2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC

Collaborators: Burri, Haran Kumar

ESC European Society of Cardiology

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2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: supplementary data

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

With the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: Theresa A. McDonagh* (Chairperson) (United Kingdom), Marco Metra * (Chairperson) (Italy), Marianna Adamo (Task Force Coordinator) (Italy), Roy S. Gardner (Task Force Coordinator) (United Kingdom), Andreas Baumbach (United Kingdom), Michael Böhm (Germany), Haran Burri

* Corresponding authors: The two chairpersons contributed equally to the document.

Theresa McDonagh, Cardiology Department, King's College Hospital, Denmark Hill, London, SE5 9RS, United Kingdom. Tel: +44 203 299 325, E-mail: theresa.mcdonagh@kcl.ac.uk;

Marco Metra, Institute of Cardiology, ASST Spedali Civili di Brescia and Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy. Tel: +39 303 07221, E-mail: metramarco@libero.it

Author/Task Force Member affiliations: listed in Author information.

ESC Clinical Practice Guidelines Committee (CPG): listed in the Appendix.

ESC subspecialty communities having participated in the development of this document:

Associations: Association for Acute CardioVascular Care (ACVC), Association of Cardiovascular Nursing & Allied Professions (ACNAP), European Association of Cardiovascular Imaging (EACVI), European Association of Preventive Cardiology (EAPC), European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA).

Councils: Council of Cardio-Oncology, Council on Basic Cardiovascular Science, Council on Valvular Heart Disease.

Working Groups: Adult Congenital Heart Disease, Cardiovascular Pharmacotherapy, Cardiovascular Regenerative and Reparative Medicine, Cardiovascular Surgery, e-Cardiology, Myocardial and Pericardial Diseases, Myocardial Function.

(Switzerland), Javed Butler (United States of America), Jelena Čelutkienė (Lithuania), Ovidiu Chioncel (Romania), John G.F. Cleland (United Kingdom), Andrew J.S. Coats (United Kingdom), Maria G. Crespo-Leiro (Spain), Dimitrios Farmakis (Greece), Martine Gilard (France), Stephane Heymans (Netherlands), Arno W. Hoes (Netherlands), Tiny Jaarsma (Sweden), Ewa A. Jankowska (Poland), Mitja Lainscak (Slovenia), Carolyn S.P. Lam (Singapore), Alexander R. Lyon (United Kingdom), John J.V. McMurray (United Kingdom), Alexandre Mebazaa (France), Richard Mindham (United Kingdom), Claudio Muneretto (Italy), Massimo Francesco Piepoli (Italy), Susanna Price (United Kingdom), Giuseppe M.C. Rosano (United Kingdom), Frank Ruschitzka (Switzerland), Anne Kathrine Skibelund (Denmark), ESC Scientific Document Group

Document Reviewers: Rudolf A. de Boer (CPG Review Coordinator) (Netherlands), P. Christian Schulze (CPG Review Coordinator) (Germany), Magdy Abdelhamid (Egypt), Victor Aboyans (France), Stamatis Adamopoulos (Greece), Stefan D. Anker (Germany), Elena Arbelo (Spain), Riccardo Asteggiano (Italy), Johann Bauersachs (Germany), Antoni Bayes-Genis (Spain), Michael A. Borger (Germany), Werner Budts (Belgium), Maja Cikes (Croatia), Jens Cosedis Nielsen (Denmark), Kevin Damman (Netherlands), Victoria Delgado (Netherlands), Paul Dendale (Belgium), Polychronis Dilaveris (Greece), Heinz Drexel (Austria), Justin Ezekowitz (Canada), Volkmar Falk (Germany), Laurent Fauchier (France), Gerasimos Filippatos (Greece), Alan Fraser (United Kingdom), Norbert Frey (Germany), Chris P. Gale (United Kingdom), Finn Gustafsson (Denmark), Julie Harris (United Kingdom), Bernard Iung (France), Stefan Janssens (Belgium), Mariell Jessup (United States of America), Aleksandra Konradi (Russia), Dipak Kotecha (United Kingdom), Ekatirini Lambrinou (Cyprus), Patrizio Lancellotti (Belgium), Ulf Landmesser (Germany), Christophe Leclercq (France), Basil S. Lewis (Israel), Francisco Leyva (United Kingdom), Aleš Linhart (Czech Republic), Maja-Lisa Løchen (Norway), Lars H. Lund (Sweden), Donna Mancini (United States of America), Josep Masip (Spain), Davor Milicic (Croatia), Christian Mueller (Switzerland), Holger Nef (Germany), Lis Neubeck (United Kingdom), Michel Noutsias (Germany), Steffen E. Petersen (United Kingdom), Anna Sonia Petronio (Italy), Piotr Ponikowski (Poland), Eva Prescott (Denmark), Amina Rakisheva (Kazakhstan), Dimitrios Richter (Greece), Evgeny Schlyakhto (Russia), Petar Seferovic (Serbia), Michele Senni (Italy), Marta Sitges (Spain), Miguel Sousa-Uva (Portugal), Carlo Gabriele Tocchetti (Italy), Rhian M. Touyz (United Kingdom), Carsten Tschoepe (Germany), Johannes Waltenberger (Germany/Switzerland)

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1 Abbreviations and acronyms

6MWT	6-minute walk test
ACE-I	Angiotensin-converting enzyme inhibitor
ACS	Acute coronary syndrome
ADVANCE	Evaluation of the HeartWare Left Ventricular Assist Device for the Treatment of Advanced Heart Failure (trial)
AF	Atrial fibrillation
AHF	Acute heart failure
Aldo-DHF	Aldosterone Receptor Blockade in Diastolic Heart Failure (trial)
AMI	Acute myocardial infarction
AO	Aorta/aortic
ARB	Angiotensin-receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor

ATLAS	Assessment of Treatment with Lisinopril And Survival (trial)
AV	Atrio-ventricular
b.i.d.	Twice daily
BMI	Body mass index
BNP	B-type natriuretic peptide
b.p.m.	Beats per minute
BTD	Bridge to decision
BTR	Bridge to recovery
BTT	Bridge to transplant
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CARE-HF	CArdiac REsynchronization in Heart Failure (trial)
CE	Conformité Européenne
CHARM-Added	Candesartan Cilexitil in Heart Failure – Assessment of Mortality and Morbidity (trial)
CHARM-Alternative	Candesartan in Heart Failure – Assessment of Reduction in Mortality and Morbidity (trial)
CHARM-Preserved	Candesartan Cilexetil in Heart Failure – Assessment of Reduction in Mortality and Morbidity (trial)
CHART-2	Congestive Heart Failure Cardiopoietic Regenerative Therapy (trial)
CI	Confidence interval
CIBIS-II	Cardiac Insufficiency Bisoprolol Study II
CKD	Chronic kidney disease
CONSENSUS	Cooperative North Scandinavian Enalapril Survival Study
COPD	Chronic obstructive pulmonary disease
COPERNICUS	Carvedilol Prospective Randomized Cumulative Survival (trial)
CPET	Cardiopulmonary exercise test
CR	Controlled release
CRT	Cardiac resynchronization therapy
CT	Computed tomography
CV	Cardiovascular
CVD	Cardiovascular disease
CYP3A4	Cytochrome P450 3A4
DAPA-CKD	Dapagliflozin and Prevention of Adverse outcomes in Chronic Kidney Disease (trial)
DAPA-HF	Dapagliflozin And Prevention of Adverse outcomes in Heart Failure (trial)
DIG	Digitalis Investigation Group (trial)
DIG-PEF	Ancillary DIG trial (effects of digoxin on morbidity and mortality in diastolic heart failure)
DT	Destination therapy
DM	Diabetes mellitus
E/e′ (ratio)	E/e′ ratio = early filling velocity on transmitral Doppler/early relaxation velocity on tissue Doppler
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EMPEROR-Reduced	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (trial)
EMPHASIS-HF	Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure (trial)
ENDURANCE	HeartWare Ventricular Assist System as Destination Therapy of Advanced Heart Failure (trial)
ESC-HF-LT	European Society of Cardiology Heart Failure Long-Term (registry)
FiO_2	Fraction of inspired oxygen
FoCUS	Focus Cardiac Ultrasound
GALACTIC-HF	Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure (trial)
GDMT	Guideline-directed medical therapy
GWTG-HF	Get With the Guidelines – Heart Failure (registry)
Hb	Haemoglobin
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HIV	Human immunodeficiency virus
HTN	Hypertension
IABP	Intra-aortic balloon pump
IABP-SHOCK-II	Intra-aortic Balloon Pump in Cardiogenic Shock II
ICD	Implantable cardioverter-defibrillator
ICU	Intensive care unit
IPD	Individual patient data
I-PRESERVE	Irbesartan in Patients with Heart Failure and PRESERVEd Ejection Fraction (trial)
i.v.	Intravenous
IVC	Inferior vena cava
IVS	Interventricular septum
K^+	Potassium
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	Left atrium/atrial
LGE	Late gadolinium enhancement
LV	Left ventricle/left ventricular
LVAD	Left ventricular assist device
LVEED	Left ventricular end-diastolic diameter
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
LVIDD	Left ventricular internal diastolic dimension
MADIT II	Multi-center Autonomic Defibrillator Implantation Trial II
MAGGIC	Meta-Analysis Global Group in Chronic Heart Failure
MCS	Mechanical circulatory support

MECKI	Metabolic Exercise test data combined with Cardiac and Kidney Indexes
mEq	Milliequivalent
MERIT-HF	Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (trial)
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MOMENTUM-3	Multicenter study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (trial)
MRA	Mineralocorticoid receptor antagonist
N	Number of patients
N/A	Not available
NIV	Non-invasive ventilation
NP	Natriuretic peptide
NS	Not significant
NSAID	Non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
NYR	Not yet reported
o.d.	Once daily
OMM	Optimal medical management
OPTIC	Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (trial)
OPTIMIZE-HF	Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (registry)
PA	Pulmonary artery
$PaCO_2$	Partial pressure of carbon dioxide
PaO_2	Partial pressure of oxygen
PARADIGM-HF	Prospective Comparison of ARNI with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure (trial)
PARAGON-HF	Prospective Comparison of ARNI with ARB Global Outcomes in HF with preserved Ejection Fraction (trial)
PARAMOUNT	LCZ696 Compared to Valsartan in Patients with Chronic Heart Failure and Preserved Left-ventricular Ejection Fraction (trial)
PCI	Percutaneous coronary intervention
Peak VO_2	Peak exercise oxygen consumption
PEP-CHF	Perindopril in Elderly People with Chronic Heart Failure (trial)
PMR	Papillary muscle rupture
Prn	As needed
PWT	Posterior wall thickness
QOL	Quality of life
QRS	Q, R, and S waves of an ECG
QT	QT interval
RA	Right atrium/atrial
RAAS	Renin-angiotensin-aldosterone system
RALES	Randomized Aldactone Evaluation Study
RELAX	Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (trial)
ROADMAP	Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients (trial)
r.p.m.	Revolutions per minute
RV	Right ventricle/right ventricular
RVF	Right ventricular failure
Sac/Val	Sacubitril/valsartan
SBP	Systolic blood pressure
SCr	Serum creatinine
SENIORS	Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisations in Seniors with Heart Failure (trial)
SGLT2	Sodium-glucose co-transporter 2
SHFM	Seattle Heart Failure Model
SHIFT	Systolic Heart failure treatment with the If inhibitor ivabradine Trial
SOLVD-Treatment	Studies of Left Ventricular Dysfunction Treatment (trial)
SpO_2	Oxygen saturation
SR	Sinus rhythm
ST	ST segment (on the ECG)
SWEDEHF	Swedish Heart Failure Registry
TAPSE	Tricuspid annular plane systolic excursion
TOE	Transoesophageal echocardiogram
t.i.d.	Three times a day
TIME-CHF	Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (trial)
VA	Veno-arterial
Val-HeFT	Valsartan Heart Failure Trial
VANISH	Ventricular Tachycardia Ablation or Escalated aNtiarrhythmic Drugs in Ischemic Heart Disease (trial)
VICTORIA	Vericiguat Global Study in Patients with Heart Failure with Reduced Ejection Fraction
vs.	Versus
VSD	Ventricular septal defect
WRF	Worsening renal function
XL	Extended release

2 Introduction

No supplementary data for this section.

3 Definition, epidemiology and prognosis

No supplementary data for this section.

4 Chronic heart failure

No supplementary data for this section.

5 Heart failure with reduced ejection fraction

Supplementary Table 1 Major clinical trials of therapeutic interventions in patients with chronic heart failure with reduced ejection fraction

Trial	Drug	Major inclusion criteria	Mean follow-up (years)	Impact of treatment on primary endpoint	Other results
ACE-Is					
CONSENSUS	Enalapril (*n* = 127) vs. placebo (*n* = 126)	Congested HF, NYHA IV, cardiomegaly on chest X-ray	0.5	All-cause mortality reduced by 40% at 6 months (26% vs. 44%, *P* = 0.002) and by 31% at 12 months (52% vs. 36%, *P* = 0.001)	–
SOLVD-Treatment[1]	Enalapril (*n* = 1285) vs. placebo (*n* = 1284)	LVEF ≤35%, NYHA I–IV (90% NYHA II–III)	3.5	All-cause mortality reduced by 16% (35% vs. 40%) (*P* = 0.004)	Reduction in combined all-cause mortality and HF hospitalization rate by 26% (*P* <0.0001)
ATLAS[2]	High (*n* = 1568) vs. low (*n* = 1596) dose of lisinopril	LVEF ≤30%, NYHA II–IV	3.8	All-cause mortality was non-significantly reduced by 8% (43% vs. 45%, *P* = 0.13)	Trend towards a reduction in CV mortality by 10% (*P* = 0.07). Reduction in combined all-cause mortality or HF hospitalization rate by 15% (*P* <0.001)
Beta-blockers					
COPERNICUS[3]	Carvedilol (*n* = 1156) vs. placebo (*n* = 1133)	LVEF <25%, NYHA IV	0.9	All-cause mortality reduced by 35% (11% vs. 17%) (*P* <0.001)	Reduction in combined all-cause mortality and any hospitalization rate by 24% (*P* <0.001)
CIBIS-II[4]	Bisoprolol (*n* = 1327 vs. placebo (*n* = 1320)	LVEF ≤35%, NYHA III–IV	1.3	All-cause mortality reduced by 34% (12% vs. 17%) (*P* <0.001)	Reduction in combined CV mortality or CV hospitalization rate by 21% (*P* <0.001)
MERIT-HF[4]	Metoprolol CR/XL (*n* = 1991) vs. placebo (*n* = 2001)	LVEF ≤40%, NYHA II–IV	1.0	All-cause mortality reduced by 34% (7% vs. 11%) (*P* <0.001)	Reduction in the risk of CV death by 38% (*P* <0.001), sudden death by 41% (*P* <0.001) and death from aggravated HF by 49% (*P* = 0.002)

Continued

Supplementary Table 1 *Continued*

Trial	Drug	Major inclusion criteria	Mean follow-up (years)	Impact of treatment on primary endpoint	Other results
SENIORS[5]	Nebivolol (*n* = 1067) vs. placebo (*n* = 1061)	Age ≥70 y, HF confirmed as HF hospitalization in recent 12 months and/or LVEF ≤35% in recent 6 months	1.8	Combined all-cause mortality and CV hospitalization rate reduced by 14% (31% vs. 35%, *P* = 0.04)	–
MRAs					
RALES[6]	Spironolactone (*n* = 822) vs. placebo (*n* = 841)	LVEF ≤35%, NYHA III–IV, and HF for >6 weeks	2.0	All-cause mortality reduced by 30% (35% vs. 46%) (*P* <0.001)	Reduction in cardiac hospitalization rate by 35% (*P*<0.001)
EMPHASIS-HF[7]	Eplerenone (*n* = 1364) vs. placebo (*n* = 1373)	NYHA II, LVEF <30% or LVEF 30–35% with QRS >130 ms, CV hospitalization in recent 6 months or BNP ≥250 pg/mL or NT-proBNP ≥500 pg/mL in men and ≥750 pg/mL in women	1.8	Combined CV mortality or HF hospitalization rate reduced by 37% (18% vs. 26%, *P* <0.001)	Reduction in all-cause mortality by 24% (*P* = 0.008) and CV mortality by 24% (*P* = 0.01). Reduction in HF hospitalization rate by 42% (*P* <0.001)
ARNIs					
PARADIGM-HF[8]	Sac/Val (*n* = 4187) vs. enalapril (*n* = 4212)	NYHA II–IV, LVEF ≤40% (amended to LVEF ≤35%), BNP ≥150 pg/mL or NT-proBNP ≥600 pg/mL, or, if HF hospitalization within recent 12 months BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL	2.3	Composite of death from CV causes or a first HF hospitalization reduced by 20% (22% vs. 27%, *P* <0.001)	Reduction in all-cause mortality by 16% (*P* <0.001) and CV mortality by 20% (*P* <0.001). Reduction in HF hospitalization rate by 21% (*P* <0.001)
I_f channel blocker					
SHIFT[9]	Ivabradine (*n* = 3268) vs. placebo (*n* = 3290)	LVEF ≤35%, NYHA II–IV, HF hospitalization in recent 12 months, SR, heart rate ≥70 b.p.m.	1.9	Combined CV mortality or HF hospitalization rate reduced by 18% (24% vs. 29%, *P* <0.001)	Reduction in HF hospitalization rate by 26% (*P*<0.001). Reduction in HF-related mortality by 26% (*P* = 0.001)
ARBs					
CHARM-Added[10]	Candesartan (*n* = 1276) vs. placebo (*n* = 1272)	LVEF ≤40%, NYHA II–IV, treatment with ACE-I	3.4	Combined CV mortality or HF hospitalization rate reduced by 15% (38% vs. 42%, *P* = 0.01)	–
CHARM-Alternative[11]	Candesartan (*n* = 1013) vs. placebo (*n* = 1015)	LVEF ≤40%, NYHA II–IV, intolerant to ACE-I	2.8	Combined CV mortality or HF hospitalization rate reduced by 23% (33% vs. 40%, *P* <0.001)	–

Continued

Supplementary Table 1 *Continued*

Trial	Drug	Major inclusion criteria	Mean follow-up (years)	Impact of treatment on primary endpoint	Other results
Val-HeFT[12]	Valsartan (n = 2511) vs. placebo (n = 2499)	LVEF <40%, NYHA II–IV, treatment with ACE-I, LVIDD >2.9 cm/body surface area	1.9	All-cause mortality was similar in both groups (19.7% vs. 19.4%, P = 0.80). Reduction in a co-primary combined endpoint of all-cause death, cardiac arrest with resuscitation, HF hospitalization or i.v. administration of inotropic or vasodilator drugs for ≥4 h without hospitalization by 13% (29% vs. 32%, P = 0.009)	–
Soluble guanylate cyclase stimulator					
VICTORIA[13]	Vericiguat (n = 2526) vs. placebo (n = 2524)	LVEF ≤45%, NYHA II–IV, recent hospitalization	0.9	Combined CV mortality or HF hospitalization reduced by 10% (35.5% vs. 38.5%, P = 0.02)	–
SGLT2 inhibitors					
DAPA-HF[14]	Dapagliflozin (n = 2373) vs. placebo (n = 2371)	LVEF ≤40%, NYHA II–IV, presence or absence of type 2 diabetes mellitus	1.5	Combined CV mortality or worsening HF reduced by 26% (16.3% vs. 21.2%, P <0.001)	Reduction in CV mortality by 18%. Reduction in all-cause mortality by 17%. Reduction in worsening HF by 30%
EMPEROR-Reduced[15]	Empagliflozin (n = 1863) vs. placebo (n = 1867)	LVEF ≤40%, NYHA II–IV, presence or absence of type 2 diabetes mellitus	1.3	Combined CV mortality or worsening HF reduced by 25% (19.4% vs. 24.7%, P <0.001)	Reduction in number of hospitalizations for HF by 30%
Cardiac myosin activator					
GALACTIC-HF[16]	Omecamtiv (n = 4120) vs. placebo (n = 4112)	In-patients and out-patients with NYHA II–IV HF and LVEF ≤35%	1.8	Combined first HF event or CV death by 8% (37% vs. 39.1%, P <0.001)	–

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; ARNI = angiotensin-receptor neprilysin inhibitor; ATLAS = Assessment of Treatment with Lisinopril And Survival (trial); BNP = B-type natriuretic peptide; b.p.m. = beats per minute; CIBIS-II = Cardiac Insufficiency Bisoprolol Study II; CHARM-Added = Candesartan Cilexitil in Heart Failure Assessment of Mortality and Morbidity (trial); CHARM-Alternative = Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (trial); CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival (trial); CR = controlled release; CV = cardiovascular; DAPA-HF = Dapagliflozin And Prevention of Adverse outcomes in Heart Failure (trial); EMPEROR-Reduced = Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (trial); EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and SurvIval Study in Heart Failure (trial); GALACTIC-HF = Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure (trial); h = hours; HF = heart failure; i.v. = intravenous; LVEF = left ventricular ejection fraction; LVIDD = left ventricular internal diastolic dimension; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; MRA = mineralocorticoid receptor antagonist; n = number of patients; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PARADIGM-HF = Prospective Comparison of ARNI with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure (trial); QRS = Q, R, and S waves of an ECG; RALES = Randomized Aldactone Evaluation Study; Sac/Val = sacubitril/valsartan; SENIORS = Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisations in Seniors with Heart Failure (trial); SGLT2 = sodium-glucose co-transporter 2; SHIFT = Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial; SOLVD-Treatment = Studies of Left Ventricular Dysfunction Treatment (trial); SR = sinus rhythm; Val-HeFT = Valsartan Heart Failure Trial; VICTORIA = Vericiguat Global Study in Patients with Heart Failure with Reduced Ejection Fraction; vs. = versus; XL = extended release.

Supplementary Table 2 Practical guidance on the use of angiotensin-converting enzyme inhibitors (or an angiotensin II receptor blocker) in patients with heart failure with reduced ejection fraction[a]

WHY?
To improve symptoms and exercise capacity, reduce the risk of HF hospitalization, and increase survival.
IN WHOM AND WHEN?
Indications: 1. Patients with HFrEF.
Contraindications: 1. History of angioedema[b]. 2. Known bilateral renal artery stenosis. 3. Pregnancy/risk of pregnancy. 4. Known allergic reaction/other adverse reaction (drug-specific).
Cautions/seek specialist advice: 1. Significant hyperkalaemia (K^+ >5.0 mmol/L). 2. Significant renal dysfunction [creatinine >221 µmol/L (>2.5 mg/dL) or eGFR <30 mL/min/1.73 m^2]. 3. Symptomatic or severe asymptomatic hypotension (SBP <90 mmHg). 4. Drug interactions to look out for: • K^+ supplements K^+-sparing diuretics, e.g. amiloride and triamterene (beware combination preparations with furosemide). • MRAs. • Renin inhibitors[c]. • NSAIDs[d]. • Trimethoprim/trimethoprim-sulfamethoxazole. • 'Low-salt' substitutes with a high K^+ content.
WHICH ACE-I AND WHAT DOSE? – see also Guidelines, Table 8
Captopril: starting dose 6.25 mg *t.i.d.*, target dose 50 mg *t.i.d.* Enalapril: starting dose 2.5 mg *b.i.d.*, target dose 10–20 mg *b.i.d.* Lisinopril: starting dose 2.5–5 mg *o.d.*, target dose 20–35 mg *o.d.* Ramipril: starting dose 2.5 mg *o.d.*, target dose 10 mg *o.d.* Trandolapril: starting dose 0.5 mg *o.d.*, target dose 4 mg *o.d.*
WHERE?
• In the community in stable patients (NYHA class IV/patients with severe HF and those with a current/recent exacerbation should be referred for specialist advice). • In patients hospitalized with worsening HF—after stabilizing, relieving congestion, and if possible, restoring 'euvolaemia' (but ideally before discharge). • Other exceptions—see '**Cautions/seek specialist advice**'.
HOW TO USE?
• Check renal function and electrolytes. • Start with a low dose (see **Guidelines, Table 8**). • Double the dose at not less than 2-week intervals in the community. More rapid dose uptitration may be carried out in patients in hospital or who are otherwise closely monitored, tolerability permitting. • Aim for the target dose (see above) or, failing that, the highest tolerated dose [remember: some ACE-I (or ARB) is better than no ACE-I]. • Re-check blood chemistry (urea/BUN, creatinine, K^+) 1–2 weeks after initiation and 1–2 weeks after final dose titration. • Monitor blood chemistry 4-monthly thereafter. • When to stop uptitration, reduce dose, stop treatment—see PROBLEM SOLVING. • It is very rarely necessary to stop an ACE-I (or ARB), and clinical deterioration is likely if treatment is withdrawn. Ideally, specialist advice should be sought before treatment discontinuation. • A specialist HF nurse may assist with education of the patient, follow-up (in person or by telephone), biochemical monitoring, and dose uptitration.

Continued

PROBLEM SOLVING

Asymptomatic low blood pressure:

- Does not usually require any change in therapy.

Symptomatic hypotension:

- Dizziness/light headedness is common and often improves with time—patients should be reassured.
- Reconsider need for nitrates, calcium-channel blockers[e] and other vasodilators and reduce dose/stop, if possible.
- If no signs or symptoms of congestion, consider reducing diuretic dose.
- If these measures do not solve problem, seek specialist advice.

Cough:

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

WRF and hyperkalaemia:

- Some rise in urea (BUN), creatinine, and K^+ is to be expected after an ACE-I; if an increase is small and asymptomatic, no action is necessary.
- An increase in creatinine of up to 50% above baseline, or 266 μmol/L (3 mg/dL)/eGFR <25 mL/min/1.73 m^2, whichever is the smaller, is acceptable.
- An increase in K^+ to ≤5.5 mmol/L is acceptable.
- If urea, creatinine, or K^+ does rise excessively, consider stopping concomitant nephrotoxic drugs (e.g. NSAIDs)[d] and other K^+ supplements or retaining agents (triamterene, amiloride) and, if no signs of congestion, reducing the dose of diuretic.
- If greater rises in creatinine or K^+ than those outlined above persist despite adjustment of concomitant medications, the dose of the ACE-I (or ARB) should be halved and blood chemistry re-checked within 1−2 weeks; if there is still an unsatisfactory response, specialist advice should be sought.
- If K^+ rises to >5.5 mmol/L or creatinine increases by >100% or to >310 μmol/L (3.5 mg/dL)/eGFR <20 mL/min/1.73 m^2, the ACE-I (or ARB) should be stopped and specialist advice sought.
- Blood chemistry should be monitored frequently and serially until K^+ and creatinine have plateaued.

ADVICE TO PATIENT

- Explain expected benefits:
  - Improved symptoms and exercise capacity.
  - Prevention of worsening of HF leading to hospital admission.
  - Increased survival.
- Symptoms improve within a few weeks to a few months after starting treatment.
- Advise patients to report principal adverse effects (i.e. dizziness/symptomatic hypotension, cough)—see PROBLEM SOLVING.
- Advise patients to avoid NSAIDs[d] not prescribed by a physician (i.e. purchased over-the-counter) and salt substitutes high in K^+—see PROBLEM SOLVING.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; *b.i.d.* = twice daily; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; K^+ = potassium; MRA = mineralocorticoid receptor antagonist; NSAID = non-steroidal anti-inflammatory drug; NYHA = New York Heart Association; *o.d.* = once daily; SBP = systolic blood pressure; *t.i.d.* = three times a day; WRF = worsening renal function.

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

[b]The safety of an ARB in patients developing angioedema with an ACE-I is uncertain.

[c]Renin inhibitors are not recommended in HF.

[d]Avoid NSAIDs unless essential.

[e]Calcium-channel blockers should be discontinued unless absolutely necessary, and diltiazem and verapamil are potentially harmful in HFrEF because of their negative inotropic action.

Supplementary Table 3 Practical guidance on the use of beta-blockers in patients with heart failure with reduced ejection fraction

WHY?
To improve symptoms, reduce the risk of HF hospitalization, and increase survival.
IN WHOM AND WHEN?
Indications: 1. Patients with stable HFrEF.
Contraindications: 1. Second- or third-degree AV block (in the absence of a permanent pacemaker). 2. Critical limb ischaemia. 3. Asthma (relative contraindication): if cardio-selective beta-blockers are indicated, asthma is not necessarily 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; COPD is not a contraindication. 4. Known allergic reaction/other adverse reaction (drug-specific).
Cautions/seek specialist advice: 1. Severe (NYHA class IV) HF. 2. Current or recent (<4 weeks) exacerbation of HF (e.g. hospital admission with worsening HF), heart block, or heart rate <50 b.p.m. 3. If persisting signs of congestion, hypotension (SBP <90 mmHg), raised jugular venous pressure, ascites, marked peripheral oedema—try to relieve congestion and achieve 'euvolaemia' before starting a beta-blocker. 4. Drug interactions to look out for (because of risk of bradycardia/AV block): • Verapamil, diltiazem (are not recommended and should be discontinued)[b]. • Digoxin. • Amiodarone. • Ivabradine.
WHICH BETA-BLOCKER AND WHAT DOSE?—see Guidelines, Table 8
Bisoprolol: starting dose 1.25 mg *o.d.*, target dose 10 mg *o.d.* Carvedilol: starting dose 3.125 mg *b.i.d.*, target dose 25 mg *b.i.d. (*target dose 50 mg* b.i.d. *if >85 kg).* Metoprolol succinate (CR/XL): starting dose 12.5–25 mg *o.d.*, target dose 200 mg *o.d.* Nebivolol: starting dose 1.25 mg *o.d.*, target dose 10 mg *o.d.*
WHERE?
• In the community in stable patients (NYHA class IV/patients with severe HF and those with a current/recent exacerbation should be referred for specialist advice). • In patients hospitalized with worsening HF—after stabilizing, relieving congestion, and, if possible, restoring 'euvolaemia' (but ideally before discharge). • Other exceptions—see 'Cautions/seek specialist advice'.
HOW TO USE?
• Start with a low dose in a stable condition (see **Guidelines, Table 8**). • Double the dose at not less than 2-week intervals (slower uptitration may be needed in some patients). • Aim for the target dose (see above) or, failing that, the highest tolerated dose (remember: some beta-blocker is better than no beta-blocker). • Monitor heart rate, blood pressure, and clinical status (symptoms, signs—especially signs of congestion, body weight). • A specialist HF nurse may assist with education of the patient, follow-up (in person or by telephone), and dose uptitration. • When to stop uptitration, reduce dose, stop treatment—see PROBLEM SOLVING.
PROBLEM SOLVING
Worsening symptoms or signs (e.g. increasing dyspnoea, fatigue, oedema, weight gain): • If increasing congestion, increase a dose of diuretic or halve a dose of beta-blocker (if increasing diuretic dose does not work). • If marked fatigue (or bradycardia—see below), halve a dose of beta-blocker (rarely necessary); review patient in 1–2 weeks; if not improved, seek specialist advice. • If serious deterioration, halve the dose of beta-blocker or stop this treatment (rarely necessary); seek specialist advice. **Low heart rate:** • If <50 b.p.m. and worsening symptoms, halve the dose of beta-blocker, or, if severe deterioration, stop beta-blocker (rarely necessary). • Review need for other heart rate-slowing drugs (e.g. digoxin, ivabradine, amiodarone, diltiazem, or verapamil[b]). • Arrange ECG to exclude heart block. • Seek specialist advice.

Continued

Asymptomatic low blood pressure:

- Does not usually require any change in therapy.

Symptomatic hypotension:

- If dizziness, light-headedness, or confusion and a low blood pressure, reconsider need for nitrates, calcium-channel blockers[b], and other vasodilators and reduce/stop, if possible.
- If no signs or symptoms of congestion, consider reducing diuretic dose.
- If these measures do not solve problem, seek specialist advice.

ADVICE TO PATIENT

- Explain expected benefits (see WHY?) and mention possibility of temporary adverse effects:
  - Treatment is given to improve symptoms, to prevent worsening of HF leading to hospital admission, and to increase survival.
  - Symptomatic improvement may develop slowly after starting treatment, sometimes taking 3–6 months or longer.
  - Temporary symptomatic deterioration may occur during initiation or uptitration phase; in the long term beta-blockers improve well-being.
- Advise patient to report deterioration (see PROBLEM SOLVING) and that deterioration (tiredness, fatigue, breathlessness) can usually be easily managed by an adjustment of other medication; patients should be advised not to stop beta-blocker therapy without consulting the physician.
- During initiation or uptitration phase to detect and to treat potential deterioration early, patients should be encouraged to weigh themselves daily (after waking, before dressing, after voiding, before eating), and to increase their diuretic dose should their weight increase, persistently (>2 days) by >1.5–2.0 kg/day.

AV = atrio-ventricular; *b.i.d.* = twice daily; b.p.m. = beats per minute; COPD = chronic obstructive pulmonary disease; CR = controlled release; ECG = electrocardiogram; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; NYHA = New York Heart Association; *o.d.* = once daily; SBP = systolic blood pressure; XL = extended release.

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

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

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

Supplementary Table 4 Practical guidance on the use of mineralocorticoid receptor antagonists in patients with heart failure with reduced ejection fraction[a]

WHY?

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

IN WHOM AND WHEN?

Indications:

1. Patients with HFrEF.

Contraindications:

1. Known allergic reaction/other adverse reaction (drug-specific).

Cautions/seek specialist advice:

1. Significant hyperkalaemia (K^+ >5.0 mmol/L)[b].
2. Significant renal dysfunction [creatinine >221 μmol/L (>2.5 mg/dL) or eGFR <30 mL/min/1.73 m^2][b].
3. Drug interactions to look out for:
   - K^+ supplements/K^+-sparing diuretics (e.g. amiloride and triamterene; beware combination preparations with furosemide).
   - ACE-Is/ARBs/renin inhibitors[c].
   - NSAIDs[d].
   - Trimethoprim/trimethoprim-sulfamethoxazole.
   - 'Low-salt' substitutes with a high K^+ content.
   - Strong CYP3A4 inhibitors, e.g. ketoconazole, itraconazole, nefazodone, telithromycin, clarithromycin, ritonavir, and nelfinavir (when eplerenone used).

WHICH MRA AND WHAT DOSE?—see Guidelines, Table 8

Eplerenone: starting dose 25 mg *o.d.*, target dose 50 mg *o.d.*

Spironolactone: starting dose 25 mg *o.d.*, target dose 50 mg *o.d.*

WHERE?

In the community or in the hospital.

Exceptions—see 'Cautions/seek specialist advice'.

HOW TO USE?

- Check renal function and electrolytes (particularly K^+).

Continued

- Start with a low dose (see above).
- Consider dose up-titration after 4–8 weeks.
- Check blood chemistry at 1 and 4 weeks after starting/increasing dose and at 8 and 12 weeks; 6, 9, and 12 months; 4-monthly thereafter.
- If K^+ rises above 5.5 mmol/L or creatinine rises to 221 µmol/L (2.5 mg/dL)/eGFR <30 mL/min/1.73 m^2, halve a dose and monitor blood chemistry closely.
- If K^+ rises to >6.0 mmol/L or creatinine to >310 µmol/L (3.5 mg/dL) eGFR <20 mL/min/1.73 m^2, stop MRA immediately and seek specialist advice.
- A specialist HF nurse may assist with education of the patient, follow-up (in person or by telephone), biochemical monitoring, and dose up-titration.

PROBLEM SOLVING

WRF/hyperkalaemia

- See HOW TO USE?
- The main concern is hyperkalaemia (>6.0 mmol/L); although this was uncommon in RALES and EMPHASIS-HF, it has been seen more commonly in clinical practice.
- Conversely, a high-normal K^+ level may be desirable in patients with HF, especially if they are taking digoxin.
- It is important to avoid other K^+-retaining drugs (e.g. K^+-sparing diuretics such as amiloride and triamterene) and nephrotoxic agents (e.g. NSAIDs[d]).
- The risk of hyperkalaemia and renal dysfunction when an MRA is given to patients already taking both an ACE-I and an ARB is higher than when an MRA is added to just an ACE-I or an ARB given singly; this triple combination of an ACE-I, ARB, and MRA is NOT recommended (see recommendations below).
- Some 'low-salt' substitutes have a high K^+ content.
- Male patients treated with spironolactone may uncommonly develop breast discomfort or gynaecomastia (switching to eplerenone should be considered).

ADVICE TO PATIENT

- Explain expected benefits (see WHY?)
  - Treatment is given to improve symptoms, to prevent worsening of HF leading to hospital admission, and to increase survival.
  - Symptomatic improvement occurs within a few weeks to a few months of starting treatment.
  - Avoid NSAIDs[d] not prescribed by a physician (i.e. purchased over-the-counter) and salt substitutes high in K^+.
  - If diarrhoea/vomiting occurs, or there is infection with fever leading to intense sweating, patients should be made aware of the risk of dehydration and electrolyte imbalance, and they should contact the physician/nurse.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; CYP3A4 = cytochrome P450 3A4; eGFR = estimated glomerular filtration rate; EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (trial); HF = heart failure; HFrEF = heart failure with reduced ejection fraction; K^+ = potassium; MRA = mineralocorticoid receptor antagonist; NSAID = non-steroidal anti-inflammatory drug; *o.d.* = once daily; RALES = Randomized Aldactone Evaluation Study; WRF = worsening renal function.

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

[b]It is extremely important to adhere to these cautions and doses to avoid serious hyperkalaemia.

[c]Renin inhibitors are not recommended in HF.

[d]Avoid NSAIDs unless essential.

Supplementary Table 5 Practical guidance on the use of sacubitril/valsartan (angiotensin receptor-neprilysin inhibitor) in patients with heart failure with reduced ejection fraction[a]

WHY?

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

IN WHOM AND WHEN?

Indications:

1. Patients with HFrEF as a replacement for ACE-I/ARB.
2. It may be considered in patients with HFrEF in those who are ACE-I/ARB naïve (*de novo* use).

Contraindications:

1. History of angioedema.[a]
2. Known bilateral renal artery stenosis.
3. Pregnancy/risk of pregnancy and breastfeeding period.
4. Known allergic reaction/other adverse reaction (drug-specific).
5. eGFR <30 mL/min/1.73 m^2.
6. Symptoms of hypotension or a SBP <90 mmHg (PARADIGM-HF enrolled patients with SBP >95 mmHg at randomization)

Continued

Cautions/seek specialist advice:

1. A washout period of at least 36 h after ACE-I therapy is required in order to minimize the risk of angioedema.
2. Significant hyperkalaemia (K^+ >5.0 mmol/L).
3. Drug interactions to look out for:
   - K^+ supplements/K^+-sparing diuretics, e.g. amiloride and triamterene (beware combination preparations with furosemide).
   - MRAs.
   - Renin inhibitors[c].
   - NSAIDs[d].
   - Trimethoprim/trimethoprim-sulfamethoxazole.
   - 'Low-salt' substitutes with a high K^+ content.

WHAT DOSE?—see also Guidelines, Table 8

Sac/Val: starting dose 49/51 mg *b.i.d.**, target dose 97/103 mg *b.i.d.*

**24/26 mg* b.i.d. *in selected patients*

WHERE?

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

HOW TO USE?

- Check renal function and electrolytes.
- Start with a low dose (see **Guidelines, Table 8**).
- In some patients, one may consider a reduced starting dose (24/26 mg *b.i.d.*), namely in those with SBP 100–110 mmHg, ACE-I/ARB naïve patients, eGFR 30–60 mL/min/1.73 m^2.
- Double the dose at not less than 2-week intervals in the community, monitoring tolerability.
- Aim for the target dose (see above) or, failing that, the highest tolerated dose.
- Re-check blood chemistry (urea/BUN, creatinine, K^+) 1–2 weeks after initiation and 1–2 weeks after final dose titration.
- Consider reducing diuretic where appropriate
- Monitor blood chemistry 4-monthly thereafter.
- When to stop uptitration, reduce dose, stop treatment—see PROBLEM SOLVING.
- It is very rarely necessary to stop an ARNI, and clinical deterioration is likely if treatment is withdrawn. Ideally, specialist advice should be sought before treatment discontinuation.
- A specialist HF nurse may assist with education of the patient, follow-up (in person or by telephone), biochemical monitoring, and dose uptitration.

PROBLEM SOLVING

Asymptomatic low blood pressure:

- Does not usually require any change in therapy.

Symptomatic hypotension:

- Dizziness/light-headedness is common and often improves with time—patients should be reassured.
- Reconsider need for any other vasodilators and reduce dose/stop, if possible.
- If no signs or symptoms of congestion, consider reducing diuretic dose.
- If these measures do not solve problem, seek specialist advice.

Cough:

- Cough is common in patients with HF, many of whom have smoking-related lung disease.
- Cough is also a symptom of pulmonary oedema, which should be excluded when a new worsening cough develops.
- When a troublesome cough does develop (e.g. one stopping the patient from sleeping) and can be proved to be due to ARNI and ACE-I (i.e. recurs after the drugs withdrawal and re-challenge), substitution of an ARB is recommended.

WRF and hyperkalaemia:

- Some rise in urea (BUN), creatinine, and K^+ is to be expected after an ARNI; if an increase is small and asymptomatic, no action is necessary.
- A reduction in eGFR up to ≤30 mL/min/1.73 m^2 is acceptable.
- An increase in K^+ up to ≤5.5 mmol/L is acceptable.
- If urea, creatinine, or K^+ does rise excessively, consider stopping concomitant nephrotoxic drugs (e.g. NSAIDs[d]) and other K^+ supplements or retaining agents (triamterene, amiloride) and, if no signs of congestion, reducing the dose of diuretic. This is particularly true in those patients on an SGLT2 inhibitor.
- If greater rises in creatinine or K^+ than those outlined above persist despite adjustment of concomitant medications, the dose of the ARNI should be halved and blood chemistry re-checked within 1–2 weeks; if there is still an unsatisfactory response, specialist advice should be sought.
- If K^+ rises to >5.5 mmol/L or eGFR lowers to <30 mL/min/1.73 m^2, the ARNI should be stopped and specialist advice sought.
- Blood chemistry should be monitored frequently and serially until K^+ and creatinine have plateaued.

Continued

ADVICE TO PATIENT
• Explain expected benefits: • Improved symptoms. • Prevention of worsening of HF leading to hospital admission. • Increased survival (reduction in both CV and all-cause mortality). • Symptoms improve within a few weeks to a few months after starting treatment. • Advise patients to report principal adverse effects (i.e. dizziness/symptomatic hypotension, cough)—see PROBLEM SOLVING. • Advise patients to avoid NSAIDs[d] not prescribed by a physician (i.e. purchased over-the-counter) and salt substitutes high in K^+—see PROBLEM SOLVING.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; ARNI = angiotensin-receptor neprilysin inhibitor; *b.i.d.* = twice daily; BUN = blood urea nitrogen; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; K^+ = potassium; MRA = mineralocorticoid receptor antagonist; NSAID = non-steroidal anti-inflammatory drug; NYHA = New York Heart Association; PARADIGM-HF = Prospective Comparison of ARNI with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure (trial); Sac/Val = sacubitril/valsartan; SBP = systolic blood pressure; SGLT2 = sodium-glucose co-transporter 2; WRF = worsening renal function.

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

[b]The safety of an ARB/ARNI in patients developing angioedema with an ACE-I is uncertain.

[c]Renin inhibitors are not recommended in HF.

[d]Avoid NSAIDs unless essential.

Supplementary Table 6 Practical guidance on the use of the sodium-glucose co-transporter 2 inhibitors dapagliflozin and empagliflozin in patients with heart failure with reduced ejection fraction[a]

WHY?
To improve QOL, reduce the risk of HF hospitalization, and increase survival.
IN WHOM AND WHEN?
Indications: 1. Patients with HFrEF (regardless of concomitant diabetes mellitus).
Contraindications: 1. Known allergic reaction/other adverse reaction (drug-specific). 2. Pregnancy/risk of pregnancy and breastfeeding period. 3. eGFR <20 mL/min/1.73 m^2.* 4. Symptoms of hypotension or a SBP <95 mmHg. **DAPA-CKD (dapagliflozin) enrolled patients with an eGFR >25 mL/min/1.73 m^2*
Cautions/seek specialist advice: 1. Type 1 diabetes mellitus is not an absolute contraindication, but an individual risk of ketoacidosis should be taken into account when starting this therapy. 2. Glycosuria (as the consequence of dapagliflozin action) may predispose to fungal genito-urinary infections. 3. Drug interactions to look out for: Insulin, sulfonylurea derivates and other antidiabetic drugs predisposing to hypoglycaemia. 4. Thiazides and loop diuretics predisposing to excessive diuresis, dehydration, symptomatic hypotension, and prerenal renal failure.
WHAT DOSE?—see Guidelines, Table 8
Dapagliflozin: starting (and target) dose 10 mg *o.d.* Empagliflozin: starting (and target) dose 10 mg *o.d.*
WHERE?
In the community or in the hospital.
HOW TO USE?
• Check renal function when starting the therapy and monitor regularly. eGFR is known to dip slightly after initiation but the SGLT2 inhibitors appear to be reno-protective. • Monitor glycaemia regularly, particularly when a patient is diabetic. Consider modification of other diabetic drugs. • Identify the risk factors predisposing to ketoacidosis and eliminate them if possible. • Monitor fluid balance regularly, particularly when a patient is taking diuretics, is old and/or frail. Consider an adjustment of diuretic therapy and fluid intake. • A specialist HF nurse may assist with education of the patient, follow-up (in person or by telephone), and biochemical monitoring.
PROBLEM SOLVING
Genito-urinary infections • Patients should be monitored in the context of symptoms and signs of genito-urinary fungal infections.

Continued

Hypoglycaemia

- Other diabetic drugs (particularly, insulin and/or sulfonylurea derivates) may predispose to hypoglycaemia; in this case, the diabetic treatment strategy needs to be modified.

Dehydration, hypotension, and prerenal renal failure

- SGLT2 inhibitors may intensify the diuresis, particularly when accompanied by Sac/Val and diuretic therapy.
- Fluid balance needs to be monitored. Diuretic doses along with fluid intake should be balanced in order to avoid dehydration, symptomatic hypotension, and prerenal renal failure.
- Elderly and frail patients are at particular risk of developing these complications.

ADVICE TO PATIENT

- Explain expected benefits (see WHY?)
  - Treatment is given to improve QOL, to prevent worsening of HF leading to hospital admission, and to increase survival (to reduce the risk of CV and all-cause deaths).
  - Improvement in QOL occurs within a few weeks to a few months of starting treatment.
- Due to action of SGLT2 inhibitors, glycosuria is an expected finding on urinalysis.
- Patients should be made aware of the risk of dehydration, hypotension, hypoglycaemia, ketoacidosis, and fungal genito-urinary infections, and in these cases they should contact the physician/nurse.

CV = cardiovascular; DAPA-CKD = Dapagliflozin and Prevention of Adverse outcomes in Chronic Kidney Disease (trial); eGFR = estimated glomerular filtration rate; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; *o.d.* = once daily; QOL = quality of life; Sac/Val = sacubitril/valsartan; SBP = systolic blood pressure; SGLT2 = sodium-glucose co-transporter 2.

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

Supplementary Table 7 Practical guidance on the use of diuretics in patients with heart failure

WHY?

To relieve breathlessness and oedema in patients with symptoms and signs of congestion.

IN WHOM AND WHEN?

Indications:

1. Potentially all patients with symptoms and signs of congestion, irrespective of LVEF.
2. When used, should always be used in a combination with an ACE-I (or an ARB), a beta-blocker, and an MRA in patients with HFrEF (unless any of these drugs is not tolerated/contraindicated), until signs of congestion have been relieved.
3. Thiazide diuretics can be used in patients with preserved renal function and mild symptoms of congestion. However, the majority of patients require loop diuretics (or combined with a thiazide diuretic and an MRA) due to the severity of HF symptoms and steadily deteriorating kidney function.

Contraindications:

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

Cautions/seek specialist advice:

1. Significant hypokalaemia ($K^+ \leq 3.5$ mmol/L)—may be made worse by diuretic.
2. Significant renal dysfunction [creatinine >221 μmol/L (>2.5 mg/dL) or eGFR <30 mL/min/1.73 m^2]—may be made worse by diuretic or patient may not respond to diuretic (especially thiazide diuretic).
3. Symptomatic or severe asymptomatic hypotension (SBP <90 mmHg)—may be made worse by diuretic-induced hypovolaemia.
4. Drug interactions to look out for:
   - Combination with an ACE-I, an ARB, or a renin inhibitor[a]—risk of hypotension (usually not a problem).
   - Combination with other diuretics (e.g. loop plus thiazide)—risk of hypovolaemia, hypotension, hypokalaemia, and renal impairment[b].
   - NSAIDs[c]—may attenuate effect of diuretic.

WHICH DIURETIC AND WHAT DAILY DOSE?

Loop diuretics:

Furosemide: starting dose 20–40 mg, usual dose 40–240 mg.

Bumetanide: starting dose 0.5–1 mg, usual dose 1–5 mg.

Torasemide: starting dose 5–10 mg, usual dose 10–20 mg.

Thiazides/thiazide-like diuretics:

Bendroflumethiazide: starting dose 2.5 mg, usual dose 2.5–10 mg.

Hydrochlorothiazide: starting dose 25 mg, usual dose 12.5–100 mg.

Metolazone: starting dose 2.5 mg, usual dose 2.5–10 mg. Can be weekly, daily, or prn.

Continued

Non-thiazide sulfonamide:

Indapamide: starting dose 2.5 mg, usual dose 2.5–5 mg.

WHERE?

In the community for most patients.

HOW TO USE?

- Check renal function and electrolytes, particularly in those on a combination of loop and thiazide diuretics.
- Start with a low dose but target an effective dose for a patient to achieve positive diuresis with a simultaneous reduction of body weight by 0.75–1.0 kg per day.
- Adjust a dose according to symptoms and/or signs of congestion, blood pressure, and renal function. Use a minimum dose necessary to maintain euvolaemia—the patient's 'dry weight' (i.e. to keep the patient free of symptoms and signs of congestion).
- Dose may need to be increased or decreased according to the patient's volume status (remember that excessive diuresis is more dangerous than oedema itself).
- Re-check blood chemistry 1–2 weeks after an initiation and after any increase in dose (urea/BUN, creatinine, K^+).
- When to stop uptitration, reduce dose, stop treatment—see PROBLEM SOLVING.
- Patients can be educated to alter their own diuretic dose, according to need (based on symptoms, signs, and weight changes).
- A specialist HF nurse may assist with education of the patient, follow-up (in person or by telephone), biochemical monitoring, and dose adjustment (including patient educated in dose adjustment).

PROBLEM SOLVING

Asymptomatic low blood pressure:

- Dose may be reduced if no symptoms or signs of congestion.

Symptomatic hypotension:

- Causing dizziness/light-headedness—reduce dose if no symptoms or signs of congestion.
- Reconsider need for nitrates, calcium-channel blockers[d] and other vasodilators.
- If these measures do not solve problem, seek specialist advice.

Hypokalaemia/hypomagnesaemia:

- Increase an ACE-I/ARB dose.
- Add an MRA, K^+ supplements; magnesium supplements.

Hyponatraemia (<135 mmol/L):

- Volume depleted:
  - Stop thiazide or switch to loop diuretic, if possible.
  - Reduce dose/stop loop diuretics if possible.
- Volume overloaded:
  - Fluid restriction.
  - Consider increasing dose of loop diuretic.
  - Consider AVP antagonist (e.g. tolvaptan if available).
  - i.v. inotropic support.
  - Consider ultrafiltration.

Hyperuricaemia/gout:

- Consider allopurinol prophylaxis (not initiated during acute exacerbation).
- For symptomatic gout use colchicine for pain relief.
- Avoid NSAIDs.

Hypovolaemia/dehydration:

- Assess volume status; consider a diuretic dosage reduction.

Insufficient diuretic response/diuretic resistance:

- Check adherence and fluid/salt intake.
- Increase a dose of diuretic.
- Consider switching from furosemide to bumetanide or torasemide.
- Add an MRA/increase dose of an MRA.
- Combine loop diuretic and thiazide/metolazone[b].
- Administer loop diuretic twice (or more times) daily or on empty stomach.
- Consider short-term i.v. infusion of loop diuretic.
- Consider ultrafiltration.

Renal impairment (rising creatinine/BUN–urea):

- Check for hypovolaemia/dehydration.
- Exclude use of other nephrotoxic agents, e.g. NSAIDs, trimethoprim.

Continued

- Withhold an MRA.
- If using concomitant loop and thiazide diuretic, stop thiazide diuretic.
- Consider reducing a dose of ACE-I/ARB.
- Consider haemofiltration/dialysis.

ADVICE TO PATIENT

- Explain expected benefits:
  - Relieves breathlessness and oedema.
  - Symptoms improve quickly—usually within days of starting treatment.
- Advise patients to report principal adverse effects [e.g. thirst (avoid excessive consumption of hypotonic fluids, which can cause hyponatraemia) and dizziness/symptomatic hypotension]—see PROBLEM SOLVING.
- Advise patients to avoid NSAIDs[c] not prescribed by a physician (i.e. purchased over-the-counter)—may cause diuretic resistance and renal impairment.
- Patient may be educated to adjust dose based on symptoms, signs, and changes in weight (if weighing regularly).
- Dose may need to be decreased if there is fluid loss (e.g. due to diarrhoea/vomiting, excessive sweating).

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; AVP = arginine vasopressin; BUN = blood urea nitrogen; LVEF = left ventricular ejection fraction; eGFR = estimated glomerular filtration rate; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; i.v. = intravenous; K^+ = potassium; MRA = mineralocorticoid receptor antagonist; NSAID = non-steroidal anti-inflammatory drug; prn = as needed; SBP = systolic blood pressure.
[a]Renin inhibitors are not recommended in HF.
[b]Usually only needed for a short period—careful monitoring of blood chemistry is essential.
[c]Avoid NSAIDs unless essential.
[d]Calcium-channel blockers should be discontinued in patients with HFrEF unless absolutely necessary, and diltiazem and verapamil are potentially harmful in patients with HFrEF because of their negative inotropic action.

Supplementary Table 8 Practical guidance on the use of ivabradine in patients with heart failure with reduced ejection fraction[a]

WHY?

To reduce the risk of HF hospitalization and CV death.

IN WHOM AND WHEN?

Indications:

1. Patients with stable symptomatic HF (NYHA class II–IV) and an EF ≤35% SR and resting heart rate ≥70 b.p.m. despite guideline-recommended treatment (in particular, an evidence-based dose of beta-blocker).

Contraindications:

1. Unstable CV conditions (ACS, stroke/TIA, severe hypotension).
2. AF.
3. Severe liver dysfunction or renal dysfunction (no evidence on safety or pharmacokinetics for creatinine clearance <15 mL/min).
4. Pregnancy or breastfeeding.
5. Known allergic reaction/other adverse reaction (drug-specific).

Cautions/seek specialist advice:

1. Severe (NYHA class IV) HF.
2. Current or recent (<4 weeks) exacerbation of HF (e.g. hospital admission with worsening HF).
3. Resting heart rate <50 b.p.m. during treatment.
4. Moderate liver dysfunction.
5. Chronic retinal diseases, including retinitis pigmentosa.
6. Drug interactions:
   - To look out for (due to a potential risk of bradycardia and an induction of long QT as a result of bradycardia):
     - Verapamil, diltiazem (both should be discontinued/not used in HFrEF).
     - Digoxin.
     - Amiodarone.
   - To look out for drugs being strong inhibitors of isoenzyme CYP3A4:
     - Antifungal azoles (such as ketoconazole, itraconazole).
     - Macrolide antibiotics (such as clarithromycin, erythromycin).
     - HIV protease inhibitors (nelfinavir, ritonavir).
     - Nefazodone.

Continued

WHAT DOSE?—see Guidelines, Table 8

Ivabradine: starting dose 5 mg *b.i.d.*, target dose 7.5 mg *b.i.d.*

WHERE?

- In the community in stable patients in NYHA class II–III.
- Patients in NYHA class IV or those with a recent HF exacerbation should be referred for specialist advice.
- Other exceptions—see 'Cautions/seek specialist advice'.

HOW TO USE?

- Start with a low dose (5 mg *b.i.d.*) (see **Guidelines, Table 8**). In patients over 75 years old, a lower starting dose of 2.5 mg *b.i.d.* can be used.
- Daily dose may be increased to 7.5 mg *b.i.d.*, decreased to 2.5 mg *b.i.d.* or stopped depending on the patient's resting heart rate. Double the dose not more frequently than at 2-week intervals (slower uptitration may be needed in some patients). Aim for the target dose (see above) or, failing that, the highest tolerated dose based on resting heart rate. If the resting heart rate is between 50 and 60 b.p.m., the current dose should be maintained.
- Monitor heart rate, blood pressure, and clinical status.
- When to stop uptitration, reduce dose, stop treatment—see PROBLEM SOLVING.
- A specialist HF nurse may assist with education of the patient, monitoring resting heart rate, follow-up (in person or by telephone), and dose uptitration.

PROBLEM SOLVING

- Treatment must be reduced or stopped if resting heart rate decreases persistently below 50 b.p.m. or if symptoms of bradycardia occur:
  - Review need for other heart rate-slowing drugs or drugs interfering with ivabradine liver metabolism.
  - Arrange ECG to exclude other than sinus bradycardia rhythm disturbances.
  - Consider screening for secondary causes of bradyarrhythmias (e.g. thyroid dysfunction).
- If a patient develops persistent/continuous AF during therapy with ivabradine, the drug should be stopped.
- Visual phenomena are usually transient and disappear during the first few months of ivabradine treatment and are not associated with serious retinal dysfunction. However, if they result in patient's discomfort, discontinuation of ivabradine should be considered.
- In case of lactose or galactose intolerance (component of the ivabradine tablet), if symptoms occur, there may be a need to stop the drug.

ADVICE TO PATIENT

- Explain expected benefits (see WHY?):
  - Treatment is given to prevent worsening of HF leading to hospital admission and to reduce the risk of CV death.
- In order to detect a potential bradycardia, patients should be encouraged to measure and record his/her pulse on a regular basis.
- Advise patient to report side effects to the physician or HF nurse. Side effects due to symptomatic bradycardia: breathlessness, fatigue, syncope, dizziness; other side effects: luminous visual phenomena.

ACS = acute coronary syndrome; AF = atrial fibrillation; *b.i.d.* = twice daily; b.p.m. = beats per minute; CV = cardiovascular; CYP3A4 = cytochrome P450 3A4; ECG = electrocardiogram; EF = ejection fraction; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HIV = human immunodeficiency virus; NYHA = New York Heart Association; QT = QT interval; SR = sinus rhythm; TIA = transient ischaemic attack.

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

Supplementary Table 9 Interventions aiming to improve quality of life and/or exercise capacity in symptomatic patients with heart failure with reduced ejection fraction

	Intervention	Additional criteria beyond the presence of symptomatic HFrEF (if any)
DRUGS	Sacubitril/valsartan[17,18]	
	Dapagliflozin[19]	
	Diuretics[20]	Fluid overload
	Ferric carboxymaltose i.v.[21–23]	Iron deficiency
	Ivabradine[24–26]	SR >70 b.p.m.
	Trimetazidine[27–29]	
DEVICES AND INVASIVE PROCEDURES	CRT[30,31]	Eligibility for CRT
	Pulmonary vein isolation[32–34]	AF
	Percutaneous correction of severe functional mitral regurgitation[35–38]	Severe functional mitral regurgitation
	Cardiac contractility modulation[39–41]	QRS <130 ms, LVEF 25–45%
	Baroreflex activation therapy[42–44]	
	Phrenic nerve stimulation[45–47]	Central sleep apnoea

Continued

Supplementary Table 9 ***Continued***

	Intervention	Additional criteria beyond the presence of symptomatic HFrEF (if any)
DEVICES AND INVASIVE PROCEDURES (*continued*)	MCS[48,49]	Advanced HF
	Heart transplantation[50–52]	Advanced HF
OTHER INTERVENTIONS	Exercise training[53–56]	
	Multidisciplinary care management programme[57,58]	
	Palliative care[59,60]	Advanced HF

AF = atrial fibrillation; b.p.m. = beats per minute; CRT = cardiac resynchronization therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; i.v. = intravenous; LVEF = left ventricular ejection fraction; MCS = mechanical circulatory support; QRS = Q, R, and S waves on ECG; SR = sinus rhythm.

6 Cardiac rhythm management for heart failure with reduced ejection fraction

No supplementary data for this section.

7 Heart failure with mildly reduced ejection fraction

Supplementary Table 10 **Heart failure with mildly reduced ejection fraction – demographics, aetiological factors, and comorbidities in registries and trials**

Clinical characteristics	GWTG -HF[61] *n* = 5626	OPTIMIZE-HF[62] *n* = 7321	SwedeHF[63] *n* = 9019	ESC -HF-LT[64] *n* = 2212	TIME -CHF[65] *n* = 108	CHART-2[66] *n* = 596
Age, years	81	74	74	64	79	69
Females, %	50	52	39	32	46	28
BMI, kg/m^2	27	–	27	29	–	23
Hypertension, %	78	74	64	60	82	90
Diabetes, %	42	44	27	31	–	–
CAD, %	57	–	53	42	80	80
AF, %	40	33	58	22	40	44
Hyperlipidaemia, %	48	35	–	–	48	80

AF = atrial fibrillation; BMI = body mass index; CAD = coronary artery disease; CHART-2 = Congestive Heart Failure Cardiopoietic Regenerative Therapy (trial); ESC-HF-LT = European Society of Cardiology Heart Failure Long-Term (registry); GWTG-HF = Get With the Guidelines – Heart Failure (registry); *n* = number of patients; OPTIMIZE-HF = Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (registry); SwedeHF = Swedish Heart Failure Registry; TIME-CHF = Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure.

Supplementary Table 11 Data from clinical trials for heart failure with mildly reduced ejection fraction

Clinical characteristics	LVEF	Symptoms	Hospitalization for HF[a]	CV death or HF hospitalization[a]	CV mortality	All-cause mortality	Comment
Diuretics							No relevant trials
ACE-I		(Improved)		**0.38 (0.19–0.75)**[b]			PEP-CHF[c]
Candesartan		(Improved)	**0.72 (0.55–0.95)**[d]	**0.76 (0.61–0.96)**	0.81 (0.60–1.11)	0.79 (0.60–1.04)	CHARM-Preserved[c]
Irbesartan				0.98 (0.85–1.12)			I-PRESERVE[c]
ARNI (Sac/Val)		Improved	NYR	**0.78 (0.64–0.95)**	NYR	NYR	PARAGON-HF[c] (compared to valsartan)
MRA			0.76 (0.46–1.27)	0.72 (0.50–1.05)	0.69 (0.43–1.12)	0.73 (0.49–1.10)	TOPCAT[c]
Beta-blocker (SR)	Improved		0.95 (0.68–1.32)	0.83 (0.60–1.13)	**0.48 (0.24–0.97)**	0.59 (0.34–1.03)	IPD Meta-analysis
Beta-blocker (AF)	Improved		1.15 (0.57–2.32)	1.06 (0.58–1.94)	0.86 (0.36–2.03)	1.30 (0.63–2.67)	IPD Meta-analysis
Digoxin			0.80 (0.63–1.03)	0.96 (0.79–1.17)	1.24 (0.94–1.64)	1.08 (0.85–1.37)	DIG[67]

ACE-I = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CHARM-Preserved = Candesartan Cilexetil in Heart Failure – Assessment of Reduction in Mortality and Morbidity (trial); CI = confidence interval; CV = cardiovascular; DIG = Digitalis Investigation Group; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; IPD = individual patient data; I-PRESERVE = Irbesartan in Patients with Heart Failure and PRESERVEd Ejection Fraction (trial); LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NP = natriuretic peptide; NYR = not yet reported; PARAGON-HF = Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (trial); PEP-CHF = Perindopril in Elderly People with Chronic Heart Failure (trial); Sac/Val = sacubitril/valsartan; SR = sinus rhythm; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (trial).

[a]Time to first event analyses.

[b]Patients with prior history of myocardial infarction—outcome was all-cause mortality or hospitalization for HF.

[c]These trials were overall neutral for their primary outcome; in TOPCAT, for the randomization stratum of patients enrolled on the basis of NP criteria (n = 981), hazard ratio for treatment effect on primary outcomes was 0.65 (95% CI, 0.49–0.87), P = 0.003) (**Supplementary Table 12**).

[d]For recurrent hospitalizations, incidence rate ratio: 0.48 (0.33–0.70).

Notes: (Improved) = improved in patients with LVEF >40% but not specifically shown for HFmrEF.

Significant effects within the subgroup of patients with HFmrEF are shown in bold.

8 Heart failure with preserved ejection fraction

Supplementary Table 12 Phase II and III clinical trials performed in patients with heart failure with preserved ejection fraction

Trial	Intervention	Major inclusion criteria	Mean follow-up	Primary endpoints	Drug effect on symptoms
PEP-CHF[68]	Perindopril vs. placebo	LV wall motion index ≥1.4 (corresponding to LVEF ≥40%), symptomatic HF treated with diuretic, diastolic dysfunction in echocardiography, age ≥70 y	2.1 y	No difference in combined all-cause mortality or CV hospitalization (36% vs. 37%, P = 0.35)	Perindopril – improvement in functional class and 6MWT
I-PRESERVE[69]	Irbesartan vs. placebo	LVEF ≥45%, NYHA III–IV with corroborative evidence, or NYHA II with HF hospitalization in recent 6 months, age ≥60 y	4.1 y	No difference in combined all-cause mortality or HF hospitalization (24% vs. 25%, P = 0.54)	Irbesartan – no improvement in MLHFQ
CHARM-Preserved[70]	Candesartan vs. placebo	LVEF >40%, NYHA II–IV, history of cardiac hospitalization	3.0 y	Trend towards a reduction in combined CV mortality or HF hospitalization by 11% (22% vs. 24%, unadjusted P = 0.12, adjusted P = 0.051)	Candesartan – not reported

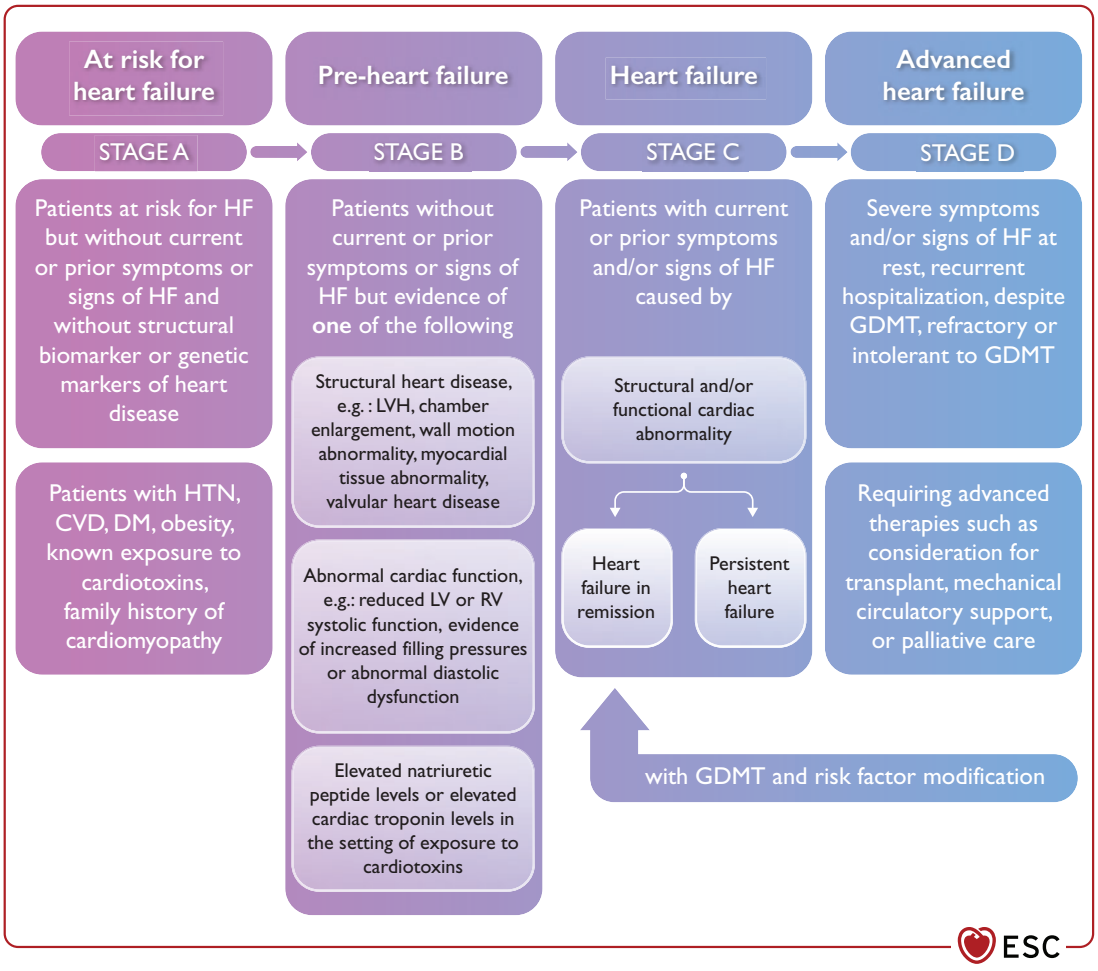
Continued

Supplementary Table 12 ***Continued***

Trial	Intervention	Major inclusion criteria	Mean follow-up	Primary endpoints	Drug effect on symptoms
Aldo-DHF[71]	Spironolactone vs. placebo	LVEF ≥50%, NYHA II–III, peak VO_2 ≤25 mL/min/kg, diastolic dysfunction on echocardiography or AF, age ≥50 y	1.0 y	Reduction in E/e′ by -1.5 (P<0.001) No change in peak VO_2 (P = 0.81)	Spironolactone – no improvement in symptoms or QOL
TOPCAT[72]	Spironolactone vs. placebo	LVEF≥45%, ≥1 HF sign, ≥1 HF symptom, HF hospitalization within recent 12 months, or BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL, age ≥50 y	3.3 y	No difference in combined CV death, aborted cardiac arrest, or HF hospitalization (19% vs. 20%, P = 0.14)	Spironolactone – not reported
DIG-PEF[73]	Digoxin vs. placebo	HF with LVEF >45%, SR	3.1 y	No difference in combined HF mortality or HF hospitalization (21% vs. 24%, P = 0.14)	Digoxin – not reported
PARAMOUNT[74]	Sac/Val vs. valsartan	HF with LVEF ≥45%, NYHA II–III, NT-proBNP >400 pg/mL	12 weeks	Reduction in NT proBNP: ratio of change Sac/Val 0.77, 95% CI, 0.64–0.92 (P = 0.005)	Sac/Val – improvement in QOL-KCCQ
RELAX[75]	Sildenafil vs. placebo	HF with LVEF ≥45%, NYHA II–IV, peak VO_2 <60% of reference values, NT-proBNP >400 pg/mL or high LV filling pressures	24 weeks	No change in peak VO_2 (P = 0.90)	Sildanefil – no improvement
PARAGON-HF[76]	Sac/Val vs. valsartan	HF with LVEF ≥45%, NYHA II–IV, left atrial enlargement OR LVH AND elevated BNP ≥300 pg/mL or NT-proBNP ≥900 pg/mL OR HF hospitalization in the last 9 months	35 months median	Trend towards a reduction in total HF hospitalizations or CV death by 13%, 95% CI, 0.75–1.01, P=0.056)	Sac/Val – no improvement in QOL-KCCQ

6MWT = 6-minute walk test; AF = atrial fibrillation; Aldo-DHF = Aldosterone Receptor Blockade in Diastolic Heart Failure (trial); ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BNP = B-type natriuretic peptide; CHARM-Preserved = Candesartan Cilexetil in Heart Failure – Assessment of Reduction in Mortality and Morbidity (trial); CI = confidence interval; CV = cardiovascular; DIG = Digitalis Investigation Group; DIG-PEF = Ancillary DIG trial (effects of digoxin on morbidity and mortality in diastolic heart failure); E/e′ ratio = early filling velocity on transmitral Doppler/early relaxation velocity on tissue Doppler; HF = heart failure, I-PRESERVE = Irbesartan in Patients with Heart Failure and PRESERVEd Ejection Fraction (trial); KCCQ = Kansas City Cardiomyopathy Questionnaire; LV = left ventricular; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PARAGON-HF = Prospective Comparison of ARNI with ARB Global Outcomes in HF with preserved Ejection Fraction (trial); PARAMOUNT = LCZ696 Compared to Valsartan in Patients with Chronic Heart Failure and Preserved Left-ventricular Ejection Fraction (trial); Peak VO_2 = peak exercise oxygen consumption; PEP-CHF = Perindopril in Elderly People with Chronic Heart Failure (trial); QOL = quality of life; RELAX = Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (trial); Sac/Val = sacubitril/valsartan; SR = sinus rhythm; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist; vs. = versus; y = year.

9 Multidisciplinary team management for the prevention and treatment of chronic heart failure



Supplementary Figure 1 Stages in the development and progression of heart failure.[77]
CVD = cardiovascular disease; DM = diabetes mellitus; GDMT = guideline-directed medical therapy; HF = heart failure; HTN = hypertension; LV = left ventricular; LVH = left ventricular hypertrophy; RV = right ventricular.

10 Advanced heart failure

Supplementary Table 13 Suggested clinical, laboratory, and echocardiographic criteria to trigger referral to a specialized heart failure or advanced heart failure unit

Clinical	Laboratory	Imaging	Risk score data
• >1 HF hospitalization in last year • NYHA class III–IV • Intolerant of optimal dose of any GDMT HF drug • Increasing diuretic requirement • SBP ≤90 mmHg • Inability to perform CPET • 6MWT <300 m • CRT non responder clinically • Cachexia, unintentional weight loss • KCCQ decrease >5 units	• eGFR <45 mL/min • SCr ≥160 µmol/L • K^+ >5.2 or <3.5 mmol/L • Hyponatraemia • Hb ≤120 g/L • Persistently elevated high BNP/NT-proBNP, e.g. NT-proBNP ≥1000 pg/mL • Abnormal liver function test • Low albumin	• LVEF ≤30% • Large area of akinesis/dyskinesis or aneurysm • Moderate[a]-severe mitral regurgitation • RV dysfunction • Systolic PA pressure ≥50 mmHg • Moderate-severe tricuspid regurgitation • Difficult to grade aortic stenosis • IVC dilated or without respiratory variation	• MAGGIC predicted survival ≤80% at 1 year • SHFM predicted survival ≤80% at 1 year • MECKI predicted survival ≤80% at 1 year

6MWT = 6-minute walk test; BNP = B-type natriuretic peptide; CPET = cardiopulmonary exercise test; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; GDMT = guideline-directed medical therapy; Hb = haemoglobin; HF = heart failure; IVC = inferior vena cava; K^+ = potassium; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MAGGIC = Meta-Analysis Global Group in Chronic Heart Failure; MECKI = Metabolic Exercise test data combined with Cardiac and Kidney Indexes; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PA = pulmonary artery; RV = right ventricular; SBP = systolic blood pressure; SCr = serum creatinine; SHFM = Seattle Heart Failure Model.
[a]Moderate mitral regurgitation alone is not sufficient but is one factor suggesting risk of progression and should be considered together with other variables.
Note that this table reflects many clinically relevant but sometimes subjective and non-specific criteria. With these criteria, sensitivity has been prioritized over specificity, i.e. many criteria may be present in patients who do not need referral, but by considering these criteria in a comprehensive assessment, there is a lower risk that high-risk patients may be missed or referred too late. While cut-offs exist for transplantation listing or LVAD implantation, there are no data to support specific cut-offs for referral to a HF centre.

Supplementary Table 14 'I Need Help' markers of advanced heart failure

I	**I**notropes	Previous or ongoing requirement for dobutamine, milrinone, dopamine, or levosimendan
N	**N**YHA class/NP	Persisting NYHA class III or IV and/or persistently high BNP or NT-proBNP
E	**E**nd-Organ Dysfunction	Worsening renal or liver dysfunction in the setting of HF
E	**E**jection Fraction	Very low EF <20%
D	**D**efibrillator shocks	Recurrent appropriate defibrillator shocks
H	**H**ospitalizations	More than 1 hospitalization with HF in the last 12 months
E	**E**dema/Escalating diuretics	Persisting fluid overload and/or increasing diuretic requirement
L	**L**ow blood pressure	Consistently low blood pressure with SBP <90 to 100 mmHg
P	**P**rognostic medication	Inability to uptitrate (or need to decrease/cease) ACE-Is, beta-blockers, ARNIs, or MRAs

ACE-I = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; BNP = B-type natriuretic peptide; EF = ejection fraction; HF = heart failure; MRA = mineralocorticoid receptor antagonist; NP = natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure. Reprinted from[78,79]

Supplementary Table 15 Overview of major devices and clinical studies on long-term mechanical circulatory support

Device	Device characteristics	Evidence from major clinical studies	Major risks
HeartMate II (Thoratec, St. Jude, Abbott)[80–90]	Axial flow pump Implanted in pre-peritoneal pocket, connected via inflow cannula to LV apex, and via outflow cannula to ascending aorta	BTT strategy (prospective, single-arm, *n* = 133): 75% survival 6 months, 68% survival 12 months.[83] HeartMate II LVAD (randomized continuous flow vs. pulsatile): improved 2-year survival free of stroke or device failure for continuous flow vs. pulsatile[87] ROADMAP (observational, *n* = 97 LVAD, *n* = 103 OMM): LVAD associated with better survival and functional capacity at 2 years[80,81]	• Device failure • Pump thrombosis[86,88,89] • Ischaemic stroke • Driveline infection[90] • Bleeding (haemorrhagic stroke) • RV failure
HeartWare (HeartWare, Medtronic)[91–98]	Continuous flow centrifugal pump Implanted and positioned completely within pericardial space, connected via driveline to controller	Single-arm (transplant candidates, NYHA class IV, *n* = 50): 84% 1-year survival[98] Post-CE mark approval registry (*n* = 254): 85% 1-year survival, 73% 3-year survival[97] ADVANCE (HeartWare vs. commercially available LVADs): non-inferior to commercially available devices;[91] continued access protocol 84% 1-year survival[96] ENDURANCE (randomized, open-label, *n* = 446 advanced HF patients ineligible for transplant, HeartWare vs. HeartMate II): non-inferiority of HeartWare vs. other devices for survival at 2 years free from disabling stroke or device removal; higher rate of stroke, RV failure, sepsis[95]	• Ischaemic stroke • Haemorrhagic stroke • RV failure • Infection • Device failure[92,93] • Pump thrombosis • Driveline infection
HeartMate 3 (St. Jude, Abbott)[99-103]	Continuous flow, centrifugal-pump, bearing-less magnetically levitated rotor, artificial pulse	Single arm (*n* = 50, BTT and DT): 98% 30-day survival, 92% 6-month survival; 92% 6-month survival; 1-year survival similar to other devices.[102,103] MOMENTUM 3 (randomized, HeartMate 3 vs. HeartMate II, both BTT and DT, *n* = 294): centrifugal flow pump non-inferior to axial-flow pump at 6 months; superiority also established (hazard ratio 0.55; 95% CI 0.32–0.95; *P* =0.04).[100] MOMENTUM 3, 2-year outcomes (*n* = 366): survival free of disabling stroke or survival free of reoperation to replace/remove device [hazard ratio 0.46; 95% CI 0.31–0.69, *P* <0.001, (superiority)].[99]	• No pump thrombosis in MOMENTUM 3 compared to 10.1% in axial flow group • RV failure • Stroke • Infection • Driveline infection • Gastrointestinal bleeding • RV failure • Stroke • Driveline infection

Continued

Supplementary Table 15 ***Continued***

Device	Device characteristics	Evidence from major clinical studies	Major risks
		HeartMate 3 CE Mark Study, 2-year results (n = 50): survival free of disabling stroke 84.9±5% 1-year and 77.3±6% 2-year; 2-year Kaplan-Meier overall survival 74±6%	

ADVANCE = Evaluation of the HeartWare Left Ventricular Assist Device for the Treatment of Advanced Heart Failure (trial); BTT = bridge to transplant; CE = Conformité Européenne; CI = confidence interval; DT = destination therapy; ENDURANCE = HeartWare Ventricular Assist System as Destination Therapy of Advanced Heart Failure (trial); HF = heart failure; LV = left ventricular; LVAD = left ventricular assist device; MOMENTUM 3 = Multicenter study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3; n = number of patients; NYHA = New York Heart Association; OMM = optimal medical management; ROADMAP = Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients (trial); RV = right ventricular; vs. = versus.

11 Acute heart failure

Supplementary Table 16 **Factors triggering acute heart failure**

ACS.
Tachyarrhythmia (e.g. AF, 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 COPD.
Pulmonary embolism.
Surgery and perioperative complications.
Increased sympathetic drive, stress-related cardiomyopathy.
Metabolic/hormonal derangements (e.g. thyroid dysfunction, diabetic ketosis, adrenal dysfunction).
Severe anaemia.
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 syndrome; AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; NSAID = non-steroidal anti-inflammatory drug.

Supplementary Table 17 Specific findings from investigations in the diagnostic workup for acute heart failure

Investigation	Specific findings	Interpretation	Practical implication
ECG	ST abnormalities	ACS	Coronary angiography/PCI
	Rapid and irregular rate	Rapid AF	Rate/rhythm control
	Low QRS voltage	Suspected tamponade	Echocardiography/Pericardiocentesis
	RV strain	Suspected pulmonary embolism	D-dimer/Echocardiogram/ CT-scan
Chest X-ray	Interstitial or alveolar oedema	Acute HF	Echocardiography
	Pleural effusion	Acute HF	Laboratory test/CT-scan
	Cardiomegaly	Dilated cardiomyopathy	
	Consolidation	Pneumonia, cancer	
Echocardiography[a]	Regional LV systolic dysfunction	ACS	Coronary angiography/PCI
	Global LV systolic dysfunction	Acute HF	D-dimer/echocardiogram/
	LV diastolic dysfunction	Acute HF	CT-scan/coronary angiography
	RV dysfunction	Pulmonary embolism or ACS or RVF	Laboratory test/TOE/emergent surgery
	Acute valve disease	PMR or endocarditis or chordae rupture	Emergent surgery
	Aortic flap	Aortic dissection	Pericardiocentesis/emergent surgery
	Pericardial effusion	Tamponade/wall rupture	MCS as bridge to surgery
	Interventricular defect	IVS rupture (ACS)	
	IVC congestion	Acute HF	
Lung ultrasound	B lines	Acute HF	
	Pleural effusion	Acute HF	

ACS = acute coronary syndrome; AF = atrial fibrillation; AMI = acute myocardial infarction; CT = computed tomography; ECG = electrocardiogram; FoCUS = Focus Cardiac Ultrasound; HF = heart failure; IVC = inferior vena cava; IVS = interventricular septum; LV = left ventricular; PCI = percutaneous coronary intervention; PMR = papillary muscle rupture; QRS = Q, R, and S waves of an ECG; RV = right ventricular; RVF = right ventricular failure; ST = ST segment (on the ECG); TOE = transoesophageal echocardiogram.
[a]Immediate/emergency echocardiography is recommended in patients with haemodynamic instability/cardiogenic shock and in suspected life-threatening structural/functional cardiac disease (i.e. mechanical complications of AMI, acute valve disease, aortic dissection). Where comprehensive echocardiography is not available, FoCUS may be used in the first instance[104] with comprehensive echocardiography being performed later, though as early as possible.

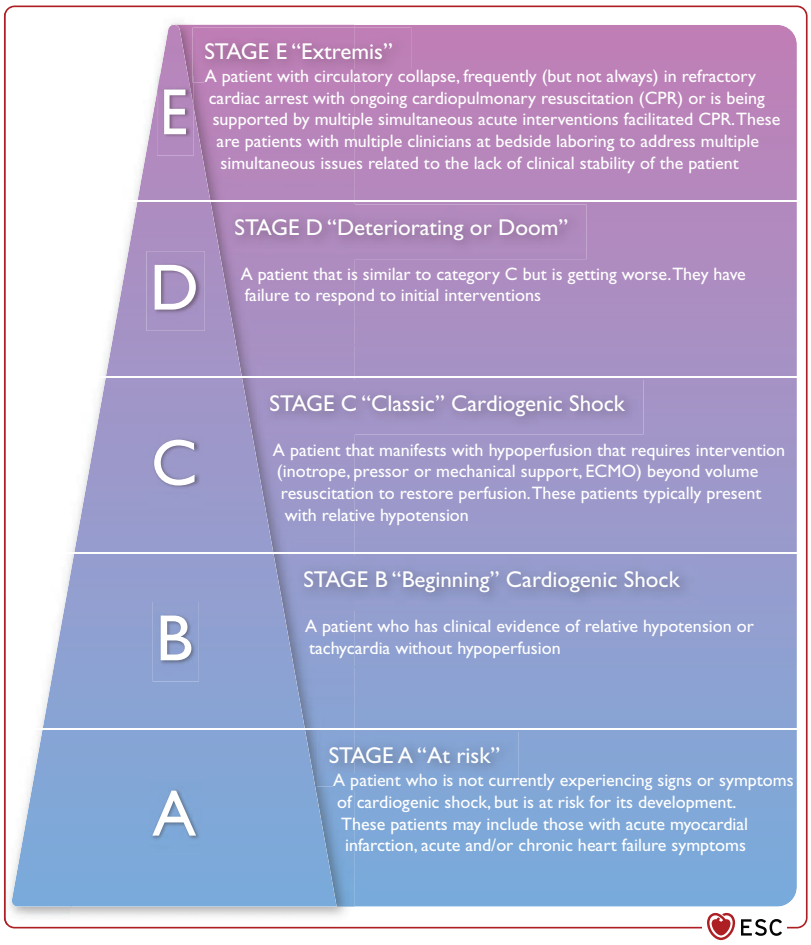
Supplementary text 11.1 Cardiogenic shock

A number of cardiogenic shock phenotypes exist, depending on the acute cardiac insult and a patient's underlying cardiac and overall medical condition.[105–108] A major difference is between cardiogenic shock related to acute coronary syndrome (ACS) and non-ACS-related cardiogenic shock, as the two entities differ significantly in terms of priorities for initial management and outcomes. A number of criteria for diagnosing cardiogenic shock exist, all of which include hypotension [systolic blood pressure (SBP) <90 mmHg despite adequate filling status or already on vasopressors to maintain SBP >90 mmHg]. Of note, hypoperfusion is not always accompanied by hypotension, as blood pressure may be preserved by compensatory vasoconstriction (with/without pressor agents), albeit at the cost of impaired tissue perfusion and oxygenation.[109] All the patients with cardiogenic shock have respiratory failure needing oxygen, and nearly 2/3 of them require invasive mechanical ventilation. A small proportion <20% may be managed with non-invasive ventilation.[110]

Five evolutive stages of cardiogenic shock have been identified (**Supplementary Figure 2**).

Depending on the local service provision, patients with cardiogenic shock may be rapidly transferred to a tertiary care centre (Shock Centre) that has a 24/7 cardiac catheterization availability, a multidisciplinary shock team, and a dedicated intensive care unit (ICU) providing short-term mechanical circulatory support (MCS).[107,111] In patients with cardiogenic shock complicating ACS, an immediate coronary angiography is recommended with the intent to perform coronary revascularization.[105–107,111–113] In the CULPRIT-SHOCK (Culprit Lesion only PCI versus Multivessel PCI in Cardiogenic Shock) trial[114–116] 'culprit lesion only percutaneous coronary intervention (PCI)' strategy with possible staged revascularization has proven superior to immediate 'multivessel PCI'.[117]

After an initial fluid challenge (if appropriate), pharmacological management consists of intravenous (i.v.) vasoactive agents, aiming to improve organ perfusion by increasing cardiac output and blood pressure **(Guidelines, Figure 10)**. Selection of pharmacological agents is largely empirical. Norepinephrine is the pressor of choice, whilst dobutamine is the most commonly used adrenergic inotrope. Levosimendan may also be used (avoiding bolus) in combination with a vasopressor such as norepinephrine.[118,119] General recommendation on inotrope use is to limit the dose and the duration to the lowest possible, due to increasing myocardial oxygen consumption and arrhythmogenic burden.[105–107,111]



Supplementary Figure 2 Stages of cardiogenic shock.
ECMO = extracorporeal membrane oxygenation.

In patients with cardiogenic shock refractory to inotropes/vasopressors, the early use of temporary MCS represents a therapeutic modality that is available as a bridge to recovery (BTR) or as a bridge to decision (BTD) for long-term ventricular assist device, transplantation or withdrawal of therapy **(Guidelines, Figure 10)**. Appropriate patient selection is influenced by the balance between efficacy, institutional experience, and device-related complications. Timing of insertion is important, preferring early use, before occurrence of extensive multiorgan failure, and avoiding futile situations.[106,107,111]

Supplementary text 11.2 Disposition decisions and intensive care unit referral

Acute heart failure (AHF) patients present to a range of medical care settings, including emergency departments, cardiology (and non-cardiology) departments, and different types of ICUs.[120] Patient disposition after complete emergency department management is one of the most important decisions to be made by emergency physicians. This would allow high-risk patients to receive prompt and aggressive in-hospital therapy, whereas low-risk patients could be safely discharged to home without exposure to potential risk associated with hospitalization and avoiding spending significant resources.[121] Consequently, some patients admitted to the emergency department with AHF, mainly those with acutely decompensated HF (see **Guidelines, section 11.2.1**), with mild symptoms and signs of congestion, no renal dysfunction, negative troponin values and very low natriuretic peptide (NP) levels, can be discharged directly home from the emergency department after a small dose of diuretics and some adjustments of oral therapy and advice to be clinically followed as outpatients.[122,123]

In the last decade, several risk scores have been developed for use in emergency departments with the aim of objectively supporting disposition decision-making process.[122,124,125] However, their implementation is not widespread, to date.[126] Two of these risk scores have been prospectively and externally validated for prediction of 30-day mortality, with 0% mortality in low-risk categories and they may be useful for disposition decisions.[127,128] Further research, including implementation testing followed by broad use of the algorithms, may improve care efficiency of those at lower risk and enhance safety by decreasing inappropriate discharge of high-risk patients.[129,130] Also, disposition decisions may not be exclusively guided by the patient risk of adverse events, and many non-medical circumstances, including socio-economic status, adequacy of family support, and feasibility of follow-up in outpatient settings, have to be considered.

With respect to the in-hospital phase, patients hospitalized for AHF may clinically experience life-threatening complications requiring immediate supportive therapies available only in the ICU.[120,131,132] Although there are large variations in definition, medical facilities and staffing, ICU offers a high-technology, life-saving care environment that supports any isolated or combined advanced organ dysfunction.[120,131–133] Intensity or the level of care (in terms of nurses, physician, techniques, environment) is graded from 1 to 3, with level 3 (critical care), offering the highest level of life-saving technology for isolated and/or multiorgan dysfunction (**Supplementary Table 18**).[131]

Immediate triage of AHF patients to the appropriate level of care at presentation potentially results in improvements in the quality of care and in-hospital outcomes.[132] Such decisions require expert judgment, balancing the clinical benefit of intensive care admission against associated risks and costs. Critical care is associated with a high risk of complications, including venous thromboembolism, upper gastrointestinal bleeding, delirium, and hospital-acquired infection with multidrug-resistant pathogens.[131,133] Criteria for critical care admission depend upon local resources and policies. They are reported in **Supplementary Table 19**. Patients who do not fulfil these criteria usually need only level 1 or 2 care.[131] A few patients admitted to the emergency department with AHF [mainly as exacerbation of heart failure (HF) symptoms with subtle signs of congestion, no renal dysfunction, negative troponin values, and very low NP level] after a small dose of diuretics and some adjustments of oral therapy can be discharged directly home from the emergency department with advice to be clinically followed as outpatients.[122,123,128]

Step-down care from the ICU is dictated by clinical stabilization and resolution of morbid conditions.[120,131] Further treatment will be continued with the involvement of a multidisciplinary team and discharge planning.

Supplementary text 11.3 Monitoring of clinical status of patients hospitalized due to acute heart failure

Initial evaluation and monitoring

Initial evaluation and continued monitoring of the patient's vital cardiorespiratory functions, including pulse oximetry, blood pressure, respiratory rate, and a continuous electrocardiogram instituted within minutes, is essential to evaluate whether ventilation, peripheral perfusion, oxygenation, and haemodynamics are acceptable.[105,134] Continuous intra-arterial blood pressure monitoring should be considered in those with persistent hypotension despite interventions. Urine output should be monitored, although routine urinary catheterization is not recommended.[134]

The intensity of any monitoring should depend on the severity of illness and haemodynamic instability. Patients with haemodynamic instability should be triaged to a location where high-end monitoring, including invasive venous and arterial pressure, and cardiac output monitoring (invasive and non-invasive) according to the level of support required/anticipated. Immediate echocardiography is mandatory in patients with haemodynamic instability and in patients suspected of acute life-threatening structural cardiac abnormalities (mechanical complications, acute valvular regurgitation, aortic dissection). Early echocardiography should be considered in all patients with new onset AHF or haemodynamic instability. Pulmonary artery (PA) catheterization may be considered in patients who, despite pharmacological interventions remain refractory (in particular with hypotension and hypoperfusion—features of cardiogenic shock, biventricular dysfunction, and/or where the echocardiographic features are discordant with the clinical picture) as the severity of illness can be underestimated when relying on clinical features alone.[134,135]

Assessment of the acid-base status is recommended in patients with respiratory failure or haemodynamic instability. Venous samples may be acceptable, providing a faster and less invasive approach than arterial ones.[136] An abnormal serum lactate >2 mmol/L is associated with higher mortality in AHF. Further, levels that do not decrease following appropriate treatment are associated with a poor outcome.[137] Lactate levels should therefore be assessed on admission in haemodynamically unstable or hypoxaemic patients with AHF, and repeated at short intervals (initially e.g. every 1–2 h) during the acute phase.[134,137]

Monitoring post-stabilization

After initial stabilization, routine monitoring of pulse, respiratory rate, blood pressure, and diuresis should continue, and in patients requiring oxygen therapy/non-invasive ventilatory support, monitoring of transcutaneous arterial oxygen saturation (SpO_2) is recommended.[134] Repeat echocardiography is not indicated unless there has been a significant change in the clinical status of the patient.[105]

Clinical signs of congestion and hypoperfusion should be monitored daily.[132,134,138–141] Patients should be examined and weighed daily and an accurate fluid balance chart should be maintained. Renal function should preferably be monitored with daily measurement of blood urea nitrogen/urea, creatinine and electrolytes,[105,134,138–140] as renal function is commonly impaired at admission, but may improve or deteriorate with diuresis. Growing evidence suggests that worsening renal function (WRF) that is due to decongestion is both reversible and not associated with harm.[142,143] Haemoconcentration may be used as a sign of negative fluid balance and response to diuretic treatment.[144]

Around 25–30% of patients with AHF are discharged with persistent signs/symptoms of congestion and/or minimal or no weight loss[145,146] as demonstrated by elevated NP levels, provoked orthopnoea, paradoxical changes of SBP in orthostasis or at Valsalva manoeuvre, and a poor 6-min walk test.[147–149] This group of patients has readmission and mortality rates higher than in those adequately decongested.[150] Residual haemodynamic congestion at the time of hospital discharge may therefore contribute to high HF readmission rates, stressing the overall importance of properly assessing and addressing filling pressures,[147,150] and treating congestion beyond signs and symptoms should be an essential target. This includes monitoring changes in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, haemoconcentration and renal function.[138–141] A reduction in NT-proBNP levels by at least 30% from admission is associated with an improvement in post-discharge outcomes whereas those with persistently elevated NT-proBNP prior to discharge have significantly higher risk for death and readmission.[138–141,151,152] Haemoconcentration is associated with reduced post-discharge mortality and rehospitalization rate in several studies, can be used to help determine the appropriate duration and

Supplementary Table 18 Intensity of care admission in patients with acute heart failure

Level 1 care
• Cardiac rhythm monitoring. • Non-invasive haemodynamic and respiratory (SpO_2) monitoring. • Specific treatments (initial administration of vasoactive drugs, non-invasive bi-level positive air-way pressure or continuous positive airway pressure, chest tube insertion and monitoring).
Level 2 care
• Central venous access. • Arterial line. • Continuous infusion of multiple drugs (because of low CV output or compromised organ perfusion). • Invasive haemodynamic monitoring. • Temporary trans-venous pacing. • Percutaneous cardiac assist device (IABP, percutaneous axial pumps). • Pericardiocentesis.
Level 3 care (critical care)
• Invasive mechanical ventilation. • Renal replacement therapy. • Short-term MCS.

CV = cardiovascular; IABP = intra-aortic balloon pump; MCS = mechanical circulatory support; SpO_2 = oxygen saturation.

Supplementary Table 19 Criteria for critical care admission

• Need for intubation (or already intubated). • Poor response to high FiO_2 or to NIV. • Signs/symptoms/markers of hypoperfusion: cold extremities, altered mentation, confusion, oliguria, lactate >2 mmol/L. • Persistent hypotension (SBP <90 mmHg). • Requirement for two or more vasoactive agents to maintain blood pressure. • Requirement for invasive cardiac output monitoring. • Requirement for MCS. • Heart rate <40 b.p.m. or persistent life-threatening arrhythmia. • Any associated non-cardiac condition requiring critical care admission (e.g. continuous venovenous hemodiafiltration and ultrafiltration).

b.p.m. = beats per minute; FiO_2 = fraction of inspired oxygen; MCS = mechanical circulatory support; NIV = non-invasive ventilation; SBP = systolic blood pressure.

Supplementary Table 20 Criteria for intubation

Cardiac or respiratory arrest
Progressive worsening of altered mental status
Progressive worsening of respiratory failure with hypoxaemia [PaO_2 <60 mmHg (8.0 kPa)], hypercapnia [$PaCO_2$ >50 mmHg (6.65 kPa)] and acidosis (pH <7.35), despite NIV
Need of airway protection
Persistent haemodynamic instability
Agitation or intolerance to NIV with progressive respiratory failure

NIV = non-invasive ventilation; $PaCO_2$ = partial pressure of carbon dioxide; PaO_2 = partial pressure of oxygen. From [154]

Supplementary Table 21 Intravenous vasodilators for acute heart failure

Vasodilator	Dosing	Main side effects	Other
Nitroglycerine	Start with 10–20 μg/min, increase up to 200 μg/min	Hypotension, headache	Tolerance in continuous use
Isosorbide dinitrate	Start with 1 mg/h, increase up to 10 mg/h	Hypotension, headache	Tolerance in continuous use
Nitroprusside	Start with 0.3 μg/kg/min and increase up to 5 μg/kg/min	Hypotension, isocyanate toxicity	Light sensitivity

intensity of decongestion therapy.[144,153] Despite WRF, patients with laboratory evidence of haemoconcentration have greater total weight loss, larger total volume of diuresis, and greater reduction in right atrial pressure and pulmonary capillary wedge pressure.[142] All these features should be considered when monitoring appropriateness for discharge.

Supplementary text 11.4 Short-term mechanical circulatory support (see also Supplementary Table 15)

Intra-aortic balloon pump (IABP) consists of a percutaneously implanted catheter with a balloon inflated with gas that is positioned in the descending aorta. The balloon is inflated in diastole and deflated during systole, facilitating coronary flow, improving oxygen supply to the myocardium, reducing afterload and oxygen consumption. The Intra-aortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK-II) trial showed no difference in 30-day, as well as in 12-month mortality between IABP and optimal medical therapy in patients with cardiogenic shock following acute myocardial infarction (AMI) who underwent early revascularization.[155] According to these results, IABP is not routinely recommended in cardiogenic shock post-myocardial infarction. However, it may still be considered in cardiogenic shock refractory to drug therapy as a BTD, BTR, bridge to bridge.[105]

Extracorporeal membrane oxygenation (ECMO) is a simplified cardiopulmonary bypass machine driven by centrifugal blood pump, which can be used in either veno-arterial (VA) or veno-venous configuration. Although VA-ECMO provides full circulatory support, it does not decompress the left ventricle. Depending on the severity of myocardial dysfunction and/or concomitant mitral or aortic regurgitation, VA-ECMO may increase left ventricular (LV) afterload with an increase in LV end-diastolic pressure and pulmonary congestion. In these cases, LV unloading is mandatory and can be achieved by means of transeptal/ventricular apex vent or adding an unloading device such as the Impella device.[156,157] Complications of percutaneous ECMO are mostly related to vascular events, bleeding, thrombosis, and infection. Randomized controlled trials comparing ECMO with IABP or medical therapy are lacking. A meta-analysis including only observational studies showed favourable outcomes in patients with cardiogenic shock or cardiac arrest treated with VA-ECMO compared to control.[158] VA-ECMO may also be considered in fulminant myocarditis with severe haemodynamic impairment[159,160] or massive pulmonary embolism and arrhythmic storm.[161,162]

Impella Ventricular Support System (Abiomed Inc., Danvers, MA, USA) is a miniaturized percutaneous micro-axial flow pump placed across the aortic valve, aspirating blood from the left ventricle and ejecting it into the ascending aorta in left assist configuration or, less often, into the PA in right assist configuration. The trans-aortic Impella unloads the left ventricle and improves haemodynamic parameters. The device is available in different sizes able to produce a cardiac output ranging from 2.5 to 5.0 L/min (2.5, CP, and 5.0 devices). CP and 5.0 devices seem more effective compared with the smaller one.[163] Major complications of Impella include vascular injury, bleeding, thrombosis, haemolysis, and device migration. Two small randomized trials and propensity-matched analyses on two large observational studies have been made to compare Impella and IABP or medical therapy with divergent results.[164–168]

TandemHeart percutaneous assist device (Cardiac Assist, Inc., Pittsburgh, PA, USA) consists of an inflow cannula, inserted via the femoral vein to the right atrium and then trans-septal into the left atrium, a centrifugal continuous extracorporeal blood pump, and an outflow arterial cannula inserted in the ilio-femoral artery. A membrane oxygenator can be added to provide respiratory support. The need for trans-septal puncture and positioning of the inflow cannula into the left atrium demands proficiency and carries a risk of complications such as atrial perforation and cannula migration or suboptimal position. TandemHeart improves haemodynamic parameters. There are no adequately powered randomized trials comparing TandemHeart with IABP or medical treatment.[169,170]

12 Cardiovascular comorbidities

Supplementary text 12.1 Antiarrhythmic drugs in patients with ventricular arrhythmias

A number of studies have shown the efficacy of d,l-sotalol for suppressing premature ventricular contractions in patients with structural heart disease.[172,173] The Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) trial randomized beta-blockers, d,l-sotalol (240 mg/day) and amiodarone plus beta-blockers in implantable cardioverter-defibrillator (ICD) patients with

Supplementary Table 22 Characteristics of short-term mechanical circulatory support. Percutaneous mechanical circulatory support can be characterized by one of four circuit configurations: 1. intra-aortic devices; 2. transvalvular aortic (Impella); 3. left atrium to systemic artery (TandemHeart); 4. right atrium to systemic artery (veno-arterial extracorporeal membrane oxygenation)

	IABP	Impella (2.5, CP, 5.0[a])	TandemHeart	VA-ECMO
Insertion	Femoral or axillary artery to AO	LV to AO	Venous cannula: femoral vein to LA Arterial cannula: iliac artery	Venous cannula: RA Arterial cannula: iliac artery
Mechanism	Diastolic augmentation of aortic pressure and improved LV performance via systolic balloon deflation (decrease in afterload)	Expels blood from LV to AO	Aspirates oxygenated blood from LA and returns to iliac artery	Drainage of deoxygenated venous blood, via an extracorporeal centrifugal pump over a membrane oxygenator and pumped back oxygenated blood to iliac artery
LV unloading	(+)	++	++	LV overloading in peripheral cannulation Only RV unloading
Technical characteristics	– Cannula size 7–8 F – Cardiac output: 0.3–0.5 L/min – Pulsatile flow	– Cannula size 12–14 F for CP and 21 F for Impella 5.0 – Cardiac output: 2.5–5.0 L/min – Continuous flow via axial pump with a maximum speed of 51000 r.p.m.	– Cannula size 21 F venous and 12–19 F arterial – Cardiac output: 4 L/min – Continuous flow via centrifugal pump; maximum pump speed 7500 r.p.m.	– Cannula size 19–25 F venous and 15–19 F arterial – Cardiac output: up to 7 L/min – Continuous flow via centrifugal pump with a maximum speed of 5000 r.p.m.
Duration	Days to weeks	10 days for Impella 2.5 and CP and 3 weeks for Impella 5.0	2–3 weeks	3–4 weeks and occasionally longer
Advantages	Easy insertion, easy to adjust, cath lab not mandatory, no extracorporeal blood; increase coronary and cerebral flow	ECG and pulse independent relatively easy insertion in cath lab, no extracorporeal blood	Rhythm independent, less artificial surface than ECMO Can be used in patients with aortic stenosis/prosthetic aortic valve; can be used even in LV thrombus	Rhythm independent, no cath lab requirement, rapid insertion, full circulatory support even in resuscitation situations or during malignant arrhythmia, providing combined support of the right and left ventricle, rapid improvement in oxygenation and the possibility of rapid application, complete cardiopulmonary bypass
Disadvantages/complications	– ECG/pulse dependent (mostly inefficient in tachycardia and irregular rhythms) – Limb ischaemia – Haemolysis – Thrombocytopenia	– Limb ischaemia – Haemolysis – Bleeding – Infection	– Limb ischaemia – Bleeding – Complex implantation requiring transseptal puncture – Infection	– Haemolysis, thromboembolic complications (large artificial surface), renal failure, limb ischaemia/amputation, infection and bleeding

Continued

Supplementary Table 22 ***Continued***

	IABP	Impella (2.5, CP, 5.0[a])	TandemHeart	VA-ECMO
	– Bleeding – Infection			– LV overloading - peripheral cannulation is associated with an increase in LV afterload, which produces LV distension and pulmonary congestion and may impair myocardial recovery. LV decompression strategies include additional procedures, such as septostomy, IABP, Impella, and hybrid circuit configuration – Harlequin syndrome (upper body hypoxia from incomplete retrograde filling and oxygenation), in which deoxygenated cerebral blood flow occurs during retrograde perfusion with peripheral cannulation. The veno-arterio-venous configuration with triple cannulation avoids upper body hypoxia
Contraindications	– Moderate to severe aortic regurgitation – Severe aortic disease	– Severe aortic stenosis – Prosthetic aortic valve – LV thrombus – VSD – Peripheral vascular disease	– Severe aortic insufficiency – Aortic dissection – Peripheral vascular disease – RV failure – VSD – Inability to tolerate systemic anticoagulation	– Severe aortic insufficiency – Aortic dissection – Inability to tolerate systemic anticoagulation

AO = aorta; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; IABP = intra-aortic balloon pump; LA = left atrial; LV = left ventricular; RA = right atrial; r.p.m. = revolutions per minute; RV = right ventricular; VA = veno-arterial; VSD = ventricular septal defect.
Percutaneous mechanical circulatory supports can be characterized by one of four circuit configurations: 1. intra-aortic devices, 2. transvalvular aortic (Impella) 3. left atrium to systemic artery (TandemHeart); 4. right atrium to systemic artery (veno-arterial extracorporeal membrane oxygenation).
[a]For Impella 5.0 surgical cut-down for cannulation is mandatory.
From [171]

spontaneous or induced ventricular tachycardia/fibrillation and left ventricular ejection fraction (LVEF) <40%, and found a trend in reduced incidence of shocks with sotalol (with a significant reduction by amiodarone).[174] However, sotalol is associated with corrected QT interval (QT) prolongation and torsades de pointes, a risk that must be balanced with its efficacy. Beneficial effects of d,l sotalol are likely mediated only by its beta-blocking activity. D-sotalol, a pure potassium (K^+)-channel blocker with no beta-blocking activity, increased mortality in patients with a recent myocardial infarction and LV dysfunction.[175]

Mexiletine is a class Ib anti-arrhythmic drug that was used in combination with amiodarone in the Ventricular Tachycardia Ablation or Escalated aNtiarrhythmic Drugs in Ischemic Heart Disease (VANISH) trial in ICD patients with ischaemic heart disease, but was not found effective for preventing recurrence of ventricular arrhythmias.[176]

13 Non-cardiovascular comorbidities

Supplementary Table 23 Comparison of the effects of interventions on outcome in patients with heart failure with or without chronic kidney disease

Trial	Intervention (sample size)	Main eligibility criteria	Follow -up (y)	Primary outcome	Overall treatment effect (95% CI)	CKD subgroups (eGFR, mL/min/ 1.73 m^2)	Treatment effect in CKD	*P*-value for treatment* CKD interaction
ACE-I								
SOLVD-Treatment[177]	Enalapril vs. placebo (*n* = 2569)	LVEF ≤ 35%; NYHA I–IV; creatinine <177 µmol/L	3.5	All-cause mortality	0.84 (0.74–0.95)	≥60 (*n* = 1466) <60 (*n* = 1036)	0.82 (0.69–0.98) 0.88 (0.73–1.06)	0.62
Beta-blockers								
CIBIS-II[178]	Bisoprolol vs. placebo (*n* = 2647)	LVEF ≤ 35%; NYHA III–IV; creatinine <300 µmol/L	1.3	All-cause mortality	0.66 (0.54–0.81)	<45 (*n* = 450) ≥45–<60 (*n* = 669) ≥60–<75 (*n* = 640) >75 (*n* = 863)	0.71 (0.48–1.05) 0.69 (0.46–1.04) 0.53 (0.34–0.82) 0.64 (0.42–0.99)	0.81
MERIT-HF[179,180]	Metoprolol vs. placebo (*n* = 3991)	LVEF ≤ 40%; NYHA II–IV; 'significant' kidney disease	1	All-cause mortality	0.66 (0.53–0.81)	<45 (*n* = 493) ≥45–≤60 (*n* = 976) >60 (*n* = 2496)	0.41 (0.25–0.68) 0.68 (0.45–1.02) 0.71 (0.54–0.95)	0.095
SENIORS[5,181]	Nebivolol vs. placebo (*n* = 2128)	LVEF <35% or hospitalization for decompensated HF; NYHA II–IV; creatinine <250 µmol/L	1.75	All-cause mortality or CV hospital admission	0.86 (0.74–0.99)	<55.5 (*n* = 704) 55.5–72.8 (*n* = 704) >72.8 (*n* = 704)	0.84 (0.67–1.07) 0.79 (0.60–1.04) 0.86 (0.65–1.14)	0.442
MRAs								
RALES[182]	Spironolactone vs. placebo (*n* = 1663)	LVEF <35%; NYHA III–IV; creatinine ≤ 221 µmol/L;	2	All-cause mortality	0.70 (0.60–0.82)	<60 (*n* = 792) ≥60 (*n* = 866)	0.68 (0.56–0.84) 0.71 (0.57–0.90)	N/A
TOPCAT[183]	Spironolactone vs. placebo (*n* = 3445)	LVEF ≥45%; HF hospitalization or elevated NP level; eGFR ≥30 mL/min/ 1.73 m^2 or creatinine ≤ 221 µmol/L	3.3	CV death or aborted cardiac arrest or hospitalization for HF	0.89 (0.77–1.04)	<45 (*n* = 411) 45–60 (*n* = 533) ≥60 (*n* = 823)	0.89 (0.66–1.21) 0.99 (0.73–1.36) 0.66 (0.50–0.88)	N/A
EMPHASIS-HF[7]	Eplerenone vs. placebo (*n* = 2737)	LVEF ≤ 35%; NYHA II; eGFR ≥30 mL/min/ 1.73 m^2	1.75	CV death or hospitalization for HF	0.63 (0.54–0.74)	<60 (*n* = 912) ≥60 (*n* = 1821)	N/A N/A	0.50
ARNI								
PARADIGM -HF[8]	Sac/Val vs. enalapril (*n* = 8442)	LVEF ≤ 40%; NYHA II–IV; eGFR ≥30 mL/min/1.73 m^2	2.25	CV death or hospitalization for HF	0.80 (0.73–0.87)	<60 (*n* = 3061) ≥60 (*n* = 5338)	N/A N/A	0.91
PARAGON -HF[76]	Sac/Val vs. enalapril (*n* = 4822)	LVEF ≥45%; NYHA II–IV; eGFR ≥30 mL/min/1.73 m^2	2.92	Total (first and recurrent) hospitalizations for HF or CV death	0.87 (0.75–1.01)	<60 (*n* = 2341) ≥60 (*n* = 2454)	0.79 (0.66–0.95) 1.01 (0.80–1.27)	NS
SGLT2 inhibitors								
DAPA-HF[14]	Dapagliflozin 10 mg o.d. vs. placebo	LVEF ≤ 40%; NYHA II–IV; eGFR ≥30 mL/min/1.73 m^2	1.5	Worsening HF or CV death	0.74 (0.65–0.85)	<60 (*n* = 1926) ≥60 (*n* = 2816)	0.72 (0.59–0.86) 0.76 (0.63–0.92)	NS
EMPEROR-Reduced[15,184]	Empagliflozin vs. placebo (*n* = 3730)	LVEF ≤ 40%; NYHA II–IV; eGFR ≥20 mL/min/1.73 m^2	1.3	HF hospitalization or CV death	0.75 (0.65– 0.86)	<60 (*n* = 1978) ≥60 (*n* = 1746)	0.78 (0.65–0.93) 0.72 (0.58–0.90)	0.63
Guanylate cyclase activators								
VICTORIA[13]	Vericiguat vs. placebo (*n* = 5050)	LVEF ≤ 45%; NYHA II–IV; recent hospitalization; eGFR ≥15 mL/min/1.73 m^2 (no more than 15% of subjects with an eGFR in the 15 L/min/1.73 m^2 to 30 mL/min/1.73 m^2 range)	0.9	First HF hospitalization or CV death	0.90 (0.82– 0.98)	≤30 (*n* = 506) >30–≤60 (*n* = 2118) >60 (*n* = 2335)	1.06 (0.83–1.34) 0.84 (0.73–0.96) 0.92 (0.80–1.07)	NS
Myosin activators								
GALACTIC-HF[16]	Omecamtiv vs. placebo (*n* = 8232)	LVEF ≤ 35%; NYHA II–IV; eGFR ≥20 mL/min/1.73 m^2	1.8	First HF event or CV death	0.92 (0.86– 0.99)	≤60 (*n* = 4321) >60 (*n* = 3911)	0.98 (0.89–1.07) 0.84 (0.75–0.94)	NS
ICD								
MADIT II[185]	Prophylactic ICD vs. conventional medical therapy (*n* = 1232)	LVEF ≤ 30%; NYHA III; eGFR ≥15 mL/min/ 1.73 m^2	2.67	All-cause mortality	0.69 (0.51–0.93)	<35 (*n* = 80) <35 (*n* = 80) 35–59 (*n* = 387)	1.09 (0.49–2.43) 1.09 (0.49–2.43) 0.74 (0.48–1.15)	0.29
CRT								
CARE-HF[186]	CRT vs. conventional medical therapy (*n* = 813)	LVEF ≤ 35%; NYHA III–IV	1.5	Death from any cause or unplanned hospitalization for a major CV event	0.63 (0.51–0.77)	<60 (*n* = 369) <60 (*n* = 369)	0.67 (0.50–0.89) 0.67 (0.50–0.89)	N/A

ACE-I = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; CARE-HF = CArdiac REsynchronization in Heart Failure (trial); CI = confidence interval; CIBIS-II = Cardiac Insufficiency Bisoprolol Study II; CKD = chronic kidney disease; CR = controlled release; CRT = cardiac resynchronization therapy; CV = cardiovascular; DAPA-HF = Dapagliflozin And Prevention of Adverse outcomes in Heart Failure (trial); eGFR = estimated glomerular filtration rate; EMPEROR-Reduced = Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction; EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (trial); GALACTIC-HF = Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure (trial); HF = heart failure; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MADIT II = Multicenter Autonomic Defibrillator Implantation Trial II; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; min = minute; MRA = mineralocorticoid receptor antagonist; N/A = not available; NP = natriuretic peptide; NYHA = New York Heart Association, o.d. = omne in die (once daily); PARADIGM-HF = Prospective Comparison of ARNI with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure (trial); PARAGON-HF = Prospective Comparison of ARNI with ARB Global Outcomes in HF with preserved Ejection Fraction (trial); RALES = Randomized Aldactone Evaluation Study; Sac/Val = sacubitril/valsartan; SENIORS = Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisations in Seniors with Heart Failure (trial); SGLT2 = sodium-glucose co-transporter 2; SOLVD-Treatment = Studies of Left Ventricular Dysfunction Treatment (trial); TOPCAT = Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (trial); VICTORIA = Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction; vs. = versus; XL = extended release; y = year.

Supplementary Table 24 Management of chronic hyperkalaemia

- In patients with chronic or recurrent hyperkalaemia on RAAS inhibitors therapy an approved K^+-lowering agent may be initiated as soon as K^+ levels are confirmed as >5.0 mEq/L. Closely monitor K^+ levels. Maintain treatment unless alternative treatable aetiology is identified.
- In patients with chronic or recurrent hyperkalaemia not on maximal tolerated guideline-recommended target dose of RAAS inhibitors, an approved K^+-lowering agent may be initiated as soon as confirmed K^+ levels are >5.0 mEq/L. Closely monitor K^+ levels. Maintain treatment unless alternative treatable aetiology is identified. RAAS inhibitors should be optimized when K^+ levels are <5.0 mEq/L.
- In patients with K^+ levels of 4.5−5.0 mEq/L not on maximal tolerated, guideline-recommended target dose of RAAS inhibitor therapy, RAAS inhibitor therapy can be initiated/uptitrated with a close monitoring of K^+ levels. If K^+ levels rise above 5.0 mEq/L, initiate an approved K^+-lowering agent.
- In patients with K^+ levels of >5.0−≤6.5 mEq/L not on maximal tolerated, guideline-recommended target dose of RAAS inhibitor therapy, an approved K^+-lowering agent should be initiated. If levels <5.0 mEq/L are detected, uptitrate RAAS inhibitor; K^+ level should be closely monitored and K^+-lowering treatment should be maintained unless another aetiology for hyperkalaemia is identified.
- In patients with K^+ levels of >5.0−≤6.5 mEq/L on maximal tolerated, guideline-recommended target dose of RAAS inhibitor therapy, treatment with a K^+-lowering agent may be initiated. K^+ level should be closely monitored and K^+-lowering treatment should be maintained unless alternative treatable aetiology for hyperkalaemia is identified.
- In patients with K^+ levels of >6.5 mEq/L on either maximal or sub-maximal tolerated, guideline-recommended target dose of RAAS inhibitor therapy, it is recommended to discontinue/reduce RAAS inhibitor. Treatment with a K^+-lowering agent may be initiated as soon as K^+ levels >5.0 mEq/L. K^+ level should be closely monitored.

K^+ = potassium; mEq = milliequivalent; RAAS = renin-angiotensin-aldosterone system.

Supplementary text 13.1 Electrolyte disorders: hypokalaemia, hyperkalaemia, hyponatraemia, hypochloraemia

Administration of the K^+ lowering agents, patiromer or sodium zirconium cyclosilicate, may allow renin-angiotensin-aldosterone system (RAAS) inhibitor initiation or uptitration in a larger proportion of patients. This hypothesis was first tested in 105 patients with HF and chronic kidney disease (CKD) or a history of hyperkalaemia resulting in discontinuation of RAAS inhibitor, in whom patiromer, compared with placebo, lowered serum K^+ levels with fewer patients developing hyperkalaemia and more patients tolerating a dose increase of spironolactone to 50 mg/day.[187] AMETHYST-DN confirmed the efficacy of patiromer as a K^+ lowering agent in patients with diabetes, CKD, mild HF and hyperkalaemia on RAAS inhibitor.[188] AMBER trial enrolled patients with resistant hypertension and CKD, including a pre-specified subgroup of patients with HF, who were randomized, double-blind, to patiromer or placebo plus open-label spironolactone. Patients assigned to patiromer were more likely to remain on spironolactone and received higher cumulative doses of this drug.[189,190] DIAMOND is testing the impact on clinical outcomes of a strategy based on patiromer administration, compared with placebo, in patients with heart failure with reduced ejection fraction (HFrEF) who are hyperkalaemic while on RAAS inhibitor or with a history of hyperkalaemia with subsequent reduction or discontinuation of a RAAS inhibitor.[191,192]

The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial showed significant decrease in dyspnoea and body weight at day 1 and oedema at day 7 with tolvaptan vs. placebo, though with no difference in the primary endpoints of all-cause mortality or cardiovascular death or HF hospitalization. In patients with hyponatraemia, serum sodium levels increased significantly.[193] Similar results were found in other studies.[194,195] A randomized placebo controlled trial in patients hospitalized for HF with estimated glomerular filtration rate <60 mL/min/1.73 m^2 and hyponatraemia or diuretic resistance showed a greater weight loss and decreased loop diuretic dose but no difference in other endpoints with tolvaptan vs. placebo.[196]

14 Special conditions

Supplementary Table 25 Echocardiographic and cardiac magnetic resonance for the diagnosis of amyloidosis

Echocardiography

Unexplained LV thickness (≥12 mm) plus 1 or 2:

1. Characteristic echocardiography findings (≥2 of a, b, and c have to be present)
   a. Grade 2 or worse diastolic dysfunction
   b. Reduced tissue Doppler s', e', and a' waves velocities (<5 cm/s)
   c. Decreased global longitudinal LV strain (absolute value <−15%).
2. Multiparametric echocardiographic score ≥8 points.
   a. Relative LV wall thickness (IVS+PWT)/LVEDD >0.6 (3 points)
   b. Doppler E wave/e' wave velocities >11 (1 point)
   c. TAPSE ≤19 mm (2 points)
   d. Global longitudinal LV strain ≤−13% (1 point)
   e. Systolic longitudinal strain apex to base ratio >2.9 (3 points)

Cardiac magnetic resonance

Characteristic findings (a and b have to be present):

a. Diffuse subendocardial or transmural LGE
b. Abnormal gadolinium kinetics*
c. ECV ≥0.40% (strongly supportive, but not essential/diagnostic)

ECG = electrocardiogram; ECV = extracellular volume; IVS = interventricular septum; LGE = late gadolinium enhancement; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; PWT = posterior wall thickness; s = second; TAPSE = tricuspid annular plane systolic excursion. From [197,198]

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