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2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: Piotr Ponikowski* (Chairperson) (Poland), Adriaan A. Voors* (Co-Chairperson) (The Netherlands), Stefan D. Anker (Germany), Héctor Bueno (Spain), John G. F. Cleland (UK), Andrew J. S. Coats (UK), Volkmar Falk (Germany), José Ramón González-Juanatey (Spain), Veli-Pekka Harjola (Finland), Ewa A. Jankowska (Poland), Mariell Jessup (USA), Cecilia Linde (Sweden), Petros Nihoyannopoulos (UK), John T. Parissis (Greece), Burkert Pieske (Germany), Jillian P. Riley (UK), Giuseppe M. C. Rosano (UK/Italy), Luis M. Ruilope (Spain), Frank Ruschitzka (Switzerland), Frans H. Rutten (The Netherlands), Peter van der Meer (The Netherlands)

Document Reviewers: Gerasimos Filippatos (CPG Review Coordinator) (Greece), John J. V. McMurray (CPG Review Coordinator) (UK), Victor Aboyans (France), Stephan Achenbach (Germany), Stefan Agewall (Norway), Nawwar Al-Attar (UK), John James Atherton (Australia), Johann Bauersachs (Germany), A. John Camm (UK), Scipione Carerj (Italy), Claudio Ceconi (Italy), Antonio Coca (Spain), Perry Elliott (UK), Çetin Erol (Turkey), Justin Ezekowitz (Canada), Covadonga Fernández-Golfín (Spain), Donna Fitzsimons (UK), Marco Guazzi (Italy),

* Corresponding authors: Piotr Ponikowski, Department of Heart Diseases, Wroclaw Medical University, Centre for Heart Diseases, Military Hospital, ul. Weigla 5, 50-981 Wroclaw, Poland, Tel: +48 261 660 279, Tel/Fax: +48 261 660 237, E-mail: piotrponikowski@4wsk.pl.

Adriaan Voors, Cardiology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, PO Box 30.001, 9700 RB Groningen, The Netherlands, Tel: +31 50 3612355, Fax: +31 50 3614391, E-mail: a.a.voors@umcg.nl.

ESC Committee for Practice Guidelines (CPG) and National Cardiac Societies document reviewers: listed in the Appendix.

ESC entities having participated in the development of this document:

Associations: Acute Cardiovascular Care Association (ACCA), European Association for Cardiovascular Prevention and Rehabilitation (EACPR), European Association of Cardiovascular Imaging (EACVI), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA).

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Maxime Guenoun (France), Gerd Hasenfuss (Germany), Gerhard Hindricks (Germany), Arno W. Hoes (The Netherlands), Bernard Iung (France), Tiny Jaarsma (Sweden), Paulus Kirchhof (UK/Germany), Juhani Knuuti (Finland), Philippe Kolh (Belgium), Stavros Konstantinides (Germany/Greece), Mitja Lainscak (Slovenia), Patrizio Lancellotti (Belgium), Gregory Y. H. Lip (UK), Francesco Maisano (Switzerland), Christian Mueller (Switzerland), Mark C. Petrie (UK), Massimo F. Piepoli (Italy), Silvia G. Priori (Italy), Adam Torbicki (Poland), Hiroyuki Tsutsui (Japan), Dirk J. van Veldhuisen (The Netherlands), Stephan Windecker (Switzerland), Clyde Yancy (USA), Jose Luis Zamorano (Spain)

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Abbreviations and acronyms

ACC/AHA	American College of Cardiology/American Heart Association
ACCF/AHA	American College of Cardiology Foundation/ American Heart Association
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ACS	acute coronary syndrome
AF	atrial fibrillation
AHF	acute heart failure
AHI	apnoea/hypopnoea index
AIDS	acquired immunodeficiency syndrome
AKI	acute kidney injury
Aldo-DHF	aldosterone receptor blockade in diastolic heart failure
AL	amyloid light chain
ALT	alanine aminotransferase

of Cardiology Working Group on Myocardial and Pericardial Diseases.[94] In most patients with a definite clinical diagnosis of HF, there is no confirmatory role for routine genetic testing to establish the diagnosis. Genetic counselling is recommended in patients with HCM, idiopathic DCM and ARVC. Restrictive cardiomyopathy and isolated non-compaction cardiomyopathies are of a possible genetic origin and should also be considered for genetic testing.

HCM is mostly inherited as an autosomal dominant disease with variable expressivity and age-related penetrance. Currently, more than 20 genes and 1400 mutations have been identified, most of which are located in the sarcomere genes encoding cardiac β-myosin heavy chain (MYH7) and cardiac myosin binding protein C (MYBPC3).[88,122]

DCM is idiopathic in 50% of cases, about one-third of which are hereditary. There are already more than 50 genes identified that are associated with DCM. Many genes are related to the cytoskeleton. The most frequent ones are titin (*TTN*), lamin (*LMNA*) and desmin (*DES*).[88,123]

ARVC is hereditary in most cases and is caused by gene mutations that encode elements of the desmosome. Desmosomal gene mutations explain 50% of cases and 10 genes are currently associated with the disease.[124]

Counselling should be performed by someone with sufficient knowledge of the specific psychological, social and medical implications of a diagnosis. Determination of the genotype is important, since some forms [e.g. mutations in *LMNA* and phospholamban (*PLN*)] are related to a poorer prognosis. DNA analysis could also be of help to establish the diagnosis of rare forms, such as mitochondrial cardiomyopathies. Screening of first-degree relatives for early detection is recommended from early adolescence onwards, although earlier screening may be considered depending on the age of disease onset in other family members.

Recently, the MOGE(S) classification of inherited cardiomyopathies has been proposed, which includes the morphofunctional phenotype (M), organ(s) involvement (O), genetic inheritance pattern (G), aetiological annotation (E), including genetic defect or underlying disease/substrate, and the functional status (S) of the disease.[125]

6. Delaying or preventing the development of overt heart failure or preventing death before the onset of symptoms

There is considerable evidence that the onset of HF may be delayed or prevented through interventions aimed at modifying risk factors for HF or treating asymptomatic LV systolic dysfunction (see recommendations table). Many trials show that control of hypertension will delay the onset of HF and some also show that it will prolong life.[126–129] Different antihypertensive drugs [diuretics, ACEIs, angiotensin receptor blockers (ARBs), beta-blockers] have been shown to be effective, especially in older people, both in patients with and without a history of myocardial infarction.[126–128] Along with the ongoing discussion on optimal target blood pressure values in hypertensive non-diabetic subjects, the recent SPRINT study has already demonstrated that treating hypertension to a lower goal [systolic blood pressure (SBP) $<$120 mmHg vs. $<$140 mmHg] in older hypertensive subjects ($\geq$75 years of age) or high-risk hypertensive patients reduces the risk of cardiovascular disease, death and hospitalization for HF.[129]

Recently, empaglifozin (an inhibitor of sodium-glucose cotransporter 2), has been shown to improve outcomes (including the reduction of mortality and HF hospitalizations) in patients with type 2 diabetes.[130] Other hypoglycaemic agents have not been shown convincingly to reduce the risk of cardiovascular events and may increase the risk of HF. Intensification of hypoglycaemic therapy to drive down glycated haemoglobin (HbA1c) with agents other than empagliflozin does not reduce the risk of developing HF (for details see Section 11.6 on diabetes).

Although smoking cessation has not been shown to reduce the risk of developing HF, the epidemiological associations with the development of cardiovascular disease[131] suggest that such advice, if followed, would be beneficial.

The association between alcohol intake and the risk of developing *de novo* HF is U-shaped, with the lowest risk with modest alcohol consumption (up to 7 drinks/week).[132–134] Greater alcohol intake may trigger the development of toxic cardiomyopathy, and when present, complete abstention from alcohol is recommended.

An inverse relationship between physical activity and the risk of HF has been reported. A recent meta-analysis found that doses of physical activity in excess of the guideline recommended minimal levels may be required for more substantial reductions in HF risk.[135]

It has been shown that among subjects $\geq$40 years of age with either cardiovascular risk factors or cardiovascular disease (but neither asymptomatic LV dysfunction nor overt HF), BNP-driven collaborative care between the primary care physician and the specialist cardiovascular centre may reduce the combined rates of LV systolic dysfunction and overt HF.[136]

Statins reduce the rate of cardiovascular events and mortality; there is also reasonable evidence that they prevent or delay the onset of HF.[137–140] Neither aspirin nor other antiplatelet agents, nor revascularization, have been shown to reduce the risk of developing HF or mortality in patients with stable CAD. Obesity is also a risk factor for HF,[141] but the impact of treatments of obesity on the development of HF is unknown.

In patients with CAD, without LV systolic dysfunction or HF, ACEIs prevent or delay the onset of HF and reduce cardiovascular and all-cause mortality, although the benefit may be small in the contemporary setting, especially in patients receiving aspirin.[142] Up-titration of renin–angiotensin system antagonists and beta-blockers to maximum tolerated dosages may improve outcomes, including HF, in patients with increased plasma concentrations of NPs.[136,143]

A primary percutaneous coronary intervention (PCI) at the earliest phase of an ST segment elevation myocardial infarction (STEMI) to reduce infarct size decreases the risk of developing a substantial reduction in LVEF and subsequent development of HFrEF.[112] Initiation of an ACEI, a beta-blocker and an MRA immediately after a myocardial infarction, especially when it is associated with LV systolic dysfunction, reduces the rate of hospitalization for HF and mortality,[144–148] as do statins.[137–139]

In asymptomatic patients with chronically reduced LVEF, regardless of its aetiology, an ACEI can reduce the risk of HF requiring hospitalization.[5,144,145] This has not yet been shown for beta-blockers or MRAs.

In patients with asymptomatic LV systolic dysfunction (LVEF <30%) of ischaemic origin who are ≥40 days after an AMI, an implantable cardioverter-defibrillator (ICD) is recommended to prolong life.[149]

Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms

Recommendations	Class [a]	Level [b]	Ref [c]
Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life.	I	A	126, 129, 150, 151
Treatment with statins is recommended in patients with or at high-risk of CAD whether or not they have LV systolic dysfunction, in order to prevent or delay the onset of HF and prolong life.	I	A	137–140, 152
Counselling and treatment for smoking cessation and alcohol intake reduction is recommended for people who smoke or who consume excess alcohol in order to prevent or delay the onset of HF.	I	C	131–134
Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.	IIa	C	130, 141, 153–155
Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.	IIa	B	130
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life.	I	A	5, 144, 145
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction without a history of myocardial infarction, in order to prevent or delay the onset of HF.	I	B	5
ACE-I should be considered in patients with stable CAD even if they do not have LV systolic dysfunction, in order to prevent or delay the onset of HF.	IIa	A	142
Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF or prolong life.	I	B	146
ICD is recommended in patients: a) with asymptomatic LV systolic dysfunction (LVEF ≤30%) of ischaemic origin, who are at least 40 days after acute myocardial infarction, b) with asymptomatic non-ischaemic dilated cardiomyopathy (LVEF ≤30%), who receive OMT therapy, in order to prevent sudden death and prolong life.	I	B	149, 156–158

ACEI = angiotensin-converting enzyme inhibitor; CAD = coronary artery disease; HF = heart failure; ICD = implantable cardioverter-defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; OMT = optimal medical therapy
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

7. Pharmacological treatment of heart failure with reduced ejection fraction

7.1 Objectives in the management of heart failure

The goals of treatment in patients with HF are to improve their clinical status, functional capacity and quality of life, prevent hospital admission and reduce mortality. The fact that several drugs for HF have shown detrimental effects on long-term outcomes, despite showing beneficial effects on shorter-term surrogate markers, has led regulatory bodies and clinical practice guidelines to seek mortality/morbidity data for approving/recommending therapeutic interventions for HF. However, it is now recognized that preventing HF hospitalization and improving functional capacity are important benefits to be considered if a mortality excess is ruled out.[159–161]

Figure 7.1 shows a treatment strategy for the use of drugs (and devices) in patients with HFrEF. The recommendations for each treatment are summarized below.

Neuro-hormonal antagonists (ACEIs, MRAs and beta-blockers) have been shown to improve survival in patients with HFrEF and are recommended for the treatment of every patient with HFrEF, unless contraindicated or not tolerated. A new compound (LCZ696) that combines the moieties of an ARB (valsartan) and a neprilysin (NEP) inhibitor (sacubitril) has recently been shown to be superior to an ACEI (enalapril) in reducing the risk of death and of hospitalization for HF in a single trial with strict inclusion/exclusion criteria.[162] Sacubitril/valsartan is therefore recommended to replace ACEIs in ambulatory HFrEF patients who remain symptomatic despite optimal therapy and who fit these trial criteria. ARBs have not been consistently proven to reduce mortality in patients with HFrEF and their use should be restricted to patients intolerant of an ACEI or those who take an ACEI but are unable to tolerate an

MRA. Ivabradine reduces the elevated heart rate often seen in HFrEF and has also been shown to improve outcomes, and should be considered when appropriate.

The above medications should be used in conjunction with diuretics in patients with symptoms and/or signs of congestion. The use of diuretics should be modulated according to the patient's clinical status.

The key evidence supporting the recommendations in this section is given in *Web Table 7.1*. The recommended doses of these disease-modifying medications are given in *Table 7.2*. The recommendations given in Sections 7.5 and 7.6 summarize drugs that should be avoided or used with caution in patients with HFrEF.

7.2 Treatments recommended in all symptomatic patients with heart failure with reduced ejection fraction

7.2.1 Angiotensin-converting enzyme inhibitors

ACEIs have been shown to reduce mortality and morbidity in patients with HFrEF[2,5,163–165] and are recommended unless contraindicated or not tolerated in all symptomatic patients. ACEIs should be up-titrated to the maximum tolerated dose in order to achieve adequate inhibition of the renin–angiotensin–aldosterone system (RAAS). There is evidence that in clinical practice the majority of patients receive suboptimal doses of ACEI.[166] ACEIs are also recommended in patients with asymptomatic LV systolic dysfunction to reduce the risk of HF development, HF hospitalization and death (see Section 6).

Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction

Recommendations	Class [a]	Level [b]	Ref [c]
An ACE-I[d] is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A	2, 163–165
A beta-blocker is recommended, in addition an ACE-I[d], for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.	I	A	167–173
An MRA is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE-I[d] and a beta-blocker, to reduce the risk of HF hospitalization and death.	I	A	174, 175

ACEI = angiotensin-converting enzyme inhibitor; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Or ARB if ACEI is not tolerated/contraindicated

Practical guidance on how to use ACE inhibitors is given in *Web Table 7.4*.

7.2.2 Beta-blockers

Beta-blockers reduce mortality and morbidity in symptomatic patients with HFrEF, despite treatment with an ACEI and, in most cases, a diuretic,[167,168,170,172,173] but have not been tested in congested or decompensated patients. There is consensus that beta-blockers and ACEIs are complementary, and can be started together as soon as the diagnosis of HFrEF is made. There is no evidence favouring the initiation of treatment with a beta-blocker before an ACEI has been started.[176] Beta-blockers should be initiated in clinically stable patients at a low dose and gradually up-titrated to the maximum tolerated dose. In patients admitted due to acute HF (AHF) beta-blockers should be cautiously initiated in hospital, once the patient is stabilized.

An individual patient data meta-analysis of all the major beta-blocker trials in HFrEF has shown no benefit on hospital admissions and mortality in the subgroup of patients with HFrEF who are in AF.[177] However, since this is a retrospective subgroup analysis, and because beta-blockers did not increase the risk, the guideline committee decided not to make a separate recommendation according to heart rhythm. Beta-blockers should be considered for rate control in patients with HFrEF and AF, especially in those with high heart rate (see Section 10.1 for details).

Beta-blockers are recommended in patients with a history of myocardial infarction and asymptomatic LV systolic dysfunction to reduce the risk of death (see Section 6).

Practical guidance on how to use beta-blockers is given in *Web Table 7.5*.

7.2.3 Mineralocorticoid/aldosterone receptor antagonists

MRAs (spironolactone and eplerenone) block receptors that bind aldosterone and, with different degrees of affinity, other steroid hormone (e.g. corticosteroids, androgens) receptors. Spironolactone or eplerenone are recommended in all symptomatic patients (despite treatment with an ACEI and a beta-blocker) with HFrEF and LVEF $\leq$35%, to reduce mortality and HF hospitalization.[174,175]

Caution should be exercised when MRAs are used in patients with impaired renal function and in those with serum potassium levels $>$5.0 mmol/L. Regular checks of serum potassium levels and renal function should be performed according to clinical status.

Practical guidance on how to use MRAs is given in *Web Table 7.6*.

7.3 Other treatments recommended in selected symptomatic patients with heart failure with reduced ejection fraction

7.3.1 Diuretics

Diuretics are recommended to reduce the signs and symptoms of congestion in patients with HFrEF, but their effects on

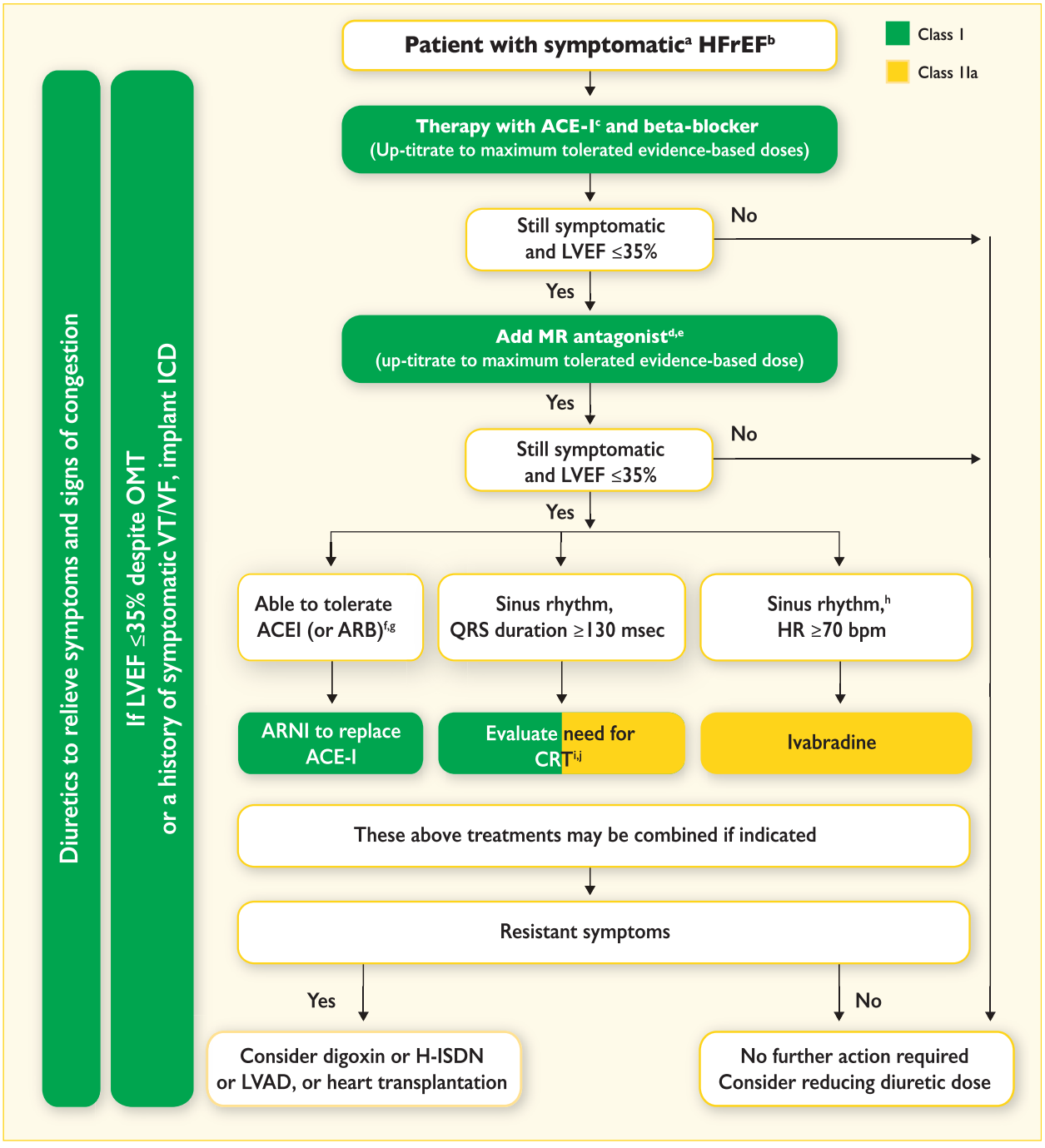

Figure 7.1 Therapeutic algorithm for a patient with symptomatic heart failure with reduced ejection fraction. Green indicates a class I recommendation; yellow indicates a class IIa recommendation. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BNP = B-type natriuretic peptide; CRT = cardiac resynchronization therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; 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 = mineralocorticoid receptor; NT-proBNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; OMT = optimal medical therapy; VF = ventricular fibrillation; VT = ventricular tachycardia. [a]Symptomatic = NYHA Class II-IV. [b]HFrEF = LVEF <40%. [c]If ACE inhibitor not tolerated/contra-indicated, use ARB. [d]If MR antagonist not tolerated/contra-indicated, use ARB. [e]With a hospital admission for HF within the last 6 months or with elevated natriuretic peptides (BNP > 250 pg/ml or NTproBNP > 500 pg/ml in men and 750 pg/ml in women). [f]With an elevated plasma natriuretic peptide level (BNP ≥ 150 pg/mL or plasma NT-proBNP ≥ 600 pg/mL, or if HF hospitalization within recent 12 months plasma BNP ≥ 100 pg/mL or plasma NT-proBNP ≥ 400 pg/mL). [g]In doses equivalent to enalapril 10 mg b.i.d. [h]With a hospital admission for HF within the previous year. [i]CRT is recommended if QRS ≥ 130 msec and LBBB (in sinus rhythm). [j]CRT should/may be considered if QRS ≥ 130 msec with non-LBBB (in a sinus rhythm) or for patients in AF provided a strategy to ensure bi-ventricular capture in place (individualized decision). For further details, see Sections 7 and 8 and corresponding web pages.

mortality and morbidity have not been studied in RCTs. A Cochrane meta-analysis has shown that in patients with chronic HF, loop and thiazide diuretics appear to reduce the risk of death and worsening HF compared with placebo, and compared with an active control, diuretics appear to improve exercise capacity.[178,179]

Table 7.2 Evidence-based doses of disease-modifying drugs in key randomized trials in heart failure with reduced ejection fraction (or after myocardial infarction)

	Starting dose (mg)	Target dose (mg)
ACE-I		
Captopril[a]	6.25 *t.i.d.*	50 *t.i.d.*
Enalapril	2.5 *b.i.d.*	20 *b.i.d.*
Lisinopril[b]	2.5–5.0 *o.d.*	20–35 *o.d.*
Ramipril	2.5 o.d.	10 *o.d.*
Trandolapril[a]	0.5 *o.d.*	4 *o.d.*
Beta-blockers		
Bisoprolol	1.25 *o.d.*	10 *o.d.*
Carvedilol	3.125 *b.i.d.*	25 *b.i.d.*[d]
Metoprolol succinate (CR/XL)	12.5–25 *o.d.*	200 o.d.
Nebivolol[c]	1.25 *o.d.*	10 *o.d.*
ARBs		
Candesartan	4–8 *o.d.*	32 *o.d.*
Valsartan	40 *b.i.d.*	160 *b.i.d.*
Losartan[b,c]	50 *o.d.*	150 *o.d.*
MRAs		
Eplerenone	25 *o.d.*	50 *o.d.*
Spironolactone	25 *o.d.*	50 *o.d.*
ARNI		
Sacubitril/valsartan	49/51 *b.i.d.*	97/103 *b.i.d.*
I_f-channel blocker		
Ivabradine	5 *b.i.d.*	7.5 *b.i.d.*

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; b.i.d. = bis in die (twice daily); MRA = mineralocorticoid receptor antagonist; o.d. = omne in die (once daily); t.i.d. = ter in die (three times a day).
[a]Indicates an ACE-I where the dosing target is derived from post-myocardial infarction trials.
[b]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 randomized, placebo-controlled trial and the optimum dose is uncertain.
[c]Indicates a treatment not shown to reduce cardiovascular or all-cause mortality in patients with heart failure (or shown to be non-inferior to a treatment that does).
[d]A maximum dose of 50 mg twice daily can be administered to patients weighing over 85 kg.

Loop diuretics produce a more intense and shorter diuresis than thiazides, although they act synergistically and the combination may be used to treat resistant oedema. However, adverse effects are more likely and these combinations should only be used with care. The aim of diuretic therapy is to achieve and maintain euvolaemia with the lowest achievable dose. The dose of the diuretic must be adjusted according to the individual needs over time. In selected asymptomatic euvolaemic/hypovolaemic patients, the use of a diuretic drug might be (temporarily) discontinued. Patients can be trained to self-adjust their diuretic dose based on monitoring of symptoms/signs of congestion and daily weight measurements.

Doses of diuretics commonly used to treat HF are provided in *Table 7.3*. Practical guidance on how to use diuretics is given in *Web Table 7.7*.

Table 7.3 Doses of diuretics commonly used in patients with heart failure

Diuretics	Initial dose (mg)		Usual daily dose (mg)	
Loop diuretics[a]				
Furosemide	20–40		40–240	
Bumetanide	0.5–1.0		1–5	
Torasemide	5–10		10–20	
Thiazides[b]				
Bendroflumethiazide	2.5		2.5–10	
Hydrochlorothiazide	25		12.5–100	
Metolazone	2.5		2.5–10	
Indapamide[c]	2.5		2.5–5	
Potassium-sparing diuretics[d]				
	+ACE-I/ ARB	-ACE-I/ ARB	+ACE-I/ ARB	-ACE-I/ ARB
Spironolactone/ eplerenone	12.5–25	50	50	100–200
Amiloride	2.5	5	5–10	10–20
Triamterene	25	50	100	200

ACE-I = angiontensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker.
[a]Oral or intravenous; dose might need to be adjusted according to volume status/weight; excessive doses may cause renal impairment and ototoxicity.
[b]Do not use thiazides if estimated glomerular filtration rate <30 mL/min/1.73 m^2, except when prescribed synergistically with loop diuretics.
[c]Indapamide is a non-thiazide sulfonamide.
[d]A mineralocorticoid antagonist (MRA) i.e. spironolactone/eplerenone is always preferred. Amiloride and triamterene should not be combined with an MRA.

Other pharmacological treatments recommended in selected patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction

Recommendations	Class [a]	Level [b]	Ref [c]
Diuretics			
Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion.	I	B	178, 179
Diuretics should be considered to reduce the risk of HF hospitalization in patients with signs and/or symptoms of congestion.	IIa	B	178, 179
Angiotensin receptor neprilysin inhibitor			
Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA[d]	I	B	162
If-channel inhibitor			
Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I (or ARB), and an MRA (or ARB).	IIa	B	180
Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contra-indications for a beta-blocker. Patients should also receive an ACE-I (or ARB) and an MRA (or ARB).	IIa	C	181
ARB			
An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE-I (patients should also receive a beta-blocker and an MRA).	I	B	182
An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a beta-blocker who are unable to tolerate an MRA.	IIb	C	-
Hydralazine and isosorbide dinitrate			
Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a beta-blocker and an MRA to reduce the risk of HF hospitalization and death.	IIa	B	183
Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE-I nor an ARB (or they are contra-indicated) to reduce the risk of death.	IIb	B	184
Other treatments with less-certain benefits			
Digoxin			
Digoxin may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE-I (or ARB), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations).	IIb	B	185
N-3 PUFA			
An n-3 PUFA[e] preparation may be considered in symptomatic HF patients to reduce the risk of cardiovascular hospitalization and cardiovascular death.	IIb	B	186

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; bpm = beats per minute; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; PUFA = polyunsaturated fatty acid. OMT = optimal medical therapy (for HFrEF this mostly comprises an ACEI or sacubitril/valsartan, a beta-blocker and an MRA).

[a]Class of recommendation.

[b]Level of evidence.

[c]Reference(s) supporting recommendations.

[d]Patient should have elevated natriuretic peptides (plasma BNP ≥150 pg/mL or plasma NT-proBNP ≥600 pg/mL, or if HF hospitalization within the last 12 months, plasma BNP ≥100 pg/mL or plasma NT-proBNP ≥400 pg/mL) and able to tolerate enalapril 10 mg *b.i.d.*

[e]Applies only to preparation studied in cited trial.

7.3.2 Angiotensin receptor neprilysin inhibitor

A new therapeutic class of agents acting on the RAAS and the neutral endopeptidase system has been developed [angiotensin receptor neprilysin inhibitor (ARNI)]. The first in class is LCZ696, which is a molecule that combines the moieties of valsartan and sacubitril (neprilysin inhibitor) in a single substance. By inhibiting neprilysin, the degradation of NPs, bradykinin and other peptides is slowed. High circulating A-type natriuretic peptide (ANP) and BNP exert physiologic effects through binding to NP receptors and the augmented generation of cGMP, thereby enhancing diuresis, natriuresis and myocardial relaxation and anti-remodelling. ANP and BNP also inhibit renin and aldosterone secretion. Selective AT1-receptor blockade reduces vasoconstriction, sodium and water retention and myocardial hypertrophy.[187,188]

A recent trial investigated the long-term effects of sacubitril/valsartan compared with an ACEI (enalapril) on morbidity

and mortality in patients with ambulatory, symptomatic HFrEF with LVEF ≤40% (this was changed to ≤35% during the study), elevated plasma NP levels (BNP ≥150 pg/mL or NT-proBNP ≥600 pg/mL or, if they had been hospitalized for HF within the previous 12 months, BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL), and an estimated GFR (eGFR) ≥30 mL/min/1.73 m^2 of body surface area, who were able to tolerate separate treatments periods with enalapril (10 mg *b.i.d.*) and sacubitril/valsartan (97/103 mg *b.i.d.*) during a run-in period.[162] In this population, sacubitril/valsartan (97/103 mg *b.i.d.*) was superior to ACEI (enalapril 10 mg *b.i.d.*) in reducing hospitalizations for worsening HF, cardiovascular mortality and overall mortality.[162] Sacubitril/valsartan is therefore recommended in patients with HFrEF who fit this profile.

Despite the superiority of sacubitril/valsartan over enalapril in the PARADIGM-HF trial, some relevant safety issues remain when initiating therapy with this drug in clinical practice. Symptomatic hypotension was more often present in the sacubitril/valsartan group (in those ≥75 years of age, it affected 18% in the sacubitril/valsartan group vs. 12% in the enalapril group), although there was no increase in the rate of discontinuation.[162] The risk of angioedema in the trial was reduced by recruiting only those who tolerated therapy with enalapril 10 mg *b.i.d.* and an sacubitril/valsartan during an active run-in phase of 5–9 weeks (it resulted in a 0.4% rate of angioedema in sacubitril/valsartan group vs. 0.2% in an enalapril group). Also, the number of African American patients, who are at a higher risk of angioedema, was relatively small in this study. To minimize the risk of angioedema caused by overlapping ACE and neprilysin inhibition, the ACEI should be withheld for at least 36 h before initiating sacubitril/valsartan. Combined treatment with an ACEI (or ARB) and sacubitril/valsartan is contraindicated. There are additional concerns about its effects on the degradation of beta-amyloid peptide in the brain, which could theoretically accelerate amyloid deposition.[189–191] However, a recent small 14-day study with healthy subjects showed elevation of the beta-amyloid protein in the soluble rather than the aggregable form, which if confirmed over longer time periods in patients with HFrEF may indicate the cerebral safety of sacubitril/valsartan.[192] Long-term safety needs to be addressed.

7.3.3 I_f-channel inhibitor

Ivabradine slows the heart rate through inhibition of the I_f channel in the sinus node and therefore should only be used for patients in sinus rhythm. Ivabradine reduced the combined endpoint of mortality and hospitalization for HF in patients with symptomatic HFrEF and LVEF ≤35%, in sinus rhythm and with a heart rate ≥70 beats per minute (bpm) who had been hospitalized for HF within the previous 12 months, receiving treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose), an ACEI (or ARB) and an MRA.[180] The European Medicines Agency (EMA) approved ivabradine for use in Europe in patients with HFrEF with LVEF ≤35% and in sinus rhythm with a resting heart rate ≥75 bpm, because in this group ivabradine conferred a survival benefit[193] based on a retrospective subgroup analysis requested by the EMA.

Practical guidance on how to use ivabradine is given in *Web Table 7.8*.

7.3.4 Angiotensin II type I receptor blockers

ARBs are recommended only as an alternative in patients intolerant of an ACEI.[182] Candesartan has been shown to reduce cardiovascular mortality.[182] Valsartan showed an effect on hospitalization for HF (but not on all-cause hospitalizations) in patients with HFrEF receiving background ACEIs.[194]

The combination of ACEI/ARB for HFrEF was reviewed by the EMA, which suggested that benefits are thought to outweigh risks only in a select group of patients with HFrEF in whom other treatments are unsuitable. Therefore, ARBs are indicated for the treatment of HFrEF only in patients who cannot tolerate an ACEI because of serious side effects. The combination of ACEI/ARB should be restricted to symptomatic HFrEF patients receiving a beta-blocker who are unable to tolerate an MRA, and must be used under strict supervision.

7.3.5 Combination of hydralazine and isosorbide dinitrate

There is no clear evidence to suggest the use of this fixed-dose combination therapy in all patients with HFrEF. Evidence on the clinical utility of this combination is scanty and comes from one relatively small RCT conducted exclusively in men and before ACEIs or beta-blockers were used to treat HF.[184] A subsequent RCT conducted in self-identified black patients (defined as being of African descent) showed that addition of the combination of hydralazine and isosorbide dinitrate to conventional therapy (ACEI, beta-blocker and MRA) reduced mortality and HF hospitalizations in patients with HFrEF and NYHA Classes III–IV.[183] The results of this study are difficult to translate to patients of other racial or ethnic origins.

Additionally, a combination of hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither ACEI nor ARB (or they are contraindicated) to reduce mortality. However, this recommendation is based on the results of the Veterans Administration Cooperative Study, which recruited symptomatic HFrEF patients who received only digoxin and diuretics.[184]

7.4 Other treatments with less certain benefits in symptomatic patients with heart failure with reduced ejection fraction

This section describes treatments that have shown benefits in terms of symptomatic improvement, reduction in HF hospitalizations or both, and are useful additional treatments in patients with HFrEF.

7.4.1 Digoxin and other digitalis glycosides

Digoxin may be considered in patients in sinus rhythm with symptomatic HFrEF to reduce the risk of hospitalization (both all-cause and HF hospitalizations),[185] although its effect on top of beta-blockers has never been tested. The effects of digoxin in patients

with HFrEF and AF have not been studied in RCTs, and recent studies have suggested potentially higher risk of events (mortality and HF hospitalization) in patients with AF receiving digoxin.[195,196] However, this remains controversial, as another recent meta-analysis concluded on the basis of non-RCTs that digoxin has no deleterious effect on mortality in patients with AF and concomitant HF, most of whom had HFrEF.[197]

In patients with symptomatic HF and AF, digoxin may be useful to slow a rapid ventricular rate, but it is only recommended for the treatment of patients with HFrEF and AF with rapid ventricular rate when other therapeutic options cannot be pursued.[196,198–201] Of note, the optimal ventricular rate for patients with HF and AF has not been well established, but the prevailing evidence suggests that strict rate control might be deleterious. A resting ventricular rate in the range of 70–90 bpm is recommended based on current opinion, although one trial suggested that a resting ventricular rate of up to 110 bpm might still be acceptable.[202] This should be tested and refined by further research.

Digitalis should always be prescribed under specialist supervision. Given its distribution and clearance, caution should be exerted in females, in the elderly and in patients with reduced renal function. In the latter patients, digitoxin should be preferred.

7.4.2 n-3 polyunsaturated fatty acids

n-3 polyunsaturated fatty acids (n-3 PUFAs) have shown a small treatment effect in a large RCT.[186] n-3 PUFA preparations differ in composition and dose. Only preparations with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as ethyl esters of at least 85% (850 mg/g) have shown an effect on the cumulative endpoint of cardiovascular death and hospitalization. No effect of n-3 PUFA preparations containing <850 mg/g has been shown in either HFrEF or post-myocardial infarction.[203] n-3 PUFA preparations containing 850–882 mg of EPA and DHA as ethyl esters in the average ratio of 1 : 1.2 may be considered as an adjunctive therapy in patients with symptomatic HFrEF who are already receiving optimized recommended therapy with an ACEI (or ARB), a beta-blocker and an MRA.

7.5 Treatments not recommended (unproven benefit) in symptomatic patients with heart failure with reduced ejection fraction

7.5.1 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors ('statins')

Although statins reduce mortality and morbidity in patients with atherosclerotic disease, statins are not effective in improving the prognosis in patients with HFrEF. Most statin trials excluded patients with HF (because it was uncertain that they would benefit).[204] The two major trials that studied the effect of statin treatment in patients with chronic HF did not demonstrate any evidence of benefit.[205] Therefore, evidence does not support the initiation of statins in most patients with chronic HF. However, in patients who already receive a statin because of underlying CAD or/and hyperlipidaemia, a continuation of this therapy should be considered.

7.5.2 Oral anticoagulants and antiplatelet therapy

Other than in patients with AF (both HFrEF and HFpEF), there is no evidence that an oral anticoagulant reduces mortality/morbidity compared with placebo or aspirin.[206,207] Studies testing the non-vitamin K antagonist oral anticoagulants (NOACs) in patients with HFrEF are currently ongoing. Patients with HFrEF receiving oral anticoagulation because of concurrent AF or risk of venous thromboembolism should continue anticoagulation. Detailed information is provided in Section 10.1.

Similarly, there is no evidence on the benefits of antiplatelet drugs (including acetylsalicylic acid) in patients with HF without accompanying CAD, whereas there is a substantial risk of gastrointestinal bleeding, particularly in elderly subjects, related with this treatment.

7.5.3 Renin inhibitors

Aliskiren (direct renin inhibitor) failed to improve outcomes for patients hospitalized for HF at 6 months or 12 months in one study[208] and is not presently recommended as an alternative to an ACEI or ARB.

Treatments (or combinations of treatments) that may cause harm in patients with symptomatic (NYHA Class II–IV) heart failure with reduced ejection fraction

Recommendations	Class [a]	Level [b]	Ref [c]
Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	A	209, 210
NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	B	211–213
Diltiazem or verapamil are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization.	III	C	214
The addition of an ARB (or renin inhibitor) to the combination of an ACE-I and an MRA is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalaemia.	III	C	

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; COX-2 inhibitor = cyclooxygenase-2 inhibitor; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; NSAIDs = non-steroidal anti-inflammatory drugs.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations

7.6 Treatments not recommended (believed to cause harm) in symptomatic patients with heart failure with reduced ejection fraction

7.6.1 Calcium-channel blockers

Non-dihydropyridine calcium-channel blockers (CCBs) are not indicated for the treatment of patients with HFrEF. Diltiazem and verapamil have been shown to be unsafe in patients with HFrEF.[214]

There is a variety of dihydropyridine CCBs; some are known to increase sympathetic tone and they may have a negative safety profile in HFrEF. There is only evidence on safety for amlodipine[215] and felodipine[216] in patients with HFrEF, and they can be used only if there is a compelling indication in patients with HFrEF.

8. Non-surgical device treatment of heart failure with reduced ejection fraction

This section provides recommendations on the use of ICDs and CRT. Currently, the evidence is considered insufficient to support specific guideline recommendations for other therapeutic technologies, including baroreflex activation therapy,[217] vagal stimulation,[218] diaphragmatic pacing[219,220] and cardiac contractility modulation;[221,222] further research is required. Implantable devices to monitor arrhythmias or haemodynamics are discussed elsewhere in these guidelines.

8.1 Implantable cardioverter-defibrillator

A high proportion of deaths among patients with HF, especially those with milder symptoms, occur suddenly and unexpectedly. Many of these are due to electrical disturbances, including ventricular arrhythmias, bradycardia and asystole, although some are due to coronary, cerebral or aortic vascular events. Treatments that improve or delay the progression of cardiovascular disease will reduce the annual rate of sudden death, but they may have little effect on lifetime risk and will not treat arrhythmic events when they occur. ICDs are effective in preventing bradycardia and correcting potentially lethal ventricular arrhythmias. Some antiarrhythmic drugs might reduce the rate of tachyarrhythmias and sudden death, but they do not reduce overall mortality and may increase it.

Recommendations for implantable cardioverter-defibrillator in patients with heart failure

Recommendations	Class [a]	Level [b]	Ref [c]
Secondary prevention An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing haemodynamic instability, and who are expected to survive for >1 year with good functional status.	I	A	223–226
Primary prevention An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA Class II–III), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than one year with good functional status, and they have:			
• IHD (unless they have had an MI in the prior 40 days – see below).	I	A	149, 156, 227
• DCM.	I	B	156, 157, 227
ICD implantation is not recommended within 40 days of an MI as implantation at this time does not improve prognosis.	III	A	158, 228
ICD therapy is not recommended in patients in NYHA Class IV with severe symptoms refractory to pharmacological therapy unless they are candidates for CRT, a ventricular assist device, or cardiac transplantation.	III	C	229–233
Patients should be carefully evaluated by an experienced cardiologist before generator replacement, because management goals and the patient's needs and clinical status may have changed.	IIa	B	234–238
A wearable ICD may be considered for patients with HF who are at risk of sudden cardiac death for a limited period or as a bridge to an implanted device.	IIb	C	239–241

CAD = coronary artery disease; CRT = cardiac resynchronization therapy; DCM = dilated cardiomyopathy; HF = heart failure; ICD = implantable cardioverter-defibrillator; IHD = ischaemic heart disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association, OMT = optimal medical therapy.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

8.1.1 Secondary prevention of sudden cardiac death

Compared with amiodarone treatment, ICDs reduce mortality in survivors of cardiac arrest and in patients who have experienced sustained symptomatic ventricular arrhythmias. An ICD is recommended in such patients when the intent is to increase survival; the decision to implant should take into account the patient's view and their quality of life, the LVEF (survival benefit is uncertain when the LVEF is >35%) and the absence of other diseases likely to cause death within the following year.[223–225]

8.1.2 Primary prevention of sudden cardiac death

Although amiodarone may have reduced mortality in older trials of HF,[242,243] contemporary studies conducted since the widespread introduction of beta-blockers suggest that it does not reduce mortality in patients with HFrEF.[227,244,245] Dronedarone[246,247] and class I antiarrhythmic agents[246,248] should not be used for prevention of arrhythmias in this population.

Some guideline-recommended therapies, including beta-blockers, MRAs, sacubitril/valsartan and pacemakers with CRT (CRT-Ps), reduce the risk of sudden death (see Section 7).

An ICD reduces the rate of sudden arrhythmic death in patients with HFrEF.[249,250] In patients with moderate or severe HF, a reduction in sudden death may be partially or wholly offset by an increase in death due to worsening HF.[227] In patients with mild HF (NYHA II), an ICD will prevent about two deaths per year for every 100 devices implanted.[227] On average, patients with IHD are at greater risk of sudden death than patients with DCM and therefore, although the relative benefits are similar, the absolute benefit is greater in patients with IHD.[249] Patients with longer QRS durations may also receive greater benefit from an ICD, but these patients should often receive a CRT device.[227,251]

Two RCTs showed no benefit in patients who had an ICD implanted within 40 days after a myocardial infarction.[158,228] Although sudden arrhythmic deaths were reduced, this was balanced by an increase in non-arrhythmic deaths. Accordingly, an ICD is contraindicated in this time period. A wearable defibrillator may be considered if the patient is deemed to be at high risk of ventricular fibrillation, although evidence from randomized trials is lacking.[239–241]

ICD implantation is recommended only after a sufficient trial (minimum 3 months) of optimal medical therapy (OMT) has failed to increase the LVEF to >35%. However, one of the two landmark papers on which these recommendations are based included patients with an LVEF >30%. Fewer than 400 patients with an LVEF of 30–35% were included in the landmark studies, and although there was no statistical interaction between treatment effect and LVEF, the evidence of benefit is less robust in this group of patients.

Conservative programming with long delays[252] between detection and the ICD delivering therapy dramatically reduces the risk of both inappropriate (due to artefacts or AF) and appropriate but unnecessary [due to self-terminating ventricular tachycardia (VT)] shocks.[252–254]

Patients with a QRS duration ≥130 ms should be considered for a defibrillator with CRT (CRT-D) rather than ICD. See the guideline on CRT for further details (Section 8.2).

ICD therapy is not recommended in patients in NYHA Class IV with severe symptoms refractory to pharmacological therapy who are not candidates for CRT, a ventricular assist device or cardiac transplantation, because such patients have a very limited life expectancy and are likely to die from pump failure.

Patients with serious co-morbidities who are unlikely to survive substantially more than 1 year are unlikely to obtain substantial benefit from an ICD.[229–233]

Patients should be counselled as to the purpose of an ICD, complications related to implantation and device activation (predominantly inappropriate shocks) and under what circumstances it might be deactivated (terminal disease) or explanted (infection, recovery of LV function).[255]

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

If the ICD generator reaches its end of life or requires explantation, it should not automatically be replaced.[234–238] Patients should be carefully evaluated by an experienced cardiologist before generator replacement. Treatment goals may have changed and the risk of fatal arrhythmia may be lower or the risk of non-arrhythmic death higher. It is a matter of some controversy whether patients whose LVEF has greatly improved and who have not required device therapy during the lifetime of the ICD should have another device implanted.[234–238]

Subcutaneous defibrillators may be as effective as conventional ICDs with a lower risk from the implantation procedure.[256,257] They may be the preferred option for patients with difficult access or who require ICD explantation due to infection. Patients must be carefully selected, as they have limited capacity to treat serious bradyarrhythmia and can deliver neither antitachycardia pacing nor CRT. Substantial RCTs with these devices and more data on safety and efficacy are awaited.[258,259]

A wearable ICD (an external defibrillator with leads and electrode pads attached to a wearable vest) that is able to recognize and interrupt VT/ventricular fibrillation may be considered for a limited period of time in selected patients with HF who are at high risk for sudden death but otherwise are not suitable for ICD implantation (e.g. those with poor LVEF after acute myocardial damage until LV function recovers, patients scheduled for heart transplantation).[239–241,260] However, no prospective RCTs evaluating this device have been reported.

For detailed recommendations on the use/indications of ICD we refer the reader to the ESC/European Heart Rhythm Association (EHRA) guidelines on ventricular tachyarrhythmias and sudden cardiac death.[260]

8.2 Cardiac resynchronization therapy

Recommendations for cardiac resynchronization therapy implantation in patients with heart failure

Recommendations	Class [a]	Level [b]	Ref [c]
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	A	261–272
CRT should be considered for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIa	B	261–272
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	B	266, 273
CRT may be considered for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIb	B	266, 273
CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing and high degree AV block in order to reduce morbidity. This includes patients with AF (see Section 10.1).	I	A	274–277
CRT should be considered for patients with LVEF ≤35% in NYHA Class III–IV[d] despite OMT in order to improve symptoms and reduce morbidity and mortality, if they are in AF and have a QRS duration ≥130 msec provided a strategy to ensure bi-ventricular capture is in place or the patient is expected to return to sinus rhythm.	IIa	B	275, 278–281
Patients with HFrEF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT and who have a high proportion of RV pacing may be considered for upgrade to CRT. This does not apply to patients with stable HF.	IIb	B	282
CRT is contra-indicated in patients with a QRS duration < 130 msec.	III	A	266, 283–285

AF = atrial fibrillation; AV = atrio-ventricular; CRT = cardiac resynchronization therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; OMT = optimal medical therapy; QRS = Q, R and S waves (combination of three of the graphical deflections); RV = right ventricular.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Use judgement for patients with end-stage HF who might be managed conservatively rather than with treatments to improve symptoms or prognosis.

CRT improves cardiac performance in appropriately selected patients and improves symptoms[286] and well-being[286] and reduces morbidity and mortality.[266] Of the improvement in quality-adjusted life-years (QALYs) with CRT among patients with moderate to severe HF, two-thirds may be attributed to improved quality of life and one-third to increased longevity.[287]

Only the COMPANION[265] and CARE-HF trials[262,263] compared the effect of CRT to guideline-advised medical therapy. Most other trials have compared CRT-D to ICD, and a few have compared CRT-P to backup pacing. The prevention of lethal bradycardia might be an important mechanism of benefit shared by all pacing devices. In CARE-HF, at baseline, 25% of patients had a resting heart rate of ≤60 bpm.[262–264] If prevention of bradycardia is important, the effect of CRT will appear greater in trials where there is no device in the control group.

Most studies of CRT have specified that the LVEF should be <35%, but RAFT[267] and MADIT-CRT[268,269] specified an LVEF <30%, while REVERSE[270–272] specified <40% and BLOCK-HF[274] <50%. Relatively few patients with an LVEF of 35–40% have been randomized, but an individual participant data (IPD) meta-analysis suggests no diminution of the effect of CRT in this group.[266]

Not all patients respond favourably to CRT.[286] Several characteristics predict improvement in morbidity and mortality, and the extent of reverse remodelling is one of the most important mechanisms of action of CRT. Patients with ischaemic aetiology will have less improvement in LV function due to myocardial scar tissue, which is less likely to undergo favourable remodelling.[288] Conversely, women may be more likely to respond than men, possibly due to smaller body and heart size.[273,285,289] QRS width predicts CRT response and was the inclusion criterion in all randomized trials. But QRS morphology has also been related to a beneficial response to CRT. Several studies have shown that patients with left bundle branch block (LBBB) morphology are more likely to respond favourably to CRT, whereas there is less certainty about patients with non-LBBB morphology. However, patients with LBBB morphology often have wider QRS duration, and there is a current debate about whether QRS duration or QRS morphology is the main predictor of a beneficial response to CRT. Evidence from two IPD meta-analyses indicates that after accounting for QRS duration, there is little evidence to suggest that QRS morphology or aetiology of disease influence the effect of CRT on morbidity or mortality.[266,273] In addition, none of the landmark trials selected patients for inclusion according to QRS morphology, sex or ischaemic aetiology, nor were they powered for subgroup analyses.

The Echo-CRT[283,284] trial and an IPD meta-analysis[266] suggest possible harm from CRT when QRS duration is <130 ms, thus implantation of CRT is not recommended if QRS duration is <130 ms.[266,283,284]

If a patient is scheduled to receive an ICD and is in sinus rhythm with a QRS duration ≥130 ms, CRT-D should be considered if QRS is between 130 and 149 ms and is recommended if QRS is ≥150 ms. However, if the primary reason for implanting a CRT is for the relief of symptoms, then the clinician should choose CRT-P or CRT-D, whichever they consider appropriate. Clinical practice varies widely among countries. The only randomized trial to compare CRT-P and CRT-D[265] failed to demonstrate a difference in morbidity or mortality between these technologies.[288] If the primary reason for implanting CRT is to improve prognosis,

then the majority of evidence lies with CRT-D for patients in NYHA Class II and with CRT-P for patients in NYHA Classes III–IV. It is unclear whether CRT reduces the need for an ICD (by reducing the arrhythmia burden) or increases the benefit from an ICD (by reducing mortality rates from worsening HF, leading to longer exposure to the risk of arrhythmia).

When LVEF is reduced, RV pacing may exacerbate cardiac dyssynchrony. This can be prevented by CRT, which might improve patient outcomes.[274,275,277,290] However, a difference in outcome was not observed between CRT and RV pacing in a subgroup analysis of RAFT[267] or in patients without HFrEF in BioPACE.[291] On balance, CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing in order to reduce morbidity, although no clear effect on mortality was observed. Patients with HFrEF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF with a high proportion of RV pacing, despite OMT, should be considered for upgrading to CRT.

Only two small trials have compared pharmacological therapy alone vs. CRT in patients with AF, with conflicting results. Several studies have indicated that CRT is superior to RV pacing in patients undergoing atrio-ventricular (AV) node ablation.[275,277,290] However, CRT is not an indication to carry out AV node ablation except in rare cases when ventricular rate remains persistently high (>110 bpm) despite attempts at pharmacological rate control. A subgroup analysis of patients with AF from the RAFT study found no benefit from CRT-D compared with ICD, although less than half of patients had >90% biventricular capture.[276] Observational studies report that when biventricular capture is <98%, the prognosis of patients with CRT declines.[277] Whether this association reflects a loss of resynchronization (which might be remedied by device programming), poor placing of the LV lead (which might be avoided at implantation) or greater difficulty in pacing severely diseased myocardium (which might not be amenable to the above) is uncertain. This observation has not been confirmed in a randomized trial.

Imaging tests for dyssynchrony have not yet been shown to be of value in selecting patients for CRT.[292] Patients with extensive myocardial scar will have less improvement in LV function with CRT, but this is true of any treatment for HFrEF and does not reliably predict less clinical benefit.[293] Pacing thresholds are higher in scarred myocardium and, if possible, lead placement should avoid such regions.[294,295] Although patients with extensive scarring have an intrinsically worse prognosis, there is little evidence that they obtain less prognostic benefit from CRT.[266]

The reader is directed to guidelines on pacing and CRT for recommendations on device implantation procedures. The value of trying to optimize AV or VV intervals after implantation using echo- or electrocardiographic criteria or blood pressure response is uncertain, but may be considered for patients who have had a disappointing response to CRT.[296,297]

8.3 Other implantable electrical devices

For patients with HFrEF who remain symptomatic despite OMT and do not have an indication for CRT, new device therapies have been proposed and in some cases are approved for clinical use in several European Union (EU) countries but remain under trial evaluation.

Cardiac contractility modulation (CCM) is similar in its mode of insertion to CRT, but it involves non-excitatory electrical stimulation of the ventricle during the absolute refractory period to enhance contractile performance without activating extra systolic contractions. CCM has been evaluated in patients with HFrEF in NYHA Classes II–III with normal QRS duration (<120 ms).[221,222] An individual patient data meta-analysis demonstrated an improvement in exercise tolerance (peak VO_2) and quality of life (Minnesota Living with Heart Failure questionnaire). Thus CCM may be considered in selected patients with HF. The effect of CCM on HF morbidity and mortality remains to be established.

Most other devices under evaluation involve some modification of the activity of the autonomic nervous system (ANS) by targeted electrical stimulation.[298,299] These include vagal nerve stimulation, spinal cord stimulation, carotid body ablation and renal denervation, but so far none of the devices has improved symptoms or outcomes in RCTs.

Devices for remote monitoring are discussed in Section 14.

9. Treatment of heart failure with preserved ejection fraction

While there is clear agreement that the diagnosis of HFrEF requires an LVEF <40%, the exact definition of HFpEF is less clear. According to the definition provided in this document (see Section 3), the diagnosis of HFpEF requires an LVEF ≥50%, whereas patients with LVEF between 40 and 49% are considered to have HFmrEF (for details, please refer to Section 3). Patients with HFmrEF have generally been included in trials of HFpEF. Accordingly, the guidance in this section applies to patients with both HFmrEF and HFpEF. As new data and analyses become available, it might be possible to make recommendations for each phenotype separately.

In clinical practice and clinical trials, compared with HFrEF patients, only slightly fewer patients with HFpEF and HFmrEF currently appear to receive diuretics, beta-blockers, MRAs and ACEIs or ARBs.[166,300–302] This may reflect treatment of cardiovascular co-morbidities, such as hypertension, CAD and AF, or extrapolation of results from trials conducted for these conditions showing a reduction in new-onset HF,[127] or failure to distinguish between guideline recommendations for HFrEF and HFmrEF/HFpEF or a belief that existing clinical trials provide some evidence of benefit with these agents.

A summary of phase II and III clinical trials of patients with HFpEF and HFmrEF is presented in *Web Table 9.1*.

The pathophysiology underlying HFpEF and HFmrEF is heterogeneous, and they are associated with different phenotypes including diverse concomitant cardiovascular diseases (e.g. AF, arterial hypertension, CAD, pulmonary hypertension) and non-cardiovascular diseases [diabetes, chronic kidney disease (CKD), anaemia, iron deficiency, COPD and obesity].[303,304] Compared with HFrEF patients, hospitalizations and deaths in patients with HFmrEF/HFpEF are more likely to be non-cardiovascular.[305,306] Therefore patients should be screened for cardiovascular and non-cardiovascular co-morbidities, which if present should be managed with interventions that have been shown to improve symptoms, well-being or outcome related to that co-morbidity and not to exacerbate HF (see Section 11).

No treatment has yet been shown, convincingly, to reduce morbidity or mortality in patients with HFpEF or HFmrEF. However, since these patients are often elderly and highly symptomatic, and often have a poor quality of life,[307] an important aim of therapy may be to alleviate symptoms and improve well-being.[308]

9.1 Effect of treatment on symptoms in heart failure with preserved ejection fraction

Diuretics will usually improve congestion, if present, thereby improving symptoms and signs of HF. The evidence that diuretics improve symptoms is similar across the spectrum of LVEF.[178,179]

Evidence that beta-blockers and MRAs improve symptoms in these patients is lacking. There is inconsistent evidence for an improvement in symptoms in those treated with ARBs (only for candesartan was there an improvement in NYHA class)[309,310] and ACEIs.[311]

9.2 Effect of treatment on hospitalization for heart failure in heart failure with preserved ejection fraction

For patients in sinus rhythm, there is some evidence that nebivolol,[173,312,313] digoxin,[314] spironolactone[301] and candesartan[310] might reduce HF hospitalizations. For patients in AF, beta-blockers do not appear to be effective and digoxin has not been studied. The evidence in support of either ARBs[315] or ACEIs[311] is inconclusive.

9.3 Effect of treatment on mortality in heart failure with preserved ejection fraction

Trials of ACEIs, ARBs, beta-blockers and MRAs have all failed to reduce mortality in patients with HFpEF or HFmrEF. However, in older patients with HFrEF, HFpEF or HFmrEF, nebivolol reduced the combined endpoint of death or cardiovascular hospitalization,[173,312] with no significant interaction between treatment effect and baseline LVEF.[313]

9.4 Other considerations

Patients in AF should receive an anticoagulant to reduce the risk of thromboembolic events (for details, see the ESC guidelines of AF[316]]. Antiplatelet agents are ineffective for this purpose. Renal dysfunction, which is common in this population, may contraindicate or increase the risk of haemorrhage with NOACs.

The optimal ventricular rate in patients with HFmrEF/HFpEF and AF is uncertain, and aggressive rate control might be deleterious. Whether digoxin, beta-blockers or rate-limiting CCBs, or a combination of these, should be preferred is unknown. Verapamil or diltiazem should not be combined with a beta-blocker. There are insufficient data to recommend ablation strategies (either pulmonary venous or AV node) for HFpEF and HFmrEF.

Circumstantial evidence suggests that treating hypertension, often predominantly systolic, is important in HFmrEF/HFpEF.[127,317] Diuretics, ACEIs, ARBs and MRAs all appear appropriate agents, but beta-blockers may be less effective in reducing SBP. A recent study suggests that patients with hypertension and HFpEF or HFmrEF should not receive an ARB (olmesartan) if they are receiving ACEIs and beta-blockers.[318]

The first-line oral hypoglycaemic drug for patients with HFpEF and HFmrEF should be metformin[319] (see also Section 11.6). Recently, a trial of empagliflozin showed a reduction in blood pressure and body weight, probably by inducing glycosuria and osmotic diuresis. Its use was associated with a reduction in hospitalization for HF and in cardiovascular mortality.[130] However, aggressive management of dysglycaemia may be harmful.[153,320]

Myocardial ischaemia may contribute to symptoms, morbidity and mortality and should be considered when assessing patients. However, there is only anecdotal evidence that revascularization improves symptoms or outcome. Patients with angina should follow the same management route as patients with HFrEF.[112]

Patients with HFpEF and HFmrEF have impaired exercise tolerance, commonly accompanied by an augmented blood pressure response to exercise and chronotropic incompetence. Combined endurance/resistance training appears safe for patients with HFpEF and HFmrEF and improves exercise capacity (as reflected by an increase in peak oxygen consumption), physical functioning score and diastolic function.[307,321]

Recommendations for treatment of patients with heart failure with preserved ejection fraction and heart failure with mid-range ejection fraction

Recommendations	Class [a]	Level [b]	Ref [c]
it is recommended to screen patients with HFpEF or HFmrEF for both cardiovascular and non-cardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis.	I	C	
Diuretics are recommended in congested patients with HFpEF or HFmrEF in order to alleviate symptoms and signs.	I	B	178, 179

HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

10. Arrhythmias and conductance disturbances

Ambulatory electrocardiographic monitoring can be used to investigate symptoms that may be due to arrhythmias,[322–324] but evidence is lacking to support routine, systematic monitoring for all patients with HF to identify tachy- and bradyarrhythmias. There is no evidence that clinical decisions based on routine ambulatory electrocardiographic monitoring improve outcomes for patients with HF.

Ambulatory electrocardiographic recording detects premature ventricular complexes in virtually all patients with HF. Episodes of asymptomatic, non-sustained VT are common, increasing in frequency with the severity of HF and ventricular dysfunction and indicating a poor prognosis in patients with HF, but provide little discrimination between sudden death or death due to progressive HF.[316,325] Bradycardia and pauses are also commonly observed, especially at night when sympathetic activity is often lower and parasympathetic activity higher; sleep apnoea may be a trigger.[326–328] Pauses are associated with a poor prognosis in patients with CAD and left ventricular dysfunction.[329] Bradyarrhythmias may make an important contribution to sudden death in HF.[330]

10.1 Atrial fibrillation

AF is the most common arrhythmia in HF irrespective of concomitant LVEF; it increases the risk of thromboembolic complications (particularly stroke) and may impair cardiac function, leading to worsening symptoms of HF.[316] Incident HF precipitated by AF is associated with a more benign prognosis,[331] but new-onset AF in a patient with established HF is associated with a worse outcome, probably because it is both a marker of a sicker patient and because it impairs cardiac function.[332,333] Patients with chronic HF and permanent AF have a worse outcome than those in sinus rhythm, although this is largely explained by more advanced age and HF severity.[332,333] Persistent ventricular rates >150 bpm may cause HFrEF that resolves with rate control or rhythm correction ('tachycardiomyopathy').[334,335] AF should be classified and managed according to the current AF guidelines (i.e. first diagnosed episode, paroxysmal, persistent, long-standing persistent or permanent), recognizing the uncertainty about the actual duration of the episode and about previous undetected episodes.[316]

The following issues need to be considered in patients with HF presenting with AF, irrespective of LVEF, especially with a first diagnosed episode of AF or paroxysmal AF:[316]

- identification of potentially correctable causes (e.g. hypothyroidism or hyperthyroidism, electrolyte disorders, uncontrolled hypertension, mitral valve disease) and precipitating factors (e.g. recent surgery, chest infection or exacerbation of COPD/asthma, acute myocardial ischaemia, alcohol binge), as this may determine management strategy;
- assessment of stroke risk and need for anticoagulation;
- assessment of ventricular rate and need for rate control;
- evaluation of symptoms of HF and AF.

For details, the reader should refer to the 2016 ESC guidelines on AF.[316]

10.1.1 Prevention of atrial fibrillation in patients with heart failure

Many treatments for HF, including ACEIs,[336] ARBs,[337] beta-blockers[177,338] and MRAs,[339,340] will reduce the incidence of AF, but ivabradine may increase it.[341] CRT has little effect on the incidence of AF.[342]

Amiodarone will reduce the incidence of AF, induce pharmacological cardioversion, maintain more patients in sinus rhythm after cardioversion and may be used to control symptoms in patients with paroxysmal AF if beta-blockers fail to do so.[343–346] Amiodarone should generally be restricted to short-term (<6 months) use in patients with paroxysmal or persistent AF to help attain sinus rhythm and to reduce the high rate of recurrent AF immediately after cardioversion. Dronedarone is contraindicated in patients with HF and AF.[246,247,347]

10.1.2 Management of new-onset, rapid atrial fibrillation in patients with heart failure

If the patient has no distressing symptoms of HF, then treatment with oral beta-blockers may be initiated to provide ventricular rate control. For patients with marked congestion who nonetheless have few symptoms at rest, initial treatment with oral or intravenous (i.v.) digoxin is preferred. For patients in haemodynamic instability, an i.v. bolus of digoxin or amiodarone[348,349] should be administered into a peripheral vein with extreme care to avoid extravasation into tissues; where uncertainty exists about venous access, amiodarone must not be given. Longer-term infusion of amiodarone should be given only by central or long-line venous access to avoid peripheral vein phlebitis. In patients with haemodynamic collapse, emergency electrical cardioversion is recommended (see also Section 12).

Recommendations for initial management of a rapid ventricular rate in patients with heart failure and atrial fibrillation in the acute or chronic setting

Recommendations	Class [a]	Level [b]	Ref [c]
Urgent electrical cardioversion is recommended if AF is thought to be contributing to the patient's haemodynamic compromise in order to improve the patient clinical condition.	I	C	
For patients in NYHA Class IV, in addition to treatment for AHF, an intravenous bolus of amiodarone or, in digoxin-naïve patients, an intravenous bolus of digoxin should be considered to reduce the ventricular rate.	IIa	B	348, 349
For patients in NYHA Class I–III, a beta-blocker, usually given orally, is safe and therefore is recommended as first-line treatment to control ventricular rate, provided the patient is euvolaemic.	I	A	177
For patients in NYHA Class I–III, digoxin, should be considered when ventricular rate remains high[d] despite beta-blockers or when beta-blockers are not tolerated or contra-indicated.	IIa	B	197
AV node catheter ablation may be considered to control heart rate and relieve symptoms in patients unresponsive or intolerant to intensive pharmacological rate and rhythm control therapy, accepting that these patients will become pacemaker dependent.	IIb	B	290
Treatment with dronedarone to improve ventricular rate control is not recommended due to safety concerns.	III	A	347

AF = atrial fibrillation; AHF = acute heart failure; AV = atrio-ventricular; bpm = beats per minute; HF = heart failure; NYHA = New York Heart Association.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]The optimal ventricular rate for patients with HF and AF has not been established, but the prevailing evidence suggests that strict rate control might be deleterious. A resting ventricular rate in the range of 60–100 bpm may be considered based on the current opinion of this Task Force,[350,351] although one trial suggested that a resting ventricular rate of up to 110 bpm might still be acceptable, and this is currently recommended by the ESC guidelines on AF.[198,316] This should be tested and refined by further research.

10.1.3 Rate control

Assessment of ventricular rate control from the radial pulse is not ideal, especially in patients with HF, as ventricular activation may not always generate a palpable pulse. Rate control should be documented electrocardiographically. A wearable device enables

ventricular rate to be assessed during rest, exercise and sleep, but the value of routine monitoring has not yet been established. Implanted devices such as pacemakers, CRT or ICDs can also be used to measure ventricular rate.

The optimal resting ventricular rate in patients with AF and HF is uncertain but may be between 60–100 bpm.[350,352–354] One trial suggested that a resting ventricular rate of up to 110 bpm might still be acceptable,[198,202] and 2016 ESC AF guidelines recommend this threshold as the target for rate control therapy.[316] However, this Task Force believes that a lower rate for patients with HF may be preferable (60–100 bpm). Ventricular rates <70 bpm are associated with a worse outcome.[351] This may explain why beta-blockers titrated to guideline-target doses failed to reduce morbidity or mortality in patients with HFrEF and AF,[177] and might also explain the association between digoxin and adverse outcomes reported in some observational studies of AF.[355–357] The optimal ventricular rate during exercise is also uncertain, but may be <110 bpm during light exercise.[354] Beta-blockers, digoxin and their combination may be used to control ventricular rate.[358] It is uncertain which approach is optimal, but beta-blockers appear safe as the first-line agent even if it is not clear that they reduce morbidity and mortality in patients with AF. Beta-blockers reduce ventricular rate during periods of activity, while digoxin exerts a greater effect at night.[358] Persistently high ventricular rates may indicate thyrotoxicosis or excessive sympathetic activity due to congestion, which might respond to diuresis. Although amiodarone and non-dihydropyridine CCBs can reduce ventricular rate, they have more adverse effects and should generally be avoided in patients with HFrEF and, with less certainty, in patients with HFpEF and HFmrEF. Rarely, ventricular rate cannot be reduced below 100–110 bpm by pharmacological means alone and AV node ablation with ventricular pacing may be considered; in this situation, for patients with HFrEF, CRT should be considered instead of conventional RV pacing. There is little evidence, other than from registries, to support a strategy of AV node ablation and CRT compared with pharmacological therapy alone in patients with AF and a resting ventricular rate <100–110 bpm (see Section 8.2).[281] However, in patients with a fast ventricular rate and intractable symptoms, AV node ablation may be considered. Also, if the patient is indicated for an ICD, AV node ablation with implantation of CRT-D may be a preferred option, especially if the patient has moderate to severe symptoms.

10.1.4 Rhythm control

In patients with chronic HF, a rhythm control strategy (including pharmacological or electrical cardioversion) has not been shown to be superior to a rate control strategy in reducing mortality or morbidity.[359] Urgent cardioversion is indicated only if the AF is life threatening, otherwise both HF and ventricular rate should be controlled prior to cardioversion. A rhythm control 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 with troublesome symptoms due to AF after optimization of rate control and HF therapy. The use of class I antiarrhythmic agents and dronedarone increases morbidity and mortality in patients with HF and AF and should be avoided.[246,247,347] Amiodarone will cause some patients with chronic AF to revert to sinus rhythm, may reduce symptomatic paroxysms of AF and will help maintain patients in sinus rhythm after spontaneous or electrical cardioversion.[343–346] When used, the need for continued administration of amiodarone should be regularly reviewed and justified.

The safety and efficacy of catheter ablation in the atria and pulmonary veins (PV) as a rhythm control strategy in HF is at present uncertain except for tachycardia induced cardiomyopathy.[316] One small study suggested that AF ablation was superior to AV node ablation and CRT.[360] Another study, including 203 patients with persistent AF, HF and an ICD or CRT device, showed that AF ablation was superior to amiodarone in correcting AF, and this was associated with fewer hospitalizations for HF and lower mortality. Two small studies of AF ablation compared with rate control met with mixed success in terms of procedural complications and success in improving symptoms.[278,279] The most recent evidence from a meta-analysis that included 914 patients suggests an encouraging success rate of PV ablation of AF in patients with LV dysfunction, with improvements in LVEF and functional capacity.[361] These results need to be confirmed in ongoing RCTs such as CASTLE AF,[362] AMICA and CABANA.

Recommendations for a rhythm control management strategy in patients with atrial fibrillation, symptomatic heart failure (NYHA Class II–IV) and left ventricular systolic dysfunction and no evidence of acute decompensation

Recommendations	Class [a]	Level [b]	Ref [c]
Electrical cardioversion or pharmacological cardioversion with amiodarone may be considered in patients with persisting symptoms and/or signs of HF, despite OMT and adequate control of ventricular rate, to improve clinical/symptomatic status.	IIb	B	344
AF ablation may be considered in order to restore sinus rhythm to improve symptoms in patients with persisting symptoms and/or signs of HF, despite OMT and adequate control of ventricular rate, to improve clinical/symptomatic status.	IIb	B	279, 363
Amiodarone may be considered prior to (and following) successful electrical cardioversion to maintain sinus rhythm.	IIb	B	342, 360
Dronedarone is not recommended because of an increased risk of hospital admissions for cardiovascular causes and an increased risk of premature death in NYHA Class III–IV patients.	III	A	247, 347
Class I antiarrhythmic agents are not recommended because of an increased risk of premature death.	III	A	248, 364, 365

AF = atrial fibrillation; HF = heart failure; NYHA = New York Heart Association, OMT = optimal medical therapy.
Patients should generally be anticoagulated for 6 weeks prior to electrical cardioversion.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

10.1.5 Thromboembolism prophylaxis

Patients with HF and AF should generally be anticoagulated and the balance of benefit and risk of bleeding (using CHA_2DS_2-VASc and HAS-BLED scores; for details, please see *Web Tables 10.1* and *10.2*.) should be evaluated as recommended in the ESC guidelines for AF.[316] A substantial proportion of patients with HF will have both benefit and risk scores ≥ 3, indicating that careful consideration should be given before prescribing an oral anticoagulant and that regular review is subsequently needed (and correctable risk factors for bleeding addressed) if an oral anticoagulant is given.

NOACs are preferred for patients with HF with non-valvular AF, as NOACs compared with vitamin K antagonists seem to be at least similarly effective and even safer (less intracranial haemorrhage) in patients with HF than in subjects without HF,[316,366,367] although concerns exist about their safety in older patients with HF and poor renal function[368,369] [for a detailed description of the interaction between NOAC and renal function, see Heidbuchel *et al.*[370]]. In patients with HF and AF who have mechanical heart valves or at least moderate mitral stenosis, only oral vitamin K antagonists should be used for prevention of thromboembolic stroke.[370]

The dabigatran dose should be reduced to 110 mg *b.i.d.* when creatinine clearance is 30–49 mL/min, rivaroxaban to 15 mg daily and edoxaban to 30 mg daily when creatinine clearance is 30–50 mL/min and apixaban to 2.5 mg twice daily if a patient has two or more of the following: age ≥ 80 years, serum creatinine ≥ 1.5 mg/dL or body weight ≤ 60 kg.[370–375] The summary of the recommendations for the prevention of thromboembolism in patients with symptomatic HF and paroxysmal or persistent/permanent AF is presented in the recommendations table. For further details, please refer to the recent ESC guidelines on AF.[316]

A left atrial occlusion device could be considered in a patient with AF as an alternative to an oral anticoagulant who is at high-risk both of thromboembolism and of bleeding in order to avoid the risk of haemorrhage due to anticoagulation risk.[381,382]

Recommendations for the prevention of thrombo-embolism in patients with symptomatic heart failure (NYHA Class II–IV) and paroxysmal or persistent/permanent atrial fibrillation

Recommendations	Class [a]	Level [b]	Ref [c]
The CHA_2DS_2-VASc and HAS-BLED scores are recommended tools in patients with HF for the estimation of the risk of thromboembolism and the risk of bleeding associated with oral anticoagulation, respectively.	I	B	376, 377
An oral anticoagulant is recommended to prevent thrombo-embolism for all patients with paroxysmal or persistent/permanent AF and a CHA_2DS_2-VASc score ≥2, without contra-indications, and irrespective of whether a rate or rhythm management strategy is used (including after successful cardioversion).	I	A	372–375, 378, 379
NOAC treatment is contra-indicated in patients with mechanical valves or at least moderate mitral stenosis.	III	B	380
In patients with AF of ≥48 h duration, or when the duration of AF is unknown, an oral anticoagulant is recommended at a therapeutic dose for ≥3 weeks prior to electrical or pharmacological cardioversion.	I	B	
Intravenous heparin or LMWH and TOE quided strategy is recommended for patients who have not been treated with an anticoagulant dose for ≥3 weeks and require urgent electrical or pharmacological cardioversion for a life threatening arrhythmia.	I	C	
Combination of an oral anticoagulant and an antiplatelet agent is not recommended in patients with chronic (>12 months after an acute event) coronary or other arterial disease, because of a high-risk of serious bleeding. Single therapy with an oral anticoagulant is preferred after 12 months.	III	C	
For patients with HF and non-valvular AF eligible for anticoagulation based on a CHA_2DS_2-VASc score, NOACs rather than warfarin should be considered for anticoagulation as NOACs are associated with a lower risk of stroke, intracranial haemorrhage and mortality, which outweigh the increased risk of gastrointestinal haemorrhage.	IIa	B	367

AF = atrial fibrillation; CHA_2DS_2-VASc = Congestive heart failure or left ventricular dysfunction, Hypertension, Age ≥ 75 (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74, Sex category (female); HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly (1 point each); HF = heart failure; LMWH = low molecular weight heparin; NOAC = non-vitamin K antagonist oral anticoagulant; NYHA = New York Heart Association; TOE = transoesophageal echocardiography.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

10.2 Ventricular arrhythmias

The initial management of asymptomatic ventricular arrhythmias is correction of electrolyte abnormalities, particularly low serum potassium and magnesium, withdrawal of agents that might provoke arrhythmias and, in patients with HFrEF, optimization of pharmacological therapy with ACEIs, beta-blockers and MRAs and sacubitril/valsartan, which all reduce the risk of sudden death.[174,177,383,384]

The clinical relevance of myocardial ischaemia for the provocation of ventricular arrhythmias is uncertain, although anecdotal cases of ischaemia-induced arrhythmias exist. Randomized trials of revascularization for patients with HFrEF have not reduced overall mortality,[107,385] even in subgroups of patients with angina or myocardial ischaemia,[115,386] but further analysis did suggest a reduction in sudden deaths.[387]

Amiodarone (often in combination with a beta-blocker) may be used to suppress symptomatic ventricular arrhythmias, but it may adversely affect prognosis, especially in patients with more severe HF.[227,244] Other antiarrhythmic drugs should be avoided.[247] Transcatheter radiofrequency modification of the arrhythmogenic substrate may reduce the number of appropriate ICD discharges and may be used to terminate arrhythmic storm in patients with

HF and frequent, recurrent ventricular tachyarrhythmias and therefore should be considered in such patients. Seeking the advice of the members of the HF Team with expertise in electrophysiology is recommended in patients with recalcitrant ventricular arrhythmias. For further details we refer the reader to the ESC/EHRA guidelines on ventricular arrhythmias and sudden cardiac death.[260]

Recommendations for the management of ventricular tachyarrhythmias in heart failure

Recommendations	Class [a]	Level [b]	Ref [c]
Potential aggravating/precipitating factors (e.g. low serum potassium/magnesium, ongoing ischaemia) should be sought and corrected in patients with ventricular arrhythmias.	IIa	C	
Treatment with beta-blocker, MRA and sacubitril/valsartan reduces the risk of sudden death and is recommended for patients with HFrEF and ventricular arrhythmias (as for other patients)(see Section 7).	I	A	162, 170–175
Implantation of an ICD or CRT-D device is recommended for selected patients with HFrEF (see Section 8).	I	A	223–226, 388
Several strategies should be considered to reduce recurrent symptomatic arrhythmias in patients with an ICD (or in those who are not eligible for ICD), including attention to risk factors and optimal pharmacological treatment of HF, amiodarone, catheter ablation and CRT.	IIa	C	
Routine use of antiarrhythmic agents is not recommended in patients with HF and asymptomatic ventricular arrhythmias because of safety concerns (worsening HF, proarrhythmia, and death).	III	A	247, 248, 364, 365

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CRT = cardiac resynchronization therapy; CRT-D = defibrillator with cardiac resynchronization therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter defibrillator; MRA = mineralocorticoid receptor antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

10.3 Symptomatic bradycardia, pauses and atrio-ventricular block

The ESC Guidelines on Pacing and CRT recommended intervention when pauses exceed 6 s, even when this is not associated with symptoms.[389] However, these recommendations were generated mainly for patients without obvious myocardial dysfunction, and shorter pauses might require intervention in patients with HFrEF.[329] If pauses >3 s are identified on electrocardiographic monitoring, medications should be reviewed and the following agents stopped or reduced in dose, starting with rate-limiting CCBs then amiodarone, digoxin and ivabradine. For patients in AF, a reduction in the dose of beta-blockers allowing the daytime resting ventricular rate to rise to 70–90 bpm may be considered, since evidence that beta-blockers improve outcome in patients with AF is lacking.[177] For patients with pauses but in sinus rhythm, a reduction in the dose of beta-blockers should be avoided unless the pauses are symptomatic, prolonged or frequent, in which case the relative merits of dose reduction, beta-blocker withdrawal and (biventricular) pacing may be considered. However, evidence is lacking to support a strategy of pacing solely to permit initiation or titration of beta-blocker therapy in the absence of a conventional pacing indication; this strategy is not recommended. For patients with HFrEF and high-degree AV block, CRT is preferred over RV pacing (Section 8.2). When the cause of bradycardia or pauses is sinus node disease with intact AV conduction, then therapeutic strategies that avoid inducing ventricular dyssynchrony are preferred, although clinical trial evidence to support this expert opinion for patients with HF is sparse. For other pacing indications, please consult the ESC Guidelines on Pacing and CRT.[389]

Recommendations for the management of bradyarrhythmias in heart failure

Recommendations	Class [a]	Level [b]	Ref [c]
When pauses >3 seconds are identified on the ECG, or if the bradycardia is symptomatic and the resting ventricular rate is <50 bpm in sinus rhythm or <60 bpm in AF, it should be considered whether there is need for any rate limiting medications prescribed; for patients in sinus rhythm beta-blockers should be reduced in dose or withdrawn only as a last resort.	IIa	C	
For patients with symptomatic, prolonged or frequent pauses despite adjustment of rate limiting medication, either beta-blocker withdrawal or pacing may be considered as the next step.	IIb	C	
Pacing solely to permit initiation or titration of beta-blocker therapy in the absence of a conventional pacing indication is not recommended.	III	C	
In patients with HFrEF who require pacing and who have high degree AV block, CRT rather than RV pacing is recommended.	I	A	274, 275, 290
In patients with HFrEF who require pacing who do not have high degree AV block, pacing modes that avoid inducing or exacerbating ventricular dyssynchrony should be considered.	IIa	C	

AF = atrial fibrillation; AV = atrio-ventricular; bpm = beats per minute; CRT = cardiac resynchronization therapy; ECG = electrocardiogram; HFrEF = heart failure with reduced ejection fraction; RV = right ventricular.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

11. Co-morbidities

11.1. Heart failure and co-morbidities

Co-morbidities are of great importance in HF (*Table 11.1*) and may affect the use of treatments for HF (e.g. it may not be possible to use renin–angiotensin system inhibitors is some patients with severe renal dysfunction) (see Section 7). The drugs used to treat co-morbidities may cause worsening of HF (e.g. NSAIDs given for arthritis, some anti-cancer drugs) (see Section 7). Management of co-morbidities is a key component of the holistic care of patients with HF (see Section 14). Many co-morbidities are actively managed by specialists in the field of the co-morbidity, and these physicians will follow their own specialist guidelines. The current guidelines will identify where the presence of HF should change the way a co-morbidity would normally be treated. This may be because either safety or efficacy may be different in the presence of HF (or may simply be unknown) or because of evidence of particular effects in an HF population, either beneficial or detrimental. HFpEF has an even higher prevalence of co-morbidities compared with HFrEF, and many of these may be instrumental in the progression of this syndrome.[398]

Table 11.1 Importance of co-morbidities in patients with heart failure

1. interfere with the diagnostic process of HF (e.g. COPD as a potentially confounding cause of dyspnoea).[390,391]
2. aggravate HF symptoms and further impair quality of life.[391,392]
3. contribute to the burden of hospitalizations and mortality,[393] as the main cause of readmissions at 1 and 3 months.[394]
4. may affect the use of treatments for HF (e.g. renin–angiotensin system inhibitors contra-indicated in some patients with severe renal dysfunction or beta-blockers relatively contra-indicated in asthma).[395,396]
5. evidence base for HF treatment is more limited as co-morbidities were mostly an exclusion criterion in trials; efficacy and safety of interventions is therefore often lacking in the presence of co-morbidities.
6. drugs used to treat co-morbidities may cause worsening HF (e.g. NSAIDs given for arthritis, some anti-cancer drugs).[397]
7. interaction between drugs used to treat HF and those used to treat co-morbidities, resulting in lower efficacy, poorer safety, and the occurrence of side effects (e.g. beta-blockers for HFrEF and beta-agonists for COPD and asthma).[391,395,396]

HF = heart failure; COPD = chronic obstructive pulmonary disease; HFrEF = heart failure with reduced ejection fraction; NSAIDs = non-steroidal anti-inflammatory drugs.

11.2 Angina and coronary artery disease

11.2.1 Pharmacological management

Beta-blockers, and in selected patients ivabradine,[180] are effective agents for angina control, as well as an essential component of HFrEF therapy. In HFpEF patients, they may also be used for angina relief, although this has never been formally tested. In the SIGNIFY trial in patients with activity-limiting angina without HF, ivabradine increased the risk of death from cardiovascular causes or non-fatal myocardial infarction and therefore is not recommended in this setting.[399]

Trimetazidine has been shown to exert some beneficial effect as an add-on to beta-blockers in patients with HF and angina.[400–406] There are data suggesting that it may improve NYHA functional capacity, exercise duration and LV function in patients with HFrEF.[402–406] Certain other effective anti-anginal drugs have been studied in sizeable numbers of HFrEF/LV dysfunction patients and shown to be safe [e.g. amlodipine,[215,407] nicorandil[408] and nitrates[183,184,409]]. The safety of other anti-anginal agents in HFrEF, such as ranolazine, is uncertain, while other drugs, specifically diltiazem and verapamil, are thought to be unsafe in patients with HFrEF (although they may be used in HFpEF).[214] Dihydropyridine CCBs may all increase sympathetic tone, and their safety in HFrEF [except amlodipine[215] and felodipine[216]] and HFpEF is uncertain.

11.2.2 Myocardial revascularization

For indications for invasive coronary angiography in patients with HF, please refer to Section 5.8.

Percutaneous and surgical revascularization are complementary approaches for symptomatic relief of angina in HFpEF, but whether these interventions improve outcomes is not entirely clear. Recent ESC guidelines on myocardial revascularization recommended coronary artery bypass grafting (CABG) for patients with significant left main stenosis and left main equivalent (proximal stenosis of both the left anterior descending and left circumflex arteries) to improve prognosis.[112,113] However, one needs to be aware of a lack of studies including patients who have well-defined HF, therefore this recommendation is solely based on expert opinion. On the basis of the results of the STICH trial [which excluded patients with left main disease and Canadian Cardiovascular Society (CCS) angina classes III–IV], CABG is also recommended in patients with HFrEF, significant CAD (left anterior descending artery or multivessel disease) and LVEF $\leq$35% to reduce death and hospitalization for cardiovascular causes.[385] Patients with >10% dysfunctional but viable LV myocardium may be more likely to benefit from myocardial revascularization (and those with $\leq$10% are less likely to benefit), although this approach to patient selection for revascularization is unproven. In the STICH trial, neither the presence of viability nor the severity of LV remodelling identified those who benefited from CABG in terms of a reduction in mortality.[118] For the assessment of techniques to assess myocardial viability, please refer to Section 5. Post hoc analyses from the STICH trial revealed that the presence of inducible myocardial ischaemia (either on radionuclide stress test or dobutamine stress echocardiogram) or angina does not identify those with worse prognosis and greater benefit from CABG over OMT.[115,386] However, CABG does improve angina to a greater extent than medical therapy alone.

The choice between CABG and PCI should be made by the Heart Team after careful evaluation of the patient's clinical status and coronary anatomy, expected completeness of revascularization, coexisting valvular disease and co-morbidities.

Recommendations for the treatment of stable angina pectoris with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction[112,113]

Recommendations	Class [a]	Level [b]	Ref [c]
Step 1			
A beta-blocker (in an evidence-based dose or maximum tolerated) is recommended as the preferred first-line treatment to relieve angina because of the associated benefits of this treatment (reducing the risk of HF hospitalization and the risk of premature death).	I	A	167–173
Step 2: on top of beta-blocker or if a beta-blocker is not tolerated			
Ivabradine should be considered as an anti-anginal drug in suitable HFrEF patients (sinus rhythm and HR ≥70 bpm) as per recommended HFrEF management.	IIa	B	180, 410, 411
Step 3: For additional angina symptom relief – except from any combination not recommended			
A short-acting oral or transcutaneous nitrate should be considered (effective anti-anginal treatment, safe in HF).	IIa	A	183, 184, 409
A long acting oral or transcutaneous nitrate should be considered (effective anti-anginal treatment, not extensively studied in HF).	IIa	B	183, 184
Trimetazidine may be considered when angina persists despite treatment with a beta-blocker (or alternative) to relieve angina (effective anti-anginal treatment, safe in HF).	IIb	A	400–403
Amlodipine may be considered in patients unable to tolerate a beta-blocker to relieve angina (effective anti-anginal treatment, safe in HF).	IIb	B	215, 407
Nicorandil may be considered in patients unable to tolerate a beta-blocker to relieve angina (effective anti-anginal treatment, but safety in HF uncertain).	IIb	C	
Ranolazine may be considered in patients unable to tolerate a beta-blocker to relieve angina (effective anti-anginal treatment, but safety in HF uncertain).	IIb	C	
Step 4: Myocardial revascularization			
Myocardial revascularization is recommended when angina persists despite treatment with anti-angina drugs.	I	A	385, 412, 413
Alternatives to myocardial revascularization: combination of ≥3 antianginal drugs (from those listed above) may be considered when angina persists despite treatment with beta-blocker, ivabradine and an extra anti-angina drug (excluding the combinations not recommended below).	IIb	C	
The following are NOT recommended:			
(1) Combination of any of ivabradine, ranolazine, and nicorandil because of unknown safety.	III	C	
(2) Combination of nicorandil and a nitrate (because of lack of additional efficacy).	III	C	
Diltiazem and verapamil are not recommended because of their negative inotropic action and risk of worsening HF.	III	C	214

bpm = beats per minute; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; NYHA = New York Heart Association.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

11.3 Cachexia and sarcopenia (for frailty, please refer to Section 14)

Cachexia is a generalized wasting process affecting all body compartments [i.e. lean tissue (skeletal muscle), fat tissue (energy reserves) and bone tissue (osteoporosis)]. It may occur in 5–15% of patients with HF, especially those with HFrEF, and more advanced disease status.[414–416] This serious complication is associated with more severe symptoms and reduced functional capacity, more frequent hospitalization and decreased survival. Cachexia in HF can be diagnosed and defined as involuntary non-oedematous weight loss ≥6% of total body weight within the previous 6–12 months.[414–417]

The causes are multifactorial, and in individual patients they are difficult to determine. These may include pro-inflammatory immune activation, neurohormonal derangements, poor nutrition and malabsorption, impaired calorie and protein balance, anabolic hormone resistance, reduced anabolic drive, prolonged immobilization and physical deconditioning, together characterized by catabolic/anabolic imbalance.[418] Skeletal muscle wasting, when associated with impaired mobility and symptoms (termed sarcopenia or myopenia), occurs in 30–50% of patients with HFrEF.[419] In its most severe form it is associated with frailty and poor morbidity and mortality.[420]

Potential treatments may include appetite stimulants, exercise training[120] and anabolic agents, including testosterone, in combination with the application of nutritional supplements and anti-catabolic interventions, although none is of proven benefit and their safety is unknown.[421]

11.4 Cancer

Certain chemotherapeutic agents can cause (or aggravate) LV systolic dysfunction and HF. The best recognized of these are the

anthracyclines (e.g. doxorubicin), trastuzumab and tyrosine kinase inhibitors.[397,422] A recent Cochrane review found that dexrazoxane may confer some cardioprotection in patients receiving anthracyclines.[423] Pre- and post-evaluation of LVEF, if available with myocardial strain imaging, is essential in patients receiving cardiotoxic chemotherapy, as detailed elsewhere.[397,422] A risk score for identifying women with breast cancer at risk of developing HF during trastuzumab therapy has been developed based on age, chemotherapy details, baseline cardiovascular status and other co-morbidities, and may be helpful.[424] Chemotherapy should be discontinued and HFrEF therapy commenced in patients developing moderate to severe LV systolic dysfunction. If LV function improves, the risks and benefits of further chemotherapy need to be reconsidered.[397,425,426] Mediastinal irradiation can also lead to a variety of long-term cardiac complications. Cardiac biomarkers (NPs and troponins) can be used to identify patients at higher risk of cardiotoxicity and may be helpful in monitoring the use and dosing of cardiotoxic cytotoxics.[397,425,426]

11.5 Central nervous system (including depression, stroke and autonomic dysfunction)

Stroke and HF commonly coexist because of an overlap of shared risk factors. Both contribute to a worse prognosis. Stroke may make self-care more difficult for the HF patient. Management of high-risk stroke patients may require balancing the risk of anticoagulant and antiplatelet therapies.

Autonomic dysfunction is common in HFrEF, especially when severe.[427] Combined with low blood pressure, it can make fainting and injuries more likely and can interfere with optimal dosing of beta-blockers, ACEIs, ARBs and MRAs. Diuretic dosage may be reduced to reduce the severity of postural hypotension.

Depression is common and is associated with worse clinical status and a poor prognosis in HF.[428–430] 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. Until now, the Beck Depression Inventory (BDI) and Cardiac Depression Scale have been formally validated as reliable tools for the assessment of depressive mood in patients with HF,[431,432] but other questionnaires have been broadly used in this group of patients (e.g. Geriatric Depression Scale, Hamilton Depression Scale, Hospital Anxiety and Depression Scale).

Psychosocial intervention and pharmacological treatment are helpful, as well as exercise training, in patients with HFrEF and depression.[433] Cognitive behavioural therapy delivered in patients with HF and major depression beyond standard care and a structured education programme were able to reduce depression severity, anxiety and fatigue symptoms, as well as improve social functioning and mental and HF-related quality of life.[434]

Selective serotonin reuptake inhibitors are thought to be safe, although the Sertraline Antidepressant Heart Attack Randomized Trial did not confirm that sertraline provides a greater reduction in depressive symptoms or improvement in cardiovascular status compared with placebo in HFrEF patients, but this trial was not powered enough to prove the latter.[435] Similarly, escitalopram had no effect on either depression or clinical outcomes during the 24-month follow-up as compared with placebo in patients with HFrEF and depression. Importantly, tricyclic antidepressants should be avoided, because they may cause hypotension, worsening HF and arrhythmias.[429,435]

11.6 Diabetes

Dysglycaemia and diabetes are very common in HF, and diabetes is associated with poorer functional status and worse prognosis. In patients with HFrEF, interventions that reduce morbidity and mortality confer similar benefit in the presence or absence of diabetes.[320] For instance, beta-blockers improve outcome similarly, whether or not the patient has diabetes, although different beta-blockers may vary in their effects on glycaemic indices.[436]

Whether strict glycaemic control alters the risk of cardiovascular events in patients with HF is uncertain.[437] Among patients with HF who have not been treated for diabetes, higher HbA1c is associated with greater risk of cardiovascular events,[438,439] but this may not be the case once treatment for diabetes has been commenced.[439]

In patients with diabetes and HF, glycaemic control should be implemented gradually and moderately, giving preference to those drugs, such as metformin, that have been shown to be safe and effective. In contrast to what was previously believed, metformin is safe to use in patients with HFrEF, and it should be the treatment of choice in patients with HF[440,441] but is contraindicated in patients with severe renal or hepatic impairment, because of the risk of lactic acidosis.

Insulin is required for patients with type 1 diabetes and to treat symptomatic hyperglycaemia in patients with type 2 diabetes and pancreatic islet β cell exhaustion. However, insulin is a powerful sodium-retaining hormone, and when combined with a reduction in glycosuria, may exacerbate fluid retention, leading to HF worsening. Sulphonylurea derivatives have also been associated with an increased risk of worsening HF and should be used with caution.

Thiazolidinediones (glitazones) cause sodium and water retention and increased risk of worsening HF and hospitalization and are not recommended in patients with HF.[209,210] Dipeptidylpeptidase-4 inhibitors (DPP4is; gliptins), which increase incretin secretion, thereby stimulating insulin release, and long-acting glucagon-like peptide 1 (GLP-1) receptor agonists, which act as incretin mimetics, improve glycaemic indices but do not reduce and may increase the risk of cardiovascular events and worsening HF.[320,442,443] Importantly, there are no data on the safety of gliptins and GLP-1 analogues in patients with HF.

Recently, empagliflozin, an inhibitor of sodium-glucose co-transporter 2, reduced hospitalization for HF and mortality, but not myocardial infarction or stroke, in patients with diabetes at high cardiovascular risk, some of whom had HF.[130] In the absence of other studies with drugs from this group, the results obtained with empaglifozin cannot be considered as a proof of a class effect.

As glycaemic derangement progresses, the judgement on glycaemic control should be made according to cardiac conditions, and if the new anti-diabetic drugs are to be prescribed, they have to be closely monitored by an HF team.

11.7 Erectile dysfunction

Erectile dysfunction is a common and important component of quality of life in men with HF.[444,445] Its treatment should include optimal therapies for underlying cardiovascular diseases and other interfering co-morbidities (e.g. diabetes) and amelioration of anxiety and depressive symptoms. Some drugs applied for HF therapy (e.g. thiazide diuretics, spironolactone and beta-blockers) may augment erectile dysfunction.[444,445] Phosphodiesterase type 5 inhibitors (PDE5Is) have been shown to have favourable haemodynamic and anti-remodelling effects and to improve exercise capacity and quality of life in patients with HFrEF,[446,447] but they are contraindicated in patients taking nitrates.

11.8 Gout and arthritis

Hyperuricaemia and gout are common in HF and may be caused or aggravated by diuretic treatment. Hyperuricaemia is associated with a worse prognosis in HFrEF.[448] The current European League Against Rheumatism (EULAR) guideline for the management of gout recommends that urate-lowering therapy (ULT) is indicated in patients with recurrent acute flares, arthropathy, tophi or radiographic changes of gout, aiming to maintain a serum urate level below the saturation point for monosodium urate [$<$357 μmol/L ($<$6 mg/dL)].[449]

Xanthine oxidase inhibitors (allopurinol, oxypurinol) may be used to prevent gout, although their safety in HFrEF is uncertain.[450] Gout attacks are better treated with colchicine rather 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 monoarticular gout, but systemic corticosteroids cause sodium and water retention.

Arthritis is a common co-morbidity and is a common cause of both self-taken and prescribed drugs that can worsen renal function and HF, especially NSAIDs. Rheumatoid arthritis is associated with an increased risk of HFpEF. The safety of disease-modifying drugs commonly given to patients with rheumatoid arthritis has not been established in HF.

11.9 Hypokalaemia and hyperkalaemia

Both hypokalaemia and hyperkalaemia are associated with HF and with many drugs used for HF treatment.[451] Both can aggravate ventricular arrhythmias.

Loop and thiazide diuretics reduce serum potassium, while ACEIs, ARBs and MRAs can all increase serum potassium. Amiloride and triamterene are sometimes used as adjunct diuretics in resistant oedema and to assist in preventing hypokalaemia. The treatment of hypokalaemia can involve recommending high potassium foods or prescribing potassium supplements.

The management of acute hyperkalaemia ($>$6.0 mmol/L) may require a short-term cessation of potassium-retaining agents and RAAS inhibitors, but this should be minimized and RAAS inhibitors should be carefully reintroduced as soon as possible while monitoring potassium levels. A Cochrane review[452] found no trial evidence of major outcome benefits for any emergency therapy regimen for hyperkalaemia. Two new potassium binders (patiromer and sodium zirconium cyclosilicate) are currently under consideration for regulatory approval.[453,454] Initial results from patients with HF are available and confirm the efficacy of these therapies in reducing serum potassium[455] and preventing recurrent hyperkalaemia in patients with HF and CKD in the context of treatment with RAAS inhibitors.[456]

11.10 Hyperlipidaemia

Elevated low-density lipoprotein cholesterol is uncommon in HFrEF; patients with advanced HFrEF 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 patients with HF with or without IHD, but it also did not increase risk, and may have reduced, hospitalizations.[205,457] Therefore there is no evidence to recommend the initiation of statins in most patients with HF. However, in patients who are already receiving a statin for CAD, a continuation of this therapy may be considered.

11.11 Hypertension

Hypertension is associated with an increased risk of developing HF; antihypertensive therapy markedly reduces the incidence of HF (with an exception of α-adrenoceptor blockers, which are less effective than other antihypertensives in preventing HF).[458] A recent prospective cohort study documented that in a population with incident HF, higher baseline systolic, diastolic and pulse pressure levels were associated with a higher rate of adverse events, which further supports the importance for optimized blood pressure control in this population.[459] Blood pressure control is an element of the holistic management of patients with HF.

Negatively inotropic CCBs (i.e. diltiazem and verapamil) should not be used to treat hypertension in patients with HFrEF (but are believed to be safe in HFpEF), and moxonidine should also be avoided in patients with HFrEF, as it increased mortality in patients in one RCT.[460] If blood pressure is not controlled with an ACEI (or an ARB), a beta-blocker, an MRA and a diuretic, then hydralazine and amlodipine[215] [or felodipine[216]] are additional blood pressure lowering agents that have been shown to be safe in systolic HF. The blood pressure targets recommended in hypertension guidelines[317] are applicable to HF. Uncontrolled hypertension in patients with HFrEF is very rare, provided they are optimally treated for HF. In contrast, treatment of hypertension is an important issue in patients with HFpEF. In patients with AHF, i.v. nitrates (or sodium nitroprusside) are recommended to lower blood pressure (see Section 12).

Recommendations for the treatment of hypertension in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction

Recommendations	Class [a]	Level [b]	Ref [c]
Step 1			
ACE-I (or ARB), a beta-blocker or an MRA (or a combination) is recommended to reduce blood pressure as first-, second- and third-line therapy, respectively, because of their associated benefits in HFrEF (reducing the risk of death and HF hospitalization). They are also safe in HFpEF.	I	A	2, 164, 165, 167, 168, 171–174, 182, 461–463
Step 2			
A thiazide diuretic (or if the patient is being treated with a thiazide diuretic, switching to a loop diuretic) is recommended to reduce blood pressure when hypertension persists despite treatment with a combination of an ACE-I (or alternatively ARB but NOT together withan ACE-I), a beta-blocker and an MRA.	I	C	
Step 3			
Amlodipine or hydralazine is recommended to reduce blood pressure when hypertension persists despite treatment with a combination of an ACE-I (or alternatively ARB but NOT together withan ACE-I), a beta-blocker, an MRA and a diuretic.	I	A	183, 184, 215, 409
Felodipine should be considered to reduce blood pressure when hypertension persists despite treatment with a combination of an ACE-I (or alternatively ARB but NOT together withan ACE-I), a beta-blocker, an MRA and a diuretic.	IIa	B	216
Moxonidine is not recommended to reduce blood pressure because of safety concerns in HFrEF patients (increased mortality).	III	B	460
Alpha-adrenoceptor antagonists are not recommended to reduce blood pressure because of safety concerns in HFrEF patients (neurohormonal activation, fluid retention, worsening HF).	III	A	458, 464, 465
Diltiazem and verapamil are not recommended to reduce blood pressure in patients with HFrEF because of their negative inotropic action and risk of worsening HF.	III	C	214

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

11.12 Iron deficiency and anaemia

Iron deficiency is common in HF, as it is with other chronic illnesses, and it can lead to anaemia and/or skeletal muscle dysfunction without anaemia.[466] Within an HF population, iron deficiency is associated with a worse prognosis.[467,468] Intravenous iron has been specifically studied in two RCTs in patients with HF and iron deficiency (serum ferritin <100 μg/L or ferritin between 100 and 299 μg/L and transferrin saturation <20%)[469,470] both with and without anaemia. Intravenous ferric carboxymaltose (FCM) has been shown to improve self-reported patient global assessment, quality of life and NYHA class (over 6 months) in the FAIR-HF trial[469] both in anaemic and non-anaemic patients with HF,[471] and in the CONFIRM-HF trial[470], exercise capacity improved over 24 weeks. In the analysis of secondary endpoints in the CONFIRM-HF trial, i.v. iron reduced the risk of HF hospitalizations in iron-deficient patients with HFrEF.[470] A meta-analysis of i.v. iron therapy in HFrEF patients with iron deficiency over up to 52 weeks showed reduced hospitalization rates and improved HF symptoms, exercise capacity and quality of life.[472] Treatment with FCM may therefore result in sustainable improvement in functional capacity, symptoms and quality of life. Treatment was also associated with a significant reduction in hospitalizations for worsening HF. The number of deaths and the incidence of adverse events were similar. Neither i.v. iron trial was powered to test for an effect on major outcomes or to evaluate separately the effects in anaemic and non-anaemic patients. The effect of treating iron deficiency in HFpEF/HFmrEF and the long-term safety of iron therapy in either HFrEF, HFmrEF or HFpEF is unknown. The safety of i.v. iron is unknown in patients with HF and haemoglobin >15 g/dL.[469,470] Patients with iron deficiency need to be screened for any potentially treatable/reversible causes (e.g. gastrointestinal sources of bleeding).

Recommendations for the treatment of other co-morbidities in patients with heart failure

Recommendations	Class [a]	Level [b]	Ref [c]
Iron deficiency			
Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L, or ferritin between 100–299 µg/L and transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.	IIa	A	469, 470
Diabetes			
Metformin should be considered as a first-line treatment of glycaemic control in patients with diabetes and HF, unless contra-indicated.	IIa	C	440 ,441

FCM = ferric carboxymaltose; HF = heart failure; HFrEF = heart failure with reduced ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
Treatments not recommended for other co-morbidities in patients with heart failure

Treatments not recommended of other co-morbidities in patients with heart failure

Recommendations	Class [a]	Level [b]	Ref [c]
Sleep apnoea			
Adaptive servo-ventilation is not recommended in patients with HFrEF and a predominant central sleep apnoea because of an increased all-cause and cardiovascular mortality.	III	B	473
Diabetes			
Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	A	209, 210
Arthritis			
NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	B	211–213

COX-2 = cyclooxygenase 2; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; NSAID = non-steroidal anti-inflammatory drug.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Anaemia (defined as a haemoglobin concentration <13.0 g/dL in men and <12.0 g/dL in women) is common in HF, particularly in hospitalized patients. It is more common in women, the elderly and in patients with renal impairment and is associated with advanced myocardial remodelling, inflammation and volume overload.[474] Anaemia is associated with advanced symptoms, worse functional status, greater risk of HF hospitalization and reduced survival. A diagnostic workup to seek a cause for any finding of anaemia is indicated (e.g. occult blood loss, iron deficiency, B12/folate deficiency, blood dyscrasias), although in many patients no specific cause is found. The erythropoietin-stimulating agent darbepoetin alfa did not improve clinical outcomes in HFrEF patients with mild to moderate anaemia, but led to an excess of thromboembolic events and is therefore not recommended.[475]

11.13 Kidney dysfunction (including chronic kidney disease, acute kidney injury, cardio-renal syndrome and prostatic obstruction)

HF and CKD frequently coexist, share many risk factors (diabetes, hypertension, hyperlipidaemia) and interact to worsen prognosis.[476,477] CKD is generally defined as an eGFR <60 mL/min/1.73 m^2 and/or the presence of albuminuria (high 30–300 or very high >300 mg albumin/1 g of urine creatinine). Patients with severe renal dysfunction (eGFR <30 mL/min/1.73m^2) have systematically been excluded from randomized clinical trials and therefore there is lack of evidence-based therapies in these patients.

A further deterioration in renal function, termed worsening renal function (WRF), is used to indicate an increase in serum creatinine, usually by >26.5 µmol/L (0.3 mg/dL) and/or a 25% increase or a 20% drop in GFR. The importance of these apparently small changes is that they are frequent, they promote the development and progression of CKD[478] and, as a consequence, can worsen the prognosis of HF. Increases in creatinine during an AHF hospitalization are not always clinically relevant, especially when they are accompanied by appropriate decongestion, diuresis and haemoconcentration.[479]

Large increases in serum creatinine, termed acute kidney injury (AKI), are relatively rare in HF and are probably associated with the combination of diuretic therapy with other potentially nephrotoxic drugs such as some antibiotics (gentamicin and trimethoprim), contrast media, ACEIs, ARBs, NSAIDs, etc. Of relevance, some of these drugs may accumulate if they are renally excreted. In HF, WRF is relatively common, especially during initiation and up-titration of RAAS inhibitor therapy. Despite the fact that RAAS blockers can frequently cause a decrease in GFR in patients with HF, this reduction is usually small and should not lead to treatment discontinuation unless there is a marked decrease, as the treatment benefit in these patients is probably largely maintained.[480] When large increases in serum creatinine occur, care should be taken to evaluate the patient thoroughly and should include assessment of a possible renal artery stenosis, excessive hyper- or hypovolaemia, concomitant medication and hyperkalaemia, which frequently coincides with WRF.

Diuretics, especially thiazides, but also loop diuretics, may be less effective in patients with a very low GFR, and if used, should be dosed appropriately (higher doses to achieve similar effects). Renally excreted drugs (e.g. digoxin, insulin and low molecular weight heparin) may accumulate in patients with renal impairment and may need dose adjustment if renal function deteriorates. Patients with HF and coronary or peripheral vascular disease are at risk of acute renal dysfunction when they undergo contrast media enhanced angiography [contrast-induced acute

kidney injury (CI-AKI)]. Renal dysfunction and worsening renal function is further discussed in the section about AHF (see Section 12).

Prostatic obstruction is common in older men and can interfere with renal function; it should therefore be ruled out in men with HF with deteriorating renal function. α-adrenoceptor blockers cause hypotension and sodium and water retention, and may not be safe in HFrEF.[458,464,465] For these reasons, 5-α-reductase inhibitors are generally preferred in the medical treatment of prostatic obstruction in patients with HF.

11.14 Lung disease (including asthma and chronic obstructive pulmonary disease)

The diagnosis of COPD and asthma may be difficult in patients with HF, due to overlap in symptoms and signs, but also problems in the interpretation of spirometry, especially in HFpEF.[48,49,391] COPD (and asthma) in patients with HF may be overdiagnosed.[481] Spirometry should be performed when patients have been stable and euvolaemic for at least 3 months, to avoid the confounding effect of pulmonary congestion causing external obstruction of alveoli and bronchioles.[482] Both correctly and incorrectly labelled COPD are associated with worse functional status and a worse prognosis in HFrEF.

Beta-blockers are only relatively contraindicated in asthma, but not in COPD, although a more selective β1-adrenoceptor antagonist (i.e. bisoprolol, metoprolol succinate, or nebivolol) is preferred.[48,49,391] The contraindication to beta-blockers in asthma, as mentioned on pharmacy leaflets, is based on small case series published in the 1980s and late 1990s with very high initial dosages in young patients with severe asthma. In clinical practice, starting with low doses of cardioselective beta-blockers combined with close monitoring for signs of airway obstruction (wheezing, shortness of breath with lengthening of the expiration) may allow the use of profoundly effective beta-blockers in HFrEF, especially in older people where true severe asthma is uncommon. Therefore, according to the 2015 GINA global strategy report,[395,396] asthma is not an *absolute* contraindication, but these medications should only be used under close medical supervision by a specialist, with consideration of the risks for and against their use. The long-term safety of cardioactive inhaled pulmonary drugs is uncertain and the need for their use should be reconsidered in patients with HFrEF, especially as their benefit in asthma and COPD may be symptomatic only without a clear effect on mortality. Oral corticosteroids can cause sodium and water retention, potentially leading to worsening of HF, but this is not believed to be a problem with inhaled corticosteroids. Pulmonary hypertension can complicate severe long-standing COPD, which, as a result, makes right-sided HF and congestion more likely. Non-invasive ventilation, added to conventional therapy, improves the outcome of patients with acute respiratory failure due to hypercapnic exacerbation of COPD or HF in situations of acute pulmonary oedema.

11.15 Obesity

Obesity is a risk factor for HF[141] and complicates its diagnosis, because it can cause dyspnoea, exercise intolerance and ankle swelling and may result in poor-quality echocardiographic images. Obese individuals also have reduced NP levels.[62] Obesity is more common in HFpEF than in HFrEF, although it is possible that misdiagnosis may explain at least some of this difference in prevalence. Although obesity is an independent risk factor for developing HF, once HF is diagnosed, it is well established that obesity is associated with lower mortality across a wide range of body mass indexes (BMIs) (see also cachexia in Section 11.3)—the so-called obesity paradox also seen in other chronic illnesses.[414,416] Obesity should be managed as recommended in the ESC guidelines on cardiovascular disease prevention,[483] if the aim is to prevent future development of HF. However, these guidelines do not refer to the HF patient in whom higher BMI is not adverse, and, although often recommended for symptom benefit and risk factor control, weight loss as an intervention has never been prospectively shown to be either beneficial or safe in HFrEF. When weight loss is occurring in HF, it is associated with high mortality and morbidity, worse symptom status and poor quality of life. In patients with HF with moderate degrees of obesity (BMI <35 kg/m^2), weight loss cannot be recommended. In more advanced obesity (BMI 35–45 kg/m^2), weight loss may be considered to manage symptoms and exercise capacity.

11.16 Sleep disturbance and sleep-disordered breathing

Sleep-disordered breathing (SDB) occurs in more than one-third of patients with HF,[484] being even more prevalent in patients with AHF.[485] The most common types are: central sleep apnoea (CSA, similar to Cheyne Stokes respiration, CSR), obstructive sleep apnoea (OSA), and a mixed pattern of the two. Other causes of sleep disturbance include anxiety, depression, decubitus or paroxysmal pulmonary congestion (orthopnoea and paroxysmal nocturnal dyspnoea) and diuretic therapy causing nocturnal diuresis. Reviewing sleep history (including asking a partner) is part of the holistic care of patients with HF (see Section 14). CSA and OSA have been shown to be associated with a worse prognosis in HF.[485,486] OSA is associated with an increased risk of incident HF in men.[487] CSA is the most common form of SDB in HFrEF, and HFrEF is the most common cause of CSA, so they are closely linked. Screening for, and the diagnosis and treatment of, sleep apnoea is discussed in detail elsewhere.[484,488] Diagnosis used to require overnight polysomnography, although advanced home testing equipment which can distinguish the type of sleep apnoea has been developed.

Nocturnal oxygen supplementation, continuous positive airway pressure (CPAP), bi-level positive airway pressure (BiPAP), and adaptive servo-ventilation (ASV) may be considered to treat nocturnal hypoxaemia in OSA as recommended in other guidelines.[489,490] An apnoea/hypopnoea index (AHI) of above 30 per hour can be treated using any of CPAP, BiPAP, ASV and nocturnal oxygen supplementation, which have all been shown to be effective in this regard. It should be noted, however, that none of these interventions has been prospectively shown to be beneficial on major outcomes in HFrEF.

CPAP in HF related CSA has been shown to reduce the frequency of episodes of apnoea and hypopnoea, and improve LVEF and 6 minute walk test distance, but did not improve prognosis or the rate of HF related hospitalizations.[491]

The recently published SERVE-HF[473] trial has shown that ASV used in patients with HFrEF and a predominantly CSA was neutral regarding the composite primary endpoint (all-cause death, lifesaving cardiovascular intervention, i.e. cardiac transplantation, implantation of a ventricular assist device, resuscitation after sudden cardiac arrest, or appropriate lifesaving shock, or unplanned hospitalization for HF worsening), but more importantly led to an increase in both all-cause and cardiovascular mortality. Therefore ASV is not recommended in patients with HFrEF and predominantly CSA.

The safety and efficacy of alternative approaches to treating CSA in HFrEF patients, such as implantable phrenic nerve stimulation,[219,220,492] are presently undergoing clinical investigation and may require additional long term study.

11.17. Valvular heart disease

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 guidelines on valvular disease for more information.[493,494]

Patients with HF and concomitant valvular heart disease constitute a high-risk population. Thus, the whole process of decision-making through a comprehensive evaluation of the risk–benefit ratio of different treatment strategies should be made by a multidisciplinary 'heart team' with a particular expertise in valvular heart disease, including cardiologists with expertise in HF, cardiac surgeons, a structural valve interventionist if a catheter-based therapy is being considered, imaging specialists, anaesthetists and, if needed, general practitioners, geriatricians, or intensive care specialists. This may be particularly beneficial in patients with HF being considered for surgery, transcatheter aortic valve implantation or transcatheter mitral valve intervention.

All patients should receive OMT. In those with HFrEF pharmacological therapy should be planned according to a previously described algorithm (see Section 7 for details). Care must be taken using vasodilators (ACEI, ARBs, CCBs, hydralazine, and nitrates) in patients with severe aortic stenosis in order not to cause hypotension.

11.17.1. Aortic stenosis

The main concern in patients with severe aortic stenosis and reduced LVEF is the entity of 'low-flow, low-gradient' aortic stenosis (valve area < 1 cm^2, LVEF $< 40\%$, mean pressure gradient < 40 mmHg). In such individuals, low-dose dobutamine stress echocardiography should be considered to differentiate between patients with moderate aortic stenosis, and those with severe stenosis and low flow across the valve due to low stroke volume, and to evaluate for contractile or flow reserve.

If the mean gradient is > 40 mmHg, there is theoretically no lower LVEF limit for aortic valve replacement in symptomatic patients with severe aortic stenosis.

Transaortic valve implantation (TAVI) is recommended in patients with severe aortic stenosis who are not suitable for surgery as assessed by a 'heart team' and have predicted post-TAVI survival > 1 year. TAVI should be also considered in high-risk patients with severe aortic stenosis who may still be suitable for surgery, but in whom TAVI is favoured by a 'heart team' based on the individual risk profile and anatomic suitability.[495,496] In a recent trial in patients with severe aortic stenosis, TAVI with a self-expanding transcatheter aortic valve bioprosthesis was associated with a significantly higher rate of survival at 1 year which was sustained at 2 years.[497,498]

11.17.2. Aortic regurgitation

In patients with severe aortic regurgitation, aortic valve repair or replacement is recommended in all symptomatic patients and in asymptomatic patients with resting LVEF $\leq 50\%$, who are otherwise fit for surgery.[499,500]

11.17.3. Mitral regurgitation

This section refers to chronic settings while acute settings are discussed in Section 12.

Primary (organic) mitral regurgitation

Surgery is indicated in symptomatic patients with severe organic mitral regurgitation with no contra-indications to surgery. The decision of whether to replace or repair depends mostly on valve anatomy, surgical expertise available, and the patient's condition.

When the LVEF 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-morbidities, 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 (including CRT in suitable patients) 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.

Combined valve and coronary surgery should be considered in symptomatic patients with LV systolic dysfunction (LVEF $< 30\%$), coronary arteries suitable for revascularization, and evidence of viability. Surgery is also recommended in patients with severe mitral regurgitation undergoing CABG with LVEF $> 30\%$.

However, a recent study in patients with moderate, secondary ischaemic mitral regurgitation did not prove that the addition of mitral valve repair to CABG would lead to a higher degree of LV reverse remodelling.[501] Also, there is no evidence favouring mitral valve repair over replacement in the context of better outcomes and magnitude of LV remodelling.[502] In the presence of AF, atrial ablation and LA 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 (LVEF $< 30\%$) 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. The decision should be based on comprehensive evaluation (including strain echocardiography or magnetic resonance imaging[499,503] and discussed within the 'heart team'.

In patients with HF with moderate-severe, secondary mitral regurgitation who are judged inoperable or at high surgical risk, percutaneous mitral valve intervention (percutaneous edge-to-edge repair) may be considered in order to improve symptoms and quality of life, although no RCT evidence of improvement has been published, only registry studies.[504–506]

11.17.4. Tricuspid regurgitation

Secondary (functional) tricuspid regurgitation (TR) frequently complicates the natural course of HF, due to annular dilatation and increased tricuspid leaflet tethering in relation to RV pressure and/or volume overload. Severe TR causes/deteriorates symptoms and signs of right HF, thus diuretics are used to reduce peripheral oedema. As hepatic congestion is often present in these patients (additionally contributing to hyperaldosteronism), an addition of an MRA (in higher natriuretic doses) may improve decongestion.[507] Management of HF which underlies secondary TR should be optimized as TR may diminish, following the treatment of its cause. Indications for surgical correction of secondary TR complicating HF are not clearly established.[493,494] The need for correction of TR is usually considered at the time of surgical correction of left-sided

Recommendations for treatment of valvular diseases in patients with heart failure

Recommendations	Class [a]	Level [b]	Ref [c]
In symptomatic patients with reduced LVEF and 'low-flow, low-gradient' aortic stenosis (valve area <1 cm^2, LVEF <40%, mean pressure gradient <40 mmHg), low-dose dobutamine stress echocardiography should be considered to identify those with severe aortic stenosis suitable for valve replacement.	IIa	C	
TAVI is recommended in patients with severe aortic stenosis who are not suitable for surgery as assessed by a 'heart team' and have predicted post-TAVI survival >1 year.	I	B	495, 496, 509
TAVI should be considered in high-risk patients with severe aortic stenosis who may still be suitable for surgery, but in whom TAVI is favoured by a 'heart team' based on the individual risk profile and anatomic suitability.	IIa	A	497, 498
In patients with severe aortic regurgitation, aortic valve repair or replacement is recommended in all symptomatic patients and in asymptomatic patients with resting LVEF ≤50%, who are otherwise fit for surgery.	I	C	317
Evidence-based medical therapy in patients with HFrEF is recommended in order to reduce functional mitral regurgitation.	I	C	
Combined surgery of secondary mitral regurgitation and coronary artery bypass grafting should be considered in symptomatic patients with LV systolic dysfunction (LVEF <30%), requiring coronary revascularization for angina recalcitrant to medical therapy.	IIa	C	
Isolated surgery of non-ischaemic regurgitant mitral valve in patients with severe functional mitral regurgitation and severe LV systolic dysfunction (LVEF <30%) may be considered in selected patients in order to avoid or postpone transplantation.	IIb	C	

HFrEF = heart failure with reduced ejection fraction; LV = left ventricular; LVEF = left ventricular ejection fraction; TAVI = transaortic valve implantation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

valve lesions.[493,494] A recent first report indicated that catheter-based interventions may be possible for TR.[508]

12. Acute heart failure

12.1 Definition and classification

AHF refers to rapid onset or worsening of symptoms and/or signs of HF. It is a life-threatening medical condition requiring urgent evaluation and treatment, typically leading to urgent hospital admission.

AHF may present as a first occurrence (*de novo*) or, more frequently, as a consequence of acute decompensation of chronic HF, and may be caused by primary cardiac dysfunction or precipitated by extrinsic factors, often in patients with chronic HF. Acute myocardial dysfunction (ischaemic, inflammatory or toxic), acute valve insufficiency or pericardial tamponade are among the most frequent acute primary cardiac causes of AHF. Decompensation of chronic HF can occur without known precipitant factors, but more often with one or more factors, such as infection, uncontrolled hypertension, rhythm disturbances or non-adherence with drugs/diet (*Table 12.1*).

A large number of overlapping classifications of AHF based on different criteria have been proposed.[510–513] In practice the most useful classifications are those based on clinical presentation at admission, allowing clinicians to identify patients at high risk of complications and to direct management at specific targets, which creates a pathway for personalized care in the AHF setting. In most cases, patients with AHF present with either preserved (90–140 mmHg) or elevated (>140 mmHg; hypertensive AHF) systolic blood pressure (SBP). Only 5–8% of all patients present with low SBP (i.e. <90 mmHg; hypotensive AHF), which is associated with poor prognosis, particularly when hypoperfusion is also present.[514,515]

Table 12.1 Factors triggering acute heart failure

Acute coronary syndrome.
Tachyarrhythmia (e.g. atrial fibrillation, ventricular tachycardia).
Excessive rise in blood pressure.
Infection (e.g. pneumonia, infective endocarditis, sepsis).
Non-adherence with salt/fluid intake or medications.
Bradyarrhythmia.
Toxic substances (alcohol, recreational drugs).
Drugs (e.g. NSAIDs, corticosteroids, negative inotropic substances, cardiotoxic chemotherapeutics).
Exacerbation of chronic obstructive pulmonary disease.
Pulmonary embolism.
Surgery and perioperative complications.
Increased sympathetic drive, stress-related cardiomyopathy.
Metabolic/hormonal derangements (e.g. thyroid dysfunction, diabetic ketosis, adrenal dysfunction, pregnancy and peripartum related abnormalities).
Cerebrovascular insult.
Acute mechanical cause: myocardial rupture complicating ACS (free wall rupture, ventricular septal defect, acute mitral regurgitation), chest trauma or cardiac intervention, acute native or prosthetic valve incompetence secondary to endocarditis, aortic dissection or thrombosis.

ACS = acute coronary syndromes; NSAIDs = non-steroidal anti-inflammatory drugs.

Another approach is to classify patients according to the presence of the following precipitants/causes leading to decompensation, which need to be treated/corrected urgently (see Section 12.3.1): ACS, hypertensive emergency, rapid arrhythmias or severe