2 Treatments recommended in potentially all patients with systolic heart failure

7.2.1 Angiotensin-converting enzyme inhibitors and beta-blockers

The pivotal trials with beta-blockers were conducted in patients with continuing symptoms and a persistently low EF, despite treatment with an ACE inhibitor and, in most cases, a diuretic. Despite this, there is consensus that these treatments are complementary and that a beta-blocker and an ACE inhibitor should both be started as soon as possible after diagnosis of HF-REF. This is in part because ACE inhibitors have a modest effect on LV remodelling whereas beta-blockers often lead to a substantial improvement in EF. Furthermore, beta-blockers are anti-ischaemic, are probably more effective in reducing the risk of sudden cardiac death, and lead to a striking and early reduction in overall mortality.

Key evidence supporting the use of angiotensin-converting enzyme inhibitors

- Two key randomized controlled trials [Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) and Studies of Left Ventricular Dysfunction (SOLVD)-Treatment] assigned ~2800 patients with mild to severely symptomatic HF to placebo or enalapril. Most were also treated with a diuretic and digoxin, but <10% of patients in each trial were treated with a beta-blocker. In CONSENSUS, which enrolled patients
Diuretics to relieve symptoms/signs of congestion

ACE inhibitor (or ARB if not tolerated)

ADD a beta-blocker

Still NYHA class II–IV?

Yes

ADD a MR antagonist

Still NYHA class II–IV?

No

LVEF ≤35%?

Yes

Sinus rhythm and HR ≥70 beats/min?

ADD ivabradine

Still NYHA class II–IV and LVEF ≤35%?

No

QRS duration ≥120 ms?

Yes

Consider CRT-P/CRT-D

Consider ICD

No

Yes

No

Still NYHA class II–IV?

No further specific treatment.

Continue in disease-management programme

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; H-ISDN = hydralazine and isosorbide dinitrate; HR = heart rate; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MR antagonist = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.

a Diuretics may be used as needed to relieve the signs and symptoms of congestion (see Section 7.5) but they have not been shown to reduce hospitalization or death.
b Should be titrated to evidence-based dose or maximum tolerated dose below the evidence-based dose.
c Asymptomatic patients with an LVEF ≤35% and a history of myocardial infarction should be considered for an ICD.
d If mineralocorticoid receptor antagonist not tolerated, an ARB may be added to an ACE inhibitor as an alternative.
e European Medicines Agency has approved ivabradine for use in patients with a heart rate ≥75 b.p.m. May also be considered in patients with a contraindication to a beta-blocker or beta-blocker intolerance.
f Not indicated in NYHA class IV.
g Digoxin may be used earlier to control the ventricular rate in patients with atrial fibrillation—usually in conjunction with a beta-blocker.
h The combination of hydralazine and isosorbide dinitrate may also be considered earlier in patients unable to tolerate an ACE inhibitor or an ARB.

Figure 2 Treatment options for patients with chronic symptomatic systolic heart failure (NYHA functional class II–IV).
Pharmacological treatments indicated in potentially all patients with symptomatic (NYHA functional class II–IV) systolic heart failure

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Classa</th>
<th>Levelb</th>
<th>Refc</th>
</tr>
</thead>
<tbody>
<tr>
<td>An ACE inhibitor is recommended, in addition to a beta-blocker, for all patients with an EF ≤40% to reduce the risk of HF hospitalization and the risk of premature death.</td>
<td>I</td>
<td>A</td>
<td>87–91</td>
</tr>
<tr>
<td>A beta-blocker is recommended, in addition to an ACE inhibitor (or ARB if ACE inhibitor not tolerated), for all patients with an EF ≤40% to reduce the risk of HF hospitalization and the risk of premature death.</td>
<td>I</td>
<td>A</td>
<td>92–98</td>
</tr>
<tr>
<td>An MRA is recommended for all patients with persisting symptoms (NYHA class II–IV) and an EF ≤35%, despite treatment with an ACE inhibitor (or an ARB if an ACE inhibitor is not tolerated) and a beta-blocker, to reduce the risk of HF hospitalization and the risk of premature death.</td>
<td>I</td>
<td>A</td>
<td>99, 100</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; EF = ejection fraction; HF = heart failure; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.

aClass of recommendation.

bLevel of evidence.

cReferences.

with severe HF, 53% of patients were treated with spironolactone.

- Both of these two RCTs showed that ACE inhibitor treatment reduced mortality [relative risk reduction (RRR) 27% in CONSENSUS and 16% in SOLVD-Treatment]. In SOLVD-Treatment there was also an RRR of 26% in HF hospitalization. These benefits were additional to those gained with conventional treatment at that time (i.e. a diuretic, digoxin, and spironolactone).

- The absolute risk reduction (ARR) in mortality in patients with mild or moderate HF (SOLVD-Treatment) was 4.5%, equating to a number needed to treat (NNT) of 22 to postpone one death (over an average of 41 months). The equivalent figures for severe HF (CONSENSUS) were 14.6% for ARR and 7 for NNT (over an average of 6 months).

- These findings are supported by a meta-analysis of smaller, short-term, placebo-controlled randomized controlled trials (RCTs), which showed a clear reduction in mortality within only 3 months.99 These RCTs also showed that ACE inhibitors improve symptoms, exercise tolerance, quality of life, and exercise performance.

- In the Assessment of Treatment with Lisinopril And Survival (ATLAS) trial,90 3164 patients with mainly moderate to severe HF were randomized to low- or high-dose lisinopril. There was an RRR of 15% in the risk of death or HF hospitalization in the high-dose lisinopril group compared with the low-dose lisinopril group.

- Additional support for the use of ACE inhibitors comes from an RCT in patients with a low EF but no symptoms of HF (‘asymptomatic LV systolic dysfunction’) and three large (5966 patients in total) placebo-controlled, randomized, outcome trials in patients with HF, LV systolic dysfunction, or both after acute myocardial infarction.91 In the SOLVD-Prevention trial (which randomized 4228 patients with asymptomatic LV systolic dysfunction), there was a 20% RRR in death or HF hospitalization. In the myocardial infarction trials, which used captopril [Survival and Ventricular Enlargement (SAVE)], ramipril [Acute Infarction Ramipril Efficacy (AIRE)], and trandolapril [TRAndolapril Cardiac Evaluation (TRACE)], there was a 26% RRR in death and a 27% RRR in death or HF hospitalization.101

- ACE inhibitors occasionally cause worsening of renal function, hyperkalaemia, symptomatic hypotension, cough, and, rarely, angioedema. An ACE inhibitor should only be used in patients with adequate renal function (creatinine ≤221 μmol/L or ≤2.5 mg/dL or eGFR ≥30 mL/min/1.73 m²) and a normal serum potassium level (see Appendix C).

Practical guidance on how to use ACE inhibitors is given in Appendix C.102

Key evidence supporting the use of beta-blockers

- More RCTs have been undertaken with beta-blockers than with ACE inhibitors in patients with HF.

- Three key trials [Cardiac Insufficiency Bisoprolol Study II (CIBIS II), Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS), and Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)] randomized nearly 9000 patients with mild to severely symptomatic HF to placebo or a beta-blocker (bisoprolol, carvedilol, or metoprolol succinate CR/XL).92–96 More than 90% of the patients were on an ACE inhibitor or ARB.

- Each of these three trials showed that beta-blocker treatment reduced mortality (RRR ~34% in each trial) and HF hospitalization (RRR 28–36%) within ~1 year of starting treatment. There was also an also an improvement in self-reported patient well-being in COPERNICUS and MERIT-HF. These benefits were additional to those gained with conventional treatment, including an ACE inhibitor.

- The ARR in mortality (after 1 year of treatment) in patients with mild to moderate HF (CIBIS II and MERIT-HF combined) was 4.3%, equating to an NNT (for 1 year to postpone one death) of 23. The equivalent figures for severe HF (COPERNICUS) were ARR 7.1% and NNT 14.

- These findings are supported by another placebo-controlled RCT [Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure (SENIORS)] in 2128 elderly (≥70 years) patients, 36% of whom had an LVEF >35%. Treatment with nebivolol resulted in an RRR of 14% in the primary composite endpoint of death or cardiovascular hospitalization, but did not reduce mortality.97
The findings of these trials were also supported by an earlier programme of studies with carvedilol (US carvedilol studies), a meta-analysis of other small beta-blocker trials, and a placebo-controlled RCT in 1959 patients with an LVEF $\leq 0.40$ after acute myocardial infarction in which the RRR in mortality with carvedilol was 23% during a mean follow-up of 1.3 years.98

One large RCT [Beta-Blocker Evaluation of Survival Trial (BEST)] with bucindolol, a beta-blocker with partial agonist properties, did not show a significant reduction in mortality, though its findings were generally consistent with the above studies.103

Another RCT [Carvedilol or Metoprolol European Trial (COMET)] showed that carvedilol increased survival compared with short-acting metoprolol tartrate (different from the long-acting succinate formulation used in MERIT-HF).104

Beta-blockers should usually be initiated in stable patients, and used only with caution in recently decompensated patients (and only initiated in hospital in these patients). Recently decompensated patients were, however, safely initiated on beta-blocker treatment in COPERNICUS.105

Continuation of beta-blocker treatment during an episode of decompensation has been shown in an RCT to be safe, although dose reduction may be necessary.106 Temporary discontinuation is advised in shocked or severely hypoperfused patients. Re-institution of treatment should be attempted before discharge.

Practical guidance on how to use beta-blockers is given in Appendix D.102

7.2.2 Mineralocorticoid/aldosterone receptor antagonists

Spironolactone and eplerenone block receptors that bind aldosterone and other corticosteroids, and are best characterized as MRAs. Although patients in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF)100 were required to have additional features elevating risk (recent cardiovascular hospitalization or elevated natriuretic peptide concentration), the benefits of MRAs probably extend to all patients with systolic HF, particularly as the two RCTs in chronic HF are supported by an additional RCT in patients with acute myocardial infarction.99,100,107

Key evidence supporting the use of mineralocorticoid receptor antagonists

- The Randomized Aldactone Evaluation Study (RALES) trial99 was undertaken with the MRA spironolactone in patients with severe HF.
- In RALES, 1663 patients with an EF $\leq 35\%$ and in NYHA functional class III (having been in class IV within the past 6 months) were randomized to placebo or spironolactone 25–50 mg once daily added to conventional treatment. At the time this trial was conducted, beta-blockers were not widely used to treat HF, and only 11% were treated with a beta-blocker.
- Treatment with spironolactone led to an RRR in death of 30% and an RRR in HF hospitalization of 35% within an average of 2 years of starting treatment. These benefits were additional to those gained with conventional treatment, including an ACE inhibitor.
- The ARR in mortality (after a mean of 2 years of treatment) in patients with severe HF was 11.4%, equating to an NNT (for 2 years to postpone one death) of 9.
- More recently the EMPHASIS-HF trial100 was undertaken in patients with systolic HF and mild symptoms.
- In EMPHASIS-HF, 2737 patients aged $\geq 55$ years with NYHA functional class II symptoms and an EF $\leq 30\%$ ($\leq 35\%$ if the QRS duration was $>130$ ms) were enrolled. Patients had to have either experienced a cardiovascular hospitalization within the previous 6 months or have an elevated plasma natriuretic peptide concentration and be treated with an ACE inhibitor, ARB, or both, and a beta-blocker.
- Treatment with eplerenone (up to 50 mg once daily) led to an RRR of 37% in cardiovascular death or HF hospitalization. Reductions were also seen in rates of death from any cause (24%), cardiovascular death (24%), hospitalization for any reason (23%), and HF hospitalization (42%). These benefits

### Table 14 Evidence-based doses of disease-modifying drugs used in key randomized trials in heart failure (or after myocardial infarction)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>ACE inhibitor</th>
<th>Beta-blocker</th>
<th>ARB</th>
<th>MRA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Starting dose (mg)</td>
<td>Target dose (mg)</td>
<td>Starting dose (mg)</td>
<td>Target dose (mg)</td>
</tr>
<tr>
<td>Captoprilb</td>
<td>6.25 t.i.d.</td>
<td>50 t.i.d.</td>
<td>Carvedilol</td>
<td>3.125 b.i.d.</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 b.i.d.</td>
<td>10–20 b.i.d.</td>
<td>Metoprolol succinate (CR/XL)</td>
<td>12.5/25 o.d.</td>
</tr>
<tr>
<td>Lisinoprilb</td>
<td>2.5–50 o.d.</td>
<td>20–35 o.d.</td>
<td>Nebivololo</td>
<td>1.25 o.d.</td>
</tr>
<tr>
<td>Ramipril</td>
<td>2.5 o.d.</td>
<td>5 b.i.d.</td>
<td>ARB</td>
<td>4 or 8 o.d.</td>
</tr>
<tr>
<td>Trandolaprilb</td>
<td>0.5 o.d.</td>
<td>4 o.d.</td>
<td>Valso</td>
<td>40 b.i.d.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Losartanb,c</td>
<td>50 o.d.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MRA</td>
<td>Eplerenone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Spironolactone</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; b.i.d. = bis in die (twice daily); MRA = mineralocorticoid receptor antagonist; o.d. = omni die (once every day); t.i.d. = ter in die (three times daily).

Indicates an ACE inhibitor where the dosing target is derived from post-myocardial infarction trials.

Indicates drugs where a higher dose has been shown to reduce morbidity–mortality compared with a lower dose of the same drug, but there is no substantive placebo-controlled randomized controlled trial and the optimum dose is uncertain.

Indicates a treatment not shown to reduce cardiovascular or all-cause mortality in patients with heart failure or after acute myocardial infarction (or shown to be non-inferior to a treatment that does).
were obtained within an average of 21 months of starting treat-
ment and were additional to those gained with conventional
treatment, including an ACE inhibitor and beta-blocker.

- The ARR in the primary composite mortality–morbidity end-
point in patients with mild symptoms was 7.7%, equating to
an NNT (for an average of 21 months to postpone one
event) of 13. The ARR in mortality was 3%, equating to an
NNT of 33.

- These findings are supported by another RCT [Eplerenone
Post-Acute Myocardial Infarction Heart Failure Efficacy and Sur-
vival Study (EPHESUS)], which enrolled 6632 patients 3–14
days after acute myocardial infarction with an EF ≤40% and
HF or diabetes. Patients were randomized to placebo or
eplerenone 25–50 mg once daily added to conventional treat-
ment including an ACE inhibitor/ARB (87%) and a beta-blocker
(75%). Treatment with eplerenone led to an RRR in death of
15%.

- Spironolactone and eplerenone can cause hyperkalaemia and
worsening renal function, which were uncommon in the
RCTs, but may occur more frequently in ordinary clinical prac-
tice, especially in the elderly. Both should only be used in
patients with adequate renal function and a normal serum po-
tassium concentration; if either is used, serial monitoring of
serum electrolytes and renal function is mandatory.

### Other treatments with less-certain benefits in patients with symptomatic (NYHA class II–IV) systolic heart failure

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class†</th>
<th>Level‡</th>
<th>Ref §</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARB</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommended to reduce the risk of HF hospitalization and the risk of premature death in patients with an EF ≤40% and unable to tolerate an ACE inhibitor because of cough (patients should also receive a beta-blocker and an MRA).</td>
<td>I</td>
<td>A</td>
<td>108, 109</td>
</tr>
<tr>
<td>Recommended to reduce the risk of HF hospitalization in patients with an EF ≤40% and persisting symptoms (NYHA class II–IV) despite treatment with an ACE inhibitor and a beta-blocker who are unable to tolerate an MRA.</td>
<td>I</td>
<td>A</td>
<td>110, 111</td>
</tr>
</tbody>
</table>

**Ivabradine**

| Should be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF ≤35%, a heart rate remaining ≥70 b.p.m., and persisting symptoms (NYHA class II–IV) despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and an MRA (or ARB). | IIa     | B      | 112   |
| May be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF ≤35% and a heart rate ≥70 b.p.m. who are unable to tolerate a beta-blocker. Patients should also receive an ACE inhibitor (or ARB) and an MRA (or ARB). | IIb     | C      | –     |

**Digoxin**

| May be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF ≤45% who are unable to tolerate a beta-blocker (ivabradine is an alternative in patients with a heart rate ≥70 b.p.m.). Patients should also receive an ACE inhibitor (or ARB) and an MRA (or ARB). | IIb     | B      | 113   |
| May be considered to reduce the risk of HF hospitalization in patients with an EF ≤45% and persisting symptoms (NYHA class II–IV) despite treatment with a beta-blocker, ACE inhibitor (or ARB), and an MRA (or ARB). | IIb     | B      | 113   |

**H-ISDN**

| May be considered as an alternative to an ACE inhibitor or ARB, if neither is tolerated, to reduce the risk of HF hospitalization and risk of premature death in patients with an EF ≤45% and dilated LV (or EF ≤35%). Patients should also receive a beta-blocker and an MRA. | IIb     | B      | 114, 115 |
| May be considered to reduce the risk of HF hospitalization and risk of premature death in patients with an EF ≤45% and dilated LV (or EF ≤35%) and persisting symptoms (NYHA class II–IV) despite treatment with a beta-blocker, ACE inhibitor (or ARB), and an MRA (or ARB). | IIb     | B      | 116 |

**An n-3 PUFA** preparation may be considered to reduce the risk of death and the risk of cardiovascular hospitalization in patients treated with an ACE inhibitor (or ARB), beta-blocker, and an MRA (or ARB).

| An n-3 PUFA preparation may be considered to reduce the risk of death and the risk of cardiovascular hospitalization in patients treated with an ACE inhibitor (or ARB), beta-blocker, and an MRA (or ARB). | IIb     | B      | 117   |

---

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CHARM-Added = Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity-Added; EF = ejection fraction; HF = heart failure; H-ISDN = hydralazine and isosorbide dinitrate; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; PUFA = polyunsaturated fatty acid.

†Class of recommendation.

‡Level of evidence.

§References.

In the CHARM-Added trial, candesartan also reduced cardiovascular mortality.

European Medicines Agency has approved ivabradine for use in patients with a heart rate ≥75 b.p.m.

Preparation studied in cited trial; the GISSI-HF trial had no EF limit.
• Spironolactone can also cause breast discomfort and enlargement in men (10% compared with 1% on placebo, in RALES); this side effect is infrequent with eplerenone.

Practical guidance on how to use MRAs is given in Appendix E.

7.2.3 Other treatments recommended in selected patients with systolic heart failure

This section describes other treatments that are valuable in patients with systolic HF. They have not, however, been shown clearly to reduce all-cause mortality [or in the case of hydralazine and isosorbide dinitrate (H-ISDN), this has only been clearly shown in African-Americans]. Most of these drugs have shown convincing benefits in terms of symptom reduction, HF hospitalization, or both, and are useful alternative or additional treatments in patients with HF.

7.2.4 Angiotensin receptor blockers

ARBs remain recommended as an alternative in patients intolerant of an ACE inhibitor. However, ARBs are no longer the first-choice recommendation in patients with HF and an EF <40% who remain symptomatic despite optimal treatment with an ACE inhibitor and beta-blocker. This is because in EMPHASIS-HF, eplerenone led to a larger reduction in morbidity–mortality than seen in the ARB ‘add-on’ trials discussed below, and because in both the Randomized Aldactone Evaluation Study (RALES) and EMPHASIS-HF, MRA treatment reduced all-cause mortality, whereas ARB ‘add-on’ treatment did not.

Key evidence

• Two key placebo-controlled RCTs [Valsartan Heart Failure Trial (Val-HeFT) and CHARM-Added] randomized ~7600 patients with mild to severely symptomatic HF to placebo or an ARB (valsartan and candesartan), added to an ACE inhibitor (in 93% of patients in Val-HeFT and all patients in CHARM-Added). In addition, 35% of patients in Val-HeFT and 55% in CHARM-Added were treated with a beta-blocker.

• Each of these two trials showed that ARB treatment reduced the risk of HF hospitalization (RRR 24% in Val-HeFT and 17% in CHARM-Added) but not all-cause hospitalization. There was a 16% RRR in the risk of cardiovascular death with candesartan in CHARM-Added. These benefits were additional to those gained with conventional treatment, including a diuretic, digoxin, an ACE inhibitor, and a beta-blocker (but few patients were taking an MRA).

• The ARR in the primary composite mortality–morbidity endpoint in patients with mild to moderate HF was 4.4%, equating to an NNT (for an average of 41 months to postpone one event) of 23 in CHARM-Added. The equivalent figures for Val-HeFT were ARR 3.3% and NNT 30 (over an average of 23 months).

• The CHARM trials and Val-HeFT also showed that ARBs improve symptoms and quality of life. Other trials showed that these agents improve exercise capacity.

• CHARM-Alternative was a placebo-controlled RCT with candesartan in 2028 patients with an LVEF ≤40%, intolerant of an ACE inhibitor. Treatment with candesartan resulted in an RRR of cardiovascular or HF hospitalization of 23% (ARR 7%, NNT 14, over 34 months of follow-up). Valsartan was also beneficial in the subset of patients in Val-HeFT not treated with an ACE inhibitor.

• Another trial [Evaluation of Losartan In The Elderly (ELITE) II] failed to show that losartan 50 mg daily was as effective as captopril 50 mg three times daily. However, a subsequent RCT [Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan (HEAAL)] showed that 150 mg daily of losartan was superior to 50 mg daily, supporting the similar findings of the Assessment of Treatment with Lisinopril And Survival (ATLAS) trial with the ACE inhibitor lisinopril—see above. In HEAAL there was an RRR of 10% in death or HF hospitalization in the high-dose losartan group (P = 0.027) over a median follow-up of 4.7 years. The results from these two trials, ATLAS and HEAAL, indicate that more benefit is obtained from using higher doses of renin–angiotensin system blockers and underscore the importance of attaining, if possible, the target doses proven to be of benefit in the key RCTs.

• Additional support for the use of ARBs comes from the Valsar- tan In Acute myocardial infarction trial (VALIANT), an RCT in which 14 703 patients with HF, LV systolic dysfunction, or both after acute myocardial infarction were assigned to treatment with captopril, valsartan, or the combination. Valsartan was found to be non-inferior to captopril. In a similar trial [Optimal Therapy in Myocardial infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL)] losartan 50 mg once daily did not demonstrate non-inferiority when compared with captopril.

Practical guidance on how to use an ARB is given in Appendix C.

7.2.5 Ivabradine

Ivabradine is a drug that inhibits the I f channel in the sinus node. Its only known pharmacological effect is to slow the heart rate in patients in sinus rhythm (it does not slow the ventricular rate in AF).

Key evidence

• The Systolic Heart failure treatment with the I f channel blocker Ivabradine (SHIFT) enrolled 6588 patients in NYHA functional class II–IV, sinus rhythm with a rate of ≥70 b.p.m., and an EF ≤35%. Patients were also required to have had a HF hospitalization in the previous 12 months. They were randomized to ivabradine (up-titrated to a maximal dosage of 7.5 mg twice daily) or placebo, added to a diuretic (in 84%), digoxin (22%), an ACE inhibitor (79%), an ARB (14%), a beta-blocker (90%), and an MRA (60%). Only 26% of patients were, however, on full-dose beta-blocker. The median follow-up was 23 months. The RRR in the primary composite outcome of cardiovascular death or HF hospitalization was 18% (P < 0.0001); the reduction in cardiovascular death (or all-cause death) was not significant, but the RRR in HF hospitalization was 26%. The ARR in the primary composite mortality–morbidity endpoint was 4.2%, equating to an NNT (for an average of 23 months to postpone one event) of 24. Ivabradine also improved LV function and quality of life.
• Five per cent of patients on ivabradine had symptomatic brady-cardia compared with 1% of the placebo group (P < 0.0001). Visual side effects (phosphenes) were reported by 3% of patients on ivabradine and 1% on placebo (P < 0.0001).
• Additional safety evidence for ivabradine comes from the MorBidity-mortality EvAlUaTion of the I inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTIFUL) trial, an RCT in which 10 917 patients with coronary heart disease and an EF ≤ 40% were assigned to treatment with ivabradine 7.5 mg twice daily or placebo and followed for a median of 19 months. Although ivabradine did not reduce the primary outcome of cardiovascular death, myocardial infarction, or HF hospitalization, it was well tolerated.122

7.2.6 Digoxin and other digitalis glycosides
In patients with symptomatic HF and AF, digoxin may be used to slow a rapid ventricular rate, although other treatments are preferred (see Section 10.1).

Digoxin may also be used in patients in sinus rhythm with symptomatic HF and an LVEF ≤ 40% as recommended below, based on the evidence summarized below.113

Key evidence
• A single large morbidity–mortality RCT [Digitalis Investigation Group (DIG)] has been undertaken with digoxin in patients with symptomatic HF and a low EF.113
• In the DIG trial, 6800 patients with an EF ≤ 45% and in NYHA functional class II–IV were randomized to placebo or digoxin (0.25 mg once daily), added to a diuretic and an ACE inhibitor. This trial was performed before beta-blockers were widely used for HF.113
• Treatment with digoxin did not alter all-cause mortality but did lead to an RRR for hospital admission for worsening HF of 28% within an average of 3 years of starting treatment. The absolute ARR was 7.9%, equating to an NNT (for 3 years to postpone one patient admission) of 13.
• These findings are supported by a meta-analysis of smaller trials suggesting that digoxin can improve symptoms and prevent deterioration.123
• Digoxin can cause atrial and ventricular arrhythmias, particularly in the context of hypokalaemia, and serial monitoring of serum electrolytes and renal function is mandatory.
• The efficacy and safety of other digitalis glycosides such as digi-toxin have not been studied properly in heart failure.

7.2.7 Combination of hydralazine and isosorbide dinitrate
In one relatively small RCT conducted exclusively in men (and before ACE inhibitor or beta-blockers were used to treat HF), this vasodilator combination led to a borderline reduction in mortality when compared with placebo.114–116 In a subsequent RCT, the addition of H-ISDN to conventional therapy (ACE inhibitor, beta-blocker, and MRA) reduced morbidity and mortality (and improved symptoms) in African-Americans with HF.116 The selected patient population studied, relatively small RCT size, and early termination (for mortality benefit) have left uncertainty about the real value of this combination therapy, especially in non-black patients.

Key evidence
• There are two placebo-controlled (V-HeFT-I and A-HeFT) RCTs and one active-controlled (V-HeFT-II) RCT with H-ISDN.114–116
• In V-HeFT-I, 642 men were randomized to placebo, prazosin, or H-ISDN added to a diuretic and digoxin.114 No patients were treated with a beta-blocker or an ACE inhibitor (and the use of MRAs was not documented). Mortality rates were not different in the placebo and prazosin groups. With H-ISDN, there was a trend to a reduction in all-cause mortality during the overall period of follow-up (mean 2.3 years): RRR 22%; ARR 5.3%; NNT 19. H-ISDN increased exercise capacity and LVEF compared with placebo.
• In A-HeFT, 1050 African-American men and women in NYHA class III or IV were randomized to placebo or H-ISDN, added to a diuretic (in 90%), digoxin (60%), an ACE inhibitor (70%), an ARB (17%), a beta-blocker (74%), and spironolactone (39%).116 The initial dose of treatment was 20 mg ISDN/37.5 mg hydralazine thrice daily, increasing to a target of 40 mg/75 mg thrice daily. The trial was discontinued prematurely, after a median follow-up of 10 months, because of a significant reduction in mortality (RRR 43%; ARR 4.0%; NNT 25). H-ISDN also reduced the risk of HF hospitalization (RRR 33%) and improved quality of life.
• In V-HeFT-II, 804 men, mainly in NYHA class II or III, were randomized to enalapril or H-ISDN, added to a diuretic and digoxin.115 No patients were treated with a beta-blocker. There was a trend in the H-ISDN group to an increase in all-cause mortality during the overall period of follow-up (mean 2.5 years): relative increase in risk was 28%.
• The most common adverse effects with H-ISDN in these trials were headache, dizziness/hypotension, and nausea. Arthralgia leading to discontinuation or reduction in dose of H-ISDN occurred in 5–10% of patients in V-HeFT I and II and a sustained increase in antinuclear antibody in 2–3% of patients (but lupus-like syndrome was rare).

7.2.8 Omega-3 polyunsaturated fatty acids
The small treatment effect of n-3 polyunsaturated fatty acids (PUFAs) in the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico-heart failure (GISSI-HF) trial was only detected after covariate adjustment in the statistical analysis and there was no effect on HF hospitalization.117 The effect of n-3 PUFAs after myocardial infarction is uncertain.117

Key evidence
• In the GISSI-HF PUFA trial, 6975 patients with NYHA class II–IV symptoms and an EF ≤ 40% (or if > 40%, HF hospitalization in the previous year) were randomized to placebo or 1 g daily of an n-3 PUFA preparation in addition to standard therapy includ-
ing an ACE inhibitor/ARB in 94%, beta-blocker in 65%, and spironolactone in 39%. The median follow-up was 3.9 years. n-3 PUFA treatment led to an RRR of 8% in the co-primary composite outcome of death or cardiovascular hospitalization in an adjusted analysis (adjusted $P = 0.009$). There was no reduction in HF hospitalization, but there was a 10% RRR in cardiovascular mortality (adjusted $P = 0.045$) and 7% RRR in cardiovascular hospitalization (adjusted $P = 0.026$).

- These findings are supported by one post-myocardial infarction RCT (GISSI-Prevenzione) but not by another (OMEGA). In GISSI-Prevenzione, involving 11,324 patients enrolled after a recent (≤3 months) myocardial infarction, patients received placebo or 1 g daily of n-3 PUFA. n-3 PUFA treatment led to an RRR of 10% in the primary composite outcome of death, myocardial infarction, or stroke (largely driven by a reduction in cardiovascular death).
- OMEGA randomized 3851 patients 3–14 days after acute myocardial infarction to placebo or 1 g n-3 PUFA daily for 1 year. Outcomes did not differ between treatment groups.
- n-3 PUFA preparations differ in composition and the dose may be important.
- The main adverse effects of n-3 PUFAs reported in these trials were nausea and other minor gastrointestinal disturbances.

### 7.3 Treatments not recommended (unproven benefit)

#### 7.3.1 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (‘statins’)

Although there is a wealth of robust evidence supporting the value of statins in patients with atherosclerotic (arterial) disease, most trials excluded patients with HF (because it was uncertain that they would benefit). Two recent trials studied statin treatment specifically in patients with chronic HF and did not demonstrate convincing evidence of benefit (although there was little evidence of harm). Despite the evidence in other areas of cardiovascular medicine, the evidence does not therefore support the initiation of statins in most patients with chronic HF.

**Key evidence**

- The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) and GISSI-HF compared rosuvastatin with placebo in patients with symptomatic HF.
- CORONA enrolled 5011 older patients (≥60 years) with symptomatic HF (NYHA class II–IV) of ischaemic aetiology with an EF ≤40%, felt by the investigator not to require cholesterol-lowering therapy. Rosuvastatin did not reduce the primary endpoint (cardiovascular death, myocardial infarction, or stroke) or all-cause mortality.
- The GISSI-HF statin trial enrolled 4574 patients with symptomatic HF (NYHA class II–IV) of ischaemic and non-ischaemic aetiology. Patients had an EF ≤40% (or if >40%, HF hospitalization in the previous year) and were randomized to placebo or rosuvastatin 10 mg daily, in addition to standard therapy including an ACE inhibitor/ARB in 94%, beta-blocker in 63% and spironolactone in 40%. The median follow-up was 3.9 years. The co-primary endpoints of all-cause mortality and the composite of all-cause death or cardiovascular hospitalization were not reduced by rosuvastatin.

#### 7.3.2 Renin inhibitors

One direct renin inhibitor (aliskiren) is currently being evaluated in two morbidity–mortality RCTs. It is not presently recommended as an alternative to an ACE inhibitor or ARB.

#### 7.3.3 Oral anticoagulants

Other than in patients with AF (both HF-REF and HF-PEF), there is no evidence that an oral anticoagulant reduces mortality–morbidity compared with placebo or aspirin (see Section 10.1).

### 7.4 Treatments not recommended (believed to cause harm)

Treatments (or combinations of treatments) that may cause harm in patients with symptomatic (NYHA class II–IV) systolic heart failure

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinediones (glitazones) should not be used as they cause worsening HF and increase the risk of HF hospitalization.</td>
<td>III</td>
<td>A</td>
<td>131–133</td>
</tr>
<tr>
<td>Most CCBs (with the exception of amiodipine and felodipine) should not be used as they have a negative inotropic effect and can cause worsening HF.</td>
<td>III</td>
<td>B</td>
<td>134</td>
</tr>
<tr>
<td>NSAIDs and COX-2 inhibitors should be avoided if possible as they may cause sodium and water retention, worsening renal function and worsening HF.</td>
<td>III</td>
<td>B</td>
<td>135, 136</td>
</tr>
<tr>
<td>The addition of an ARB (or renin inhibitor) to the combination of an ACE inhibitor AND a mineralocorticoid antagonist is NOT recommended because of the risk of renal dysfunction and hyperkalaemia.</td>
<td>III</td>
<td>C</td>
<td>–</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium-channel blocker; COX = cyclo-oxygenase; EF = ejection fraction; HF = heart failure; NSAID = non-steroidal anti-inflammatory drug; NYHA = New York Heart Association.

*Class of recommendation.

References.
7.5 Diuretics

The effects of diuretics on mortality and morbidity have not been studied in patients with HF, unlike ACE inhibitors, beta-blockers, and MRAs (and other treatments). However, diuretics relieve dyspnoea and oedema and are recommended for this reason in patients with signs and symptoms of congestion, irrespective of EF.

Loop diuretics produce a more intense and shorter diuresis than thiazides, which cause a more gentle and prolonged diuresis. Thiazides may be less effective in patients with reduced kidney function. Loop diuretics are usually preferred to thiazides in HF-REF although they act synergistically and the combination may be used (usually on a temporary basis) to treat resistant oedema.

The aim of using diuretics is to achieve and maintain euvolaemia (the patient’s ‘dry weight’) with the lowest achievable dose. This means that the dose must be adjusted, particularly after restoration of dry body weight, to avoid the risk of dehydration leading to hypotension and renal dysfunction. This may reduce cardiac output in patients with HF-PEF and often needlessly leads to oedema.

Thiazides may be used (usually on a temporary basis) to treat resistant oedema. Thiazides may be less effective in patients with reduced kidney function. Loop diuretics are usually preferred to thiazides, which cause a more gentle and prolonged diuresis than thiazides, which cause a more gentle and prolonged diuresis. Thiazides may be less effective in patients with reduced kidney function. Loop diuretics are usually preferred to thiazides in HF-REF although they act synergistically and the combination may be used (usually on a temporary basis) to treat resistant oedema.

The key mortality–morbidity trials to date are:

- The 4128 patient Irbesartan in heart failure with preserved systolic function trial (I-Preserve) which showed no reduction in the primary composite endpoint of death or HF hospitalization.
- The 850-patient Perindopril for Elderly People with Chronic Heart failure trial (PEP-CHF), which showed no reduction in the primary composite endpoint of death or HF hospitalization.

Use of potassium-sparing diuretics and potassium supplements

- If a potassium-losing diuretic is used with the combination of an ACE inhibitor and an MRA (or ARB), potassium replacement is usually not required.
- Serious hyperkalaemia may occur if potassium-sparing diuretics or supplements are taken in addition to the combination of an ACE inhibitor (or ARB) and MRA.
- The use of all three of an ACE inhibitor, MRA and ARB is not recommended.

8. Pharmacological treatment of heart failure with ‘preserved’ ejection fraction (diastolic heart failure)

No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HF-PEF. Diuretics are used to control sodium and water retention and relieve breathlessness and oedema as in HF-REF. Adequate treatment of hypertension and myocardial ischaemia is also considered to be important, as is control of the ventricular rate in patients with AF (see Section 11). Two very small studies (<30 patients each) have shown that the heart rate-limiting calcium-channel blocker (CCB) verapamil may improve exercise capacity and symptoms in these patients. Rate-limiting CCBs may also be useful for ventricular rate control in patients with AF and in the treatment of hypertension and myocardial ischaemia (which is not the case in patients with HF-REF where their negative inotropic action can be dangerous). Beta-blockers may also be used to control the ventricular rate in patients with HF-PEF and AF.

The drugs that should be avoided in HF-REF (see Section 7.4) should also be avoided in HF-PEF, with the exception of CCBs. The key mortality–morbidity trials to date are:

- The 3023-patient Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved trial, which showed no reduction in the primary composite endpoint (cardiovascular death or HF hospitalization).
- The 850-patient Perindopril for Elderly People with Chronic Heart failure trial (PEP-CHF), which showed no reduction in the primary composite endpoint of death or HF hospitalization.
- The 4128 patient Irbesartan in heart failure with preserved systolic function trial (I-Preserve) which showed no reduction in the primary composite outcome of death or cardiovascular...
hospitalization (specifically, HF, myocardial infarction, unstable angina, arrhythmia, or stroke). 141

9. Non-surgical device treatment of heart failure with reduced ejection fraction (systolic heart failure)

This section discusses the use of ICDs and CRT. While no new ICD RCT has completed since publication of the 2008 guidelines, 7 there have been several important RCTs using CRT that have changed the recommendations (see below). Other technologies including a wearable defibrillator vest 142 and implantable monitors (either ‘stand-alone’ or incorporated into other devices) are of research interest, but do not yet have enough evidence behind them to support guideline recommendations.

9.1 Implantable cardioverter-defibrillator

Approximately half of the deaths in patients with HF, especially in those with milder symptoms, occur suddenly and unexpectedly, and many, if not most, of these are related to ventricular arrhythmias (whereas others may be related to bradycardia and asystole). Prevention of sudden death is therefore an important goal in HF. While the key disease-modifying neurohumoral antagonists mentioned earlier reduce the risk of sudden death, they do not abort it. Specific antiarrhythmic drugs do not decrease this risk (and may even increase it). 143 For this reason, ICDs have an important role to play in reducing the risk of death from ventricular arrhythmias.

9.1.1 Secondary prevention of sudden cardiac death

Key evidence

ICDs reduce mortality in survivors of cardiac arrest and in patients with sustained symptomatic ventricular arrhythmias. Consequently, an ICD is recommended in such patients, irrespective of EF, with good functional status, a life expectancy of >1 year, and where the intent is to increase survival. 144,147

9.1.2 Primary prevention of sudden cardiac death

Key evidence

- The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) enrolled 2521 patients with non-ischaemic dilated cardiomyopathy or ischaemic HF, no prior symptomatic ventricular arrhythmia, and an EF ≤ 35% who were in NYHA functional class II or III. These patients were randomized to placebo, amiodarone, or an ICD, in addition to conventional treatment including an ACE inhibitor or ARB (96%) and a beta-blocker (69%); MRA use was not reported. 149
- ICD treatment led to an RRR in death of 23% (P = 0.007) over a median follow-up of 45.5 months. This benefit was additional to that gained with conventional treatment, including an ACE inhibitor and a beta-blocker. Amiodarone did not reduce mortality.

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) to support guideline recommendations.

- Additional support for the use of ICDs comes from the Multi-center Automatic Defibrillator Implantation Trial II (MADIT-II), 148 an RCT in which patients with a prior myocardial infarction and an EF ≤ 30% (59% of which were in NYHA class II or III) were assigned to receive either conventional treatment or conventional treatment plus an ICD. Use of an ICD led to a 31% RRR in mortality. Two other RCTs showed no benefit in patients treated with an ICD early (<40 days) after myocardial infarction. 150,151 This is why ICD use in patients with coronary heart disease receives level of evidence A, but only in patients >40 days after acute myocardial infarction.
- There is less evidence in patients with non-ischaemic HF, with one moderate sized trial [Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation (DEFINITE), n = 458] showing only a non-significant trend to a reduction in mortality; hence the evidence level of B. 152
- ICD implantation should be considered only after a sufficient period of optimization of medical therapy (at least 3 months) and only if the EF remains persistently low.

### Recommendations for the use of implanted cardioverter defibrillators in patients with heart failure

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Classa</th>
<th>Levelb</th>
<th>Refc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary prevention</td>
<td>An ICD is recommended in a patient with a ventricular arrhythmia causing haemodynamic instability, who is expected to survive for &gt;1 year with good functional status, to reduce the risk of sudden death.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Primary prevention</td>
<td>An ICD is recommended in a patient with symptomatic HF (NYHA class II–III) and an EF ≤ 35% despite ≥3 months of treatment with optimal pharmacological therapy, who is expected to survive for &gt;1 year with good functional status, to reduce the risk of sudden death.</td>
<td>(i) Ischaemic aetiology and &gt;40 days after acute myocardial infarction</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>(ii) Non-ischaemic aetiology</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

HF = heart failure; ICD = implantable cardioverter defibrillator; NYHA = New York Heart Association.

aClass of recommendation.
bLevel of evidence.
cReferences.
ICD therapy is not indicated in patients in NYHA class IV with severe, drug-refractory, symptoms who are not candidates for CRT, a ventricular assist device, or cardiac transplantation (because such patients have a very limited life expectancy and are more likely to die from pump failure).

Patients should be counselled as to the purpose of an ICD and the complications related to its use (predominantly inappropriate shocks).

If HF deteriorates, deactivation of a patient’s ICD may be considered after appropriate discussion with the patient and caregiver(s).

### 9.2 Cardiac resynchronization therapy

Two large RCTs have shown that CRT is of benefit in patients with mild (NYHA class II) symptoms as well as in those who are more severely symptomatic. There is little doubt that patients expected to survive with good functional status for >1 year should receive CRT if they are in sinus rhythm, their LVEF is low (<30%), QRS duration is markedly prolonged (>150 ms), and an ECG shows a left bundle branch morphology, irrespective of symptom severity. There is less consensus about patients with right bundle branch block or interventricular conduction delay (based on subgroup analyses) and those in AF (because most trials excluded these patients and because a high ventricular rate will prevent resynchronization). Another area of debate is what to do in an HF-REF patient without an indication for CRT who needs a conventional pacemaker. The possibility that patients with a QRS duration of <120 ms may have ‘mechanical dyssynchrony’ (detectable by imaging) and might benefit from CRT is another area of research interest but remains to be proven.

#### Recommendations for the use of CRT where the evidence is strong—patients in sinus rhythm with NYHA functional class III and ambulatory class IV heart failure and a persistently reduced ejection fraction, despite optimal pharmacological therapy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBBB QRS morphology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT-P/CRT-D is recommended in patients in sinus rhythm with a QRS duration of ≥120 ms, LBBB QRS morphology, and an EF ≤35%, who are expected to survive with good functional status for &gt;1 year, to reduce the risk of HF hospitalization and the risk of premature death.</td>
<td>I</td>
<td>A</td>
<td>156, 157</td>
</tr>
<tr>
<td>Non-LBBB QRS morphology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT-P/CRT-D should be considered in patients in sinus rhythm with a QRS duration of ≥150 ms, irrespective of QRS morphology, and an EF ≤35%, who are expected to survive with good functional status for &gt;1 year, to reduce the risk of HF hospitalization and the risk of premature death.</td>
<td>IIa</td>
<td>A</td>
<td>156, 157</td>
</tr>
</tbody>
</table>

**Bold terms:** CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; EF = ejection fraction; HF = heart failure; LBBB = left bundle branch block; NYHA = New York Heart Association.

**References:**

*Class of recommendation.

*Level of evidence.

*References.
9.2.1 Recommendations for cardiac resynchronization therapy where the evidence is certain

Key evidence supporting the use of cardiac resynchronization therapy

Moderate to severely symptomatic heart failure

- Two key placebo-controlled RCTs [Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) and Cardiac Resynchronization in Heart Failure Study (CARE-HF)] randomized 2333 patients with moderate to severely symptomatic HF (NYHA class III or IV) to either optimal medical therapy or optimal medical therapy plus CRT.154,155 Patients in COMPANION were required to be in sinus rhythm, to have an EF ≤ 35% and a QRS duration of at least 120 ms, and a HF hospitalization or equivalent in the preceding year. Patients in CARE-HF were required to be in sinus rhythm and to have an EF ≤ 35%, a QRS duration ≥ 120 ms (if the QRS duration was 120–149 ms other echocardiographic criteria for dys synchrony had to be met), and an LV end-diastolic dimension of at least 30 mm (indexed to height).

- Each of these two trials showed that CRT reduced the risk of death from any cause and hospital admission for worsening HF [RRR in death of 24% with a CRT-pacemaker (CRT-P) and of 36% with CRT-defibrillator (CRT-D) in COMPANION and of 36% with CRT-P in CARE-HF]. In CARE-HF, the RRR in HF hospitalization with CRT-P was 52%. These benefits were additional to those gained with conventional treatment, including a diuretic, digoxin, an ACE inhibitor, a beta-blocker, and an MRA.

- The ARR with CRT-D in the composite outcome of cardiovascular death or cardiovascular hospitalization in COMPANION was 8.6%, equating to an NNT (over a median duration of follow-up of ~16 months) to postpone one event of 12. The corresponding figures for CRT-P in CARE-HF (over a mean follow-up of 29 months) were an ARR of 16.6% and an NNT of 6.

- These trials also showed that CRT improves symptoms, quality of life, and ventricular function. Other trials showed that these agents improve exercise capacity.

- Because these severely symptomatic patients have much to gain and because there was no subgroup of patients that clearly did not benefit from CRT, individuals in NYHA functional class III and IV have been given the broadest indication for CRT.

Mild to moderately symptomatic HF

- Two key placebo-controlled RCTs randomized 3618 patients with mild (MADIT-CRT, 15% NYHA class I and 85% NYHA class II) to moderately [Resynchronization/Defibrillation for Ambulatory Heart Failure Trial (RAFT), 80% NYHA class II and 20% NYHA class III] symptomatic HF to either optimal medical therapy plus an ICD or optimal medical therapy plus a CRT-D.154,155 Patients in MADIT-CRT were required to have an EF ≤ 30%, a QRS duration ≥ 130 ms, and to be in sinus rhythm. Patients in RAFT were required to have an EF ≤ 30% and a QRS duration ≥ 120 ms (13% of enrolled patients had AF with a well-controlled ventricular rate).

- Each of these two trials showed that CRT reduced the risk of the primary composite endpoint of death or HF hospitalization (HF event in MADIT-CRT) (RRR of 34% in MADIT-CRT and 25% in RAFT). There was a 25% reduction in all-cause mortality in RAFT (P = 0.003), but mortality was not reduced in MADIT-CRT. These benefits were additional to those gained with conventional treatment, including a diuretic, digoxin, an ACE inhibitor, a beta-blocker, an MRA, and an ICD.

- The ARR in the primary composite mortality–morbidity endpoint in MADIT-CRT was 8.1%, equating to an NNT (for an average of 2.4 years to postpone one event) of 12. The equivalent figures for RAFT were ARR 7.1% and NNT 14 (over an average of 40 months).

- These trials also showed that CRT improves symptoms, quality of life, and ventricular function. Other trials showed that these agents improve exercise capacity.

- Both MADIT-CRT and RAFT showed a significant treatment-by-subgroup interaction whereby QRS duration modified the treatment effect (CRT appeared more effective in patients with a QRS ≥ 150 ms) and patients with LBBB also seemed to obtain more benefit than those with right bundle branch block or an interventricular conduction defect (these groups overlap considerably, as patients with LBBB are more likely to have a QRS duration ≥ 150 ms). These findings are supported by echocardiographic analyses.161 For these reasons, in patients with milder symptoms, CRT is recommended only in those with either a QRS duration ≥ 150 ms or ≥ 130 ms plus an LBBB pattern.

9.2.2 Recommendations for cardiac resynchronization therapy where the evidence is uncertain

Two commonly encountered clinical situations where there is little robust evidence for (or against) CRT are AF and when a patient with a reduced EF has an indication for conventional pacing and no other indication for CRT.

Atrial fibrillation

One small, single-blind study [Multisite Stimulation in Cardiomyopathies (MUSTIC)] included 59 HF-REF patients with persistent/permanent AF, a slow ventricular rate necessitating permanent ventricular pacing, and a paced QRS duration ≥ 200 ms.162 The study had a crossover design (3 months conventional pacing vs. 3 months CRT). There was a high drop-out rate (42%) and there was no difference in the primary endpoint of 6-min walk distance. The key large RCTs of CRT all excluded patients in AF, with the exception of RAFT.158 RAFT included 229 patients with permanent AF or flutter either with a controlled ventricular rate (≤ 60 b.p.m. at rest and ≤ 90 b.p.m. during a 6-min walk test) or with planned AV junction ablation. Further analysis did not show a significant interaction between baseline rhythm and treatment effect, but this subgroup represented only a small proportion of the overall population. Other data suggesting that patients with AF (without AV nodal ablation) may benefit from CRT are limited by being observational in nature.163

Patients with an indication for conventional pacing

All the major RCTs of CRT, with the exception of RAFT, excluded patients with a conventional indication for pacing. RAFT included...
Recommendations for the use of CRT where the evidence is uncertain—patients with symptomatic HF (NYHA functional class II–IV) and a persistently reduced EF despite optimal pharmacological therapy and in AF or with a conventional pacing indication

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients in permanent AF</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| CRT/P/CRT-D may be considered in patients in NYHA functional class III or ambulatory class IV with a QRS duration ≥120 ms and an EF ≤35%, who are expected to survive with good functional status for >1 year, to reduce the risk of HF worsening if:  
  - The patient requires pacing because of an intrinsically slow ventricular rate  
  - The patient is pacemaker dependent as a result of AV nodal ablation  
  - The patient’s ventricular rate is ≤60 b.p.m. at rest and ≤90 b.p.m. on exercise. | IIb   | C     | 163a |
| Patients with an indication for conventional pacing and no other indication for CRT |       |       |     |
| In patients who are expected to survive with good functional status for >1 year:  
  - CRT should be considered in those in NYHA functional class III or IV with an EF ≤35%, irrespective of QRS duration, to reduce the risk of worsening of HF  
  - CRT may be considered in those in NYHA functional class II with an EF ≤35%, irrespective of QRS duration, to reduce the risk of worsening of HF. | IIa   | C     | –    |

CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; EF = ejection fraction; HF = heart failure; NYHA = New York Heart Association.

Class of recommendation.

Level of evidence.

References.

135 patients with a paced QRS duration ≥200 ms, a subgroup too small for meaningful analysis. Conventional right ventricular pacing, however, alters the normal sequence of cardiac activation in a similar way to LBBB, and experimental and observational data suggest that this may lead to deterioration in LV systolic function. It is on this basis that CRT is recommended as an alternative to conventional right ventricular pacing in patients with HF-REF who have a standard indication for pacing or who require a generator change or revision of a conventional pacemaker.

10. Arrhythmias, bradycardia, and atrioventricular block in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction

The management of arrhythmias is discussed in other ESC guidelines, and this section focuses only on aspects that are particularly relevant to patients with HF.

10.1 Atrial fibrillation

AF is the most common arrhythmia in HF; it increases the risk of thrombo-embolic complications (particularly stroke) and may lead to worsening of symptoms. Whether AF is an independent predictor of mortality is less certain, as is whether it can cause systolic HF (‘tachycardiomyopathy’).

AF should be classified and managed according to the current AF guidelines (i.e. first episode, paroxysmal, persistent, longstanding persistent, or permanent), recognizing the uncertainty about the actual duration of the episode and about previous undetected episodes.

The following issues need to be considered in patients with HF and AF, especially a first episode of AF or paroxysmal AF:

- Identification of correctable causes (e.g. hyperthyroidism, electrolyte disorders, uncontrolled hypertension, mitral valve disease).
- Identification of potential precipitating factors (e.g. recent surgery, chest infection or exacerbation of chronic pulmonary disease/asthma, acute myocardial ischaemia, alcohol binge) as this may determine whether a rhythm-control strategy is preferred to a rate-control strategy.
- Assessment for thromboembolism prophylaxis.

10.1.1 Rate control

An approach to controlling the ventricular rate in patients with HF and AF is shown in Figure 3. Recommendations for stepwise use of individual treatments in patients with HF-REF are given below.

For rate control in patients with HF-REF, a beta-blocker is preferred over digoxin as the latter does not provide rate control during exercise. Furthermore, beta-blockers have favourable effects on mortality and morbidity in systolic HF per se (see above). The combination of digoxin and a beta-blocker is more effective than a beta-blocker alone in controlling the ventricular rate at rest.

In patients with HF-PEF, rate-limiting CCBs (verapamil and diltiazem) are an effective alternative to a beta-blocker (but their use is not recommended in patients with HF-REF as their negative inotropic action may further depresses LV systolic function).
The combination of digoxin and a rate-limiting CCB is more effective than a CCB alone in controlling the ventricular rate at rest. Assessment of control of the ventricular rate on exertion requires either ambulatory ECG monitoring or measurement of the rate during moderate exercise. The optimum ventricular rate in patients with HF and AF is uncertain because the one RCT comparing strict with lenient rate control included very few patients with HF. In the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) study (which showed similar outcomes for a rate-control compared with a rhythm-control strategy) the target rate was <80 b.p.m. at rest and <110 b.p.m. during a 6-min walk test.

In extreme cases, AV node ablation and pacing may be required; in this situation in patients with systolic HF, CRT may be considered instead of conventional pacing (see Section 9.2).

10.1.2 Rhythm control

In patients with chronic HF, a rhythm-control strategy (including pharmacological or electrical cardioversion) has not been demonstrated to be superior to a rate-control strategy in reducing
mortality or morbidity. This strategy is probably best reserved for patients with a reversible secondary cause of AF (e.g. hyperthyroidism) or an obvious precipitant (e.g. recent pneumonia) and in patients who cannot tolerate AF after optimization of rate control and HF therapy. Amiodarone is the only antiarrhythmic that should be used in patients with systolic HF. The role of catheter ablation as a rhythm control strategy in HF is at present uncertain.

In patients with AHF, emergency cardioversion may be required to correct profound haemodynamic instability (see Section 12.2).

10.1.3 Thrombo-embolism prophylaxis
Thrombo-embolism prophylaxis in patients with HF and AF should be based on the Cardiac failure, Hypertension, Age ≥75 (Doubled), Diabetes, Stroke (Doubled)-Vascular disease, Age 65–74 and Sex category (Female) (CHA₂DS₂-VASc) score (see Table 17), in keeping with the 2010 ESC AF guidelines. A substantial proportion of patients with HF will have a score ≥3, indicating that careful consideration should be given before prescribing an oral anticoagulant and that regular review is needed (and correctable risk factors addressed) if an oral anticoagulant is given.

Some new anticoagulant drugs such as the oral direct thrombin inhibitors and oral factor Xa inhibitors are contraindicated in severe renal impairment (creatinine clearance ≤30 mL/min). This is clearly a concern in many patients with HF and, if these drugs are used, serial monitoring of renal function is required. There is no known way to reverse the anticoagulant action of these new drugs.

10.2 Ventricular arrhythmias
Ventricular arrhythmias are frequent in HF patients, particularly in those with a dilated left ventricle and reduced EF. Ambulatory ECG recording detects premature ventricular complexes in virtually all HF patients, and episodes of asymptomatic, non-sustained ventricular tachycardia are common. Historical studies have suggested that ‘complex ventricular arrhythmias’ (frequent premature ventricular complexes and non-sustained ventricular
tachycardia) are associated with a poor outcome in HF. Certain recommendations from the American College of Cardiology/American Heart Association/ESC guidelines on the management of ventricular arrhythmias and sudden death, which may be particularly relevant to patients with HF, are summarized below. The role of catheter ablation in patients with HF other than as an adjunct in the treatment of refractory ventricular arrhythmias is uncertain. The reader is also referred to the section on ICDs (Section 9.1).

10.3 Symptomatic bradycardia and atrioventricular block

Although the indications for pacing in patients with HF are similar to those in other patients, as described in the ESC guidelines on pacing, there are issues specific to HF, including:

- Before implanting a conventional pacemaker in a patient with HF-REF, consider whether there is an indication for an ICD, CRT-P, or CRT-D (see Sections 9.1 and 9.2).

- Because right ventricular pacing may induce dyssynchrony and worsen symptoms, CRT should be considered instead of conventional pacing in patients with HF-REF (see Section 9.2).
### Recommendations for the prevention of thromboembolism in patients with symptomatic HF (NYHA functional class II–IV) and paroxysmal or persistent/permanent AF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>The CHA2DS2-VASc and HAS-BLED scores (Tables 17 and 18) are recommended to determine the likely risk–benefit (thrombo-embolism prevention vs. risk of bleeding) of oral anticoagulation.</td>
<td>I</td>
<td>B</td>
<td>179, 180</td>
</tr>
<tr>
<td>An oral anticoagulant is recommended for all patients with paroxysmal or persistent/permanent AF and a CHA2DS2-VASc score ≥1, without contraindications, and irrespective of whether a rate- or rhythm-management strategy is used (including after successful cardioversion).</td>
<td>I</td>
<td>A</td>
<td>184</td>
</tr>
<tr>
<td>In patients with AF of &gt;48 h duration, or when the known duration of AF is unknown, an oral anticoagulant is recommended at a therapeutic dose for ≥3 weeks prior to electrical or pharmacological cardioversion.</td>
<td>I</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>Intravenous heparin or LMWH is recommended for patients who have not been treated with an anticoagulant and require urgent electrical or pharmacological cardioversion.</td>
<td>I</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>Alternative to i.v. heparin or LMWH</td>
<td>IIb</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>A TOE-guided strategy may be considered for patients who have not been treated with an anticoagulant and require urgent electrical or pharmacological cardioversion.</td>
<td>III</td>
<td>A</td>
<td>185</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; CHA2DS2-VASc = Cardiac failure, Hypertension, Age ≥75 (Doubled), Diabetes, Stroke (Doubled); Vascular disease, Age 65–74 and Sex category (Female); EF = ejection fraction; HAS-BLED = Hypertension, Abnormal renal/liver function (1 point each), Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (≥65); Drugs/alcohol concomitantly (1 point each); HF = heart failure; i.v. = intravenous; LMWH = low molecular weight heparin; LV = left ventricular; NYHA = New York Heart Association; TOE = transoesophageal echocardiography.

*aClass of recommendation.

*bLevel of evidence.

*cReferences.

### Recommendations for the management of ventricular arrhythmias in heart failure

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended that potential aggravating/precipitating factors (e.g. electrolyte disorders, use of proarrhythmic drugs, myocardial ischaemia) should be sought and corrected in patients with ventricular arrhythmias.</td>
<td>I</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>It is recommended that treatment with an ACE inhibitor (or ARB), beta-blocker, and MRA should be optimized in patients with ventricular arrhythmias.</td>
<td>I</td>
<td>A</td>
<td>87–100</td>
</tr>
<tr>
<td>It is recommended that coronary revascularization is considered in patients with ventricular arrhythmias and coronary artery disease (see Section 13.2).</td>
<td>I</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>It is recommended that an ICD is implanted in a patient with symptomatic or sustained ventricular arrhythmia (ventricular tachycardia or ventricular fibrillation), reasonable functional status, and in whom a goal of treatment is to improve survival.</td>
<td>I</td>
<td>A</td>
<td>144–149</td>
</tr>
<tr>
<td>Amiodarone is recommended in patients with an ICD, who continue to have symptomatic ventricular arrhythmias or recurrent shocks despite optimal treatment and device re-programming.</td>
<td>I</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>Catheter ablation is recommended in patients with an ICD who continue to have ventricular arrhythmias causing recurrent shocks not preventable by optimal treatment device re-programming and amiodarone.</td>
<td>I</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>Amiodarone may be considered as a treatment to prevent recurrence of sustained symptomatic ventricular arrhythmias in otherwise optimally treated patients in whom an ICD is not considered appropriate.</td>
<td>IIb</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>Routine use of amiodarone is not recommended in patients with non-sustained ventricular arrhythmias because of lack of benefit and potential drug toxicity.</td>
<td>III</td>
<td>A</td>
<td>172, 173</td>
</tr>
<tr>
<td>Other antiarrhythmic drugs (particularly class IC agents and dronedarone) should not be used in patients with systolic HF because of safety concerns (worsening HF, proarrhythmia, and death).</td>
<td>III</td>
<td>A</td>
<td>176, 178</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HF = heart failure; ICD = implantable cardioverter-defibrillator; MRA = mineralocorticoid receptor antagonist.

*aClass of recommendation.

*bLevel of evidence.

*cReferences.
Physiological pacing to maintain an adequate chronotropic response and maintain atrial–ventricular coordination with a DDD system is preferable to VVI pacing in patients with both HF-REF and HF-PEF.  

Pacing solely in order to permit initiation or titration of beta-blocker therapy in the absence of a conventional indication is not recommended.

11. Importance and management of other co-morbidity in heart failure with reduced ejection fraction and heart failure with preserved ejection fraction

11.1 Heart failure and co-morbidities

Co-morbidities are important in patients with HF for four main reasons. First, co-morbidities may affect the use of treatments for HF (e.g., it may not be possible to use renin–angiotensin system inhibitors in some patients with renal dysfunction) (see Section 7.2). Secondly, the drugs used to treat co-morbidities may cause worsening of HF (e.g., NSAIDs given for arthritis) (see Section 7.4). Thirdly, the drugs used to treat HF and those used to treat co-morbidities may also interact with one another [e.g., beta-blockers and beta-agonists for chronic obstructive pulmonary disease (COPD) and asthma] and reduce patient adherence. Lastly, most co-morbidities are associated with worse clinical status and are predictors of poor prognosis in HF (e.g., diabetes). This has led to some co-morbidities themselves becoming targets for treatment (e.g., anaemia).  

Management of co-morbidities is a key component of the holistic care of patients with HF (see Section 14).

11.2 Anaemia

Anaemia (defined as a haemoglobin concentration <13 g/dL in men and <12 g/dL in women) is common in HF, particularly in hospitalized patients. It is more frequent in women, the elderly, and in patients with renal impairment. Anaemia is associated with more symptoms, worse functional status, greater risk of HF hospitalization, and reduced survival. A standard diagnostic work-up should be undertaken in anaemic patients. Correctable causes should be treated in the usual way, although no definite aetiology is identified in many patients. Correction of iron deficiency using i.v. iron has been specifically studied in patients with HF (see Section 11.14). The value of erythropoietin-stimulating agents as a treatment for anaemia of unknown aetiology is unknown but is currently being tested in a large mortality RCT.

11.3 Angina

Beta-blockers are effective agents for angina as well as an essential treatment for systolic HF. Certain other effective antianginal drugs have been studied in large numbers of patients with systolic HF and shown to be safe (e.g., amiodpine, 188,189 ivabradine,112,122 and nitrates114–116). The safety of other antianginal agents such as nicorandil and ranolazine is uncertain, while other drugs, specifically dilatiazem and verapamil, are thought to be unsafe in patients with HF-REF (although they may be used in HF-PEF).  

11.4 Asthma: see chronic obstructive pulmonary disease

See Section 11.7.

11.5 Cachexia

A generalized process, wasting all body compartments [i.e. lean tissue (skeletal muscle), fat tissue (energy reserves), and bone tissue (osteoporosis)], may occur in 10–15% of patients with HF, especially those with HF-REF. This serious complication is associated with worse symptoms and functional capacity, more frequent hospitalization, and decreased survival. Cachexia is specifically defined as involuntary non-oedematous weight loss ≥6% of total body weight within the previous 6–12 months. The causes are uncertain, but may include poor nutrition, malabsorption, impaired calorie and protein balance, hormone resistance, pro-inflammatory immune activation, neurohormonal derangements, and reduced anabolic drive. Potential treatments include appetite stimulants, exercise training, and anabolic agents (insulin, anabolic steroids) in combination with the application of nutritional supplements, although none is of proven benefit and their safety is unknown.

11.6 Cancer

Certain chemotherapeutic agents can cause (or aggravate) LV systolic dysfunction and HF. The best recognized of these are the anthracyclines (e.g. doxorubicin) and trastuzumab. Dexamethoxzane may confer some cardioprotection in patients receiving anthracyclines. Pre- and post-evaluation of EF is essential in patients receiving cardiotoxic chemotherapy, as detailed elsewhere. Patients developing LV systolic dysfunction should not receive further chemotherapy and should receive standard treatment for HF-REF. Mediastinal irradiation can also lead to a variety of long-term cardiac complications, although the less frequent use of high-dose, wide-field radiotherapy has led to a decline in these problems.

11.7 Chronic obstructive pulmonary disease

COPD and asthma may cause diagnostic difficulties, especially in HF-PEF. These conditions are associated with worse functional status and a worse prognosis. Beta-blockers are contraindicated in asthma but not in COPD, although a selective beta-1 adrenoceptor antagonist (i.e., bisoprolol, metoprolol succinate, or nebivolol) is preferred. Oral corticosteroids cause sodium and water retention, potentially leading to worsening of HF, but this is not believed to be a problem with inhaled corticosteroids. COPD is an independent predictor of worse outcomes in HF.
11.8 Depression
Depression is common and is associated with worse clinical status and a poor prognosis in HF. It may also contribute to poor adherence and social isolation. A high index of suspicion is needed to make the diagnosis, especially in the elderly. Routine screening using a validated questionnaire is good practice. Psychosocial intervention and pharmacological treatment are helpful. Selective serotonin reuptake inhibitors are thought to be safe, whereas tricyclic antidepressants are not because they may cause hypotension, worsening HF, and arrhythmias.

11.9 Diabetes
Dysglycaemia and diabetes are very common in HF, and diabetes is associated with poorer functional status and worse prognosis.
Diabetes may be prevented by treatment with ARBs and possibly ACE inhibitors. Beta-blockers are not contraindicated in diabetes and are as effective in improving outcome in diabetic patients as in non-diabetic individuals, although different beta-blockers may have different effects on glycaemic indices. Thiazolidinediones (glitazones) cause sodium and water retention and increased risk of worsening HF and hospitalization, and should be avoided (see recommendations, Section 7.4). Metformin is not recommended in patients with severe renal or hepatic impairment because of the risk of lactic acidosis, but is widely (and apparently safely) used in other patients with HF. The safety of newer anti-diabetic drugs in HF is unknown.

11.10 Erectile dysfunction
Erectile dysfunction should be treated in the usual way; phosphodiesterase V inhibitors are not contraindicated other than in patients taking nitrates. Indeed short-term studies have shown that these agents have favourable haemodynamic and other effects in patients with HF-REF. There are, however, reports of phosphodiesterase V inhibitors causing worsening LV outflow tract obstruction in patients with hypertrophic cardiomyopathy, which may be a concern in some patients with HF-PEF.

11.12 Gout
Hyperuricaemia and gout are common in HF and may be caused or aggravated by diuretic treatment. Hyperuricaemia is associated with a worse prognosis in HF-REF. Xanthine oxidase inhibitors (allopurinol, oxypurinol) may be used to prevent gout, although their safety in HF-REF is uncertain. Gout attacks are better treated by colchicine than with NSAIDs (although colchicine should not be used in patients with very severe renal dysfunction and may cause diarrhoea). Intra-articular corticosteroids are an alternative for monarticular gout, but systemic corticosteroids cause sodium and water retention.

11.13 Hyperlipidaemia
Elevated low-density lipoprotein cholesterol is uncommon in HF-REF; patients with advanced HF-REF often have low concentrations of low-density lipoprotein, which is associated with a worse prognosis. Rosuvastatin did not reduce the primary composite mortality–morbidity endpoints in two large RCTs in HF.

11.14 Hypertension
Hypertension is associated with an increased risk of developing HF; antihypertensive therapy markedly reduces the incidence of HF (with an exception of alpha-adrenoceptor blockers, which are less effective than other antihypertensives in preventing HF). Negatively inotropic CCBs (i.e. diltiazem and verapamil) should not be used to treat hypertension in patients with HF-REF (but are believed to be safe in HF-PEF), and moxonidine should also be avoided in patients with HF-REF as it increased mortality in patients in one RCT. If blood pressure is not controlled with an ACE inhibitor (or ARB), a beta-blocker, MRA, and diuretic, hydralazine and amlodipine (or felodipine), are additional options.

Recommendations for the treatment of hypertension in patients with symptomatic HF (NYHA functional class II–IV) and LV systolic dysfunction

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class*</th>
<th>Levelb</th>
<th>Ref c</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One or more of an ACE inhibitor (or ARB), beta-blocker, and MRA is recommended as first-, second-, and third-line therapy, respectively, because of their associated benefits (reducing the risk of HF hospitalization and reducing the risk of premature death).</td>
<td>I</td>
<td>A</td>
<td>87, 108–111</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A thiazide diuretic (or if the patient is treated with a thiazide diuretic, switching to a loop diuretic) is recommended when hypertension persists despite treatment with a combination of as many as possible of an ACE inhibitor (or ARB), beta-blocker, and MRA.</td>
<td>I</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine is recommended when hypertension persists despite treatment with a combination of as many as possible of an ACE inhibitor (or ARB), beta-blocker, MRA, and diuretic.</td>
<td>I</td>
<td>A</td>
<td>188, 189</td>
</tr>
<tr>
<td>Hydralazine is recommended when hypertension persists despite treatment with a combination of as many as possible of an ACE inhibitor (or ARB), beta-blocker, MRA, and diuretic.</td>
<td>I</td>
<td>A</td>
<td>114–116</td>
</tr>
<tr>
<td>Felodipine should be considered when hypertension persists despite treatment with a combination of as many as possible of an ACE inhibitor (or ARB), beta-blocker, MRA, and diuretic.</td>
<td>IIa</td>
<td>B</td>
<td>204</td>
</tr>
<tr>
<td>Moxonidine is NOT recommended because of safety concerns (increased mortality).</td>
<td>III</td>
<td>B</td>
<td>203</td>
</tr>
<tr>
<td>Alpha-adrenoceptor antagonists are NOT recommended because of safety concerns (neurohumoral activation, fluid retention, worsening HF).</td>
<td>III</td>
<td>A</td>
<td>202, 206, 207</td>
</tr>
</tbody>
</table>

*Class of recommendation.
*Level of evidence.
*References.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HF = heart failure; LV = left ventricular; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.
blood pressure-lowering agents shown to be safe in systolic HF. The blood pressure targets recommended in hypertension guidelines are applicable to HF.

In patients with AHF, i.v. nitrates (or sodium nitroprusside) are recommended to lower blood pressure (see Section 12).

11.14 Iron deficiency
Iron deficiency may contribute to muscle dysfunction in HF and causes anaemia. In a single RCT, 459 patients with NYHA class II or III systolic HF, a haemoglobin concentration between 9.5 and 13.5 g/dL, and iron deficiency (see below) were randomized 2:1 to i.v. ferric carboxymaltose or saline. In this trial, iron deficiency was diagnosed when serum ferritin was <100 μg/L or when the ferritin concentration was between 100 and 299 μg/L and transferrin saturation was <20%. Over 6 months of treatment, iron therapy improved self-reported patient global assessment and NYHA class (as well as 6-min walk distance and health-related quality of life) and may be considered as a treatment for these patients. The effect of treating iron deficiency in HF-PEF and the long-term safety of iron therapy in HF is unknown.

11.15 Kidney dysfunction and cardiorenal syndrome
The GFR is reduced in most patients with HF, especially if advanced, and renal function is a powerful independent predictor of prognosis in HF. Renin–angiotensin–aldosterone blockers (ACE inhibitors, renin inhibitors, ARBs, and MRAs) frequently cause a fall in GFR, although any reduction is usually small and should not lead to treatment discontinuation unless marked (see Appendix C). Conversely, an immediate and large fall in GFR should raise the suspicion of renal artery stenosis. Sodium and water depletion (due to the excessive diuresis or fluid loss due to vomiting or diarrhoea) and hypotension are well recognized causes of renal dysfunction, but less well known is that volume overload, right heart failure, and renal venous congestion may also cause renal dysfunction. Other causes of kidney dysfunction are prostatic obstruction and nephrotoxic drugs such as NSAIDs and certain antibiotics (e.g., trimethoprim and gentamicin), all of which should be considered (and corrected or avoided) in HF patients with worsening renal function. Thiazide diuretics may be less effective in patients with a very low eGFR, and certain renally excreted drugs (e.g., digoxin, insulin, and low molecular weight heparin) may accumulate in patients with renal impairment. Sometimes the term ‘cardiorenal syndrome’ is used to describe concurrent heart and renal failure (and ‘cardiorenal–anaemia syndrome’ if there is concomitant anaemia).

Chronic or acute renal dysfunction is a particular problem in patients with AHF, and is discussed further in that section (see Section 12).

11.16 Obesity
Obesity is a risk factor for HF and complicates its diagnosis because it causes dyspnoea, effort intolerance, and ankle swelling, and may result in poor-quality echocardiographic images. Obese individuals also have reduced natriuretic peptide levels. Obesity is more common in HF-PEF than in HF-REF, although it is possible that misdiagnosis may explain at least some of this difference in prevalence. Obesity should be managed as recommended in other guidelines.

11.17 Prostatic obstruction
Alpha-adrenoceptor blockers cause hypotension, and sodium and water retention, and may not be safe in systolic HF (see Section 11.13). For these reasons, 5-alpha reductase inhibitors are generally preferred. Prostatic obstruction should be ruled out in men with deteriorating renal function.

11.18 Renal dysfunction
See Section 11.15.

11.19 Sleep disturbance and sleep-disordered breathing
Patients with HF frequently have sleep disturbance; the causes are many, including pulmonary congestion (leading to orthopnoea and paroxysmal nocturnal dyspnoea) and diuretic therapy causing nocturnal diuresis. Anxiety and other psychological problems can also lead to insomnia, and reviewing sleep history is part of the holistic care of patients with HF (see Section 14). Up to one-third of patients with HF have sleep-disordered breathing. Sleep apnoea is of concern in patients with HF because it leads to intermittent hypoxaemia, hypercapnia, and sympathetic excitation. Obstructive sleep apnoea also causes recurrent episodes of negative intrathoracic pressure and increases in LV afterload. It is more common in patients who are obese and whose sleeping partners report that the patient snores or exhibits daytime somnolence (the patient may not be aware of these). However, not all patients with obstructive sleep apnoea are obese. The prevalence of central sleep apnoea (including Cheyne–Stokes respiration) in HF is uncertain and may have declined since the widespread use of beta-blockers and CRT. Screening for and the diagnosis and treatment of sleep apnoea is discussed in detail elsewhere. Diagnosis currently requires overnight polysomnography. Nocturnal oxygen supplementation, continuous positive airway pressure, bi-level positive airway pressure, and adaptive servo-ventilation may be used to treat nocturnal hypoxaemia.

12. Acute heart failure
Acute heart failure (AHF) is the term used to describe the rapid onset of, or change in, symptoms and signs of HF. It is a life-threatening condition that requires immediate medical attention and usually leads to urgent admission to hospital. In most cases, AHF arises as a result of deterioration in patients with a previous diagnosis of HF (either HF-REF or HF-PEF), and all of the aspects of chronic management described in these guidelines apply fully to these patients. AHF may also be the first presentation of HF (‘de novo’ AHF). AHF may be caused by an abnormality of any aspect of cardiac function. In patients with pre-existing HF there is often a clear precipitant or trigger (e.g., an arrhythmia or discontinuation of diuretic therapy in a patient with HF-REF and volume overload or severe hypertension in patients with HF-PEF) (Table 19). The ‘acuteness’ may
Table 19  Precipitants and causes of acute heart failure

<table>
<thead>
<tr>
<th>Events usually leading to rapid deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rapid arrhythmia or severe bradycardia/conduction disturbance</td>
</tr>
<tr>
<td>• Acute coronary syndrome</td>
</tr>
<tr>
<td>• Mechanical complication of acute coronary syndrome (e.g. rupture of interventricular septum, mitral valve chordal rupture, right ventricular infarction)</td>
</tr>
<tr>
<td>• Acute pulmonary embolism</td>
</tr>
<tr>
<td>• Hypertensive crisis</td>
</tr>
<tr>
<td>• Cardiac tamponade</td>
</tr>
<tr>
<td>• Aortic dissection</td>
</tr>
<tr>
<td>• Surgery and perioperative problems</td>
</tr>
<tr>
<td>• Peripartum cardiomyopathy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Events usually leading to less rapid deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Infection (including infective endocarditis)</td>
</tr>
<tr>
<td>• Exacerbation of COPD/asthma</td>
</tr>
<tr>
<td>• Anaemia</td>
</tr>
<tr>
<td>• Kidney dysfunction</td>
</tr>
<tr>
<td>• Non-adherence to diet/drug therapy</td>
</tr>
<tr>
<td>• Iatrogenic causes (e.g. prescription of an NSAID or corticosteroid; drug interactions)</td>
</tr>
<tr>
<td>• Arrhythmias, bradycardia, and conduction disturbances not leading to sudden, severe change in heart rate</td>
</tr>
<tr>
<td>• Uncontrolled hypertension</td>
</tr>
<tr>
<td>• Hypothyroidism or hyperthyroidism</td>
</tr>
<tr>
<td>• Alcohol and drug abuse</td>
</tr>
</tbody>
</table>

AHF = acute heart failure; COPD = chronic obstructive pulmonary disease; NSAID = non-steroidal anti-inflammatory drug.

12.1 Initial assessment and monitoring of patients

Three parallel assessments must be made during the initial evaluation of the patient, aided by the investigations listed in Figure 4.

(i) Does the patient have HF or is there an alternative cause for their symptoms and signs (e.g. chronic lung disease, anaemia, kidney failure, or pulmonary embolism)?

(ii) If the patient does have HF, is there a precipitant and does it require immediate treatment or correction (e.g. an arrhythmia or acute coronary syndrome)?

(iii) Is the patient’s condition immediately life-threatening because of hypoxaemia or hypotension leading to underperfusion of the vital organs (heart, kidneys, and brain)?

12.2 Treatment of acute heart failure

Often treatment must be administered in parallel with the diagnostic work-up (see treatment algorithm, Figure 5). Although not ‘evidence based’ in the same way as treatments for chronic HF, the key drugs are oxygen, diuretics, and vasodilators. Opiates and inotropes are used more selectively, and mechanical support of the circulation is required only rarely. Non-invasive ventilation is used commonly in many centres, but invasive ventilation is required in only a minority of patients.

Systolic blood pressure, heart rhythm and rate, saturation of peripheral oxygen (SpO₂) using a pulse oximeter, and urine output should be monitored on a regular and frequent basis until the patient is stabilized (see also Sections 12.3 and 12.4).

12.2.1 Pharmacological therapy

12.2.1.1 Acute management

Oxygen

Oxygen may be given to treat hypoxaemia (SpO₂ <90%), which is associated with an increased risk of short-term mortality. Oxygen should not be used routinely in non-hypoxaemic patients as it causes vasodilatation and a reduction in cardiac output.224

Diuretics

Most patients with dyspnoea caused by pulmonary oedema obtain rapid symptomatic relief from administration of an i.v. diuretic, as a result of both an immediate venodilator action and subsequent removal of fluid. The optimum dose and route of administration (bolus or continuous infusion) are uncertain. A recent, small, prospective RCT compared 12-hourly bolus injection with continuous infusion and low-dose (equal to pre-existing oral dose) with high-dose (×2.5 times previous oral dose) using a 2 × 2 factorial design.213 There was no difference between either of the treatment comparisons for the co-primary endpoints (patient global assessment of symptoms and change in serum creatinine). Compared with the low-dose strategy, the high-dose strategy was, however, associated with greater improvement in a number of secondary outcomes (including dyspnoea) but at the expense of more transient worsening of renal function.

In patients with resistant peripheral oedema (and ascites), a combination of a loop and a thiazide (e.g. bendroflumethiazide)
or thiazide-like diuretic (metolazone) may be needed to achieve an adequate diuresis (see Appendix F). This potent combination is usually only needed for a few days and requires careful monitoring to avoid hypokalaemia, renal dysfunction, and hypovolaemia.

Opiates

Opiates such as morphine may be useful in some patients with acute pulmonary oedema as they reduce anxiety and relieve distress associated with dyspnoea. Opiates are also thought to be venodilators, reducing preload, and may also reduce sympathetic drive. Conversely, opiates induce nausea (necessitating the concomitant administration of an antiemetic, one of which, cyclizine, has vasoconstrictor activity) and depress respiratory drive, potentially increasing the need for invasive ventilation.

Vasodilators

Although vasodilators such as nitroglycerine (Table 20) reduce preload and afterload and increase stroke volume, there is no robust evidence that they relieve dyspnoea or improve other clinical outcomes. Vasodilators are probably most useful in patients with hypertension and should be avoided in patients with a systolic blood pressure <110 mmHg. Excessive falls in blood pressure should also be avoided because hypotension is associated with higher mortality in patients with AHF. Vasodilators should be used with caution in patients with significant mitral or aortic stenosis.

<table>
<thead>
<tr>
<th>Table 20</th>
<th>Intravenous vasodilators used to treat acute heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vasodilator</strong></td>
<td><strong>Dosing</strong></td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>Start with 10–20 µg/min, increase up to 200 µg/min</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>Start with 1 mg/h, increase up to 10 mg/h</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>Start with 0.3 µg/kg/min and increase up to 5 µg/kg/min</td>
</tr>
<tr>
<td>Nesiritide</td>
<td>Bolus 2 µg/kg + infusion 0.01 µg/kg/min</td>
</tr>
</tbody>
</table>

*Not available in many European Society of Cardiology countries.*
Nesiritide
Nesiritide—a human BNP that acts mainly as a vasodilator—was recently shown to reduce dyspnoea by a small but statistically significant amount when added to conventional treatment (mainly diuretic).228

Inotropes
Use of an inotrope such as dobutamine (Table 21) should usually be reserved for patients with such severe reduction in cardiac output that vital organ perfusion is compromised. Such patients are almost always hypotensive (‘shocked’). Inotropes cause sinus tachycardia and may induce myocardial ischaemia and arrhythmias. There is long-standing concern that they may increase mortality. There is pharmacological rationale to use levosimendan (or a phosphodiesterase III inhibitor such as milrinone) if it is felt necessary to counteract the effect of a beta-blocker.

Vaspressors
Drugs with prominent peripheral arterial vasoconstrictor action such as norepinephrine (Table 21) are sometimes given to severely ill patients with marked hypotension. These agents are given to raise blood pressure and redistribute cardiac output from the extremities to the vital organs. However, this is at the expense of an increase in LV afterload, and these agents have adverse effects similar to those of inotropes (and the most commonly used of these agents, norepinephrine and epinephrine, have inotropic activity). Their use should be restricted to patients with persistent hypoperfusion despite adequate cardiac filling pressures.

Table 21 Drugs used to treat acute heart failure that are positive inotropes or vasopressors or both

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bolus</th>
<th>Infusion rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>No</td>
<td>2–20 µg/kg/min (£+)</td>
</tr>
<tr>
<td>Dopamine</td>
<td>No</td>
<td>&lt;3 µg/kg/min; renal effect (£+)</td>
</tr>
<tr>
<td>Milrinone</td>
<td>25–75 µg/kg over 10–20 min</td>
<td>0.375–0.75 µg/kg/min (£+)</td>
</tr>
<tr>
<td>Enoximone</td>
<td>0.5–1.0 mg/kg over 5–10 min</td>
<td>5–20 µg/kg/min (£+)</td>
</tr>
<tr>
<td>Levosimendan</td>
<td>12 µg/kg over 10 min (optional)</td>
<td>0.1 µg/kg/min, which can be decreased to 0.05 or increased to 0.2 µg/kg/min (£+)</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>No</td>
<td>0.2–1.0 µg/kg/min (£+)</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Bolus: 1 mg can be given i.v. during resuscitation, repeated every 3–5 min</td>
<td>0.05–0.5 µg/kg/min (£+)</td>
</tr>
</tbody>
</table>

Dopamine
In large doses (>5 µg/kg/min) dopamine has inotropic and vasoconstrictor activity. At lower doses (<3 µg/kg/min) dopamine may have a selective renal arterial vasodilator activity and promote natriuresis, although this is uncertain. Dopamine may cause hypoxaemia.229 Arterial oxygen saturation should be monitored, and supplemental oxygen administered as required.

Other pharmacological therapy
Thrombo-embolism prophylaxis with heparin or another anti-coagulant should be used, unless contraindicated or unnecessary (because of existing treatment with oral anti-coagulants).214–216 Tolvaptan (a vasopressin V2-receptor antagonist) may be used to treat patients with resistant hyponaetraemia (thirst and dehydration are recognized adverse effects).230

12.2.1.2 After stabilization
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker
In patients with reduced EF not already receiving an ACE inhibitor (or ARB), this treatment should be started as soon as possible, blood pressure and renal function permitting (see recommendations in Section 7.2.1 and Appendix C). The dose should be up-titrated as far as possible before discharge, and a plan made to complete dose up-titration after discharge.

Beta-blocker
In patients with reduced EF not already receiving a beta-blocker, this treatment should be started as soon as possible after stabilization, blood pressure and heart rate permitting (see recommendations in Section 7.1 and Appendix D). The dose should be up-titrated as far as possible before discharge, and a plan made to complete dose up-titration after discharge. It has been shown that beta-blocker treatment may be continued in many patients during an episode of decompensation and started safely before discharge after an episode of decompensation.

Mineralocorticoid (aldosterone) receptor antagonist
In patients with reduced EF not already receiving an MRA, this treatment should be started as soon as possible, renal function and potassium permitting (see recommendations in Section 7.2 and Appendix E). As the dose of MRA used to treat HF has a minimal effect on blood pressure, even relatively hypotensive patients may be started on this therapy during admission. The dose should be up-titrated as far as possible before discharge, and a plan made to complete dose up-titration after discharge.

Digoxin
In patients with reduced EF, digoxin may be used to control the ventricular rate in AF, especially if it has not been possible to up-titrade the dose of beta-blocker. Digoxin may also provide symptom benefit and reduce the risk of HF hospitalization in patients with severe systolic HF (see recommendations in Section 7.2.6).

12.2.2 Non-pharmacological/non-device therapy
It is common to restrict sodium intake to <2 g/day and fluid intake to <1.5–2.0 L/day, especially (the latter in hyponatraemic
Recommendations for the treatment of patients with acute heart failure

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class$^a$</th>
<th>Level$^b$</th>
<th>Ref$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with pulmonary congestion/oedema without shock</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>An i.v. loop diuretic is recommended to improve breathlessness and relieve congestion. Symptoms, urine output, renal function, and electrolytes should be monitored regularly during use of i.v. diuretic.</td>
<td>I</td>
<td>B</td>
<td>213</td>
</tr>
<tr>
<td>High-flow oxygen is recommended in patients with a capillary oxygen saturation &lt;90% or PaO$_2$ &lt;60 mmHg (8.0 kPa) to correct hypoxaemia.</td>
<td>I</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>Thrombo-embolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism.</td>
<td>I</td>
<td>A</td>
<td>214-216</td>
</tr>
<tr>
<td>Non-invasive ventilation (e.g. CPAP) should be considered in dyspnoeic patients with pulmonary oedema and a respiratory rate &gt;20 breaths/min to improve breathlessness and reduce hypercapnia and acidosis. Non-invasive ventilation can reduce blood pressure and should not generally be used in patients with a systolic blood pressure &lt;85 mmHg (and blood pressure should be monitored regularly when this treatment is used).</td>
<td>IIa</td>
<td>B</td>
<td>217</td>
</tr>
<tr>
<td>An i.v. opiate (along with an anxiolytic) should be considered in particularly anxious, restless, or distressed patients to relieve these symptoms and improve breathlessness. Alertness and ventilatory effort should be monitored frequently after administration because opiates can depress respiration.</td>
<td>IIa</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>An i.v. infusion of a nitrates should be considered in patients with pulmonary congestion/oedema and a systolic blood pressure &gt;110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Nitrates may also relieve dyspnoea and congestion. Symptoms and blood pressure should be monitored frequently during administration of i.v. nitrates.</td>
<td>IIa</td>
<td>B</td>
<td>218,219</td>
</tr>
<tr>
<td>An i.v. infusion of sodium nitroprusside may be considered in patients with pulmonary congestion/oedema and a systolic blood pressure &gt;110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Caution is recommended in patients with acute myocardial infarction. Nitroprusside may also relieve dyspnoea and congestion. Symptoms and blood pressure should be monitored frequently during administration of i.v. nitroprusside.</td>
<td>IIb</td>
<td>B</td>
<td>220</td>
</tr>
<tr>
<td>Inotropic agents are NOT recommended unless the patient is hypotensive (systolic blood pressure &lt;85 mmHg), hypoperfused, or shocked because of safety concerns (atrial and ventricular arrhythmias, myocardial ischaemia, and death).</td>
<td>III</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td><strong>Patients with hypotension, hypoperfusion or shock</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrical cardioversion is recommended if an atrial or ventricular arrhythmia is thought to be contributing to the patient’s haemodynamic compromise in order to restore sinus rhythm and improve the patient’s clinical condition.</td>
<td>I</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>An i.v. infusion of an inotrope (e.g. dobutamine) should be considered in patients with hypotension (systolic blood pressure &lt;85 mmHg) and/or hypoperfusion to increase cardiac output, increase blood pressure, and improve peripheral perfusion. The ECG should be monitored continuously because inotropic agents can cause arrhythmias and myocardial ischaemia.</td>
<td>IIa</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>Short-term mechanical circulatory support should be considered (as a ‘bridge to recovery’) in patients remaining severely hypoperfused despite inotropic therapy and with a potentially reversible cause (e.g. viral myocarditis) or a potentially surgically correctable cause (e.g. acute interventricular septal rupture).</td>
<td>IIa</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>An i.v. infusion of levosimendan (or a phosphodiesterase inhibitor) may be considered to reverse the effect of beta-blockade if beta-blockade is thought to be contributing to hypoperfusion. The ECG should be monitored continuously because inotropic agents can cause arrhythmias and myocardial ischaemia, and, as these agents are also vasodilators, blood pressure should be monitored carefully.</td>
<td>IIb</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>A vasopressor (e.g. dopamine or norepinephrine) may be considered in patients who have cardiogenic shock, despite treatment with an inotrope, to increase blood pressure and vital organ perfusion. The ECG should be monitored as these agents can cause arrhythmias and/or myocardial ischaemia. Intra-arterial blood pressure measurement should be considered.</td>
<td>IIb</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>Short-term mechanical circulatory support may be considered (as a ‘bridge to decision’) in patients deteriorating rapidly before a full diagnostic and clinical evaluation can be made.</td>
<td>IIb</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td><strong>Patients with an ACS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate primary PCI (or CABG in selected cases) is recommended if there is an ST elevation or a new LBBB ACS in order to reduce the extent of myocyte necrosis and reduce the risk of premature death.</td>
<td>I</td>
<td>A</td>
<td>221</td>
</tr>
<tr>
<td><strong>Alternative to PCI or CABG:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous thrombolytic therapy is recommended, if PCI/CABG cannot be performed, if there is ST-segment elevation or new LBBB, to reduce the extent of myocyte necrosis and reduce the risk of premature death.</td>
<td>I</td>
<td>A</td>
<td>222</td>
</tr>
<tr>
<td>Early PCI (or CABG in selected patients) is recommended if there is non-ST elevation ACS in order to reduce the risk of recurrent ACS. Urgent revascularization is recommended if the patient is haemodynamically unstable.</td>
<td>I</td>
<td>A</td>
<td>221</td>
</tr>
<tr>
<td>Eplerenone is recommended to reduce the risk of death and subsequent cardiovascular hospitalization in patients with an EF &lt;40%.</td>
<td>I</td>
<td>B</td>
<td>107</td>
</tr>
</tbody>
</table>
Recommended for the treatment of patients with acute heart failure (Cont.)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with an ACS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>An ACE inhibitor (or ARB) is recommended in patients with an EF ≤40%, after stabilization, to reduce the risk of death, recurrent myocardial infarction, and hospitalization for HF.</td>
<td>I</td>
<td>A</td>
<td>101</td>
</tr>
<tr>
<td>A beta-blocker is recommended in patients with an EF ≤40%, after stabilization, to reduce the risk of death and recurrent myocardial infarction.</td>
<td>I</td>
<td>B</td>
<td>223</td>
</tr>
<tr>
<td>An i.v. opiate (along with an antiemetic) should be considered in patients with ischaemic chest pain to relieve this symptom (and improve breathlessness). Alertness and ventilatory effort should be monitored frequently after administration because opiates can depress respiration.</td>
<td>IIa</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>Patients with AF and a rapid ventricular rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients should be fully anticoagulated (e.g. with i.v. heparin), if not already anticoagulated and with no contraindication to anticoagulation, as soon as AF is detected to reduce the risk of systemic arterial embolism and stroke.</td>
<td>I</td>
<td>A</td>
<td>184</td>
</tr>
<tr>
<td>Electrical cardioversion is recommended in patients haemodynamically compromised by AF and in whom urgent restoration of sinus rhythm is required to improve the patient’s clinical condition rapidly.</td>
<td>I</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>Electrical cardioversion or pharmacological cardioversion with amiodarone should be considered in patients when a decision is made to restore sinus rhythm non-urgently (‘rhythm control’ strategy). This strategy should only be employed in patients with a first episode of AF of ≤48 h duration (or in patients with no evidence of left atrial appendage thrombus on TOE).</td>
<td>I</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>Intravenous administration of a cardiac glycoside should be considered for rapid control of the ventricular rate.</td>
<td>I</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>Dronedarone is not recommended because of safety concerns (increased risk of hospital admission for cardiovascular causes and an increased risk of premature death), particularly in patients with an EF ≤40%.</td>
<td>III</td>
<td>A</td>
<td>176</td>
</tr>
<tr>
<td>Class I antiarrhythmic agents are not recommended because of safety concerns (increased risk of premature death), particularly in patients with LV systolic dysfunction.</td>
<td>III</td>
<td>A</td>
<td>178</td>
</tr>
<tr>
<td>Patients with severe bradycardia or heart block</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacing is recommended in patients haemodynamically compromised by severe bradycardia or heart block to improve the patient’s clinical condition.</td>
<td>I</td>
<td>C</td>
<td>–</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; CPAP = continuous positive airway pressure; ECG = electrocardiogram; EF = ejection fraction; HF = heart failure; i.v. = intravenous; LBBB = left bundle branch block; LMWH = low molecular weight heparin; LV = left ventricular; PaO₂ = partial pressure of oxygen; PCI = percutaneous coronary intervention; TOE = transoesophageal echocardiography.

1. Class of recommendation.
2. Level of evidence.
3. References.

patients) during the initial management of an acute episode of HF associated with volume overload, although there is no firm evidence to support this practice.

12.2.2.1 Ventilation

Non-invasive ventilation

Continuous positive airway pressure (CPAP) and non-invasive positive pressure ventilation (NIPPV) relieve dyspnoea and improve certain physiological measures (e.g. oxygen saturation) in patients with acute pulmonary oedema. However, a recent large RCT showed that neither type of non-invasive ventilation reduced mortality or the rate of endotracheal intubation when compared with standard therapy, including nitrates (in 90% of patients) and opiates (in 51% of patients). This result is in contrast to the findings of meta-analyses of earlier, smaller studies. Non-invasive ventilation may be used as adjunctive therapy to relieve symptoms in patients with pulmonary oedema and severe respiratory distress or who fail to improve with pharmacological therapy. Contraindications include hypotension, vomiting, possible pneumothorax, and depressed consciousness.

Endotracheal intubation and invasive ventilation

The primary indication for endotracheal intubation and invasive ventilation is respiratory failure leading to hypoxaemia, hypercapnia, and acidosis. Physical exhaustion, diminished consciousness, and inability to maintain or protect the airway are other reasons to consider intubation and ventilation.

12.2.2.2 Mechanical circulatory support

Intra-aortic balloon pump

The conventional indications for an intra-aortic balloon pump (IABP) are to support the circulation before surgical correction of specific acute mechanical problems (e.g. interventricular septal rupture and acute mitral regurgitation), during severe acute myocarditis and in selected patients with acute myocardial ischaemia or infarction before, during, and after percutaneous or surgical revascularization. There is no good evidence that an IABP is of benefit in other causes of cardiogenic shock. More recently, balloon pumps (and other types of short-term, temporary circulatory support) have been used to bridge patients until implantation of a ventricular assist device or heart transplantation (see Section 13.5).
Acute pulmonary oedema/congestion

- Invasive bolus of loop diuretic
  - Hypoalbuminemia
    - Yes
    - Oxygen
  - No

- Measure systolic blood pressure
  - SBP <85 mmHg or shock
    - Add non-vasodilating inotrope
    - No additional therapy until response assessed
  - SBP 85–110 mmHg
    - No additional therapy until response assessed
  - SBP >110 mmHg
    - Consider vasodilator (e.g. NTG)

- Adequate response to treatment
  - Yes
  - Continue present treatment
  - No

- Re-evaluation of patient’s clinical status
  - SBP <85 mmHg
    - Stop vasodilator
    - Stop beta-blocker if hypotensive
    - Consider non-vasodilating inotrope or vasopressor
    - Consider right-heart catheterization
    - Consider mechanical circulatory support
  - Yes

- Urine output <20 mL/h
  - Yes
  - Bladder catheterization to confirm adequate diuresis
  - Increase dose of diuretic or use combination of diuretics
  - Consider low-dose dopamine
  - Consider right-heart catheterization
  - Consider ultrafiltration

- Oxygen
  - Yes
  - Consider IVF
  - Consider TTE and invasive ventilation

- Severe anxiety/distress
  - Yes
  - Consider i.v. opiate

- Cold skin, low pulse volume, poor urine output, confusion, myocardial ischaemia

- A dose of >100 µg/min is rarely needed.

- An adequate response includes reduction in dyspnoea and adequate diuresis (>100 mL/hr urine production in first 2 h), accompanied by an increase in oxygen saturation (if hypoxaemic) and usually reduction in heart and respiratory rate (which should occur in 1–2 h). Peripheral blood flow may also increase as indicated by a reduction in skin vasoconstriction, an increase in skin temperature, and improvement in skin colour. There may also be a decrease in lung crackles.

- Once the patient is comfortable and a stable diuresis has been established, withdrawal of i.v. therapy can be considered (with substitution of oral diuretic treatment).

- For symptoms relevant to HF (dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea), associated co-morbidity (e.g. chest pain due to myocardial ischaemia), and treatment-related adverse effects (e.g. symptomatic hypotension). Assess for signs of peripheral and pulmonary congestion/oedema, heart rate and rhythm, blood pressure, peripheral perfusion, respiratory rate, and respiratory effort. An ECG (rhythm/arrhythmia and infarction) and blood chemistry/biochemistry (sodium, electrolyte disturbances, kidney failure) should also be examined. Pulse oximetry (or arterial blood gas measurements) should be checked and echocardiography performed (if not already carried out).

- Less than 100 mL/h over 1–2 h is an inadequate initial response to i.v. diuretic (confirm is inadequate by catheterizing bladder).

- In patients with persistently low blood pressure/shock, consider alternative diagnoses (e.g. pulmonary embolism), acute mechanical problems, and severe valve disease (particularly aortic stenosis). Pulmonary artery catheterization may identify patients with an inadequate left ventricular filling pressure (and characterize the patient’s haemodynamic pattern, enabling more precise tailoring of vasoactive therapy).

- An intra-aortic balloon pump or other mechanical circulatory support should be considered in patients without contraindications.

- CRP or NPPV (see Section 12.2.2.1) should be considered in patients without contraindications.

- Consider endotracheal intubation and invasive ventilation if worsening hypoxaemia, failing respiratory effort, increasing confusion, etc.

- Double dose of loop diuretic up to equivalent of furosemide 500 mg (doses of 250 mg and above should be given by infusion over 4 h).

- No response to doubling of dose of diuretics despite adequate left ventricular filling pressure (either inferred or measured directly) start i.v. infusion of dopamine 2.5 µg/kg/min. Higher doses are not recommended to enhance diuresis.

- If steps 17 and 18 do not result in an adequate diuresis and the patient remains in pulmonary oedema, venousous isolated ultrafiltration should be considered.

CRP = C-reactive protein; PaO2 = partial pressure of oxygen; SBP = systolic blood pressure; SpO2 = saturation of peripheral oxygen.

Figure 5 Algorithm for management of acute pulmonary oedema/congestion.
Ventricular assist devices

Ventricular assist devices and other forms of mechanical circulatory support (MCS) may be used as a ‘bridge to decision’ or longer term in selected patients (see Section 13.5).

12.2.2.3 Ultrafiltration

Venovenous isolated ultrafiltration is sometimes used to remove fluid in patients with HF, although is usually reserved for those unresponsive or resistant to diuretics.

12.3 Invasive monitoring

12.3.1 Intra-arterial line

Insertion of an intra-arterial line should only be considered in patients with persistent HF and a low systolic blood pressure despite treatment.

12.3.2 Pulmonary artery catheterization

Right heart catheterization does not have a general role in the management of AHF, but may help in the treatment of a minority of selected patients with acute (and chronic) HF. Pulmonary artery catheterization should only be considered in patients: (i) who are refractory to pharmacological treatment; (ii) who are persistently hypotensive; (iii) in whom LV filling pressure is uncertain; or (iv) who are being considered for cardiac surgery. A primary concern is to ensure that hypotension (and worsening renal function) is not due to inadequate LV filling pressure, in which case diuretic and vasodilator therapy should be reduced (and volume replacement may be required). Conversely, a high LV filling pressure and/or systemic vascular resistance may suggest an alternative pharmacological strategy (e.g. inotropic or vasodilator therapy), depending on blood pressure. Measurement of pulmonary vascular resistance (and its reversibility) is a routine part of the surgical work-up before cardiac transplantation.

12.4 Monitoring after stabilization

Heart rate, rhythm, blood pressure, and oxygen saturation should be monitored continuously for at least the first 24 h of admission, and frequently thereafter. Symptoms relevant to HF (e.g. dyspnoea) and related to the adverse effects of treatments used (e.g. dizziness) should be assessed at least daily. Fluid intake and output, weight, and the jugular venous pressure and extent of pulmonary and peripheral oedema (and ascites if present) should be measured daily to evaluate the correction of volume overload. Blood urea nitrogen, creatinine, potassium, and sodium should be monitored daily during i.v. therapy and when renin–angiotensin–aldosterone system antagonists are being initiated or if the dose of any of these drugs is changed.

12.5 Other in-patient assessments

After initial treatment of the acute episode, every patient should be assessed for possible causes of HF (if the HF is new) and precipitants of worsening (if the HF has previously been diagnosed). The focus is detection of reversible or treatable causes (Table 19).

12.6 Readiness for discharge

Before discharge is contemplated, the acute episode of HF should have resolved and, in particular, congestion should be absent and a stable oral diuretic regimen established for at least 48 h.

Long-term disease-modifying therapy (including a beta-blocker) should be optimized as much as possible and appropriate education provided to the patient and family/caregivers. Pre- and post-discharge management should follow the standards of care laid out by the Heart Failure Association. The goals of treatment during the different stages of management of patients with HF are summarized in Table 22.

<table>
<thead>
<tr>
<th>Table 22</th>
<th>Goals of treatment in acute heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate (ED/ICU/CCU)</td>
<td>• Treat symptoms&lt;br&gt;• Restore oxygenation&lt;br&gt;• Improve haemodynamics and organ perfusion&lt;br&gt;• Limit cardiac and renal damage&lt;br&gt;• Prevent thrombo-embolism&lt;br&gt;• Minimize ICU length of stay</td>
</tr>
<tr>
<td>Intermediate (in hospital)</td>
<td>• Stabilize patient and optimize treatment strategy&lt;br&gt;• Initiate and up-titrade disease-modifying pharmacological therapy&lt;br&gt;• Consider device therapy in appropriate patients&lt;br&gt;• Identify etiology and relevant co-morbidities</td>
</tr>
<tr>
<td>Pre-discharge and long-term management</td>
<td>• Plan follow-up strategy&lt;br&gt;• Enrol in disease management programme, educate, and initiate appropriate lifestyle adjustments&lt;br&gt;• Plan to up-titrade optimize dose of disease-modifying drugs&lt;br&gt;• Ensure assessed for appropriate device therapy&lt;br&gt;• Prevent early readmission&lt;br&gt;• Improve symptoms, quality of life, and survival</td>
</tr>
</tbody>
</table>

CCU = coronary care unit; ED = emergency department; ICU = intensive care unit.

12.7 Special patient populations

12.7.1 Patients with a concomitant acute coronary syndrome

Patients with a concomitant acute coronary syndrome should be assessed and treated according to the current acute coronary syndrome guidelines. They should undergo coronary angiography and revascularization as appropriate. This should be undertaken as an urgent procedure in patients with haemodynamic instability and as an emergency procedure in those in cardiogenic shock. If haemodynamic instability persists despite optimal medical treatment, an IABP should be inserted before coronary angiography and revascularization. Persistent haemodynamic instability may also be caused by mechanical complications of infarction (e.g. mitral valve papillary muscle rupture), which may be identified using echocardiography and may require urgent corrective surgery.
12.7.2 Isolated right ventricular failure

New-onset isolated right ventricular failure may occur secondarily to an acute coronary syndrome (and is managed as described above) and following massive pulmonary embolism (see pulmonary embolism guidelines). In both situations, diuretics and vasodilators should be used cautiously or avoided so as not to reduce right ventricular filling.

Progressive isolated right ventricular failure may occur in patients with pulmonary hypertension. Type V phosphodiesterase inhibitors, endothelin antagonists, and prostacyclin analogues may help by decreasing pulmonary arterial resistance (see guidelines).

12.7.3 Acute heart failure with ‘cardiorenal syndrome’

Acutely worsening HF, or its treatment, or both may cause acute worsening of renal function (the so-called ‘type 1 cardiorenal syndrome’) in up to one-third of patients, and is associated with worse outcomes.66,244 An acute renal cardiorenal syndrome (the so-called ‘type 3 cardiorenal syndrome’), characterized by worsening cardiac function secondary to volume overload resulting from acute kidney injury, may also occur, but is less common. The main management issues with these patients are that renal dysfunction may limit the use of renin–angiotensin–aldosterone system blockers and that progressive uraemia and volume overload may necessitate renal replacement therapy. Often these patients are best cared for jointly with a nephrologist.

12.7.4 Perioperative acute heart failure

AHF may occur in patients before (e.g., because of pre-operative infarction), during (‘failure to wean’), and after (mechanical complications and pericardial tamponade must be excluded) cardiac surgery. The specialized management of this group of patients is described in detail elsewhere and may involve use of mechanical support, including extracorporeal membrane oxygenation (ECMO).

12.7.5 Peripartum cardiomyopathy

A high index of suspicion is needed to avoid late diagnosis of this serious condition, the management of which is described in detail in a Heart Failure Association statement and elsewhere.

12.7.6 Adult congenital heart disease

Patients with adult congenital heart disease (ACHD) are a very heterogeneous patient population. The diagnosis and management of HF in these patients can be very complex, and close collaboration with a tertiary referral centre is mandatory.

Patients with ACHD may present with HF due to a reduced systolic LVEF, reduced systemic right ventricular EF, or isolated sub-pulmonary right ventricular failure (see Section 12.7.2). Patients with univentricular hearts, either unoperated or palliated by a Fontan procedure, are particularly difficult to evaluate and treat. CMR and cardiopulmonary exercise testing are especially valuable in their assessment, but the acquisition and interpretation of data require special expertise.

There is a lack of multicentre RCTs to guide the treatment of HF in patients with ACHD. There are, however, a number of general empirical principles of management: (i) residual (post-repair) or new haemodynamic lesions should always be sought first; (ii) the value of ACE inhibitors, ARBs, and beta-blockers in ACHD is controversial and these drugs may even be harmful in certain patients, e.g. those with a Fontan circulation (see ESC guidelines); (iii) pulmonary arterial vasodilators may be useful in certain patients with pulmonary hypertension (see ESC guidelines); (iv) the role of CRT is unknown; and (v) heart transplantation is an option but may be precluded by factors such as complex cardiovascular anatomy, and renal and hepatic dysfunction.

13. Coronary revascularization and surgery, including valve surgery, ventricular assist devices, and transplantation

13.1 Coronary revascularization

Surgical (and percutaneous) coronary revascularization is indicated for the relief of angina pectoris in patients with either HF-REF or HF-PEF, and surgical coronary revascularization is indicated for ‘prognostic’ reasons in other patients with severe CAD, particularly those with three-vessel disease or left-main stenosis. The detailed indications for coronary revascularization are covered elsewhere.

This section focuses on recent developments relevant to HF. The Surgical Treatment for Ischemic Heart Failure (STICH) trial addressed the broader role of surgical revascularization in patients with HF-REF and less severe CAD. Patients with an EF ≤35% and CAD who were suitable for surgery were randomized to coronary artery bypass graft (CABG) plus medical therapy or medical therapy alone. The patients enrolled were young (average age 60 years), predominantly male (88%), and were in NYHA class I (11%), II (52%), or III (34%). Their Canadian Cardiovascular Society angina class was 0 in 36%, I in 16%, II in 43%, III in 4%, and IV in 1%. Most patients had two-vessel (31%) or three-vessel (60%) CAD, and 68% had a severe proximal left anterior descending stenosis; very few (2%) had a left-main stenosis. The primary outcome (all-cause death) was not reduced by CABG. CABG did, however, reduce the secondary outcomes of cardiovascular death (RRR 19%) and death from any cause or cardiovascular hospitalization (RRR 26%). This trial may therefore extend the indication for CABG to ‘STICH-like’ patients with two-vessel CAD, including a left anterior descending stenosis, who are otherwise suitable for surgery and expected to survive >1 year with good functional status.

The benefit–risk balance for CABG in patients without angina/ischaemia or without viable myocardium remains uncertain. Patients with >10% of dysfunctional but viable LV myocardium may be more likely to benefit from myocardial revascularization (and those with ≤10% less likely to benefit) although this approach to patient selection for revascularization is unproven. Several non-invasive techniques can be used to assess myocardial viability (Table 7). Nuclear imaging has a high sensitivity, whereas techniques evaluating contractile reserve have lower sensitivity but higher specificity. CMR is excellent for assessing the transmural extent of scar, but is not better at detecting viability or predicting recovery of wall motion.

The choice between percutaneous coronary intervention and CABG should be made by the Heart Team, including a HF specialist, and be based on the extent of CAD, expected completeness of...
13.2 Ventricular reconstruction

The value of surgical ventricular reconstruction during which scar tissue is removed from the LV wall, with the aim of restoring a more physiological LV volume and shape, is uncertain and was not shown to be of benefit in STICH.\textsuperscript{246} This technique is not recommended for routine use and is discussed further in the revascularization guidelines.\textsuperscript{71} External containment devices are not recommended.

13.3 Valvular surgery

Valvular heart disease may cause or aggravate HF. This section briefly addresses problems particularly relevant to HF, and the reader is referred to the recent ESC/European Association for Cardio-Thoracic Surgery guidelines on valvular disease for more information.\textsuperscript{247}

13.3.1 Aortic stenosis

The main concern in patients with LV systolic dysfunction is the entity of ‘low-flow, low-gradient’ aortic stenosis (valve area $<1$ cm$^2$, EF $<40\%$, mean gradient $<40$ mmHg) because some may have severe aortic stenosis and others ‘pseudo-aortic stenosis’ (i.e. where the low flow across the aortic valve is not caused by a severe fixed obstruction but by low stroke volume). In such individuals, low-dose dobutamine stress echocardiography may help differentiate between these two types of patient and provide information about contractile reserve which is of prognostic importance. In patients with severe aortic stenosis and a low EF, individuals with contractile reserve have a lower operative mortality and better long-term prognosis.

If the mean gradient is $>$40 mmHg, there is theoretically no lower EF limit for aortic valve replacement in symptomatic patients with severe aortic stenosis. However, substantial recovery of LV function is only likely when the reduced EF is caused by excessive afterload and is not due to scar.

Medical treatment should be optimized, although vasodilators (ACE inhibitors, ARBs, renin inhibitors, CCBs, hydralazine, and nitrates) may cause substantial hypotension in patients with severe aortic stenosis and should only be used with great caution. Optimization of treatment should not delay surgical decision-making. In patients not medically fit for surgery (e.g. because of severe pulmonary disease), transcatheter aortic valve replacement should be considered.\textsuperscript{248,249}

13.3.2 Aortic regurgitation

Aortic valve repair or replacement is recommended in all symptomatic patients and in asymptomatic patients with severe aortic regurgitation and an EF $<50\%$, who are otherwise fit for surgery. Surgery should also be considered in patients with severe aortic regurgitation and an LV end-diastolic diameter $>70$ mm or end-systolic diameter $>50$ mm (or $>25$ mm/m$^2$ body surface area if small stature).\textsuperscript{31} Surgery is indicated to reduce the risk of death, and HF and LV function usually improve after aortic valve repair.

It is important not to confuse mild to moderate aortic incompetence secondary to LV dilatation with LV dilatation and systolic dysfunction due to primary severe aortic regurgitation.

13.3.3 Mitral regurgitation

Assessment of mitral regurgitation is complex, particularly in patients with systolic dysfunction (and assessment of systolic function is complicated in the presence of mitral regurgitation—see Section 4.1). Differentiating between primary and secondary mitral regurgitation is crucial (see below).

The decision to recommend surgery should take account of symptoms, age, concurrent AF, reduced LV systolic function, pulmonary hypertension, and the suitability of the valve for repair, which are the most important predictors of post-operative outcome.

Primary (organic) mitral regurgitation

In primary mitral regurgitation due to flail leaflets, an LV end-systolic diameter $\geq 40$ mm is associated with increased mortality whether the patient is treated medically or surgically. When the EF is $<30\%$, a durable surgical repair may improve symptoms,
although its effect on survival is unknown. In this situation, the decision to operate should take account of response to medical therapy, co-morbidity, and the likelihood that the valve can be repaired (rather than replaced).

**Secondary mitral regurgitation**

This occurs because LV enlargement and remodelling lead to reduced leaflet closing. Effective medical therapy leading to reverse remodelling of the LV may reduce functional mitral regurgitation, and every effort should be made to optimize medical treatment in these patients.

Ischaemic mitral regurgitation is a particular type of secondary mitral regurgitation that may be more suitable for surgical repair. As it is often a dynamic condition, stress testing is important in its evaluation. An exercise-induced increase of effective regurgitant orifice (≥13 mm²) is associated with a worse prognosis. Combined valve and coronary surgery should be considered in symptomatic patients with LV systolic dysfunction, coronary arteries suitable for revascularization, and evidence of viability. Predictors of late failure of valve repair include large interpapillary muscle distance, severe posterior mitral leaflet tethering, and marked LV dilatation (LV end-diastolic diameter ≥65 mm). In these patients, mitral valve replacement, rather than repair, may be advisable. In the presence of AF, atrial ablation and left atrial appendage closure may be considered at the time of mitral valve surgery.

The role of isolated mitral valve surgery in patients with severe functional mitral regurgitation and severe LV systolic dysfunction who cannot be revascularized or have non-ischaemic cardiomyopathy is questionable, and in most patients conventional medical and device therapy are preferred. In selected cases, repair may be considered in order to avoid or postpone transplantation.

In patients with an indication for valve repair but judged inoperable or at unacceptably high surgical risk, percutaneous edge-to-edge repair may be considered in order to improve symptoms.250

### 13.4 Heart transplantation

Heart transplantation is an accepted treatment for end-stage HF.251,252 Although controlled trials have never been conducted, there is consensus that transplantation—provided that proper selection criteria are applied—significantly increases survival, exercise capacity, quality of life, and return to work compared with conventional treatment.

Apart from the shortage of donor hearts, the main challenges in transplantation are the consequences of the limited effectiveness and complications of immunosuppressive therapy in the long term (i.e. antibody-mediated rejection, infection, hypertension, renal failure, malignancy, and coronary artery vasculopathy). The indications for and contraindications to heart transplantation are summarized in Table 23.

#### 13.5 Mechanical circulatory support

MCS is an umbrella term describing a number of different technologies used to provide both short- and longer term assistance in patients with either chronic HF or AHF. A variety of terms have been used to describe the use of these technologies (Table 24).251,253 The most experience is with MCS in end-stage

---

### Table 23 Heart transplantation: indications and contraindications

<table>
<thead>
<tr>
<th>Patients to consider</th>
<th>End-stage heart failure with severe symptoms, a poor prognosis, and no remaining alternative treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Motivated, well informed, and emotionally stable</td>
</tr>
<tr>
<td></td>
<td>Capable of complying with the intensive treatment required post-operatively</td>
</tr>
</tbody>
</table>

**Contraindications**

- Active infection
- Severe peripheral arterial or cerebrovascular disease
- Current alcohol or drug abuse
- Treated cancer in previous 5 years
- Unhealed peptic ulcer
- Recent thrombo-embolism
- Significant renal failure (e.g. creatinine clearance <50 mL/min)
- Significant liver disease
- Systemic disease with multiorgan involvement
- Other serious co-morbidity with poor prognosis
- Emotional instability or untreated mental illness
- High, fixed pulmonary vascular resistance (>4–5 Wood Units and mean transpulmonary gradient >15 mmHg)

**HF** = heart failure.

### Table 24 Terms describing various uses of mechanical circulatory support (MCS)

<table>
<thead>
<tr>
<th>Bridge to decision (BTD):</th>
<th>Use of MCS in patients with drug-refractory acute circulatory collapse and at immediate risk of death to sustain life until a full clinical evaluation can be completed and additional therapeutic options can be evaluated.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bridge to candidacy (BTC):</td>
<td>Use of MCS to improve end-organ function in order to make an ineligible patient eligible for transplantation.</td>
</tr>
<tr>
<td>Bridge to transplantation (BTT):</td>
<td>Use of MCS to keep a patient at high risk of death before transplantation alive until a donor organ becomes available.</td>
</tr>
<tr>
<td>Bridge to recovery (BTR):</td>
<td>Use of MCS to keep a patient alive until intrinsic cardiac function recovers sufficiently to remove MCS.</td>
</tr>
<tr>
<td>Destination therapy (DT):</td>
<td>Long-term use of MCS as an alternative to transplantation in patients with end-stage heart failure ineligible for transplantation.</td>
</tr>
</tbody>
</table>

MCS = mechanical circulatory support.
HF, initially as bridge to transplantation (BTT), but more recently as destination therapy (DT).

### 13.5.1 End-stage heart failure

For selected patients with end-stage HF, transplantation remains the gold-standard treatment, with good long-term survival. However, because of the increasing numbers of patients with end-stage HF, limited organ donation, and technological advances, MCS with an LV assist device (LVAD) or bi-ventricular assist device (BiVAD) is increasingly seen as an alternative for some of these individuals. Initially MCS was used as a short-term BTT treatment (Table 24), but is now being used long-term, as so-called ‘destination therapy (DT)’, in patients not eligible for transplantation. Ventricular assist devices may ultimately become a more general alternative to transplantation, as current 2- to 3-year survival rates in carefully selected patients receiving the latest continuous flow devices are much better than with medical therapy only.\(^{254,255}\) Patients receiving these devices also have a post-transplant survival rate similar to those not requiring bridging. However, despite technological improvements, bleeding, thromboembolism (both of which can cause stroke), infection, and device failure remain significant problems; these issues, plus the high cost of devices and implantation, have limited their wider use. It is recommended that such devices are only implanted and managed at tertiary heart failure centres with appropriately trained, specialist HF physicians and surgeons. Ideally these centres should also undertake transplantation.

In some patients, LV reverse remodelling and functional improvement during MCS permit removal of the ventricular assist devices (‘bridge-to-recovery, BTR’). This outcome may occur in some patients with non-ischaemic cardiomyopathy, but is more likely in patients with an acute fulminant, but reversible, cause of HF such as acute myocarditis.\(^{256}\) Another concept is using MCS to permit recovery of end-organ dysfunction, so-called ‘bridge to candidacy (BTC)’, which may allow ineligible patients to become eligible for transplantation. The difficult decision to withdraw MCS may need to be made if the patient does not become eligible and DT is not possible.

### Table 25 Patients potentially eligible for implantation of a ventricular assist device

<table>
<thead>
<tr>
<th>Patients with &gt;2 months of severe symptoms despite optimal medical and device therapy and more than one of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• LVEF &lt;25% and, if measured, peak VO(_2) &lt; 12 mL/kg/min</td>
</tr>
<tr>
<td>• &gt;3 HF hospitalizations in previous 12 months without an obvious precipitating cause</td>
</tr>
<tr>
<td>• Dependence on i.v. inotropic therapy</td>
</tr>
<tr>
<td>• Progressive end-organ dysfunction (worsening renal and/or hepatic function) due to reduced perfusion and not to inadequate ventricular filling pressure (PCWP ≥20 mm Hg and SBP ≤80–90 mmHg or CI ≤2 L/min/m(^2))</td>
</tr>
<tr>
<td>• Deteriorating right ventricular function</td>
</tr>
</tbody>
</table>

\(\text{CI} = \text{cardiac index}; \text{HF} = \text{heart failure}; \text{i.v.} = \text{intravenous}; \text{LVEF} = \text{left ventricular ejection fraction}; \text{PCWP} = \text{pulmonary capillary wedge pressure}; \text{SBP} = \text{systolic blood pressure}.\)

### Recommendations for surgical implantation of LVADs in patients with systolic heart failure

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class(^a)</th>
<th>Level(^b)</th>
<th>Ref(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>An LVAD or BiVAD is recommended in selected patients(^d) with end-stage HF despite optimal pharmacological and device therapy and who are otherwise suitable for heart transplantation, to improve symptoms and reduce the risk of HF hospitalization for worsening HF and to reduce the risk of premature death while awaiting transplantation.</td>
<td>I</td>
<td>B</td>
<td>254, 255, 258</td>
</tr>
<tr>
<td>An LVAD should be considered in highly selected patients(^d) who have end-stage HF despite optimal pharmacological and device therapy and who are not suitable for heart transplantation, but are expected to survive &gt;1 year with good functional status, to improve symptoms, and reduce the risk of HF hospitalization and of premature death.</td>
<td>IIa</td>
<td>B</td>
<td>254</td>
</tr>
</tbody>
</table>

\(\text{LVAD} = \text{left ventricular assist device}; \text{BiVAD} = \text{bi-ventricular assist device}; \text{HF} = \text{heart failure}; \text{LVAD} = \text{left ventricular assist device}.\)

\(^a\)Level of evidence.

\(^b\)Class of recommendation.

\(^c\)References.

Typically, patients with end-stage HF considered for MCS are on continuous inotropic support (Table 25).\(^{211,253,257}\) Evaluation of right ventricular function is crucial as post-operative right ventricular failure greatly increases perioperative mortality and reduces survival to, and after, transplantation. Consequently, BiVAD, rather than LVAD, support should be considered for BTT in patients with biventricular failure or at high risk of developing right ventricular failure after LVAD implantation. Referral before right ventricular failure develops is preferable. Indeed, earlier ventricular assist device implantation in less severely ill patients (e.g. with an EF <25%, peak oxygen consumption <12 mL/kg/min, and only requiring intermittent inotropic support), and before right ventricular or multiorgan failure develops, leads to better surgical outcomes.

Patients with active infection, severe renal, pulmonary, or hepatic dysfunction, or uncertain neurological status after cardiac arrest or due to cardiogenic shock are not usually candidates for BTT or DT, but may be candidates for BTC.

### 13.5.2 Acute heart failure

In addition to ventricular assist devices, other forms of short-term, temporary MCS may be used in selected patients with AHF, including intra-aortic balloon counterpulsation, other percutaneous cardiac support, and ECMO. In addition to the uses described...
above, MCS, particularly ECMO, can be used as a ‘bridge to decision (BTD)’ in patients with acute and rapidly deteriorating HF where full evaluation has not been possible and in whom death will occur without MCS. However, the difficult decision to withdraw MCS may need to be made if the patient is not eligible for conventional corrective surgery or longer term MCS.

14. Holistic management, including exercise training and multidisciplinary management programmes, patient monitoring, and palliative care

Non-pharmacological non-device/surgical interventions used in the management of HF (both HF-REF and HF-PEF) are summarized in Tables 26 and 27, and detailed practical recommendations on their use have been published by the Heart Failure Association.259 There is no evidence that most of these improve mortality or morbidity, and some long-cherished approaches may not be beneficial, e.g. advice to restrict sodium intake and self-management counselling.260,261 For this reason, these interventions have not been given a recommendation with an evidence level. The exceptions are implementation of care in a multidisciplinary framework and exercise training, both of which are discussed further below.

14.1 Exercise training

Several systematic reviews and meta-analyses of small studies have shown that physical conditioning by exercise training improves exercise tolerance, health-related quality of life, and HF hospitalization rates in patients with HF. Recently, a single large RCT [Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION)] investigated the effects of exercise training in 2331 relatively young (mean age 59 years) medically stable patients with mild to moderately severe symptoms (NYHA class II 63% and class III 35%) and an EF ≤ 35%.262 The intervention comprised 36 supervised sessions in the initial 3 months followed by home-based training. The median follow-up was 30 months. In an adjusted analysis, exercise training led to an 11% reduction in the primary composite outcome of all-cause mortality or all-cause hospitalization (unadjusted \( P = 0.13 \); adjusted \( P = 0.03 \)). There was also a 15% RRR in a secondary composite outcome of cardiovascular death or HF hospitalization (unadjusted \( P = 0.06 \); adjusted \( P = 0.03 \)). There was no reduction in mortality, and no safety concerns were raised. Adherence to exercise declined substantially after the period of supervised training.

Collectively, the evidence suggests that physical training is beneficial in HF, although typical elderly patients were not enrolled in many studies and the optimum exercise ‘prescription’ is uncertain. Furthermore, the single large trial showed a borderline treatment effect that was only obtained with a very intensive intervention that may not be practical to deliver in every centre. Exercise training is

### Recommendations for exercise prescription and multidisciplinary management

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class (^a)</th>
<th>Level (^b)</th>
<th>Ref (^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended that regular aerobic exercise is encouraged in patients with heart failure to improve functional capacity and symptoms.</td>
<td>I</td>
<td>A</td>
<td>262, 263</td>
</tr>
<tr>
<td>It is recommended that patients with heart failure are enrolled in a multidisciplinary-care management programme to reduce the risk of heart failure hospitalization.</td>
<td>I</td>
<td>A</td>
<td>236, 259, 264</td>
</tr>
</tbody>
</table>

\(^a\)Class of recommendation.  
\(^b\)Level of evidence.  
\(^c\)References.

### Table 26 Characteristics and components of management programmes for patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Should employ a multidisciplinary approach (cardiologists, primary care physicians, nurses, pharmacists, etc.)</th>
<th>Should target high-risk symptomatic patients</th>
<th>Should include competent and professionally educated staff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Components</td>
<td>Optimized medical and device management</td>
<td>Adequate patient education, with special emphasis on adherence and self-care</td>
<td>Patient involvement in symptom monitoring and flexible diuretic use</td>
</tr>
<tr>
<td></td>
<td>Follow-up after discharge (regular clinic and/or home-based visits; possibly telephone support or remote monitoring)</td>
<td>Increased access to healthcare (through in-person follow-up and by telephone contact; possibly through remote monitoring)</td>
<td>Facilitated access to care during episodes of decompensation</td>
</tr>
<tr>
<td></td>
<td>Assessment of (and appropriate intervention in response to) an unexplained increase in weight, nutritional status, functional status, quality of life, and laboratory findings</td>
<td>Access to advanced treatment options</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Provision of psychosocial support to patients and family and/or caregivers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
discussed in more detail in a recent Heart Failure Association consensus paper.263

14.2 Organization of care and multidisciplinary management programmes

The goal of management of HF is to provide a ‘seamless’ system of care, embracing both the community and hospital, to ensure that the management of every patient is optimal, from the beginning to the end of their healthcare journey. The standards of care that patients with HF should expect have been published by the Heart Failure Association.236 To achieve this goal, other services, such as cardiac rehabilitation and palliative care, must be integrated into the overall provision for patients with HF. Fundamental to the delivery of this complete package of care are multidisciplinary management programmes designed to improve outcomes through structured follow-up with patient education, optimization of medical treatment, psychosocial support, and improved access to care.264 Key to the success of these programmes is coordination of care along the continuum of HF and throughout the chain-of-care delivered by the various services within the healthcare system. This

<table>
<thead>
<tr>
<th>Educational topic</th>
<th>Patient skills and self-care behaviours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition and aetiology</td>
<td>• Understand the cause of heart failure and why symptoms occur</td>
</tr>
<tr>
<td>Prognosis</td>
<td>• Understand important prognostic factors and make realistic decisions</td>
</tr>
<tr>
<td>Symptom monitoring and self-care</td>
<td>• Monitor and recognize signs and symptoms</td>
</tr>
<tr>
<td></td>
<td>• Record daily weight and recognize rapid weight gain</td>
</tr>
<tr>
<td></td>
<td>• Know how and when to notify healthcare provider</td>
</tr>
<tr>
<td></td>
<td>• In the case of increasing dyspnoea or oedema or a sudden unexpected weight gain of &gt;2 kg in 3 days, patients may increase their diuretic dose and/or alert their healthcare team</td>
</tr>
<tr>
<td></td>
<td>• Use flexible diuretic therapy if appropriate and recommended after appropriate education and provision of detailed instructions</td>
</tr>
<tr>
<td>Pharmacological treatment</td>
<td>• Understand indications, dosing, and effects of drugs</td>
</tr>
<tr>
<td></td>
<td>• Recognize the common side effects of each drug prescribed</td>
</tr>
<tr>
<td>Adherence</td>
<td>• Understand the importance of following treatment recommendations and maintaining motivation to follow treatment plan</td>
</tr>
<tr>
<td></td>
<td>• Sodium restriction may help control the symptoms and signs of congestion in patients with symptomatic heart failure classes III and IV</td>
</tr>
<tr>
<td>Diet</td>
<td>• Avoid excessive fluid intake: fluid restriction of 1.5–2 L/day may be considered in patients with severe heart failure to relieve symptoms and congestion. Restriction of hypotonic fluids may improve hyponatraemia. Routine fluid restriction in all patients with mild to moderate symptoms is probably not of benefit. Weight-based fluid restriction (30 mL/kg body weight, 35 mL/kg if body weight &gt;85 kg) may cause less thirst</td>
</tr>
<tr>
<td></td>
<td>• Monitor and prevent malnutrition</td>
</tr>
<tr>
<td></td>
<td>• Eat healthily and keep a healthy weight (see Section 11)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>• Modest intake of alcohol abstinence is recommended in patients with alcohol-induced cardiomyopathy. Otherwise, normal alcohol guidelines apply (2 units per day in men or 1 unit per day in women). 1 unit is 10 mL of pure alcohol (e.g. 1 glass of wine, 1/2 pint of beer, 1 measure of spirit)</td>
</tr>
<tr>
<td>Smoking and drugs</td>
<td>• Stop smoking and/or taking illicit drugs</td>
</tr>
<tr>
<td>Exercise</td>
<td>• Understand the benefits of exercise</td>
</tr>
<tr>
<td></td>
<td>• Perform exercise training regularly</td>
</tr>
<tr>
<td></td>
<td>• Be reassured and comfortable about physical activity</td>
</tr>
<tr>
<td>Travel and leisure</td>
<td>• Prepare travel and leisure activities according to physical capacity</td>
</tr>
<tr>
<td></td>
<td>• When travelling, carry a written report of medical history and current medication regimen and carry extra medication. Monitor and adapt fluid intake particularly during flights and in hot climates. Beware adverse reactions to sun exposure with certain medications (e.g. amiodarone)</td>
</tr>
<tr>
<td>Sexual activity</td>
<td>• Be reassured about engaging in sex and discuss problems with healthcare professionals. Stable patients can undertake normal sexual activity that does not provoke undue symptoms. For treatment of erectile dysfunction, see Section 11.10</td>
</tr>
<tr>
<td>Immunization</td>
<td>• Receive immunization against influenza and pneumococcal disease according to local guidelines and practice</td>
</tr>
<tr>
<td>Sleep and breathing disorders</td>
<td>• Recognize preventive behaviour such as reducing weight in obese patients, smoking cessation, and abstinence from alcohol</td>
</tr>
<tr>
<td></td>
<td>• Learn about treatment options if appropriate</td>
</tr>
<tr>
<td>Psychosocial aspects</td>
<td>• Understand that depressive symptoms and cognitive dysfunction are common in patients with heart failure and the importance of social support</td>
</tr>
<tr>
<td></td>
<td>• Learn about treatment options if appropriate</td>
</tr>
</tbody>
</table>
necessitates close collaboration between HF practitioners (cardiologists and HF nurses) and experts in allied health professions, including pharmacists, dieticians, physiotherapists, psychologists, primary care providers, and social workers. Although the content and structure of HF management programmes may vary in different countries and healthcare settings, the components shown in Tables 26 and 27 are recommended.

### 14.3 Serial natriuretic peptide measurement

High natriuretic peptide concentrations are associated with a poor prognosis, and a fall in peptide levels correlates with a better prognosis. However, several RCTs that evaluated natriuretic peptide-guided treatment (intensifying treatment in order to lower peptide levels) have given conflicting results. It is uncertain whether outcome is better using this approach than by simply optimizing treatment (combinations and doses of drugs, devices) according to guidelines.

### 14.4 Remote monitoring (using an implanted device)

Management adapted in response to monitoring thoracic impedance (as an indirect measure of intrathoracic fluid) has not been shown to improve outcomes. Treatment adjusted in response to pulmonary artery pressure measured using an implanted monitor did reduce hospital admission for HF in one RCT, but the general applicability of this approach is uncertain and a guideline recommendation is not yet possible.

### 14.5 Remote monitoring (no implanted device)

The optimum approach to non-invasive remote monitoring is uncertain, and RCTs performed to date have given inconsistent results and do not yet support a guideline recommendation.

### 14.6 Structured telephone support

Although a meta-analysis of RCTs suggests that structured telephone support in addition to conventional care may reduce the risk of hospitalization in patients with HF, few individual RCTs showed this benefit, and the evidence is not robust enough to support a guideline recommendation.

### 14.7 Palliative/supportive/end-of-life care

HF has an unpredictable disease trajectory and it is often difficult to identify a specific time point to consider palliative care. Features that should trigger consideration of palliative care are listed in Tables 28 and 29. At this point in a patient’s disease trajectory, the focus should be on improvement in quality of life, control of symptoms, early detection, and treatment of episodes of deterioration, and on pursuing a holistic approach to patient care, encompassing physical, psychological, social, and spiritual well-being. Liaison between the specialist palliative care service and the HF team and/or the primary care physician, using a shared-care approach, is required in order to address and coordinate the patients’ care optimally. Palliative care has been discussed in detail in a position paper from the Heart Failure Association.

### 15. Gaps in evidence

Clinicians responsible for managing patients with HF must frequently make treatment decisions without adequate evidence or a consensus of expert opinion. The following is a shortlist of selected, common issues that deserve to be addressed in future clinical research.

#### 15.1 Diagnosis

The diagnosis of HF-PEF remains a particular challenge, and the optimum approach incorporating symptoms, signs, imaging, biomarkers, and other investigations is uncertain.

- **Strain/speckle imaging**—value in diagnostic and prognostic assessment of both HF-REF and HF-PEF?
- **Diastolic stress test**—value in diagnosis of HF-PEF?

#### 15.2 Co-morbidity

The long-term safety and efficacy of many treatments for co-morbidities are unknown, but are of great interest and importance.

- **Anaemia**—erythropoiesis-stimulating agents, iron?
- **Depression**—selective serotonin reuptake inhibitors, cognitive therapy?
- **Diabetes**—metformin, GLP-1 agonists/analogues, DPP IV inhibitors, SGLT-2 inhibitors?
- **Sleep-disordered breathing**—positive airways pressure therapies?
15.3 Non-pharmacological, non-interventional therapy
Salt restriction—is it effective and safe?
Cardiac cachexia—is there an effective and safe treatment?

15.4 Pharmacological therapy
Digoxin—efficacy and safety in modern era of pharmacological and device therapy?
Hydralazine and ISDN—efficacy and safety in non-black patients?
Renin inhibition—is it an effective and safe alternative to/addition to ACE inhibition?
New oral anticoagulants—efficacy and safety compared with aspirin in patients in sinus rhythm?
Clopidogrel and other novel antiplatelet agents—efficacy and safety compared with aspirin in patients in sinus rhythm?
Dual neprilysin/angiotensin receptor inhibitors—efficacy and safety compared with an ACE inhibitor?

15.5 Devices
CRT—the efficacy and safety of CRT remains unknown in certain groups of patients.

15.6 Acute heart failure
The treatment of acute heart failure remains largely opinion-based with little good evidence to guide therapy.

Intravenous nitrates—efficacy and safety still uncertain.
Levosimendan—efficacy and safety still uncertain.
Omecamtiv mecarbil—is it effective and safe?
Ultrafiltration—efficacy and safety unknown.

15.7 End-of-life care
What is the optimum palliative care package?
When should palliative care be started?

The CME text ‘European Guidelines on cardiovascular disease prevention in clinical practice (version 2012)’ is accredited by the European Board for Accreditation in Cardiology (EBAC). EBAC works according to the quality standards of the European Accreditation Council for Continuing Medical Education (EACCME), which is an institution of the European Union of Medical Specialists (UEMS). In compliance with EBAC/EACCME guidelines, all authors participating in this programme have disclosed potential conflicts of interest that might cause a bias in the article. The Organizing Committee is responsible for ensuring that all potential conflicts of interest relevant to the programme are declared to the participants prior to the CME activities.

CME questions for this article are available at: European Heart Journal http://www.oxfordlearning.com/eurheartj and European Society of Cardiology http://www.escardio.org/guidelines.

References


Appendix A: Aetiology of heart failure

There is no agreed or satisfactory classification for the causes of HF, with much overlap between potential categories.

**Myocardial disease**
1. Coronary artery disease
2. Hypertension
3. Cardiomyopathy
   - Familial
     - Hypertrophic
     - Dilated
     - Arrhythmogenic right ventricular cardiomyopathy
   - Restrictive
   - Left ventricular non-compaction
4. Acquired
   - Myocarditis (inflammatory cardiomyopathy)
     - Infective
       - Bacterial
       - Spirochaetal
       - Fungal
       - Protozoal
       - Parasitic
       - Viral
     - Immune-mediated
       - Tetanus toxoid, vaccines, serum sickness
       - Drugs
       - Lymphocytic/giant cell myocarditis
       - Sarcoidosis
       - Autoimmune
       - Eosinophilic (Churg-Strauss)
   - Toxic
     - Drugs (e.g. chemotherapy, cocaine)
     - Alcohol
     - Heavy metals (copper, iron, lead)
   - Endocrine/nutritional
     - Phaeochromocytoma
     - Vitamin deficiency (e.g. thiamine)
     - Selenium deficiency
     - Hypophosphataemia
     - Hypocalcaemia
   - Pregnancy
   - Infiltration
     - Amyloidosis
     - Malignancy

**Valvular heart disease**
- Mitral
- Aortic
- Tricuspid
- Pulmonary

**Pericardial disease**
- Constrictive pericarditis
- Pericardial effusion

**Endocardial disease**
- Endomyocardial diseases with hypereosinophilia (hypereosinophilic syndromes (HES))
- Endomyocardial disease without hypereosinophilia (e.g. endomyocardial fibrosis (EMF))
- Endocardial fibroelastosis

**Congenital heart disease**

**Arrhythmia**
- Tachyarrhythmia
- Atrial
- Ventricular
- Bradyarrhythmia
- Sinus node dysfunction

**Conduction disorders**
- Atrioventricular block

**High output states**
- Anaemia
- Sepsis
- Thyrotoxicosis
- Paget’s disease
- Arteriovenous fistula

**Volume overload**
- Renal failure
- Isotonic (e.g. post-operative fluid infusion)

AV = atrioventricular; HF = heart failure.
*Both peripheral arterial and myocardial factors contribute to the development of heart failure.
*Other inherited diseases may have cardiac effects e.g. Fabry disease.
Appendix B: Prognostic variables in heart failure

A very large number of variables have been shown to relate to outcome in HF (and new prognostic markers are regularly identified). This table lists some of the more commonly described prognostic variables.

### Demographics, history, and physical examination
- Age, sex, ethnicity, NYHA class, body mass index.
- Signs of congestion, increased jugular venous pressure, third heart sound, low systolic blood pressure, higher heart rate.
- Diabetes mellitus, renal dysfunction, depression, COPD.
- Ischaemic aetiology, history of myocardial infarction.

### Routine laboratory tests
- Serum sodium
- Liver enzymes, bilirubin
- Serum creatinine/creatinine clearance/eGFR
- BUN/urea and markers of tubular injury
- Serum albumin
- Uric acid
- Haemoglobin
- Red cell distribution width
- Troponin I/T
- Urinary albumin creatinine ratio

### Neurohormones, cytokines, and related factors
- Plasma renin activity
- Angiotensin II
- Aldosterone
- Catecholamines
- (Big) endothelin-1
- Adrenomedullin
- Natriuretic peptides
- Vasopressin/Co-peptin
- Cytokines
- sST-2
- Galectin-3
- Collagen markers

### Electrical variables
- QRS width
- LV hypertrophy
- Atrial fibrillation
- Complex ventricular arrhythmias
- Heart rate variability

### Imaging variables
- LV internal dimensions and fractional shortening
- Cardiorespiratory ratio on chest X-ray
- Wall motion index (various)
- Ejection fraction
- Left atrial size
- Restrictive filling pattern/short deceleration time
- Right ventricular function (various)
- Inflammation (contrast-enhanced CMR), iron content (in thalassaemia: CMR)
- Amyloidosis (contrast kinetics in CMR)
- Ischaemia and viability imaging, arrhythmogenic substrates

### Exercise test/haemodynamic variables (rest/exercise)
- VO$_2$
- VE/VO$_2$ slope
- Max/peak (normal >20 mL/kg/min)
- 6-min walk distance (normal >600 m)
- Cardiac index (normal >2.5 L/min/m$^2$)
- LV end-diastolic pressure/pulmonary artery wedge pressure (normal <12 mmHg)

---

BUN = blood urea nitrogen; CMR = cardiac magnetic resonance; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HF = heart failure; LV = left ventricular; NYHA = New York Heart Association; sST-2 = soluble ST-2; VO2 = peak oxygen consumption.

*This list is not intended to be comprehensive and other circulating factors may also be associated with prognosis.

*Various measures/classifications can be used, and no single threshold for normal/abnormal can be given.

*Functional capacity varies greatly according to prior fitness, age, and sex; values given are a guideline for older (>65 years) adults.
Appendix C: Practical guidance on the use of angiotensin-converting enzyme inhibitors (or an angiotensin II receptor blocker) in patients with systolic heart failure

**WHY?**
To improve symptoms and exercise capacity, reduce the risk of HF hospitalization, and increase survival

**IN WHOM AND WHEN?**

**Indications**
- Potentially all patients with HF and an EF ≤40%
  - First-line treatment (along with beta-blockers and an MRA) in patients with NYHA class II–IV HF; start as early as possible in the course of disease.
  - ACE inhibitors are also of benefit in patients with asymptomatic LV systolic dysfunction (NYHA class I)

**Contraindications**
- History of angioedema
- Known bilateral renal artery stenosis
- Pregnancy/risk of pregnancy

**Cautions/seek specialist advice**
- Significant hyperkalaemia (K⁺ >5.0 mmol/L)
- Significant renal dysfunction (creatinine >221 µmol/L >2.5 mg/dL) or eGFR <30 mL/min/1.73 m²
- Symptomatic or severe asymptomatic hypotension (systolic blood pressure <90 mmHg)

**Drug interactions to look out for**
- K⁺ supplements; K⁺-sparking diuretics, e.g. amiloride and triamterene (beware combination preparations with furosemide), MRAs and renin inhibitors
- NSAIDs
- Trimethoprim/trimethoprim-sulfamethoxazole
- 'Low-salt' substitutes with a high K⁺ content

**WHERE?**
In the community for most patients
Exceptions—see Cautions/see specialist advice

**WHICH ACE INHIBITOR AND WHAT DOSE?** — see Table 14

**HOW TO USE?**
- Check renal function and electrolytes
  - Start with a low dose (see Table 14)
  - Double the dose at not less than 2-week intervals in the community. More rapid dose up-titration may be carried out in patients in hospital or who are otherwise closely monitored, tolerability permitting
  - Aim for target dose (see above) or, failing that, the highest tolerated dose

**Re-check blood chemistry (urea/BUN, creatinine, K⁺) 1–2 weeks after initiation and 1–2 weeks after final dose titration**

**Monitor blood chemistry 4 monthly thereafter**
- When to stop up-titration, reduce dose, stop treatment—see PROBLEM SOLVING
  - A specialist HF nurse may assist with education of the patient, follow-up (in person or by telephone), biochemical monitoring and dose up-titration

**ADVICE TO PATIENT**
- Explain expected benefits
  - Treatment is given to improve symptoms, to prevent worsening of HF leading to hospital admission, and to increase survival
  - Symptoms improve within a few weeks to a few months after starting treatment
  - Advise patients to report principal adverse effects, (i.e. dizziness/symptomatic hypotension, cough)—see PROBLEM SOLVING
  - Advise patients to avoid NSAIDs not prescribed by a physician (i.e. purchased over-the-counter) and salt substitutes high in K⁺—see PROBLEM SOLVING

**PROBLEM SOLVING**

**Asymptomatic low blood pressure**
- Doses not usually require any change in therapy
- Symptomatic hypotension
  - Dizziness/light headedness is common and often improves with time—patients should be reassured
  - Reconsider need for nitrates, calcium-channel blockers, and other vasodilators and reduce dose/stop, if possible
  - If no signs of symptoms of congestive, consider reducing diuretic dose
  - If these measures do not solve problem, seek specialist advice

**Cough**
- Cough is common in patients with HF, many of whom have smoking-related lung disease
- Cough is also a symptom of pulmonary oedema, which should be excluded when a new worsening cough develops
- ACE inhibitor-induced cough does not always require treatment discontinuation
  - When a troublesome cough does develop (e.g. one stopping the patient from sleeping) and can be proved to be due to ACE inhibitor (i.e. recurs after ACE inhibitor withdrawal and re-challenge), substitution of an ARB is recommended

**Worsening renal function and hyperkalaemia**
- Some rise in urea (BUN), creatinine, and potassium is to be expected after an ACE inhibitor; if an increase is small and asymptomatic, no action is necessary
  - An increase in potassium to ≤5.5 mmol/L is acceptable
  - If urea, creatinine, or potassium does rise excessively, consider stopping concomitant nephrotoxic drugs (e.g. NSAIDs) and other potassium supplements or retaining agents (triamterene, amiloride) and, if no signs of congestion, reducing the dose of diuretic
  - If greater rises in creatinine or potassium than those outlined above persist despite adjustment of concomitant medications, the dose of the ACE inhibitor (or ARB) should be halved and blood chemistry re-checked within 1–2 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 >310 µmol/L (3.5 mg/dL)eGFR <20 mL/min/1.73 m², the ACE inhibitor (or ARB) should be stopped and specialist advice sought

**Blood chemistry should be monitored frequently and serially until potassium and creatinine have plateaued**

---

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BUN = blood urea nitrogen; EF = ejection fraction; HF = heart failure; LV = left ventricular; MRA = mineralocorticoid receptor antagonist; NSAID = non-steroidal anti-inflammatory drug; NYHA = New York Heart Association.

*Note: it is very rarely necessary to stop an ACE inhibitor (or ARB), and clinical deterioration is likely if treatment is withdrawn. Ideally, specialist advice should be sought before treatment discontinuation.*

*The recommendations in this table represent expert opinion based upon relevant clinical trials (drugs, titration schedules, target doses, patient monitoring, treatment benefits, and reported adverse effects) and clinical experience.

*The safety of an ARB in patients developing angioedema with an ACE inhibitor is uncertain.*

*Renin inhibitors are not recommended in heart failure.*

*Avoid NSAIDs unless essential.*

*Calcium-channel blockers should be discontinued unless absolutely necessary, and diltiazem and verapamil are potentially harmful because of their negative inotropic action.*
Appendix D: Practical guidance on the use of beta-blockers in patients with systolic heart failure

WHY?
To improve symptoms, reduce the risk of HF hospitalization and increase survival

IN WHOM AND WHEN?
Indications
- Potentially all patients with stable mild or moderate systolic HF (EF ≤ 40%); patients with severe HF also benefit from beta-blockers but treatment should be started under the care of a specialist
- First-line treatment, along with an ACE inhibitor and an MRA, in patients with stabilized HF; start as early as possible in the course of disease

Contraindications
- Asthma (COPD is not a contraindication)
- Second- or third-degree AV block (in the absence of a permanent pacemaker)
- Severe (NYHA class IV) HF
- Current or recent (<4 weeks) exacerbation of HF (e.g. hospital admission with worsening HF), heart block, or heart rate <60 b.p.m.
- Persisting signs of congestion, hypotension/low blood pressure (systolic <90 mmHg), raised jugular venous pressure, ascites, marked peripheral oedema—try to relieve congestion and achieve 'euvolaemia' before starting beta-blocker

Drug interactions to look out for (because of risk of bradycardia/atrioventricular block)
- Verapamil, diltiazem (should be discontinued)
- Digoxin, amiodarone, ivabradine

WHERE?
In the community in stable patients (NYHA class I/II); severe HF patients and those with a current/recent exacerbation should be referred for specialist advice.
In patients hospitalized with worsening HF—after stabilizing, relieving congestion, and, if possible, restoring ‘euvolaemia’ (but ideally before discharge).
Other exceptions—see Cautions/see specialist advice

WHICH BETA-BLOCKER AND WHAT DOSE? - see Table 14

HOW TO USE?
- Start with a low dose (see Table 14)
- Double the dose at not less than 2-week intervals (slower up-titration may be needed in some patients)
- Aim for target dose (see above) or, failing that, the highest tolerated dose
- Monitor heart rate, blood pressure, and clinical status (symptoms, signs—especially signs of congestion, body weight)
- When to stop up-titration, reduce dose, stop treatment—see PROBLEM SOLVING

A specialist HF nurse may assist with education of the patient, follow-up (in person or by telephone), and dose up-titration

ADVICE TO PATIENT
- Explain expected benefits (see WHY?) and mention possibility of temporary adverse effects
- Treatment is given to improve symptoms, to prevent worsening of HF leading to hospital admission, and to increase survival
- Symptomatic improvement may develop slowly after starting treatment, sometimes taking 3–6 months or longer
- Temporary symptomatic deterioration may occur during initiation or up-titration phase; in the long term, beta-blockers improve well-being
- Advise patient to report deterioration (see PROBLEM SOLVING) 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 the physician
- To detect and to 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 (>2 days), by >1.5–2.0 kg

PROBLEM SOLVING
- Worsening symptoms or signs (e.g. increasing dyspnoea, fatigue, oedema, weight gain)
  - If increasing congestion, increase dose of diuretic or halve dose of beta-blocker (if increasing diuretic dose does not work)
  - If marked fatigue (or bradycardia—see below), halve dose of beta-blocker (rarely necessary); review patient in 1–2 weeks; if not improved, seek specialist advice
  - If serious deterioration, halve dose of beta-blocker or stop this treatment (rarely necessary); seek specialist advice
- Low heart rate
  - If <50 b.p.m. and worsening symptoms, halve dose of beta-blocker, or, if severe deterioration, stop beta-blocker (rarely necessary)
  - Review need for other heart rate-slowing drugs (e.g. digoxin, amiodarone, diltiazem, or verapamil*)
  - Arrange electrocardiogram to exclude heart block
  - Seek specialist advice
- Asymptomatic low blood pressure
  - Does not usually require any change in therapy
- Symptomatic hypotension
  - If dizziness, light headedness, or confusion and a low blood pressure, reconsider need for nitrates, calcium-channel blockers,* and other vasodilators and reduce/stop, if possible
  - If no signs or symptoms of congestion, consider reducing diuretic dose
  - If these measures do not solve problem, seek specialist advice

ACE = angiotensin-converting enzyme; AV = atrioventricular; COPD = chronic obstructive pulmonary disease; HF = heart failure; LV = left ventricular; MRA = mineralocorticoid receptor antagonist; NSAID = non-steroidal anti-inflammatory drug; NYHA = New York Heart Association.

Note: Beta-blockers should not be stopped suddenly unless absolutely necessary (there is a risk of a ‘rebound’ increase in myocardial ischaemia or infarction and arrhythmias). Ideally, specialist advice should be sought before treatment discontinuation.

*The recommendations in this table represent expert opinion based upon relevant clinical trials (drugs, titration schedules, target doses, patient monitoring, treatment benefits, and reported adverse effects) and clinical experience.

†Calcium-channel blockers should be discontinued unless absolutely necessary, and diltiazem and verapamil are potentially harmful because of their negative inotropic effect.

‡Metoprolol tartrate should not be used in preference to an evidence-based beta-blocker in HF.

§This is generally good advice for all patients with HF.
Appendix E: Practical guidance on the use of mineralocorticoid receptor antagonists in patients with systolic heart failure

WHY?
To improve symptoms, reduce the risk of HF hospitalization, and increase survival

IN WHOM AND WHEN?
Indications
Potentially all patients with persisting symptoms (NYHA Class II-IV) and an EF \( \leq 35\% \) despite treatment with an ACE inhibitor (or ARB) and beta-blocker

Cautions/seek specialist advice
Significant hyperkalaemia (K+ >5.0 mmol/L)

Significant renal dysfunction (creatinine >221 \( \mu \text{mol/L} \) [>2.5 mg/dL] or eGFR <30 mL/min/1.73 m\(^2\))

Drug interactions to look out for
K+ supplements/ K+-sparing diuretics (e.g. amiloride and triamterene; beware combination preparations with furosemide)
ACE inhibitors/ARBs/renin inhibitors
NSAIDs
Trimethoprim/trimethoprim-sulfamethoxazole

‘Low-salt’ substitutes with a high K+ content

Contraindication
Eplerenone–strong CYP3A4 inhibitors, e.g. ketoconazole,itraconazole, nefazodone, telithromycin, clarithromycin, ritonavir, and nelfinavir

WHERE?
In the community or in the hospital
Exceptions—see Cautions/seek specialist advice

WHICH MRA AND WHAT DOSE? - see Table 14

HOW TO USE?
Check renal function and electrolytes (particularly K+)
Start with a low dose (see above)
Consider dose up-titration after 4–8 weeks
Check blood chemistry at 1 and 4 weeks after starting/increasing dose and at 8 and 12 weeks; 6, 9, and 12 months; 4-monthly thereafter
If K+ rises to >6.0 mmol/L or creatinine to >310 \( \mu \text{mol/L} \) (3.5 mg/dL) eGFR <20 mL/min/1.73 m\(^2\), stop MRA immediately and seek specialist advice

A specialist HF nurse may assist with education of the patient, follow-up (in person or by telephone), biochemical monitoring, and dose up-titration

ADVICE TO PATIENT
Explain expected benefits (see WHY?)
Treatment is given to improve symptoms, to prevent worsening of HF leading to hospital admission, and to increase survival
Symptomatic improvement occurs within a few weeks to a few months of starting treatment
Avoid NSAIDs not prescribed by a physician (i.e. purchased over-the-counter) and salt substitutes high in K+
If diarrhoea or vomiting occurs, patients should stop the MRA and contact the physician/nurse

PROBLEM SOLVING
Worsening renal function/hyperkalaemia
See HOW TO USE!
The main concern is hyperkalaemia (>6.0 mmol/L); although this was uncommon in RALES and EMPHASIS-HF, it has been seen more commonly in clinical practice
Conversely, a high-normal K+ level may be desirable in patients with HF, especially if they are taking digoxin
It is important to avoid other K+-retaining drugs (e.g. K+-sparing diuretics such as amiloride and triamterene) and nephrotoxic agents (e.g. NSAIDs)

The risk of hyperkalaemia and renal dysfunction when an MRA is given to patients already taking both an ACE inhibitor and ARB is higher than when an MRA is added to just an ACE inhibitor or ARB given singly; this triple combination of an ACE inhibitor, ARB and MRA is NOT recommended

(see recommendations below)
Some ‘low-salt’ substitutes have a high K+ content
Male patients treated with spironolactone may uncommonly develop breast discomfort or gynaecomastia (switching to eplerenone should be considered)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; NSAID = non-steroidal anti-inflammatory drug;
NYHA = New York Heart Association.
\( ^a \)The recommendations in this table represent expert opinion based upon relevant clinical trials (drugs, titration schedules, target doses, patient monitoring, treatment benefits, and reported adverse effects) and clinical experience.
\( ^b \)It is extremely important to adhere to these cautions and doses to avoid serious hyperkalaemia.
\( ^c \)Renin inhibitors are not recommended in heart failure.
\( ^d \)Avoid NSAIDs unless essential.
\( ^{cAn} \)Canrenoic acid is not recommended in heart failure.
Appendix F: Practical guidance on the use of diuretics in patients with heart failure
(with a reduced or preserved ejection fraction)

**WHY?**
To relieve breathlessness and oedema in patients with symptoms and signs of congestion

**IN WHOM AND WHEN?**

**Indications**
- Potentially all patients with symptoms and signs of congestion, irrespective of EF
- Should always be used in combination with an ACE inhibitor (or ARB), beta-blocker, and an MRA in patients with a reduced EF
- Use minimum dose necessary to maintain euvolaemia—the patient’s ‘dry weight’ (i.e. to keep the patient free of symptoms and signs of congestion)
- Dose may need to be increased or decreased according to the patient’s volume status; patients can be educated and trained to alter their own diuretic dose, according to need (based on symptoms, signs and weight changes—see Section 14)

**Contraindications**
- Not indicated if the patient has never had symptoms or signs of congestion
- Known allergic reaction/other adverse reaction (drug-specific)

**Cautions/seek specialist advice**
- Significant hypokalaemia (K⁺ ≤ 3.5 mmol/L)—may be made worse by diuretic
- Significant renal dysfunction (creatinine >221 µmol/L [>2.5 mg/dL] or eGFR <30 mL/min/1.73 m²)—may be made worse by diuretic or patient may not respond to diuretic (especially thiazide diuretic)
- Symptomatic or severe asymptomatic hypotension (systolic blood pressure <90 mmHg)—may be made worse by diuretic-induced hypovolaemia

**Drug interactions to look out for**
- Combination with ACE inhibitor ARB or renin inhibitors—a risk of hypotension (usually not a problem)
- Combination with other diuretics (e.g. loop plus thiazide)—risk of hypovolaemia, hypotension, hypokalaemia, and renal impairment
- NSAIDs—may attenuate effect of diuretic

**WHERE?**
- In the community for most patients

**WHICH DIURETIC AND WHAT DOSE?** - see Table 16

**HOW TO USE?**
- Check renal function and electrolytes
- Start with a low dose (see Table 16)
- Adjust dose according to symptoms and signs of congestion, blood pressure, and renal function
- Re-check blood chemistry 1–2 weeks after initiation and after any increase in dose (urea/BUN, creatinine, K⁺)
- When to stop up-titration, reduce dose, stop treatment—see PROBLEM SOLVING

**Hypokalaemia/hypomagnesaemia**
- Increase ACE inhibitor/ARB dose, add MRA, potassium supplements; magnesium supplements
- Hypoanaemia
- Volume depleted: stop thiazide or switch to loop diuretic, if possible; reduce dose/stop loop diuretics if possible; volume overloaded: fluid restriction; increase dose of loop diuretic; consider AVP antagonist (e.g. tolvaptan if available); i.v. inotropic support; consider ultrafiltration
- Hypouricaemia/gout
- Consider allopurinol prophylaxis; for symptomatic gout use colchicine for pain relief; avoid NSAIDs
- Hypovolaemia/dehydration
- Assess volume status; consider diuretic dosage reduction

**PROBLEM SOLVING**

**Asymptomatic low blood pressure**
- Dose may be reduced if no symptoms or signs of congestion

**Symptomatic hypotension**
- Causing dizziness/light headedness—reduce dose if no symptoms or signs of congestion
- Reconsider need for nitrates, CCBs, and other vasodilators
- If these measures do not solve problem, seek specialist advice

**Potentially all patients with symptoms and signs of congestion, irrespective of EF**
- Avoid NSAIDs unless essential
- Renin inhibitors are not recommended in heart failure
- Caution should be discontinued in patients with systolic HF unless absolutely necessary, and diltiazem and verapamil are potentially harmful in patients with systolic heart failure because of their negative inotropic action

---

**Key Points**
- **EF = ejection fraction; HF = heart failure; i.v. = intravenous; MRA = mineralocorticoid receptor antagonist; NSAIDs = non-steroidal anti-inflammatory drugs.**
- **ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; AVP = arginine vasopressin; BUN = blood urea nitrogen; CCBs = calcium-channel blockers; EF = ejection fraction; HF = heart failure; i.v. = intravenous; MRA = mineralocorticoid receptor antagonist; NSAIDs = non-steroidal anti-inflammatory drugs.**
- **Renin inhibitors are not recommended in heart failure.**
- **Avoid NSAIDs unless essential.**
- **CCBs should be discontinued in patients with systolic HF unless absolutely necessary, and diltiazem and verapamil are potentially harmful in patients with systolic heart failure because of their negative inotropic action.**