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ESC GUIDELINES

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

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Patient Forum

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For the Supplementary Data which include background information and detailed discussion of the data that have provided the basis for the guidelines see *European Heart Journal* online

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Abbreviations and acronyms

6MWT	6-minute walk test
^{99m}Tc-PYP	Technetium-labelled pyrophosphate
AATAC	Ablation vs. Amiodarone for Treatment of Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted ICD/CRTD (trial)
AC	Arrhythmogenic cardiomyopathy
ACE	Angiotensin-converting enzyme
ACE-I	Angiotensin-converting enzyme inhibitor
ACHD	Adult congenital heart disease
ACS	Acute coronary syndrome
ADHF	Acutely decompensated heart failure
AF	Atrial fibrillation
AF-CHF	Atrial fibrillation – Congestive Heart Failure (trial)

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AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management (trial)
AFFIRM-AHF	A Randomized, Double-blind Placebo-controlled Trial Comparing the Effect of Intravenous Ferric Carboxymaltose on Hospitalizations and Mortality in Iron-deficient Subjects Admitted for Acute Heart Failure (trial)
AHF	Acute heart failure
AL	Light chain immunoglobulin
AL-CA	Light chain immunoglobulin cardiac amyloidosis
AMICA	Atrial Fibrillation Management in Congestive Heart Failure With Ablation (trial)
ANCA	Antineutrophil cytoplasmic antibody
ARB	Angiotensin-receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
ARVC	Arrhythmogenic right ventricular cardiomyopathy
ATTR	Transthyretin amyloidosis
AV	Atrio-ventricular
b.i.d.	Bis in die (twice daily)
BAG3	Bcl2-associated athanogene 3
BiVAD	Biventricular assist device
BMI	Body mass index
BNP	B-type natriuretic peptide
BP	Blood pressure
b.p.m.	Beats per minute
BTB	Bridge to bridge
BTC	Bridge to candidacy
BTD	Bridge to decision
BTR	Bridge to recovery
BTT	Bridge to transplantation
CA	Cardiac amyloidosis (or amyloid cardiomyopathy)
CABANA	Catheter ABlation vs. ANti-arrhythmic drug therapy for Atrial fibrillation (trial)
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CANVAS-R	CANagliflozin cardioVascular Assessment Study - Renal
CARE-HF	CArdiac REsynchronization in Heart Failure
CASTLE-AF	Catheter Ablation versus Standard conventional Treatment in patients with LEft ventricular and Atrial Fibrillation (trial)
CCB	Calcium channel blocker
CCS	Chronic coronary syndrome
CHA_2DS_2-VASc	Congestive heart failure or left ventricular dysfunction, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74, Sex category (female) (score)
CHAMPIT	Acute Coronary syndrome/Hypertension emergency/Arrhythmia/acute Mechanical cause/Pulmonary embolism/Infections/Tamponade
CHARM	Candesartan in Heart Failure - Assessment of moRtality and Morbidity (trial)
CHF	Chronic heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CMP	Cardiomyopathy
CMR	Cardiac magnetic resonance
CMV	Cytomegalovirus
COAPT	Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for HF patients with functional mitral regurgitation (trial)
COC	Cardio-Oncology Council (part of the European Society of Cardiology)
COMMANDER-HF	A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction or Stroke in Participants With Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure (trial)
COMPASS	Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease (trial)
COPD	Chronic obstructive pulmonary disease
CORONA	COntrolled ROsuvastatin multiNAtional (trial)
COVID-19	Coronavirus disease 2019
CR	Controlled release
CREDENCE	Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (trial)
CRT	Cardiac resynchronization therapy
CRT-D	Cardiac resynchronization therapy with defibrillator
CRT-P	Cardiac resynchronization therapy pacemaker
CSA	Central sleep apnoea
CT	Computed tomography
CTCA	Computed tomography coronary angiography
CV	Cardiovascular
DAPA-HF	Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (trial)
DCM	Dilated cardiomyopathy
DECLARE-TIMI 58	Dapagliflozin Effect on CardiovascuLAR Events (Thrombolysis in Myocardial Infarction) (trial)
DIAMOND	Patiromer for the Management of Hyperkalemia in Subjects Receiving RAASi Medications for the Treatment of Heart Failure (trial)
DIG	Digitalis Investigation Group (trial)
DNA	Deoxyribonucleic acid
DOAC	Direct-acting oral anticoagulant
DPD	3,3-diphosphono-1,2-propanodicarboxylic acid

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DPP-4	Dipeptidyl peptidase-4
DSC2	Desmocollin 2
DSG2	Desmoglein 2
DSP	Desmoplakin
DT	Destination therapy
E/e′ (ratio)	E/e′ (ratio) = early filling velocity on transmitral Doppler/early relaxation velocity on tissue Doppler
EACVI	European Association of Cardiovascular Imaging (part of the European Society of Cardiology)
EAST-AFNET 4	Early Treatment of Atrial Fibrillation for Stroke Prevention Trial 4 (trial)
ECG	Electrocardiogram
EchoCRT	Echocardiography Guided Cardiac Resynchronization Therapy (trial)
ECLS	Extracorporeal life support
ECMO	Extracorporeal membrane oxygenation
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EHRA	European Heart Rhythm Association
EMA	European Medicines Agency
EMB	Endomyocardial biopsy
EMPA-REG OUTCOME	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (trial)
EMPEROR-Reduced	EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (trial)
EROA	Effective regurgitant orifice area
ESC	European Society of Cardiology
EU	European Union
EuroSCORE II	European System for Cardiac Operative Risk Evaluation II (score)
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FiO_2	Fraction of inspired oxygen
FLN	Filamin
FLNC	Filamin C
GGT	Gamma-glutamyl transferase
GISSI-HF	Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico – Heart Failure (trial)
GLP-1	Glucagon-like peptide-1
GUIDE-HF	Hemodynamic-GUIDEd Management of Heart Failure (trial)
h	Hour/hours
H_2FPEF	Heavy (BMI>30 kg/m^2), Hypertensive (use of ≥2 antihypertensive medications), atrial Fibrillation (paroxysmal or persistent), Pulmonary hypertension (Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure >35 mmHg), Elderly (age >60 years), Filling pressure (Doppler Echocardiographic E/e′ >9) (score)
HbA1c	Glycated haemoglobin
HCM	Hypertrophic cardiomyopathy
HEART	Heart Failure Revascularisation Trial
HER2	Human epidermal growth factor receptor 2
HF	Heart failure
HFA	Heart Failure Association
HFA-PEFF	Heart Failure Association of ESC diagnostic algorithm, P – Initial Workup (Step 1: Pretest Assessment), E - Diagnostic Workup (Step 2: Echocardiographic and Natriuretic Peptide score), F1 – Advanced Workup (Step 3: Functional testing in Case of Uncertainty), F2 – Aetiological Workup (Step 4: Final Aetiology)
HF-MP	Heart failure management programme
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HHV	Human herpes virus
HIV	Human immunodeficiency virus
HLA-DR	Human leukocyte antigen-DR isotype
HMDP	Hydroxyl-methylene-diphosphonate
HR	Hazard ratio
HT	Heart transplantation
HTM	Home telemonitoring
i.v.	Intravenous
IABP	Intra-aortic balloon pump
ICCU	Intensive coronary care unit
ICD	Implantable cardioverter-defibrillator
ICU	Intensive care unit
IHD	Ischaemic heart disease
INR	International normalized ratio
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
INTrEPID	Investigation of Nontransplant-Eligible Patients Who Are Inotrope Dependent (trial)
IOCM	Iron overload cardiomyopathy
IPD	Individual patient data
I-PRESERVE	Irbesartan in Patients with Heart Failure and PRESERVEd Ejection Fraction (trial)
KCNH2	Potassium voltage-gated channel subfamily H member 2
KCNQ1	Potassium voltage-gated channel subfamily Q member 1
LA	Left atrium/atrial
LAE	Left atrial enlargement
LBBB	Left bundle branch block
LDB3	LIM domain binding 3
LFT	Liver function test
LGE	Late gadolinium enhancement
LMNA	Lamin A/C
LMWH	Low-molecular-weight heparin
LUS	Lung ultrasound
LV	Left ventricular/ventricle
LVAD	Left ventricular assist device

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LVEDP	Left ventricular end-diastolic pressure
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end-systolic diameter
LVH	Left ventricular hypertrophy
LVNC	Left ventricular non-compaction
LVOT	Left ventricular outflow tract
LVOTO	Left ventricular outflow tract obstruction
MADIT-CRT	Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (trial)
MADIT-II	Multicenter Automatic Defibrillator Implantation Trial II (trial)
MADIT-RIT	Multicenter Automatic Defibrillator Implantation Trial – Reduce Inappropriate Therapy (trial)
MAGGIC	Meta-Analysis Global Group in Chronic Heart Failure
MCS	Mechanical circulatory support
MEK	Mitogen-activated protein kinase
MI	Myocardial infarction
MITRA-FR	Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (trial)
MMR	Mismatch repair
MR	Mitral regurgitation
MRA	Mineralocorticoid receptor antagonist
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MR-proANP	Mid-regional pro-atrial natriuretic peptide
MT	Medical therapy
MV	Mitral valve
mWHO	Modified World Health Organization
MYPC	Myosin-binding protein C
NICM	Non-ischaemic cardiomyopathy
NKX2-5	NK2 transcription factor related, locus 5
NP	Natriuretic peptide
NSAID	Non-steroidal anti-inflammatory drug
NSVT	Non-sustained ventricular tachycardia
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
o.d	Omne in die (once daily)
OMT	Optimal medical therapy
OSA	Obstructive sleep apnoea
PA	Pulmonary artery
PaO_2	Partial pressure of oxygen
PARADIGM-HF	Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (trial)
pCO_2	Partial pressure of carbon dioxide
PCI	Percutaneous coronary intervention
PCR	Polymerase chain reaction
PCWP	Pulmonary capillary wedge pressure
PEP-CHF	Perindopril in Elderly People with Chronic Heart Failure (trial)
PET	Positron emission tomography
PKP2	Plakophilin 2
PLN	Phospholamban
PPCM	Peripartum cardiomyopathy
PREVEND	Prevention of REnal and Vascular ENd-stage Disease (trial)
PV	Pulmonary vein
PVC	Premature ventricular contraction
PVI	Pulmonary vein isolation
pVO_2	Peak exercise oxygen consumption
QI	Quality indicator
QOL	Quality of life
QRS	Q, R, and S waves on an ECG
RAAS	Renin-angiotensin-aldosterone system
RACE II	Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II (trial)
RAFT	Resynchronization/Defibrillation for Ambulatory Heart Failure Trial (trial)
RASi	Renin-angiotensin system inhibitor
RATE-AF	Rate Control Therapy Evaluation in Permanent Atrial Fibrillation (trial)
RBM20	Ribonucleic acid binding motif 20
RCT	Randomized controlled trial
REMATCH	Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (trial)
REVERSE	REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (trial)
REVIVED	REVascularization for Ischaemic VEntricular Dysfunction (trial)
RNA	Ribonucleic acid
RRT	Renal replacement therapy
RV	Right ventricular/ventricle
RVAD	Right ventricular assist device
RVEDP	Right ventricular end-diastolic pressure
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAVR	Surgical aortic valve replacement
SBP	Systolic blood pressure
SCORED	Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (trial)
SCN5a	Sodium channel alpha subunit 5
SENIORS	Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalizations in Seniors with Heart Failure (trial)
SERVE-HF	Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure (trial)
SGLT2	Sodium-glucose co-transporter 2
S-ICD	Subcutaneous implantable cardioverter-defibrillator
SMR	Secondary mitral regurgitation
SPECT	Single-photon emission computed tomography

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SpO_2	Transcutaneous oxygen saturation
SR	Sinus rhythm
STEMI	ST-elevation myocardial infarction
STICH	Surgical Treatment for Ischemic Heart Failure (trial)
STICHES	Extended follow-up of patients from the STICH trial
STS-PROM	Society of Thoracic Surgeons Predicted Risk of Mortality
SZC	Sodium zirconium cyclosilicate
T2DM	Type 2 diabetes mellitus
TAVI	Transcatheter aortic valve implantation
TFT	Thyroid function test
t.i.d.	Ter in die (three times a day)
TKI	Tyrosine kinase inhibitor
TMEM43	Transmembrane protein 43
TNNT	Troponin-T
TR	Tricuspid regurgitation
TRPM4	Transient receptor potential cation channel subfamily M member 4
TSAT	Transferrin saturation
TSH	Thyroid-stimulating hormone
TTN	Titin
TTR	Transthyretin
UK	United Kingdom
US	United States
VAD	Ventricular assist device
Val-HeFT	Valsartan Heart Failure Trial (trial)
VEGF	Vascular endothelial growth factor
VERTIS-CV	Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease (trial)
VEST	Vest Prevention of Early Sudden Death Trial (trial)
VKA	Vitamin K antagonist
VO_2	Oxygen consumption
VPB	Ventricular premature beat
vs	Versus
VV interval	Interventricular delay interval
WARCEF	Warfarin and Aspirin in Reduced Cardiac Ejection Fraction (trial)
wtTTR-CA	Wild-type transthyretin cardiac amyloidosis
XL	Extended release

1 Preamble

Guidelines summarize and evaluate available evidence with the aim of assisting health professionals in proposing the best management strategies for an individual patient with a given condition. Guidelines and their recommendations should facilitate decision making of health professionals in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

A great number of guidelines have been issued in recent years by the European Society of Cardiology (ESC), as well as by other societies and organizations. Because of their impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (https://www.escardio.org/Guidelines). The ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

In addition to the publication of Clinical Practice guidelines, the ESC carries out the EURObservational Research Programme of international registries of cardiovascular (CV) diseases and interventions which are essential to assess diagnostic/therapeutic processes, use of resources and adherence to guidelines. These registries aim at providing a better understanding of medical practice in Europe and around the world, based on high-quality data collected during routine clinical practice.

Furthermore, the ESC has developed and embedded in this document a set of quality indicators (QIs), which are tools to evaluate the level of implementation of the guidelines and may be used by the ESC, hospitals, healthcare providers and professionals to measure clinical practice as well as used in educational programmes, alongside the key messages from the guidelines, to improve quality of care and clinical outcomes.

The Members of this Task Force were selected by the ESC, including representation from its relevant ESC sub-specialty groups, in order to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management of a given condition according to ESC Clinical Practice Guidelines (CPG) Committee policy. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined below.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. Their declarations of interest were reviewed according to the ESC declaration of interest rules and can be found on the ESC website (http://www.escardio.org/guidelines) and have been compiled in a report and published in a supplementary document simultaneously to the guidelines.

This process ensures transparency and prevents potential biases in the development and review processes. Any changes in declarations of interest that arise during the writing period were notified to the ESC and updated. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new guidelines. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts. After appropriate revisions the guidelines are signed-off by all the experts involved in the Task Force. The finalized document is signed-off by the CPG for publication in the European Heart Journal. The guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing ESC Guidelines also includes the creation of educational tools and implementation programmes for the recommendations including condensed pocket guideline versions, summary slides, summary cards for non-specialists and an electronic version for digital

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Table 1 **Classes of recommendations**

Classes of recommendations	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

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Table 2 **Levels of evidence**

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

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applications (smartphones, etc.). These versions are abridged and thus, for more detailed information, the user should always access to the full text version of the guidelines, which is freely available via the ESC website and hosted on the EHJ website. The National Cardiac Societies of the ESC are encouraged to endorse, adopt, translate and implement all ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic, or therapeutic medical strategies. However, the ESC Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable in each country to drugs and devices at the time of prescription.

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2 Introduction

The aim of this ESC Guideline is to help health professionals manage people with heart failure (HF) according to the best available evidence. Fortunately, we now have a wealth of clinical trials to help us select the best management to improve the outcomes for people with HF; for many, it is now both preventable and treatable. This guideline provides practical, evidence-based recommendations.

We have revised the format of the previous 2016 ESC HF Guidelines[1] to make each phenotype of HF stand-alone in terms of its diagnosis and management. The therapy recommendations mention the treatment effect supported by the class and level of evidence and are presented in tables. For HF with reduced ejection fraction (HFrEF), the tabular recommendations focus on mortality and morbidity outcomes. Where there are symptomatic benefits, these are highlighted in the text and/or in the web appendices. Detailed summaries of the trials underpinning the recommendations are available in the web appendices. For diagnostic indications, we have suggested investigations that all patients with HF should receive, and investigations that can be targeted to specific circumstances. As diagnostic tests have rarely been subject to randomized controlled trials (RCTs), most of the evidence would be regarded as level C. However, that does not mean that there has not been appropriate rigorous evaluation of diagnostic tests.

In this guideline, we have decided to focus on the diagnosis and treatment of HF, not on its prevention. Management of CV risk and many CV diseases [especially systemic hypertension, diabetes mellitus, coronary artery disease, myocardial infarction (MI), atrial fibrillation (AF), and asymptomatic left ventricular (LV) systolic dysfunction] will reduce the risk of developing HF, which is addressed by many other ESC Guidelines and in section 9.1 of the current guideline.[2–7]

This guideline is the result of a collaboration between the Task Force (including two patient representatives), the reviewers, and the ESC CPG Committee. As such, it is a consensus/majority opinion of the experts consulted in its development.

2.1 What is new

In addition to the recommendations listed below, the following table lists some new concepts compared with the 2016 version.

New concepts

A change of the term 'heart failure with mid-range ejection fraction' to 'heart failure with mildly reduced ejection fraction' (HFmrEF).
A new simplified treatment algorithm for HFrEF.
The addition of a treatment algorithm for HFrEF according to phenotypes.
Modified classification for acute HF.
Updated treatments for most non-cardiovascular comorbidities including diabetes, hyperkalaemia, iron deficiency, and cancer.
Updates on cardiomyopathies including the role of genetic testing and new treatments.
The addition of key quality indicators.

HF = heart failure.

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New recommendations

Recommendations	Class
Recommendations for the diagnosis of HF	
Right heart catheterization should be considered in patients where HF is thought to be due to constrictive pericarditis, restrictive cardiomyopathy, congenital heart disease, and high output states.	IIa
Right heart catheterization may be considered in selected patients with HFpEF to confirm the diagnosis.	IIb
Recommendations for treatment of chronic HF	
HFrEF	
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I
Vericiguat may be considered in patients in NYHA class II–IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization.	IIb
HFmrEF	
An ACE-I may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb
An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb
A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb
An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb
Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb
HFpEF	
Screening for, and treatment of, aetiologies, and CV and non-CV comorbidities are recommended in patients with HFpEF (see relevant sections of this document).	I
Prevention and monitoring	
Self-management strategies are recommended to reduce the risk of HF hospitalization and mortality.	I
Either home-based and/or clinic-based programmes improve outcomes and are recommended to reduce the risk of HF hospitalization and mortality.	I
Influenza and pneumococcal vaccinations should be considered in order to prevent HF hospitalizations.	IIa
A supervised, exercise-based, cardiac rehabilitation programme should be considered in patients with more severe disease, frailty, or with comorbidities.	IIa
Non-invasive HTM may be considered for patients with HF in order to reduce the risk of recurrent CV and HF hospitalizations and CV death.	IIb
Recommendations for management of patients with advanced HF	
Patients being considered for long-term MCS must have good compliance, appropriate capacity for device handling and psychosocial support.	I

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Heart transplantation is recommended for patients with advanced HF, refractory to medical/device therapy and who do not have absolute contraindications.	I
Continuous inotropes and/or vasopressors may be considered in patients with low cardiac output and evidence of organ hypoperfusion as bridge to MCS or heart transplantation.	IIb
Recommendations for management of patients after HF hospitalization	
It is recommended that patients hospitalized for HF be carefully evaluated to exclude persistent signs of congestion before discharge and to optimize oral treatment.	I
It is recommended that evidence-based oral medical treatment be administered before discharge.	I
An early follow-up visit is recommended at 1–2 weeks after discharge to assess signs of congestion, drug tolerance, and start and/or uptitrate evidence-based therapy.	I
Recommendations for management of patients with HF and atrial fibrillation	
Long-term treatment with an oral anticoagulant should be considered for stroke prevention in AF patients with a CHA_2DS_2-VASc score of 1 in men or 2 in women.	IIa
Recommendations for management of patients with HF and CCS	
CABG should be considered as the first-choice revascularization strategy, in patients suitable for surgery, especially if they have diabetes and for those with multivessel disease.	IIa
In LVAD candidates needing coronary revascularization, CABG should be avoided, if possible.	IIa
Coronary revascularization may be considered to improve outcomes in patients with HFrEF, CCS, and coronary anatomy suitable for revascularization, after careful evaluation of the individual risk to benefit ratio, including coronary anatomy (i.e. proximal stenosis >90% of large vessels, stenosis of left main or proximal LAD), comorbidities, life expectancy, and patient's perspectives.	IIb
PCI may be considered as alternative to CABG, based on Heart Team evaluation, considering coronary anatomy, comorbidities, and surgical risk.	IIb
Recommendations for management of patients with HF and valvular heart disease	
Aortic valve intervention, TAVI or SAVR is recommended in patients with HF and severe high-gradient aortic stenosis to reduce mortality and improve symptoms.	I
It is recommended that the choice between TAVI and SAVR be made by the Heart Team, according to individual patient preference and features including age, surgical risk, clinical, anatomical and procedural aspects, weighing the risks and benefits of each approach.	I
Percutaneous edge-to-edge mitral valve repair should be considered in carefully selected patients with secondary mitral regurgitation, not eligible for surgery and not needing coronary revascularization, who are symptomatic despite OMT and who fulfil criteria to achieve a reduction in HF hospitalizations.	IIa
Percutaneous edge-to-edge mitral valve repair may be considered to improve symptoms in carefully selected patients with secondary mitral regurgitation, not eligible for surgery and not needing coronary revascularization, who are highly symptomatic despite OMT and who do not fulfil criteria for reducing HF hospitalization.	IIb

Continued

Recommendations for management of patients with HF and diabetes	
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with T2DM at risk of CV events to reduce hospitalizations for HF, major CV events, end-stage renal dysfunction, and CV death.	I
SGLT2 inhibitors (dapagliflozin, empagliflozin, and sotagliflozin) are recommended in patients with T2DM and HFrEF to reduce hospitalizations for HF and CV death.	I
The DPP-4 inhibitor saxagliptin is not recommended in patients with HF.	III
Recommendations for management of patients with HF and iron deficiency	
It is recommended that all patients with HF are periodically screened for anaemia and iron deficiency with a full blood count, serum ferritin concentration, and TSAT.	I
Intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic HF patients recently hospitalized for HF and with LVEF ≤50% and iron deficiency, defined as serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with TSAT <20%, to reduce the risk of HF hospitalization.	IIa
Treatment of anaemia in HF with erythropoietin stimulating agents is not recommended in the absence of other indications for this therapy.	III
Recommendations for management of patients with HF and cancer	
It is recommended that cancer patients at increased risk for cardiotoxicity, defined by a history or risk factors of CV disease, previous cardiotoxicity or exposure to cardiotoxic agents, undergo CV evaluation before scheduled anticancer therapy, preferably by a cardiologist with experience/interest in Cardio-Oncology.	I
Treatment with an ACE-I and a beta-blocker (preferably carvedilol) should be considered in cancer patients developing LV systolic dysfunction, defined as a 10% or more decrease in LVEF and to a value lower than 50%, during anthracycline chemotherapy.	IIa
A baseline CV risk assessment should be considered in all cancer patients scheduled to receive a cancer treatment with the potential to cause HF.	IIa
Recommendations for treatment of patients with HF and amyloidosis	
Tafamidis is recommended in patients with genetic testing proven hereditary hTTR-CMP and NYHA class I or II symptoms to reduce symptoms, CV hospitalization and mortality.	I
Tafamidis is recommended in patients with wtTTR-CA and NYHA class I or II symptoms to reduce symptoms, CV hospitalization and mortality.	I

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CABG = coronary artery bypass graft; CCS = chronic coronary syndrome; CHA_2DS_2-VASc = congestive heart failure or left ventricular dysfunction, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74, Sex category (female) (score); CMP = cardiomyopathy; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HTM = home telemonitoring; hTTR = hereditary transthyretin; LAD = left anterior descending artery; LV = left ventricular; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MCS = mechanical circulatory support; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; OMT = optimal medical therapy; PCI = percutaneous coronary intervention; SAVR = surgical aortic valve replacement; SGLT2 = sodium-glucose co-transporter 2; T2DM = type 2 diabetes mellitus; TAVI = transcatheter aortic valve implantation; TSAT = transferrin saturation; wtTTR-CA = wild-type transthyretin cardiac amyloidosis.

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Changes in recommendations

2021	Class	2016	Class
Recommendations for diagnosis of HF			
Invasive coronary angiography may be considered in patients with HFrEF with an intermediate to high pre-test probability of CAD and the presence of ischaemia in non-invasive stress tests.	IIb	Invasive coronary angiography should be considered in patients with HF and intermediate to high pre-test probability of CAD and the presence of ischaemia in non-invasive stress tests (who are considered suitable for potential coronary revascularization) in order to establish the diagnosis of CAD and its severity.	IIa
CTCA should be considered in patients with a low to intermediate pre-test probability of CAD or those with equivocal non-invasive stress tests in order to rule out coronary artery stenosis.	IIa	Cardiac CT may be considered in patients with HF and low to intermediate pre-test probability of CAD or those with equivocal non-invasive stress tests in order to rule out coronary artery stenosis.	IIb
Right heart catheterization may be considered in patients with probable pulmonary hypertension, assessed by echo in order to confirm the diagnosis and assess its reversibility before the correction of valve/structural heart disease.	IIb	Right heart catheterization with a pulmonary artery catheter should be considered in patients with probable pulmonary hypertension assessed by echocardiography in order to confirm pulmonary hypertension and its reversibility before the correction of valve/structural heart disease.	IIa
Recommendations for device therapy in HFrEF			
An ICD should be considered to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II–III) of a non-ischaemic aetiology, and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status.	IIa	Primary prevention An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II–III), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status, and they have DCM.	I
CRT should be considered for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 ms and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIa	CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 ms and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I
Patients with an LVEF ≤35% who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT and who have a significant proportion of RV pacing should be considered for 'upgrade' to CRT.	IIa	Patients with HFrEF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT and who have a high proportion of RV pacing may be considered for upgrade to CRT. This does not apply to patients with stable HF.	IIb
Recommendations for management of patients with acute HF			
Combination of a loop diuretic with thiazide-type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses.	IIa	Combination of loop diuretic with either thiazide-type diuretic or spironolactone may be considered in patients with resistant oedema or insufficient symptomatic response.	IIb
In patients with AHF and SBP >110 mmHg, i.v. vasodilators may be considered as initial therapy to improve symptoms and reduce congestion.	IIb	In patients with hypertensive AHF, i.v. vasodilators should be considered as initial therapy to improve symptoms and reduce congestion.	IIa
Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety.	III	Opiates may be considered for cautious use to relieve dyspnoea and anxiety in patients with severe dyspnoea but nausea and hypopnea may occur.	IIb
Short-term MCS should be considered in patients with cardiogenic shock as a BTR, BTD, BTB. Further indications include treatment of the cause of cardiogenic shock or long-term MCS or transplantation.	IIa	Short-term MCS may be considered in refractory cardiogenic shock depending on patient age, comorbidities, and neurological function.	IIb

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Recommendations for management of patients with HF and AF			
DOACs are recommended in preference to VKAs in patients with HF, except in those with moderate or severe mitral stenosis or mechanical prosthetic heart valves.	I	For patients with HF and non-valvular AF eligible for anticoagulation based on a CHA_2DS_2-VASc score, NOACs rather than warfarin should be considered for anticoagulation as NOACs are associated with a lower risk of stroke, intracranial haemorrhage, and mortality, which outweigh the increased risk of gastrointestinal haemorrhage.	IIa
Beta-blockers should be considered for short- and long-term rate control in patients with HF and AF.	IIa	For patients in NYHA class I–III, a beta-blocker, usually given orally, is safe and therefore is recommended as first-line treatment to control ventricular rate, provided the patient is euvolaemic.	I
In cases of a clear association between paroxysmal or persistent AF and worsening of HF symptoms, which persist despite medical therapy, catheter ablation should be considered for the prevention of AF.	IIa	AV node catheter ablation may be considered to control heart rate and relieve symptoms in patients unresponsive or intolerant to intensive pharmacological rate and rhythm control therapy, accepting that these patients will become pacemaker-dependent.	IIb
Recommendations for management of patients with HF and CCS			
Coronary revascularization should be considered to relieve persistent symptoms of angina (or an angina-equivalent) in patients with HFrEF, CCS, and coronary anatomy suitable for revascularization, despite OMT including anti-anginal drugs.	IIa	Myocardial revascularization is recommended when angina persists despite treatment with anti-anginal drugs.	I
Recommendations for management of patients with HF and diabetes			
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with T2DM at risk of CV events to reduce hospitalizations for HF, major CV events, end-stage renal dysfunction, and CV death.	I	Empagliflozin should be considered in patients with T2DM in order to prevent or delay the onset of HF and prolong life.	IIa

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AF = atrial fibrillation; AHF = acute heart failure; AV = atrio-ventricular; BTB = bridge to bridge; BTD = bridge to decision; BTR = bridge to cardiac recovery; CAD = coronary artery disease; CCS = chronic coronary syndrome; CHA_2DS_2-VASc = congestive heart failure or left ventricular dysfunction, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74, Sex category (female) (score); CRT = cardiac resynchronization therapy; CT = computed tomography; CTCA = computed tomography coronary angiography; CV = cardiovascular; DCM = dilated cardiomyopathy; DOAC = direct oral anticoagulant; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MCS = mechanical circulatory support; NOAC = non-vitamin K antagonist oral anticoagulant; NYHA = New York Heart Association; OMT = optimal medical therapy; QRS = Q, R, and S waves (combination of three of the graphical deflections); RV = right ventricular/ventricle; SBP = systolic blood pressure; SGLT2 = sodium-glucose co-transporter 2; T2DM = type 2 diabetes mellitus; VKA = vitamin K antagonist.

3 Definition, epidemiology and prognosis

3.1 Definition of heart failure

Heart failure is not a single pathological diagnosis, but a clinical syndrome consisting of cardinal symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema). It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise.

Identification of the aetiology of the underlying cardiac dysfunction is mandatory in the diagnosis of HF as the specific pathology can determine subsequent treatment. Most commonly, HF is due to myocardial dysfunction: either systolic, diastolic, or both. However, pathology of the valves, pericardium, and endocardium, and abnormalities of heart rhythm and conduction can also cause or contribute to HF.

3.2 Terminology

3.2.1 Heart failure with preserved, mildly reduced, and reduced ejection fraction

Traditionally, HF has been divided into distinct phenotypes based on the measurement of left ventricular ejection fraction (LVEF) (*Table 3*). The rationale behind this relates to the original treatment trials in HF that demonstrated substantially improved outcomes in patients with LVEF ≤40%. However, HF spans the entire range of LVEF (a normally distributed variable), and measurement by echocardiography is subject to substantial variability. We have decided on the following classification of HF (*Table 3*):

- Reduced LVEF is defined as ≤40%, i.e. those with a significant reduction in LV systolic function. This is designated as HFrEF.
- Patients with a LVEF between 41% and 49% have *mildly* reduced LV systolic function, i.e. HFmrEF. Retrospective analyses from RCTs in HFrEF or HF with preserved ejection fraction (HFpEF) that have included patients with ejection fractions in the 40–50% range suggest that they may benefit from similar

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Table 3 Definition of heart failure with reduced ejection fraction, mildly reduced ejection fraction and preserved ejection fraction

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricle; LVEF = left ventricular ejection fraction.
[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in optimally treated patients.
[b]For the diagnosis of HFmrEF, the presence of other evidence of structural heart disease (e.g. increased left atrial size, LV hypertrophy or echocardiographic measures of impaired LV filling) makes the diagnosis more likely.
[c]For the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF.

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therapies to those with LVEF ≤40%.[8–13] This supports the renaming of HFmrEF from 'heart failure with mid-range ejection fraction' to 'heart failure with mildly reduced ejection fraction'.[14]
- Those with symptoms and signs of HF, with evidence of structural and/or functional cardiac abnormalities and/or raised natriuretic peptides (NPs), and with an LVEF ≥50%, have HFpEF.

The diagnosis of HFrEF, HFmrEF, and HFpEF is covered in more detail in their respective sections (sections 5, 7, and 8, respectively). These definitions are consistent with a recent report on the Universal Definition of Heart Failure.[15]

Patients with non-CV disease, e.g. anaemia, pulmonary, renal, thyroid, or hepatic disease may have symptoms and signs very similar to those of HF, but in the absence of cardiac dysfunction, they do not fulfil the criteria for HF. However, these pathologies can coexist with HF and exacerbate the HF syndrome.

3.2.2 Right ventricular dysfunction

Heart failure can also be a result of right ventricular (RV) dysfunction. RV mechanics and function are altered in the setting of either pressure or volume overload.[16] Although the main aetiology of chronic RV failure is LV dysfunction-induced pulmonary hypertension, there are a number of other causes of RV dysfunction [e.g. MI, arrhythmogenic right ventricular cardiomyopathy (ARVC), or valve disease].[17] The diagnosis is determined by a quantitative assessment of global RV function, most commonly by echocardiography, using at least one of the following measurements: fractional area change (FAC); tricuspid annular plane systolic excursion (TAPSE); and Doppler tissue imaging-derived systolic S′ velocity of the tricuspid annulus. The diagnosis and management of RV dysfunction is covered comprehensively in a recent Heart Failure Association (HFA) position paper.[18]

3.2.3 Other common terminology used in heart failure

Heart failure is usually divided into two presentations: chronic heart failure (CHF) and acute heart failure (AHF). CHF describes those who have had an established diagnosis of HF or who have a more gradual onset of symptoms. If CHF deteriorates, either suddenly or slowly, the episode may be described as 'decompensated' HF. This can result in a hospital admission or treatment with intravenous (i.v.) diuretic therapy in the outpatient setting. In addition, HF can present more acutely. Both of these are considered in the section on AHF (section 11).

Some individuals with HF may recover completely [e.g. those due to alcohol-induced cardiomyopathy (CMP), viral myocarditis, Takotsubo syndrome, peripartum cardiomyopathy (PPCM), or tachycardiomyopathy]. Other patients with LV systolic dysfunction may show a substantial or even complete recovery of LV systolic function after receiving drug and device therapy.

3.2.4 Terminology related to the symptomatic severity of heart failure

The simplest terminology used to describe the severity of HF is the New York Heart Association (NYHA) functional classification (*Table 4*). However, this relies solely on symptoms and there are many other better prognostic indicators in HF.[19] Importantly, patients with mild symptoms may still have a high risk of hospitalization and death.[20] Predicting outcome is particularly important in advanced HF to guide selection of cardiac transplantation and device therapies. This will be covered in detail in the section on advanced HF (section 10).

3.3 Epidemiology and natural history of heart failure

3.3.1 Incidence and prevalence

In developed countries, the age-adjusted incidence of HF may be falling, presumably reflecting better management of CV disease, but due to ageing, the overall incidence is increasing.[21–24] Currently, the incidence of HF in Europe is about 3/1000 person-years (all age-groups) or about 5/1000 person-years in adults.[25,26] The prevalence of HF appears to be 1–2% of adults.[21,27–31] As studies only usually include recognized/diagnosed HF cases, the true prevalence is likely to be higher.[32] The prevalence increases with age: from around 1% for those aged <55 years to >10% in those aged 70 years or over.[33–36] It

Table 4 New York Heart Association functional classification based on severity of symptoms and physical activity

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

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is generally believed that, of those with HF, about 50% have HFrEF and 50% have HFpEF/HFmrEF, mainly based on studies in hospitalized patients.[32,35,37,38] The ESC Long-Term Registry, in the outpatient setting, reports that 60% have HFrEF, 24% have HFmrEF, and 16% have HFpEF.[39] Somewhat more than 50% of HF patients are female.[21,40,41]

3.3.2 Aetiology of heart failure

The most common causes (as well as some key investigations) of HF are shown in *Table 5*. The aetiology of HF varies according to geography. In Western-type and developed countries, coronary artery disease (CAD) and hypertension are predominant factors.[27]

With regard to ischaemic aetiology, HFmrEF resembles HFrEF, with a higher frequency of underlying CAD compared to those with HFpEF.[38,42,43]

3.3.3 Natural history and prognosis

The prognosis of patients with HF has improved considerably since the publication of the first treatment trials a few decades ago. However, it remains poor, and quality of life (QOL) is also markedly reduced. The improvement in prognosis has been confined to those with HFrEF.

Mortality rates are higher in observational studies than in clinical trials.[44] In the Olmsted County cohort, 1-year and 5-year mortality rates after diagnosis, for all types of HF patients, were 20% and 53%, respectively, between 2000 and 2010.[45] A study combining the Framingham Heart Study (FHS) and Cardiovascular Health Study (CHS) cohorts reported a 67% mortality rate within 5 years following diagnosis.[46] Despite receiving less evidence-based treatment, women have a better survival than men.[47]

Overall prognosis is better in HFmrEF compared to HFrEF.[39] Of note, transition in ejection fraction over time is common, and patients who progress from HFmrEF to HFrEF have a worse prognosis than those who remain stable or transition to a higher ejection fraction category.[48–52]

HFpEF is generally considered to confer a better survival than HFrEF, but most observational studies show that this difference is negligible.[45,46] In contrast, the large MAGGIC meta-analysis concluded that the adjusted mortality risk for patients with HFpEF was considerably lower than in patients with HFrEF.[53]

Studies from several countries have shown that between 1980 and 2000 survival in HF patients has improved markedly.[41,54–57] However, this positive trend may have levelled off since then.[45]

After the initial diagnosis, HF patients are hospitalized once every year on average.[54] From 2000 to 2010, the mean rate of hospitalization in the Olmsted County cohort was 1.3 per person-year. Interestingly, the majority (63%) of hospitalizations were related to non-CV causes.[45] Studies from several European countries and the United States (US) have shown that HF hospitalization rates peaked in the 1990s, and then declined.[54,55,*,58–60] However, in a recent study of incident HF conducted between 1998 and 2017 in the United Kingdom (UK), age-adjusted rates of first hospitalizations increased by 28% for both all-cause and HF admissions, and by 42% for non-CV admissions.[61] These increases were higher in women, perhaps related to higher comorbidity rates. The risk of HF hospitalization is 1.5 times higher in patients with diabetes compared to controls. AF, a higher body mass index (BMI), and higher glycated haemoglobin (HbA1c), as well as a low estimated glomerular filtration rate (eGFR) are strong predictors of HF hospitalizations.[29]

Due to population growth, ageing, and the increasing prevalence of comorbidities, the absolute number of hospital admissions for HF is expected to increase considerably in the future, perhaps by as much as 50% in the next 25 years.[24,62]

4 Chronic heart failure

4.1 Key steps in the diagnosis of chronic heart failure

The diagnosis of CHF requires the presence of symptoms and/or signs of HF and objective evidence of cardiac dysfunction (*Figure 1*). Typical symptoms include breathlessness, fatigue, and ankle swelling (*Table 6*). Symptoms and signs lack sufficient accuracy to be used alone to make the diagnosis of HF.[63–66]

The diagnosis of CHF is made more likely in patients with a history of MI, arterial hypertension, CAD, diabetes mellitus, alcohol misuse, chronic kidney disease (CKD), cardiotoxic chemotherapy, and in those with a family history of CMP or sudden death.

The following diagnostic tests are recommended for the assessment of patients with suspected chronic HF:

(1) Electrocardiogram (ECG). A normal ECG makes the diagnosis of HF unlikely.[63] The ECG may reveal abnormalities such as AF, Q waves, LV hypertrophy (LVH), and a widened QRS complex (*Table 7*) that increase the likelihood of a diagnosis of HF and also may guide therapy.

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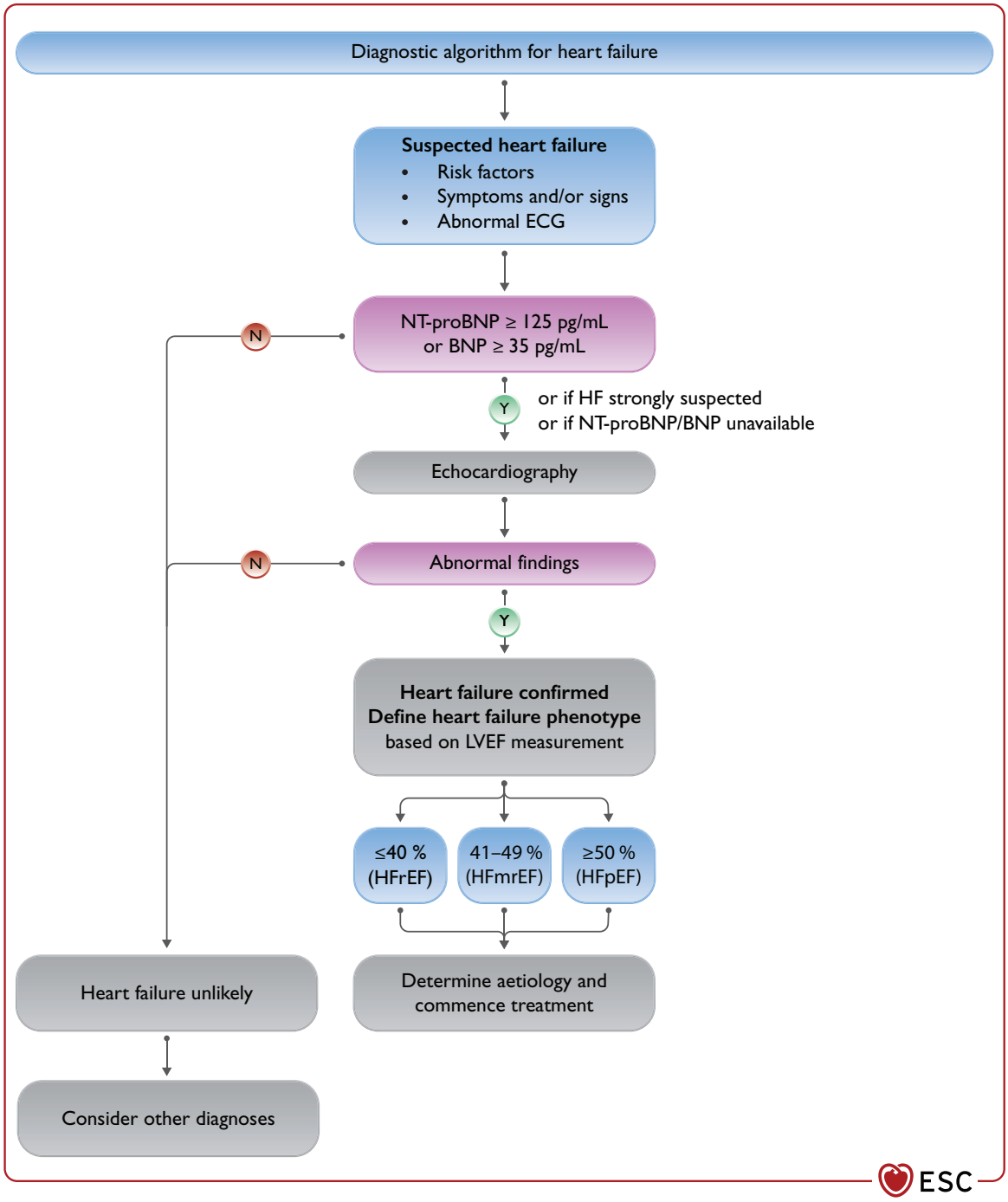

Figure 1 The diagnostic algorithm for heart failure. BNP = B-type natriuretic peptide; ECG = electrocardiogram; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B type natriuretic peptide. The abnormal echocardiographic findings are described in more detail in the respective sections on HFrEF (section 5), HFmrEF (section 7), and HFpEF (section 8).

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Table 5 Causes of heart failure, common modes of presentation and specific investigations

Cause	Examples of presentations	Specific investigations
CAD	Myocardial infarction	Invasive coronary angiography
	Angina or "angina-equivalent"	CT coronary angiography
	Arrhythmias	Imaging stress tests (echo, nuclear, CMR)
Hypertension	Heart failure with preserved systolic function	24 h ambulatory BP
	Malignant hypertension/acute pulmonary oedema	Plasma metanephrines, renal artery imaging
		Renin and aldosterone
Valve disease	Primary valve disease e.g., aortic stenosis	Echo − transoesophageal/stress
	Secondary valve disease, e.g. functional regurgitation	
	Congenital valve disease	
Arrhythmias	Atrial tachyarrhythmias	Ambulatory ECG recording
	Ventricular arrhythmias	Electrophysiology study, if indicated
CMPs	All	CMR, genetic testing
	Dilated	
	Hypertrophic	
	Restrictive	Right and left heart catheterization
	ARVC	
	Peripartum	
	Takotsubo syndrome	CMR, angiography
	Toxins: alcohol, cocaine, iron, copper	Trace elements, toxicology, LFTs, GGT
Congenital heart disease	Congenitally corrected/repaired transposition of great arteries	CMR
	Shunt lesions	
	Repaired tetralogy of Fallot	
	Ebstein's anomaly	
Infective	Viral myocarditis	CMR, EMB
	Chagas disease	
	HIV	Serology
	Lyme disease	
Drug-induced	Anthracyclines	
	Trastuzumab	
	VEGF inhibitors	
	Immune checkpoint inhibitors	
	Proteasome inhibitors	
	RAF+MEK inhibitors	
Infiltrative	Amyloid	Serum electrophoresis and serum free light chains, Bence Jones protein, Bone scintigraphy, CMR, CT-PET, EMB
	Sarcoidosis	Serum ACE, CMR, FDG-PET, chest CT, EMB
	Neoplastic	CMR, EMB
Storage disorders	Haemochromatosis	Iron studies, genetics, CMR (T2* imaging), EMB
	Fabry disease	α-galactosidase A, genetics, CMR (T1 mapping)
	Glycogen storage diseases	
Endomyocardial disease	Radiotherapy	CMR
	Endomyocardial fibrosis/eosinophilia	EMB
	Carcinoid	24 h urine 5-HIAA
Pericardial disease	Calcification	Chest CT, CMR, Right and Left heart catheterisation
	Infiltrative	
Metabolic	Endocrine disease	TFTs, plasma metanephrines, renin and aldosterone, cortisol
	Nutritional disease (thiamine, vitamin B1 and selenium deficiencies)	Specific plasma nutrients
	Autoimmune disease	ANA, ANCA, rheumatology review
Neuromuscular disease	Friedreich's ataxia	Nerve conduction studies, electromyogram, genetics
	Muscular dystrophy	CK, electromyogram, genetics

5-HIAA = 5-hydroxyindoleacetic acid; ACE = angiotensin-converting enzyme; ANA = anti-nuclear antibody; ANCA = anti-nuclear cytoplasmic antibody; ARVC = arrhythmogenic right ventricular cardiomyopathy; BP = blood pressure; CAD = coronary artery disease; CMP = cardiomyopathy; CMR = cardiac magnetic resonance; CK = creatinine kinase; CT = computed tomography; ECG = electrocardiogram; Echo = echocardiography; EMB = endomyocardial biopsy; FDG = fluorodeoxyglucose; GGT = gamma-glutamyl transferase; HIV = human immunodeficiency virus; h = hour; LFT = liver function test; LGE = late gadolinium enhancement; MEK = mitogen-activated protein kinase; PET = positron emission tomography; TFT = thyroid function test; VEGF = vascular endothelial growth factor.

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(2) Measurement of NPs are recommended, if available. A plasma concentration of B-type natriuretic peptide (BNP) <35 pg/mL, N-terminal pro-B-type natriuretic peptide (NT-proBNP) <125 pg/mL, or mid-regional pro-atrial natriuretic peptide (MR-proANP) <40 pmol/L[68] make a diagnosis of HF unlikely. These will be discussed in more detail in section 4.2.[69,70]

(3) Basic investigations such as serum urea and electrolytes, creatinine, full blood count, liver and thyroid function tests are recommended to differentiate HF from other conditions, to provide prognostic information, and to guide potential therapy.

(4) Echocardiography is recommended as the key investigation for the assessment of cardiac function. As well as the determination of the LVEF, echocardiography also provides information on other parameters such as chamber size, eccentric or concentric LVH, regional wall motion abnormalities (that may suggest underlying CAD, Takotsubo syndrome, or myocarditis), RV function, pulmonary hypertension, valvular function, and markers of diastolic function.[16,71]

(5) A chest X-ray is recommended to investigate other potential causes of breathlessness (e.g. pulmonary disease). It may also provide supportive evidence of HF (e.g. pulmonary congestion or cardiomegaly).

Recommended diagnostic tests in all patients with suspected chronic heart failure

Recommendations	Class[a]	Level[b]
BNP/NT-proBNP[c]	I	B
12-lead ECG	I	C
Transthoracic echocardiography	I	C
Chest radiography (X-ray)	I	C
Routine blood tests for comorbidities, including full blood count, urea and electrolytes, thyroid function, fasting glucose and HbA1c, lipids, iron status (TSAT and ferritin)	I	C

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BNP = B-type natriuretic peptide; ECG = electrocardiogram; HbA1c = glycated haemoglobin; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TSAT = transferrin saturation.
[a]Class of recommendation.
[b]Level of evidence.
[c]References are listed in section 4.2 for this item.

4.2 Natriuretic peptides

Plasma concentrations of NPs are recommended as initial diagnostic tests in patients with symptoms suggestive of HF to rule out the diagnosis. Elevated concentrations support a diagnosis of HF, are useful for prognostication,[72] and may guide further cardiac investigation.[73] However, it should be noted that there are many causes of an elevated NP—both CV and non-CV—that might reduce their diagnostic accuracy (*Table 7*). These causes include AF, increasing age, and acute or chronic kidney disease.[74] Conversely, NP concentrations may be disproportionately low in obese patients.[75]

Table 6 Symptoms and signs typical of heart failure

Symptoms	Signs
Typical	**More specific**
Breathlessness	Elevated jugular venous pressure
Orthopnoea	Hepatojugular reflux
Paroxysmal nocturnal dyspnoea	Third heart sound (gallop rhythm)
Reduced exercise tolerance	Laterally displaced apical impulse
Fatigue, tiredness, increased time to recover after exercise	
Ankle swelling	
Less typical	**Less specific**
Nocturnal cough	Weight gain (>2 kg/week)
Wheezing	Weight loss (in advanced HF)
Bloated feeling	Tissue wasting (cachexia)
Loss of appetite	Cardiac murmur
Confusion (especially in the elderly)	Peripheral oedema (ankle, sacral, scrotal)
Depression	Pulmonary crepitations
Palpitation	Pleural effusion
Dizziness	Tachycardia
Syncope	Irregular pulse
Bendopnea[a]	Tachypnoea
	Cheyne-Stokes respiration
	Hepatomegaly
	Ascites
	Cold extremities
	Oliguria
	Narrow pulse pressure

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HF = heart failure.
[a]This symptom of advanced HF corresponds to shortness of breath when leaning forward.[67]

4.2.1 Use in the non-acute setting

The diagnostic value of NPs, in addition to signs and symptoms and other diagnostic tests, such as an ECG, has been assessed in several studies in the primary care setting.[68,76–80] The aim of these studies was to either exclude or establish a diagnosis of HF. The Task Force considered studies of adequate quality that included NP cut-off points in their diagnostic algorithms, below which the probability of having HF was extremely low. The upper limits of normal in the non-acute setting are 35 pg/mL for BNP, and 125 pg/mL for NT-proBNP. In these studies, the negative predictive values of NP concentrations below these thresholds range from 0.94 to 0.98.[76–78] Fewer data are available for MR-proANP in CHF than in AHF. A concentration of <40 pmol/L can be used to rule out HF.[68]

4.3 Investigations to determine the underlying aetiology of chronic heart failure

Recommended tests to determine the underlying aetiology of CHF are summarized in *Table 5*.

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Table 7 Causes of elevated concentrations of natriuretic peptides[86-88]

Cardiac	Heart failure ACS Pulmonary embolism Myocarditis Left ventricular hypertrophy Hypertrophic or restrictive cardiomyopathy Valvular heart disease Congenital heart disease Atrial and ventricular tachyarrhythmias Heart contusion Cardioversion, ICD shock Surgical procedures involving the heart Pulmonary hypertension
Non-cardiac	Advanced age Ischaemic stroke Subarachnoid haemorrhage Renal dysfunction Liver dysfunction (mainly liver cirrhosis with ascites) Paraneoplastic syndrome COPD Severe infections (including pneumonia and sepsis) Severe burns Anaemia Severe metabolic and hormone abnormalities (e.g. thyrotoxicosis, diabetic ketosis)

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ACS = acute coronary syndrome; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter-defibrillator.

Exercise or pharmacological stress echocardiography may be used for the assessment of inducible ischaemia in those who are considered suitable for coronary revascularization.[81] In patients with HFpEF, valve disease, or unexplained dyspnoea, stress echocardiography might help clarify the diagnosis.[82]

Cardiac magnetic resonance (CMR) imaging with late gadolinium enhancement (LGE), T1 mapping and extracellular volume will identify myocardial fibrosis/scar, which are typically subendocardial for patients with ischaemic heart disease (IHD) in contrast to the mid-wall scar typical of dilated cardiomyopathy (DCM). In addition, CMR allows myocardial characterization in, e.g. myocarditis, amyloidosis, sarcoidosis, Chagas disease, Fabry disease, LV non-compaction CMP, haemochromatosis, and arrhythmogenic cardiomyopathy (AC).[83,84]

Computed tomography coronary angiography (CTCA) may be considered in patients with a low to intermediate pre-test probability of CAD, or those with equivocal non-invasive stress tests in order to exclude the diagnosis of CAD.[5]

Single-photon emission CT (SPECT) can also be used to assess myocardial ischaemia and viability, myocardial inflammation or infiltration. Scintigraphy with technetium (Tc)-labelled bisphosphonate has shown high sensitivity and specificity for imaging cardiac transthyretin amyloid.[85]

Recommendations for specialized diagnostic tests for selected patients with chronic heart failure to detect reversible/treatable causes of heart failure

Recommendations	Class[a]	Level[b]
CMR		
CMR is recommended for the assessment of myocardial structure and function in those with poor echocardiogram acoustic windows.	I	C
CMR is recommended for the characterization of myocardial tissue in suspected infiltrative disease, Fabry disease, inflammatory disease (myocarditis), LV non-compaction, amyloid, sarcoidosis, iron overload/haemochromatosis.	I	C
CMR with LGE should be considered in DCM to distinguish between ischaemic and non-ischaemic myocardial damage.	IIa	C
Invasive coronary angiography (in those who are considered eligible for potential coronary revascularization)		
Invasive coronary angiography is recommended in patients with angina despite pharmacological therapy or symptomatic ventricular arrhythmias.[5]	I	B
Invasive coronary angiography may be considered in patients with HFrEF with an intermediate to high pre-test probability of CAD and the presence of ischaemia in non-invasive stress tests.[89]	IIb	B
Non-invasive testing		
CTCA should be considered in patients with a low to intermediate pre-test probability of CAD or those with equivocal non-invasive stress tests in order to rule out coronary artery stenosis.	IIa	C
Non-invasive stress imaging (CMR, stress echocardiography, SPECT, PET) may be considered for the assessment of myocardial ischaemia and viability in patients with CAD who are considered suitable for coronary revascularization.[90–93]	IIb	B
Exercise testing may be considered to detect reversible myocardial ischaemia and investigate the cause of dyspnoea.[94–96]	IIb	C
Cardiopulmonary exercise testing		
Cardiopulmonary exercise testing is recommended as a part of the evaluation for heart transplantation and/or MCS.[94–96]	I	C
Cardiopulmonary exercise testing should be considered to optimize prescription of exercise training.[94–96]	IIa	C
Cardiopulmonary exercise testing should be considered to identify the cause of unexplained dyspnoea and/or exercise intolerance.[94–96]	IIa	C
Right heart catheterization		
Right heart catheterization is recommended in patients with severe HF being evaluated for heart transplantation or MCS.	I	C

Continued

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Right heart catheterization should be considered in patients where HF is thought to be due to constrictive pericarditis, restrictive cardiomyopathy, congenital heart disease, and high output states.	IIa	C
Right heart catheterization should be considered in patients with probable pulmonary hypertension, assessed by echo in order to confirm the diagnosis and assess its reversibility before the correction of valve/structural heart disease.	IIa	C
Right heart catheterization may be considered in selected patients with HFpEF to confirm the diagnosis.	IIb	C
EMB		
EMB should be considered in patients with rapidly progressive HF despite standard therapy when there is a probability of a specific diagnosis, which can be confirmed only in myocardial samples.[97,98]	IIa	C

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CAD = coronary artery disease; CMR = cardiac magnetic resonance; CTCA = computed tomography coronary angiography; DCM = dilated cardiomyopathy; EMB = endomyocardial biopsy; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LGE = late gadolinium enhancement; LV = left ventricular; MCS = mechanical circulatory support; PET = positron emission tomography; SPECT = single-photon emission computed tomography.
[a]Class of recommendation.
[b]Level of evidence.

Coronary angiography is recommended in patients with HF, who have angina pectoris or an 'angina equivalent' despite pharmacological therapy, in order to establish the diagnosis of CAD and its severity. Coronary angiography may also be considered in patients with HFrEF who have an intermediate to high pre-test probability of CAD and who are considered potentially suitable for coronary revascularization.[5]

5 Heart failure with reduced ejection fraction

5.1 The diagnosis of heart failure with reduced ejection fraction

The diagnosis of HFrEF requires the presence of symptoms and/or signs of HF and a reduced ejection fraction (LVEF ≤40%). This is most usually obtained by echocardiography. Details about the quality standards that should be adhered to when determining the presence of reduced LV systolic function by echocardiography can be found in the European Association of Cardiovascular Imaging (EACVI) position paper.[99] If assessment of EF is not possible by echocardiography, then CMR or rarely, nuclear techniques can be employed.

An algorithm for the diagnosis of HFrEF is depicted in *Figure 1*. For the investigation of the underlying aetiology, please refer to *Table 5*.

5.2 Pharmacological treatments for patients with heart failure with reduced ejection fraction

5.2.1 Goals of pharmacotherapy for patients with heart failure with reduced ejection fraction

Pharmacotherapy is the cornerstone of treatment for HFrEF and should be implemented before considering device therapy, and alongside non-pharmacological interventions.

There are three major goals of treatment for patients with HFrEF: (i) reduction in mortality, (ii) prevention of recurrent hospitalizations due to worsening HF, and (iii) improvement in clinical status, functional capacity, and QOL.[100–102]

The key evidence supporting the recommendations in this section for patients with symptomatic HFrEF is given in *Supplementary Table 1*.

Figure 2 depicts the algorithm for the treatment strategy, including drugs and devices in patients with HFrEF, for Class I indications for the reduction of mortality (either all-cause or CV). The recommendations for each treatment are summarized below.

5.2.2 General principles of pharmacotherapy for heart failure with reduced ejection fraction

Modulation of the renin-angiotensin-aldosterone (RAAS) and sympathetic nervous systems with angiotensin-converting enzyme inhibitors (ACE-I) or an angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers, and mineralocorticoid receptor antagonists (MRA) has been shown to improve survival, reduce the risk of HF hospitalizations, and reduce symptoms in patients with HFrEF. These drugs serve as the foundations of pharmacotherapy for patients with HFrEF. The triad of an ACE-I/ARNI, a beta-blocker, and an MRA is recommended as cornerstone therapies for these patients, unless the drugs are contraindicated or not tolerated.[103–105] They should be uptitrated to the doses used in the clinical trials (or to maximally tolerated doses if that is not possible). This guideline still recommends the use of ARNI as a replacement for ACE-I in suitable patients who remain symptomatic on ACE-I, beta-blocker, and MRA therapies; however, an ARNI may be considered as a first-line therapy instead of an ACE-I.[106,107] The recommended doses of these drugs are given in *Table 8*. Angiotensin-receptor blockers (ARBs) still have a role in those who are intolerant to ACE-I or ARNI.

The sodium-glucose co-transporter 2 (SGLT2) inhibitors dapagliflozin and empagliflozin added to therapy with ACE-I/ARNI/beta-blocker/MRA reduced the risk of CV death and worsening HF in patients with HFrEF.[108,109] Unless contraindicated or not tolerated, dapagliflozin or empagliflozin are recommended for all patients with HFrEF already treated with an ACE-I/ARNI, a beta-blocker, and an MRA, regardless of whether they have diabetes or not.

Other drugs may be used for selected patients with HFrEF. These are discussed in section 5.4.

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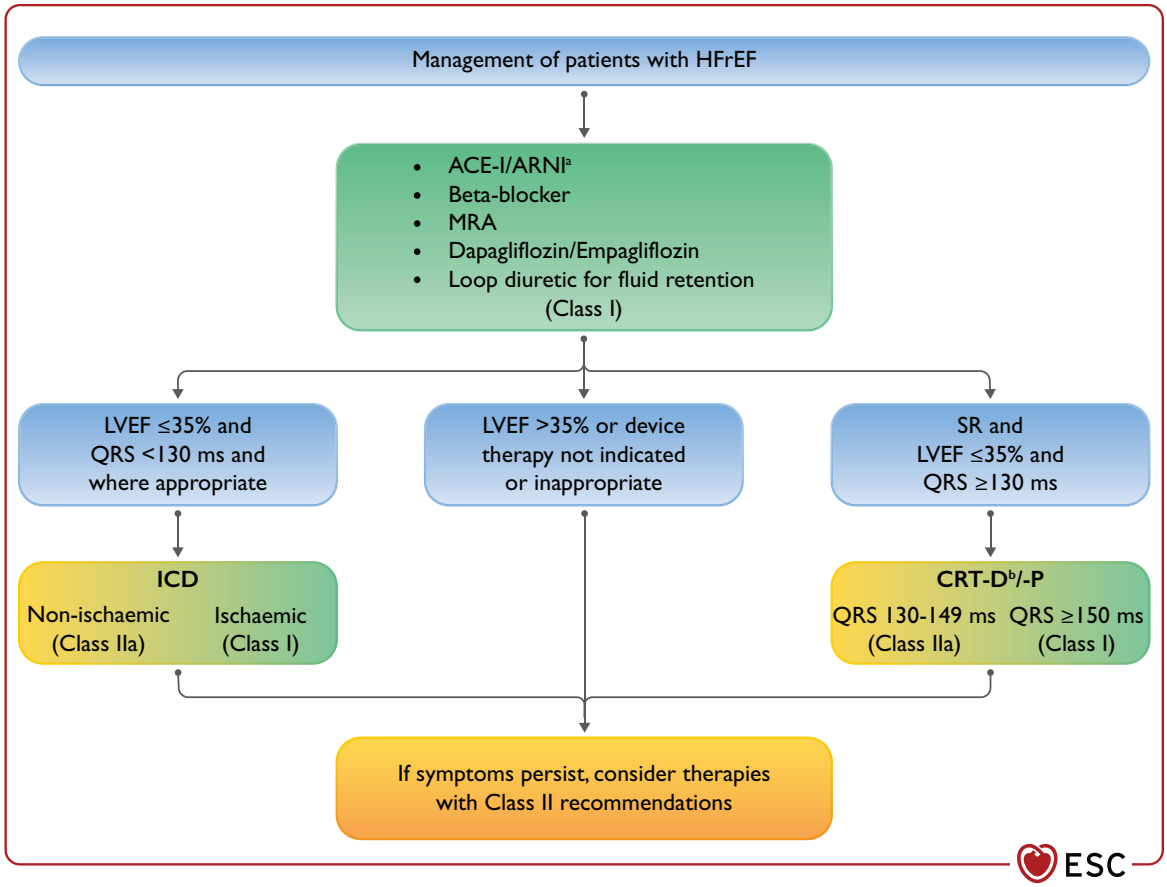

Figure 2 Therapeutic algorithm of Class I Therapy Indications for a patient with heart failure with reduced ejection fraction. ACE-I = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; CRT-D =cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; ICD = implantable cardioverter-defibrillator; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; QRS = Q, R, and S waves (on a 12-lead electrocardiogram); SR = sinus rhythm. [a]As a replacement for ACE-I. [b]Where appropriate. Class I = green. Class IIa = Yellow.

5.3 Drugs recommended in all patients with heart failure with reduced ejection fraction

Pharmacological treatments indicated in patients with (NYHA class II–IV) heart failure with reduced ejection fraction (LVEF ≤40%)

Recommendations	Class[a]	Level[b]
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113]	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120]	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122]	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.[105]	I	B

ACE-I = angiotensin-converting enzyme inhibitor; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.
[a]Class of recommendation.
[b]Level of evidence.

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Table 8 Evidence-based doses of disease-modifying drugs in key randomized trials in patients with heart failure with reduced ejection fraction

	Starting dose	Target dose
ACE-I		
Captopril[a]	6.25 mg *t.i.d.*	50 mg *t.i.d.*
Enalapril	2.5 mg *b.i.d.*	10–20 mg *b.i.d.*
Lisinopril[b]	2.5–5 mg *o.d.*	20–35 mg *o.d.*
Ramipril	2.5 mg *b.i.d.*	5 mg *b.i.d.*
Trandolapril[a]	0.5 mg *o.d.*	4 mg *o.d.*
ARNI		
Sacubitril/valsartan	49/51 mg *b.i.d.*[c]	97/103 mg *b.i.d.*
Beta-blockers		
Bisoprolol	1.25 mg *o.d.*	10 mg *o.d.*
Carvedilol	3.125 mg *b.i.d.*	25 mg *b.i.d.*[e]
Metoprolol succinate (CR/XL)	12.5–25 mg *o.d.*	200 mg *o.d.*
Nebivolol[d]	1.25 mg *o.d.*	10 mg *o.d.*
MRA		
Eplerenone	25 mg *o.d.*	50 mg *o.d.*
Spironolactone	25 mg *o.d.*[f]	50 mg *o.d.*
SGLT2 inhibitor		
Dapagliflozin	10 mg *o.d.*	10 mg *o.d.*
Empagliflozin	10 mg *o.d.*	10 mg *o.d.*
Other agents		
Candesartan	4 mg *o.d.*	32 mg *o.d.*
Losartan	50 mg *o.d.*	150 mg *o.d.*
Valsartan	40 mg *b.i.d.*	160 mg *b.i.d.*
Ivabradine	5 mg *b.i.d.*	7.5 mg *b.i.d.*
Vericiguat	2.5 mg *o.d.*	10 mg *o.d.*
Digoxin	62.5 µg *o.d.*	250 µg *o.d.*
Hydralazine/ Isosorbide dinitrate	37.5 mg *t.i.d.*/20 mg *t.i.d.*	75 mg *t.i.d.*/40 mg *t.i.d.*

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ACE-I = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; *b.i.d.* = bis in die (twice daily); CR = controlled release; CV = cardiovascular; MRA = mineralocorticoid receptor antagonist; *o.d.* = omne in die (once daily); SGLT2 = sodium-glucose co-transporter 2; *t.i.d.* = ter in die (three times a day); XL = extended release.

[a]Indicates an ACE-I where the dosing target is derived from post-myocardial infarction trials.

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

[c]Sacubitril/valsartan may have an optional lower starting dose of 24/26 mg *b.i.d.* for those with a history of symptomatic hypotension.

[d]Indicates a treatment not shown to reduce CV or all-cause mortality in patients with heart failure (or shown to be non-inferior to a treatment that does).

[e]A maximum dose of 50 mg twice daily can be administered to patients weighing over 85 kg.

[f]Spironolactone has an optional starting dose of 12.5 mg in patients where renal status or hyperkalaemia warrant caution.

5.3.1 Angiotensin-converting enzyme inhibitors

ACE-Is were the first class of drugs shown to reduce mortality and morbidity in patients with HFrEF.[110–113] They have also been shown to improve symptoms.[111] They are recommended in all patients unless contraindicated or not tolerated. They should be uptitrated to the maximum tolerated recommended doses.

Practical guidance on how to use ACE-Is is given in *Supplementary Table 2*.

5.3.2 Beta-blockers

Beta-blockers have been shown to reduce mortality and morbidity in patients with HFrEF, in addition to treatment with an ACE-I and diuretic.[114–120] They also improve symptoms.[123] There is consensus that ACE-I and beta-blockers can be commenced together as soon as the diagnosis of symptomatic HFrEF is established. There is no evidence favouring the initiation of a beta-blocker before an ACE-I and vice versa.[124] Beta-blockers should be initiated in clinically stable, euvolaemic, patients at a low dose and gradually uptitrated to the maximum tolerated dose. In patients admitted with AHF, beta-blockers should be cautiously initiated in hospital, once the patient is haemodynamically stabilized.

An individual patient data (IPD) meta-analysis of all major beta-blocker trials in HFrEF has shown no benefit on hospital admissions and mortality in the subgroup of patients with HFrEF with AF.[125] However, since this is a retrospective subgroup analysis, and because beta-blockers did not increase risk, the guideline committee decided not to make a separate recommendation according to heart rhythm.

Practical guidance on how to use beta-blockers is given in *Supplementary Table 3*.

5.3.3 Mineralocorticoid receptor antagonists

MRAs (spironolactone or eplerenone) are recommended, in addition to an ACE-I and a beta-blocker, in all patients with HFrEF to reduce mortality and the risk of HF hospitalization.[121,122] They also improve symptoms.[121] MRAs block receptors that bind aldosterone and, with different degrees of affinity, other steroid hormones (e.g. corticosteroid and androgen) receptors. Eplerenone is more specific for aldosterone blockade and, therefore, causes less gynaecomastia.

Caution should be exercised when MRAs are used in patients with impaired renal function and in those with serum potassium concentrations >5.0 mmol/L.

Practical guidance on how to use MRAs is given in *Supplementary Table 4*.

5.3.4 Angiotensin receptor-neprilysin inhibitor

In the PARADIGM-HF trial, sacubitril/valsartan, an ARNI, was shown to be superior to enalapril in reducing hospitalizations for worsening HF, CV mortality, and all-cause mortality in patients with ambulatory HFrEF with LVEF ≤40% (changed to ≤35% during the study). Patients in the trial had elevated plasma NP concentrations, an eGFR ≥30 mL/min/1.73 m^2 and were able to tolerate enalapril and then sacubitril/valsartan during the run-in period.[105] Additional benefits of sacubitril/valsartan included an improvement in symptoms and QOL,[105] a reduction in the incidence of diabetes requiring insulin treatment,[126] and a reduction in the decline in eGFR,[127] as well as a reduced rate of hyperkalaemia.[128] Additionally, the use of sacubitril/valsartan may allow a reduction in loop diuretic requirement.[129] Symptomatic hypotension was reported more commonly in patients treated with sacubitril/valsartan as compared to enalapril, but despite developing hypotension, these patients also gained clinical benefits from sacubitril/valsartan therapy.[128,130]

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Therefore, it is recommended that an ACE-I or ARB is replaced by sacubitril/valsartan in ambulatory patients with HFrEF, who remain symptomatic despite optimal treatment outlined above. Two studies have examined the use of ARNI in hospitalized patients, some of whom had not been previously treated with ACE-I. Initiation in this setting appears safe and reduces subsequent CV death or HF hospitalizations by 42% compared to enalapril.[106,107,131] As such, initiation of sacubitril/valsartan in ACE-I naive (i.e. *de novo*) patients with HFrEF may be considered (class of recommendation IIb, level of evidence B). Patients being commenced on sacubitril/valsartan should have an adequate blood pressure (BP), and an eGFR ≥30 mL/min/1.73 m^2. A washout period of at least 36 h after ACE-I therapy is required in order to minimize the risk of angioedema.

Practical guidance on how to use ARNI is given in *Supplementary Table 5*.

5.3.5 Sodium-glucose co-transporter 2 inhibitors

The DAPA-HF trial investigated the long-term effects of dapagliflozin (SGLT2 inhibitor) compared to placebo in addition to optimal medical therapy (OMT), on morbidity and mortality in patients with ambulatory HFrEF.[108] Patients participated in the trial if they were in NYHA class II–IV, and had an LVEF ≤40% despite OMT. Patients were also required to have an elevated plasma NT-proBNP and an eGFR ≥30 mL/min/1.73 m^2.[108]

Therapy with dapagliflozin resulted in a 26% reduction in the primary endpoint: a composite of worsening HF (hospitalization or an urgent visit resulting in i.v. therapy for HF) or CV death. Both of these components were significantly reduced. Moreover, dapagliflozin reduced all-cause mortality,[108] alleviated HF symptoms, improved physical function and QOL in patients with symptomatic HFrEF.[132] Benefits were seen early after the initiation of dapagliflozin, and the absolute risk reduction was large. Survival benefits were seen to the same extent in patients with HFrEF with and without diabetes, and across the whole spectrum of HbA1c values.[108]

Subsequently, the EMPEROR-Reduced trial found that empagliflozin reduced the combined primary endpoint of CV death or HF hospitalization by 25% in patients with NYHA class II–IV symptoms, and an LVEF ≤40% despite OMT.[109] This trial included patients with an eGFR >20 mL/min/1.73 m^2 and there was also a reduction in the decline in eGFR in individuals receiving empagliflozin. It was also associated with an improvement in QOL.[133] Although there was not a significant reduction in CV mortality in the EMPEROR-Reduced trial, a recent meta-analysis of the DAPA-HF and EMPEROR-Reduced trials found no heterogeneity in CV mortality.[134]

Therefore, dapagliflozin or empagliflozin are recommended, in addition to OMT with an ACE-I/ARNI, a beta-blocker and an MRA, for patients with HFrEF regardless of diabetes status. The diuretic/natriuretic properties of SGLT2 inhibitors may offer additional benefits in reducing congestion and may allow a reduction in loop diuretic requirement.[135]

The combined SGLT-1 and 2 inhibitor, sotagliflozin, has also been studied in patients with diabetes who were hospitalized with HF. The drug reduced CV death and hospitalization for HF.[136] It is discussed further in the AHF and comorbidity sections.

Therapy with SGLT2 inhibitors may increase the risk of recurrent genital fungal infections. A small reduction in eGFR following initiation is expected and is reversible and should not lead to premature discontinuation of the drug.

Practical guidance on how to use the SGLT2 inhibitors dapagliflozin and empagliflozin are given in *Supplementary Table 6*.

5.4 Other drugs recommended or to be considered in selected patients with heart failure with reduced ejection fraction

Other pharmacological treatments indicated in selected patients with NYHA class II–IV heart failure with reduced ejection fraction (LVEF ≤40%)

Recommendations	Class[a]	Level[b]
Loop diuretics		
Diuretics are recommended in patients with HFrEF with signs and/or symptoms of congestion to alleviate HF symptoms, improve exercise capacity, and reduce HF hospitalizations.[137]	I	C
ARB		
An ARB[c] is recommended to reduce the risk of HF hospitalization and CV death in symptomatic patients unable to tolerate an ACE-I or ARNI (patients should also receive a beta-blocker and an MRA).[138]	I	B
I_f-channel inhibitor		
Ivabradine should be considered in symptomatic patients with LVEF ≤35%, in SR and a resting heart rate ≥70 b.p.m. despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I/(or ARNI), and an MRA, to reduce the risk of HF hospitalization and CV death.[139]	IIa	B
Ivabradine should be considered in symptomatic patients with LVEF ≤35%, in SR and a resting heart rate ≥70 b.p.m. who are unable to tolerate or have contraindications for a beta-blocker to reduce the risk of HF hospitalization and CV death. Patients should also receive an ACE-I (or ARNI) and an MRA.[140]	IIa	C
Soluble guanylate cyclase receptor stimulator		
Vericiguat may be considered in patients in NYHA class II–IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization.[141]	IIb	B
Hydralazine and isosorbide dinitrate		
Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated left ventricle in NYHA class III–IV despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of HF hospitalization and death.[142]	IIa	B

Continued

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Hydralazine and isosorbide dinitrate may be considered in patients with symptomatic HFrEF who cannot tolerate any of an ACE-I, an ARB, or ARNI (or they are contraindicated) to reduce the risk of death.[143]	IIb	B
Digoxin		
Digoxin may be considered in patients with symptomatic HFrEF in sinus rhythm despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF hospitalizations).[144]	IIb	B

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ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; b.p.m. = beats per minute; CV = cardiovascular; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; SR = sinus rhythm.
[a]Class of recommendation.
[b]Level of evidence.
[c]The ARBs with evidence in HFrEF are candesartan, losartan, and valsartan.

5.4.1 Diuretics

Loop diuretics are recommended to reduce the signs and/or symptoms of congestion in patients with HFrEF. The quality of the evidence regarding diuretics is poor and their effects on morbidity and mortality have not been studied in RCTs. However, it should also be remembered that the major disease-modifying treatment trials for HFrEF were conducted with a high background use of loop diuretic therapy. One meta-analysis has shown that in patients with HFrEF, loop and thiazide diuretics appear to reduce the risk of death and worsening HF compared with a placebo, and compared with an active control, diuretics improve exercise capacity.[137]

Loop diuretics produce a more intense and shorter diuresis than thiazides, although they act synergistically (sequential nephron blockade) and the combination may be used to treat diuretic resistance. However, adverse effects are more likely, and these combinations should only be used with care. Of note, ARNI, MRAs, and SGLT2 inhibitors may also possess diuretic properties.[129,145]

The aim of diuretic therapy is to achieve and maintain euvolaemia with the lowest diuretic dose. In some euvolaemic/hypovolaemic patients, the use of a diuretic drug might be reduced or discontinued.[146] Patients should be trained to self-adjust their diuretic dose based on monitoring of symptoms/signs of congestion and daily weight measurements.

Practical guidance on how to use diuretics is given in *Supplementary Table 7*.

5.4.2 Angiotensin II type I receptor blockers

The place of ARBs in the management of HFrEF has changed over the last few years. They are now recommended for patients who cannot tolerate ACE-I or ARNI because of serious side effects. Candesartan in the CHARM-Alternative study reduced CV deaths and HF hospitalizations in patients who were not receiving an ACE-I due to previous intolerance.[138] Valsartan, in addition to usual therapy, including ACE-I, reduced HF hospitalizations in the Val-HeFT trial.[147] However, no ARB has reduced all-cause mortality in any trial.

5.4.3 I_f-channel inhibitor

Ivabradine slows heart rate by inhibition of the I_f channel in the sinus node and is therefore only effective in patients in SR. Ivabradine reduced the combined endpoint of CV mortality and HF hospitalization in patients with symptomatic HFrEF with an LVEF ≤35%, with HF hospitalization in recent 12 months, in sinus rhythm (SR) and with a heart rate ≥70 b.p.m. who were on evidence-based therapy including an ACE-I (or ARB), a beta-blocker, and an MRA.[139,140] Our recommendation is based on the heart rate of ≥70 b.p.m. used in the SHIFT trial. However, the European Medicines Agency (EMA) approved ivabradine for use in Europe in patients with HFrEF with LVEF ≤35% and in SR with a resting heart rate ≥75 b.p.m., because in this group ivabradine conferred a survival benefit[148] based on a retrospective subgroup analysis. Every effort should be made to commence and uptitrate beta-blocker therapy to guideline recommended/maximally tolerated doses prior to considering ivabradine.

Practical guidance on how to use ivabradine is given in *Supplementary Table 8*.

5.4.4 Combination of hydralazine and isosorbide dinitrate

There is no clear evidence to suggest the use of this fixed-dose combination therapy in all patients with HFrEF. A small RCT conducted in self-identified black patients showed that an addition of the combination of hydralazine and isosorbide dinitrate to conventional therapy (an ACE-I, a beta-blocker, and an MRA) reduced mortality and HF hospitalizations in patients with HFrEF and NYHA classes III–IV.[142] These results are difficult to translate to patients of other racial or ethnic origins.

Additionally, a combination of hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who cannot tolerate any of an ACE-I, ARNI, or an ARB (or if they are contraindicated) to reduce mortality. However, this recommendation is based on the results of the relatively small Veterans Administration Cooperative Study, which included only male patients with symptomatic HFrEF who were treated with digoxin and diuretics.[143]

5.4.5 Digoxin

Digoxin may be considered in patients with HFrEF in SR to reduce the risk of hospitalization,[144] although its effect on those routinely treated with beta-blockers has not been tested. In the DIG trial, the overall effect on mortality with digoxin was neutral.

The effects of digoxin in patients with HFrEF and AF have not been studied in RCTs. Some studies have suggested a potentially higher risk of events in patients with AF receiving digoxin,[149,150] whereas another meta-analysis concluded, on the basis of non-RCTs, that digoxin has no deleterious effect on mortality in patients with AF and HF, most of whom had HFrEF.[151] Therefore, in patients with symptomatic HF and AF, digoxin may be useful for the treatment of patients with HFrEF and AF with rapid ventricular rate, when other therapeutic options cannot be pursued.[150,152–155]

Digoxin has a narrow therapeutic window and so levels should be checked aiming for a serum digoxin concentration <1.2 ng/mL.[156,157] Caution should also be exercised when using it in females, the elderly, frail, hypokalaemic, and malnourished subjects. In patients with reduced renal function, digitoxin could be considered. Digitoxin use in HF and SR is currently being investigated.[158]

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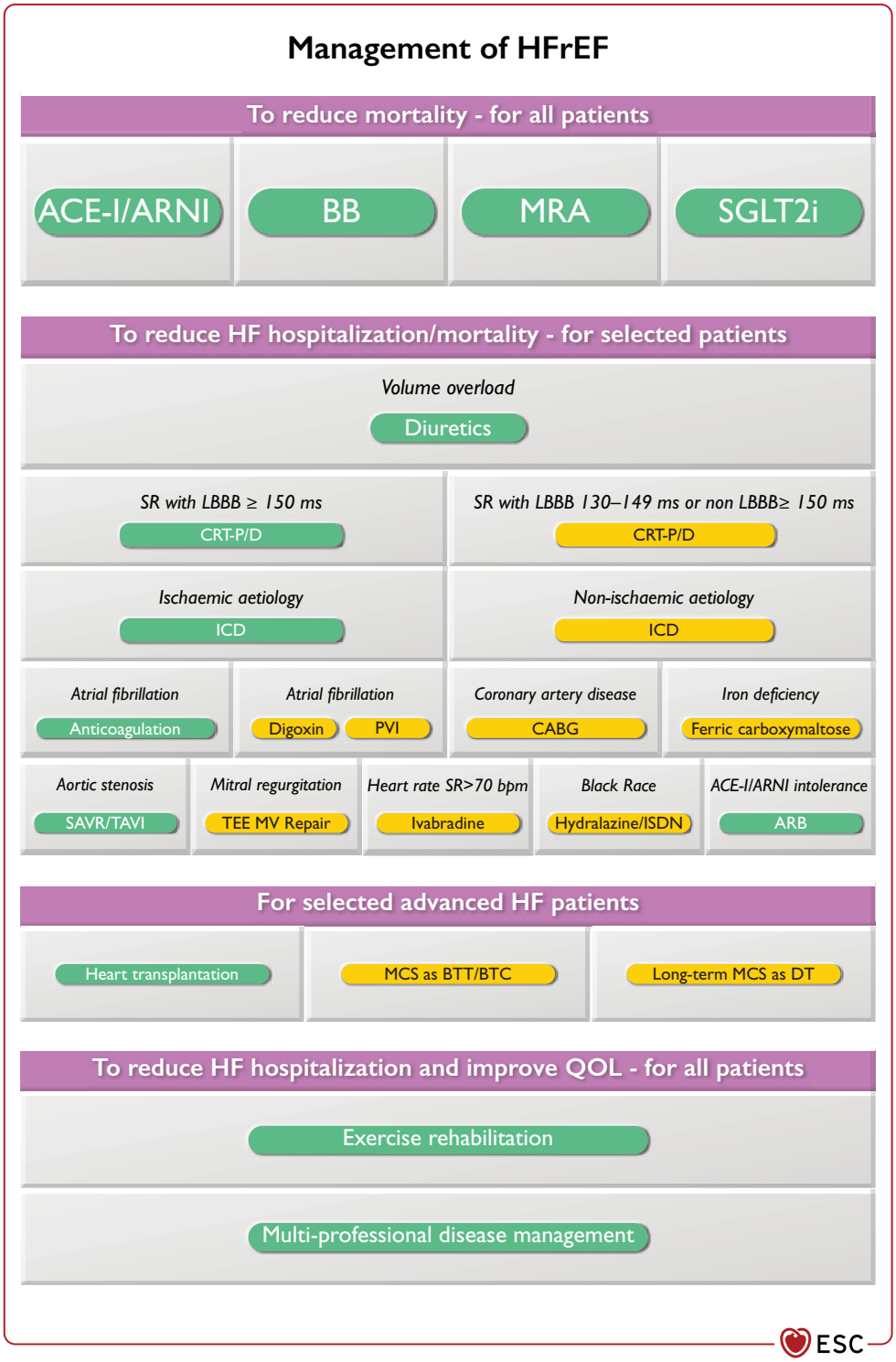

Figure 3 Central illustration. Strategic phenotypic overview of the management of heart failure with reduced ejection fraction. ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta-blocker; b.p.m. = beats per minute; BTC = bridge to candidacy; BTT = bridge to transplantation; CABG = coronary artery bypass graft; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; DT = destination therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; ISDN = isosorbide dinitrate; LBBB = left bundle branch block; MCS = mechanical circulatory support; MRA = mineralocorticoid receptor antagonist; MV = mitral valve; PVI = pulmonary vein isolation; QOL = quality of life; SAVR = surgical aortic valve replacement; SGLT2i = sodium-glucose co-transporter 2 inhibitor; SR = sinus rhythm; TAVI = transcatheter aortic valve replacement; TEE = transcatheter edge to edge. Colour code for classes of recommendation: Green for Class of recommendation I; Yellow for Class of recommendation IIa (see *Table 1* for further details on classes of recommendation). The Figure shows management options with Class I and IIa recommendations. See the specific Tables for those with Class IIb recommendations.

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5.4.6 Recently reported advances from trials in heart failure with reduced ejection fraction

Soluble guanylate cyclase receptor stimulator

The VICTORIA study assessed the efficacy and safety of the oral soluble guanylate cyclase receptor stimulator, vericiguat, in patients with a reduced EF and recently decompensated CHF. The incidence of the primary endpoint of death from CV causes or hospitalization for HF was lower among those who received vericiguat than among those who received placebo.[141] There was no reduction in either all-cause or CV mortality. Thus, vericiguat may be considered, in addition to standard therapy for HFrEF, to reduce the risk of CV mortality and hospitalizations for HF.

Cardiac myosin activator

The GALACTIC-HF study assessed the efficacy and safety of the cardiac myosin activator, omecamtiv mecarbil, in HFrEF patients, enrolling patients in both the inpatient and outpatient settings. The primary endpoint of a first HF event or CV death was reduced by 8%. There was no significant reduction in CV mortality. Currently, this drug is not licensed for use in HF. However, in the future it may be able to be considered, in addition to standard therapy for HFrEF to reduce the risk of CV mortality and hospitalization for HF.[159]

5.5 Strategic phenotypic overview of the management of heart failure with reduced ejection fraction

In addition to the general therapies considered in section 5, other therapies are appropriate to consider in selected patients. These are covered in detail in later sections. Some of the main ones (i.e. those with Class I and IIa Mortality/Hospitalization indications) are depicted in *Figure 3*. The effect of some interventions on symptoms/QOL are outlined in *Supplementary Table 9*.

6 Cardiac rhythm management for heart failure with reduced ejection fraction

This section provides recommendations on the use of implantable cardioverter-defibrillators (ICD) and cardiac resynchronization therapy (CRT). Other implantable devices will be discussed at the end of this section.

6.1 Implantable cardioverter-defibrillator

A high proportion of deaths among patients with HF, especially in those with milder symptoms, occur suddenly and unexpectedly. Many of these may be due to electrical disturbances, including ventricular arrhythmias, bradycardia, and asystole, although some are due to other acute vascular events. Treatments that improve or delay the progression of CV disease have been shown to reduce the annual rate of sudden death,[105,160] but they do not treat arrhythmic events when they occur. ICDs are effective at correcting potentially lethal ventricular arrhythmias, and in the case of transvenous systems, also prevent bradycardia. Some antiarrhythmic drugs might reduce the rate of tachyarrhythmias and sudden death, but they do not reduce overall mortality,[161] and may increase it.

Recommendations for an implantable cardioverter-defibrillator in patients with heart failure

Recommendations	Class[a]	Level[b]
Secondary prevention		
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing haemodynamic instability, and who are expected to survive for >1 year with good functional status, in the absence of reversible causes or unless the ventricular arrhythmia has occurred <48 h after a MI.[162–164]	I	A
Primary prevention		
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II–III) of an ischaemic aetiology (unless they have had a MI in the prior 40 days—see below), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status.[161,165]	I	A
An ICD should be considered to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II–III) of a non-ischaemic aetiology, and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status.[161,166,167]	IIa	A
Patients should be carefully evaluated by an experienced cardiologist before generator replacement, because management goals, the patient's needs and clinical status may have changed.[168–172]	IIa	B
A wearable ICD may be considered for patients with HF who are at risk of sudden cardiac death for a limited period or as a bridge to an implanted device.[173–176]	IIb	B
ICD implantation is not recommended within 40 days of a MI as implantation at this time does not improve prognosis.[177,178]	III	A
ICD therapy is not recommended in patients in NYHA class IV with severe symptoms refractory to pharmacological therapy unless they are candidates for CRT, a VAD, or cardiac transplantation.[179–183]	III	C

CRT = cardiac resynchronization therapy; HF = heart failure; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; OMT = optimal medical therapy; VAD = ventricular assist device.
[a]Class of recommendation.
[b]Level of evidence.

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6.1.1 Secondary prevention of sudden cardiac death

Compared with amiodarone treatment, ICDs reduce mortality in survivors of cardiac arrest and in patients who have experienced sustained symptomatic ventricular arrhythmias. An ICD is recommended in such patients when the intent is to increase survival; the decision to implant should take into account the patient's view and their QOL, the LVEF (survival benefit is uncertain when LVEF >35%) and the absence of other diseases likely to cause death within the following year.[162–164,184]

6.1.2 Primary prevention of sudden cardiac death

In an analysis of over 40 000 patients from 12 pivotal HF trials, rates of sudden cardiac death decreased by 44% over the 20-year period (from the mid-1990s to 2015).[160] This is almost certainly due to advances in HF treatment, as many key guideline-recommended therapies, including beta-blockers, MRAs, sacubitril/valsartan, and CRT pacemakers (CRT-P), reduce the risk of sudden death. While the afore-mentioned HF therapies have been shown to reduce mortality in patients with HFrEF, amiodarone has not.[161] However, if it is to be used, it should be with caution due to its significant side-effect profile. Conversely, dronedarone[185] and the class I antiarrhythmic agents disopyramide, encainide, and flecainide[186] should not be used for prevention of arrhythmias due to the increase in mortality seen in clinical studies.

Although an ICD reduces the rate of sudden arrhythmic death in patients with HFrEF,[187] it would be expected that, in well-managed patients, the additional benefit afforded by an ICD would be lower. In the DANISH trial, rates of sudden death were low in patients with non-ischaemic cardiomyopathy (NICM); only 70 patients out of 1116 followed up over 5 years had sudden death.[166] Whilst there was a modest absolute reduction in sudden death with a defibrillator-containing device, this did not significantly improve the overall risk of mortality. However, subgroup analysis suggested there was a benefit in those ≤70 years.[188] In a recent meta-analysis of studies that examined the effect of ICDs in NICM a survival benefit was still seen, although the effect was significantly weakened by the inclusion of the DANISH trial.[167]

On average, patients with IHD are at greater risk of sudden death than patients with NICM and therefore, although the relative benefits are similar, the absolute benefit is greater in patients with IHD.[187] Two RCTs showed no benefit in patients who had an ICD implanted within 40 days after a MI.[177,178] Although sudden arrhythmic deaths were reduced, this was balanced by an increase in non-arrhythmic deaths. Accordingly, an ICD for primary prevention is contraindicated in this time period. Furthermore, ICD implantation is recommended only if a minimum of 3 months of OMT has failed to increase the LVEF to >35%. OMT ideally includes the use of Class I recommended drugs for HFrEF. However, the ICD trials we cite predate the use of ARNI and SGLT2 inhibitors. Whether implantation of ICDs reduces mortality in those with an LVEF >35% is unknown. There is an ongoing trial of ICD therapy in such patients with the presence of scar on CMR imaging.[189]

6.1.3 Patient selection for implantable cardioverter-defibrillator therapy

Patients with HFrEF and a QRS duration ≥130 ms can be considered for CRT with a defibrillator (CRT-D) rather than ICD. See the section on CRT for further details (section 6.2).

In patients with moderate or severe HF, a reduction in sudden death may be partially or wholly offset by an increase in death due to worsening HF.[161] As such, ICD therapy is not recommended in patients in NYHA class IV, with severe symptoms refractory to pharmacological therapy, who are not candidates for a ventricular assist device (VAD) or cardiac transplantation. Such patients have a very limited life expectancy and are likely to die from pump failure. Similarly, patients with serious comorbidities who are unlikely to survive substantially more than 1 year with good QOL are unlikely to obtain substantial benefit from an ICD.[179–183]

Although the DANISH trial did not show a significant benefit from ICD therapy in patients with NICM, it should be remembered that NICM is a heterogeneous condition, and certain subgroups (e.g. laminopathies, sarcoidosis) are at higher risk of sudden death and therefore merit careful consideration of ICD implantation. Tools to help risk stratification (e.g. scar burden on magnetic resonance imaging) can be helpful in that regard.[190–192]

Patients should be counselled as to the purpose of an ICD and involved in the decision-making process. They should also be aware of the potential complications related to implantation, any additional implications for driving, and the risk of inappropriate shocks. Furthermore, patients should be informed about the circumstances where the defibrillator (or defibrillator component of a CRT-D) might be deactivated (e.g. terminal disease) or explanted (e.g. infection or recovery of LV function).[193] Subsequent timely conversations regarding defibrillator deactivation should be held with the patient and caregiver(s).

When an ICD generator reaches its end of life or requires explantation, it should not be replaced automatically. Rather, shared decision making should be undertaken.[168–172] Patients should be carefully evaluated by an experienced cardiologist as treatment goals may have changed since implantation (the risk of fatal arrhythmia may be lower, or the risk of non-arrhythmic death may be higher). It is a matter of some controversy whether patients whose LVEF has greatly improved and who have not required device therapy during the lifetime of the ICD should have another device implanted.[168–172]

6.1.4 Implantable cardioverter-defibrillator programming

Routine defibrillation threshold testing is no longer performed following implantation of an ICD or CRT-D as it does not improve shock efficacy or reduce arrhythmic death.[194] Conservative programming with long delays[195] between detection and the ICD delivering therapy dramatically reduces the risk of both inappropriate and appropriate but unnecessary shocks.[194,196,197] Generally, for primary prevention, defibrillators are programmed to minimize pacing (e.g. ventricular demand pacing VVI at 40/min), and with a tachycardia treatment zone >200/min.[194,198] Ultimately—and particularly for secondary prevention—programming should be adapted according to the patient's specific needs.

6.1.5 Subcutaneous and wearable implantable cardioverter-defibrillators

Subcutaneous ICDs (S-ICDs) appear to be as effective as conventional transvenous ICDs with a similar complication rate. Although the risk of inappropriate shocks appeared to be higher initially,

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improved patient selection has shown S-ICDs are non-inferior to transvenous ICDs in this regard.[199–202] They may be the preferred option for patients with difficult venous access or those who require ICD explantation due to infection. Patients must be carefully selected, as S-ICDs cannot treat bradyarrhythmia (except post-shock pacing) and cannot deliver either anti-tachycardia pacing or CRT. Substantial RCTs with these devices and more long-term data on safety and efficacy are awaited.

A wearable cardioverter-defibrillator that is able to recognize and treat ventricular arrhythmias may be considered for a limited period of time in selected patients with HF who are at high risk for sudden death but otherwise are not suitable for ICD implantation.[162,175,176,203] However, the large VEST trial failed to show that the wearable cardioverter-defibrillator reduced arrhythmic death in patients with an LVEF ≤35% following a recent acute MI.[204]

For more detailed recommendations on the use/indications of ICD we refer the reader to the ESC/European Heart Rhythm Association (EHRA) Guidelines on ventricular tachyarrhythmias and sudden cardiac death.[201]

6.2 Cardiac resynchronization therapy

Recommendations for cardiac resynchronization therapy implantation in patients with heart failure

Recommendations	Class[a]	Level[b]
CRT is recommended for symptomatic patients with HF in SR with a QRS duration ≥150 ms and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.[205–215]	I	A
CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class or QRS width who have an indication for ventricular pacing for high degree AV block in order to reduce morbidity. This includes patients with AF.[216–219]	I	A
CRT should be considered for symptomatic patients with HF in SR with a QRS duration ≥150 ms and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.[205–215]	IIa	B
CRT should be considered for symptomatic patients with HF in SR with a QRS duration of 130–149 ms and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.[211,220]	IIa	B
Patients with an LVEF ≤35% who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT and who have a significant proportion of RV pacing should be considered for 'upgrade' to CRT.[221]	IIa	B
CRT may be considered for symptomatic patients with HF in SR with a QRS duration of 130–149 ms and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.[208,213]	IIb	B
CRT is not recommended in patients with a QRS duration <130 ms who do not have an indication for pacing due to high degree AV block.[222–224]	III	A

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AF = atrial fibrillation; AV = atrio-ventricular; CRT = cardiac resynchronization therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; OMT = optimal medical therapy (class I recommended medical therapies for at least 3 months); QRS = Q, R, and S waves (combination of three of the graphical deflections); RV = right ventricular; SR = sinus rhythm.
[a]Class of recommendation.
[b]Level of evidence.

In appropriately selected individuals, CRT reduces morbidity and mortality.[211] Furthermore, CRT improves cardiac function, and enhances QOL.[209,225]

Whilst the CARE-HF[206,208] and COMPANION[210] trials compared the effect of CRT with medical therapy (MT), the majority of CRT studies have compared CRT-D with ICD, and a few have compared CRT-P with backup pacing. The prevention of fatal bradycardia might be an important mechanism of benefit shared by all pacing devices. In CARE-HF, at baseline, 25% of patients had a resting heart rate of ≤60 b.p.m.[206,208,209] If prevention of bradycardia is important, the effect of CRT will appear greater in trials where there is no device in the control group. However, in MADIT-II, 35% of those who died with an ICD did so suddenly even though they were protected from both brady- and tachyarrhythmia.[226]

Most studies of CRT have specified that the LVEF should be ≤35%, but RAFT[212] and MADIT-CRT[213,214] specified an LVEF ≤30%, while REVERSE[207,215,227] specified ≤40% and BLOCK-HF[216] ≤50%. Relatively few patients with an LVEF of 35–40% have been randomized, but an IPD meta-analysis suggests no diminution of the effect of CRT in this group.[211]

Assessing the 'response' to CRT is challenging. Indeed, many who do not appear to 'respond' favourably in terms of their symptoms or LV function may well have experienced the mortality benefit. Several characteristics predict improvement in morbidity and mortality. The extent of reverse remodelling is one of the most important mechanisms of action of CRT. Patients with HFrEF of an ischaemic aetiology have less improvement in LV function due to myocardial scar tissue, which is less likely to undergo favourable remodelling.[228] Conversely, women may be more likely to respond than men, possibly due to smaller body and heart size.[220,224,229] QRS width predicts CRT response and was the inclusion criterion in all randomized trials,[211] but QRS morphology has also been related to a beneficial response to CRT. Several studies have shown that patients with left bundle branch block (LBBB) morphology are more likely to respond favourably to CRT, whereas there is less certainty about patients with non-LBBB morphology.[230] This latter group is also underrepresented in the large CRT trials.[206,210,213] However, patients with LBBB

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morphology often have wider QRS durations, and there is a current debate about whether QRS durations or QRS morphology is the main predictor of a beneficial response to CRT. Evidence from two IPD meta-analyses indicates that after accounting for QRS duration, there is little evidence to suggest that QRS morphology or aetiology of disease influence the effect of CRT on morbidity or mortality.[211,220] In addition, none of the landmark trials selected patients for inclusion according to QRS morphology, sex, or ischaemic aetiology, nor were they powered for subgroup analyses.

The Echo-CRT trial[222,223] and an IPD meta-analysis[213] suggest possible harm from CRT when QRS duration is <130 ms, thus implantation of CRT is not recommended if QRS duration is <130 ms.

If a patient is scheduled to receive an ICD and is in SR, with a LBBB, CRT-D should be considered if the QRS is between 130 and 149 ms and is recommended if QRS is ≥150 ms. However, clinical practice varies widely among countries and if the primary reason for implanting CRT is for the relief of symptoms, then the clinician should choose CRT-P or CRT-D, whichever they consider appropriate. The only randomized trial to compare CRT-P and CRT-D[210] did not demonstrate a difference in morbidity or mortality between these technologies (although the trial was not powered to show such a difference). Furthermore, in the DANISH study in patients with NICM where 58% of patients received CRT there was no suggestion from subgroup analysis that CRT-P was inferior to CRT-D.[166,167]

When LVEF is reduced, RV pacing may exacerbate cardiac dyssynchrony. This can be prevented by CRT, which might improve patient outcomes.[216–218,231] However, a difference in outcome was not observed between CRT and RV pacing in a subgroup analysis of RAFT.[212] On balance, CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing in order to reduce morbidity, although no clear effect on mortality was observed. Patients with HFrEF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF with a high proportion of RV pacing, despite OMT, should be considered for 'upgrading' to CRT.

Only two small trials have compared pharmacological therapy alone vs. CRT in patients with AF, with conflicting results. Several studies have indicated that CRT is superior to RV pacing in patients undergoing atrio-ventricular (AV) node ablation.[217,218,231] However, AF is not an indication to carry out AV node ablation in patients with CRT except in a few cases when ventricular rate remains persistently high despite attempts at pharmacological rate control. A subgroup analysis of patients with AF from the RAFT study found no benefit from CRT-D compared with ICD, although less than half of patients had >90% biventricular capture.[219] In view of the paucity of evidence for the efficacy of CRT in patients with AF, it may be an option in selected patients—particularly those with a QRS ≥150 ms—ensuring a proportion of biventricular pacing as high as possible.

Observational studies report that when biventricular capture is <98%, the prognosis of patients with CRT declines.[218,232] Whether this association reflects a loss of resynchronization (which might be remedied by device programming), poor placement of the LV lead, or greater difficulty in pacing severely diseased myocardium is uncertain. This observation has not been confirmed in any randomized trial.

Early studies suggested that imaging tests for dyssynchrony were not of value in selecting patients for CRT.[233] However, a recent study has suggested that two novel markers of dyssynchrony (apical rocking and septal flash) are associated with a response to CRT, but these have not been tested as selection criteria or as prespecified subgroups in a randomized trial.[234] Patients with extensive myocardial scar will have less improvement in LV function with CRT, but this is true of any treatment for HFrEF and does not reliably predict less clinical benefit. Pacing thresholds are higher in scarred myocardium and, if possible, lead placement should avoid such regions.[235,236] Although patients with extensive scarring have an intrinsically worse prognosis, there is little evidence that they obtain less prognostic benefit from CRT.[211]

The value of trying to optimize AV intervals or interventricular delay intervals (VV intervals) after implantation using echo- or electrocardiographic criteria or BP response is uncertain but may be considered for patients who have had a disappointing response to CRT.[237,238] Other options to consider to optimize response to CRT are covered in a recently published practical article.[239]

Following CRT implantation, a review of diuretic therapy is advised as a reduction in dose or its discontinuation may be required. In addition, CRT implantation may afford an opportunity to further optimize MT for HFrEF.[240]

The reader is directed to guidelines on pacing and CRT for recommendations on device implantation procedures.[240a]

6.3 Devices under evaluation

Cardiac contractility modulation (CCM) has been evaluated in patients with NYHA class III–IV HF, with an LVEF ≥25% to ≤45% and QRS duration <130 ms, and was associated with a small improvement in exercise tolerance and QOL.[241,242]

Technologies that involve modification of the activity of the autonomic nervous system, e.g. baroreflex activation therapy,[243,244] have also been shown to offer a modest improvement in effort capacity and QOL. However, currently, the evidence is considered insufficient to support specific guideline recommendations for a reduction in mortality or hospitalization for these and a variety of other implantable electrical therapeutic technologies (see also Gaps in Evidence in section 16).

7 Heart failure with mildly reduced ejection fraction

7.1 The diagnosis of heart failure with mildly reduced ejection fraction

The diagnosis of HFmrEF requires the presence of symptoms and/or signs of HF, and a mildly reduced EF (41–49%) The presence of elevated NPs (BNP ≥35 pg/mL or NT-proBNP ≥125 pg/mL) and other evidence of structural heart disease [e.g. increased left atrial (LA) size, LVH or echocardiographic measures of LV filling] make the diagnosis more likely but are not mandatory for diagnosis if there is certainty regarding the measurement of LVEF.

An algorithm for the diagnosis of HFmrEF is depicted in *Figure 1*. For the investigation of the underlying aetiology, please refer to *Table 5* (which refers to investigations regardless of LVEF).

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7.2 Clinical characteristics of patients with heart failure with mildly reduced ejection fraction

There is a substantial overlap of clinical characteristics, risk factors, patterns of cardiac remodelling, and outcomes among the LVEF categories in HF. Patients with HFmrEF have, on average, features that are more similar to HFrEF than HFpEF, in that they are more commonly men, younger, and are more likely to have CAD (50–60%),[38,42,43] and less likely to have AF and non-cardiac comorbidities (*Supplementary Table 10*). However, ambulatory patients with HFmrEF have a lower mortality than those with HFrEF, more akin to those with HFpEF.

Patients with HFmrEF may include patients whose LVEF has improved from ≤40% or declined from ≥50%.[50]

7.3 Treatments for patients with heart failure with mildly reduced ejection fraction

As in other forms of HF, diuretics should be used to control congestion. No substantial prospective RCT has been performed exclusively in patients with HFmrEF (*Supplementary Table 11*). Some data can be gleaned from subgroup analysis of trials in HFpEF, none of which have met their primary endpoint. Although strong recommendations cannot be made about specific therapies at this point in time, we have included a Table of Recommendations to help guide the management of patients in this category.

Pharmacological treatments to be considered in patients with (NYHA class II–IV) heart failure with mildly reduced ejection fraction

Recommendations	Class[a]	Level[b]
Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs.[137]	I	C
An ACE-I may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[11]	IIb	C
An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[245]	IIb	C
A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[12,119]	IIb	C
An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[246]	IIb	C
Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[13,247]	IIb	C

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.
[a]Class of recommendation.
[b]Level of evidence.

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7.3.1 Angiotensin-converting enzyme inhibitors

There are no specific trials of ACE-I in patients with HFmrEF. Although, the PEP-CHF trial was conducted in patients with HFpEF and included patients with an LVEF >40%, it did not report outcomes according to LVEF.[11]

However, in patients with HFmrEF, many will also have CAD, hypertension, or post-MI LV systolic dysfunction and will, therefore, already be treated with ACE-I.

Therefore, ACE-I use may be considered in patients with HFmrEF.

7.3.2 Angiotensin receptor II type 1 receptor blockers

There are no specific trials of ARBs in HFmrEF. The CHARM-Preserved trial missed its primary endpoint of CV death or HF hospitalizations.[245] However, a retrospective analysis showed that candesartan reduced the number of patients hospitalized for HF among those with HFmrEF (with similar trends for CV and all-cause mortality).[8] Moreover, a recurrent-event analysis suggested a reduction in hospitalizations for HF among the entire CHARM-Preserved cohort, including those with HFmrEF.[248]

As for ACE-I, many with HFmrEF will already be on an ARB for other CV indications. Therefore, treatment with ARBs may be considered in patients with HFmrEF.

7.3.3 Beta-blockers

There is no specific trial of beta-blockade in HFmrEF. An IPD meta-analysis of landmark trials of beta-blockers suggested similar reductions in CV and all-cause mortality (of 50%) for patients in SR with HFrEF and HFmrEF.[12] This IPD meta-analysis included the SENIORS trial where nebivolol reduced the composite primary endpoint of all-cause mortality or CV hospital admissions in the overall population. No interaction between LVEF (35% of patients had an LVEF of 35–50%) and the effect of nebivolol on the primary outcome was observed.[119,249] Many patients with HFmrEF may have another CV indication, such as AF or angina, for a beta-blocker. Therefore, treatment with beta-blockers may be considered in patients with HFmrEF.

7.3.4 Mineralocorticoid receptor antagonists

There is no specific trial of MRAs in HFmrEF. In a retrospective analysis of the TOPCAT trial in patients with an LVEF ≥45%,[9] spironolactone reduced hospitalizations for HF in those with an LVEF <55%. There was a similar trend for CV but not all-cause mortality.

Treatment with an MRA may be considered in patients with HFmrEF.

7.3.5 Angiotensin receptor-neprilysin inhibitor

There is no specific trial of ARNI in HFmrEF. In the PARAGON-HF trial, which included patients with EF ≥45%, although the trial missed its primary endpoint overall, a significant EF-by-treatment interaction was observed. Sacubitril/valsartan, compared with valsartan, reduced the likelihood of the primary composite outcome of CV death and total HF hospitalizations by 22% in those with an EF below or equal to the median of 57%.[13] Further data are available from a combined analysis of the PARADIGM-HF and PARAGON-HF trials showing that sacubitril/valsartan, compared to other forms of RAAS blockade, has a beneficial effect, especially on hospitalizations for HF in those with HFmrEF.[247]

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Treatment with an ARNI may be considered in patients with HFmrEF.

7.3.6 Other drugs

In the DIG trial,[10] for those with HFmrEF in SR, there was a trend to fewer hospitalizations for HF in those assigned to digoxin, but no reduction in mortality and a trend to an excess of CV deaths. Therefore, there are insufficient data to recommend its use.

There are also insufficient data on ivabradine in HFmrEF to draw any conclusions.

7.3.7 Devices

While post hoc analyses of landmark CRT trials suggest that CRT may benefit patients with LVEF >35%, trials of CRT for HFmrEF were abandoned due to poor recruitment.[250] There are no substantial trials of ICDs for primary prevention of ventricular arrhythmias for HFmrEF; trials conducted more than 20 years ago suggested no benefit from ICD implantation for secondary prevention of ventricular arrhythmias for HFmrEF.

Therefore, there is insufficient evidence to advise CRT or ICD therapy in patients with HFmrEF.

In HF patients with an LVEF ≥40%, the implantation of an interatrial shunt device was found to be safe, and this device is subject to investigation in a larger study before any recommendation on their use in HFpEF or HFmrEF can be given.[251]

8 Heart failure with preserved ejection fraction

8.1 The background to heart failure with preserved ejection fraction

This guideline acknowledges the historical changes in nomenclature and the lack of consensus on the optimal LVEF cut-off to define the group of patients with HF without overtly reduced EF. The term 'preserved' was originally proposed in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) Programme to refer to patients with an EF (>40%) that was not clearly 'reduced' or completely 'normal'.[252] While the current guidelines have designated patients with an LVEF 41–49% as HFmrEF, we recognize that there will be debate about what constitutes 'mildly reduced' EF, what these EF cut-offs should be, and whether they should be different for men and women.[14,253] The EACVI defines systolic dysfunction as being <52% for males and <54% for females.[16]

Whether patients with higher EFs and HF should be named HF with 'normal' EF has also been considered.[14,254] However, given the known variability of echocardiographic measurements of LVEF, the difficulties in interpreting LVEF measured using different imaging modalities, and remaining controversies regarding the precise LVEF cut-off to define 'normal' , which may vary not only with sex but also with other factors such as age and ethnicity,[255] this guideline has kept the nomenclature of HFpEF using an EF cut-off of 50%. Importantly, clinicians should be aware that LVEF is a continuous variable with a normal distribution in the general population, and the EF cut-offs used in definitions are therefore arbitrary. Moreover, while the LVEF cut-off to define 'normal' will likely be higher than 50%, the presence of a very high EF (e.g. above 65–70%) should also prompt a search for pathology, such as cardiac amyloidosis (CA) or hypertrophic cardiomyopathy (HCM), where a 'supra-normal' EF may result from shrinkage of the LV end-diastolic volume (denominator of EF).[256,257]

8.2 Clinical characteristics of patients with heart failure with preserved ejection fraction

HFpEF differs from HFrEF and HFmrEF in that HFpEF patients are older and more often female. AF, CKD, and non-CV comorbidities are more common in patients with HFpEF than in those with HFrEF.[258]

There are numerous potential causes of HFpEF (*Table 5*). The pathophysiology of various HFpEF syndromes differs, and thus they require distinct therapies. Red flags for the potential presence of CA include low normal BP in patients with a history of hypertension, intolerance to beta-blockers or ACE-I, history of bilateral carpal tunnel syndrome, low voltage on ECG and echocardiographic features such as thickening of the septum, posterior wall, or RV wall, enlarged atria, a small pericardial effusion, or valve thickening [for more details see the section on CMP (section 14.2)]. Furthermore, it is important to exclude other conditions that might mimic the HFpEF syndrome (e.g. lung disease, anaemia, obesity, and deconditioning). For a more comprehensive overview on HFpEF, see the ESC/HFA position statement.[259]

8.3 The diagnosis of heart failure with preserved ejection fraction

The diagnosis of HFpEF remains challenging. Several diagnostic criteria have been proposed by societies and in clinical trials.[260] These criteria vary widely in their sensitivities and specificities for diagnosing HFpEF. More recently, two score-based algorithms (H_2FPEF and HFA-PEFF) have been proposed to aid the diagnosis.[259,261] While the generalizability of the scores has been tested in various trial and observational cohorts, their diagnostic performance has varied.[262–269]

Both scores assign a substantial proportion of suspected HFpEF patients as intermediate likelihood, wherein additional diagnostics are proposed. Thus, depending on which score is used, different patients will be referred for additional testing or allocated as having HFpEF. Furthermore, physicians may not have access to all the specialized tests recommended by the specific diagnostic algorithms. This limits the broad clinical applicability of the scores and demonstrates the ongoing diagnostic uncertainty in HFpEF.[267]

To facilitate broad clinical application, this guideline recommends a simplified pragmatic approach that distils the common major elements in prior diagnostic criteria and emphasizes the most frequently used variables widely available to clinicians. Some of these variables, in particular, LA size (LA volume index >32 mL/m^2), mitral E velocity <90 cm/s, septal e′ velocity <9 cm/s, E/e′ ratio >9 have been shown to be pivot points beyond which the risk of CV mortality is increased, underscoring their value.[270] This recommendation is therefore consistent with the consensus document of the HFA, and does not represent a new algorithm or diagnostic score but rather a simplified approach. Physicians with access to expertise may refer to the full diagnostic approach recommended by the HFA.[259]

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This simplified diagnostic approach starts with assessment of pre-test probability (see clinical characteristics above). The diagnosis should include the following:

(1) Symptoms and signs of HF.
(2) An LVEF ≥50%.*
(3) Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised NPs (*Table 9*).

*Of note, patients with a history of overtly reduced LVEF (≤40%), who later present with LVEF ≥50%, should be considered to have recovered HFrEF or 'HF with improved LVEF' (rather than HFpEF). Continued treatment for HFrEF is recommended in these patients.[271] It is not known whether starting HF therapy in patients with recovered LVEF is beneficial. Patients with HFpEF tend to have stable trajectory of LVEF over time.[272] However, in those who develop a clinical indication for a repeat echo during follow-up, around one third have a decline in LVEF.[273]

In the presence of AF, the threshold for LA volume index is >40 mL/m^2. Exercise stress thresholds include E/e′ ratio at peak stress ≥15 or tricuspid regurgitation (TR) velocity at peak stress >3.4 m/s.[275] LV global longitudinal strain <16% has a sensitivity of 62% and a specificity of 56% for the diagnosis of HFpEF by invasive testing.[261]

The approach to the diagnosis should involve additional confirmatory tests in cases of diagnostic uncertainty, such as cardiopulmonary exercise testing (to confirm a reduction in exercise capacity and to help differentiate the cause of dyspnoea), exercise stress testing, and invasive haemodynamic testing.[259]

If resting echocardiographic and laboratory markers are equivocal, a diastolic stress test is recommended.[259,274] The confirmatory test for the diagnosis of HFpEF is invasive haemodynamic exercise testing. An invasively measured pulmonary capillary wedge pressure (PCWP) of ≥15 mmHg (at rest) or ≥25 mmHg (with exercise) or LV end-diastolic pressure ≥16 mmHg (at rest) is generally considered diagnostic.[266] However, instead of an exercise PCWP cut-off, some have used an index of PCWP to cardiac output for the invasive diagnosis of HFpEF[260,276]. Recognizing that invasive haemodynamic exercise testing is not available in many centres worldwide, and is associated with risks, its main use is limited to the research setting. In the absence of any disease-modifying treatments, the current guidelines do not mandate gold standard testing in every patient to make the diagnosis, but emphasize that the greater the number of objective non-invasive markers of raised LV filling pressures (*Table 9*), the higher the probability of a diagnosis of HFpEF.

8.4 Treatment of heart failure with preserved ejection fraction

To date, no treatment has been shown to convincingly reduce mortality and morbidity in patients with HFpEF, although improvements have been seen for some specific phenotypes of patients within the overall HFpEF umbrella. However, none of the large RCTs conducted in HFpEF have achieved their primary endpoints. These include PEP-CHF (perindopril),[277] CHARM-Preserved (candesartan),[245] I-PRESERVE (irbesartan),[278] TOPCAT (spironolactone),[246] DIG-Preserved (digoxin),[279] and PARAGON-HF (sacubitril/valsartan)[13] (see *Supplementary Table 12* for the details about these and additional trials). Hospitalizations for HF were reduced by candesartan and spironolactone and there was a trend towards reduction with sacubitril/valsartan, although as these trials were neutral for their primary endpoints, these are hypothesis-generating findings only. Although nebivolol significantly reduced the combined primary endpoint of all-cause mortality or CV hospital admission in the SENIORS trial, this trial included only 15% with an LVEF >50%.[119,249] Trials targeting the nitric oxide-cyclic guanosine monophosphate pathway have also failed to improve exercise

Table 9 Objective evidence of cardiac structural, functional and serological abnormalities consistent with the presence of left ventricular diastolic dysfunction/raised left ventricular filling pressures[259,261]

Parameter[a]	Threshold	Comments
LV mass index **Relative wall thickness**	≥**95** g/m^2 (Female), ≥**115** g/m^2 (Male) >**0.42**	Although the presence of concentric LV remodelling or hypertrophy is supportive, the absence of LV hypertrophy does not exclude the diagnosis of HFpEF
LA volume index[a]	>**34** mL/m^2 (SR)	In the absence of AF or valve disease, LA enlargement reflects chronically elevated LV filling pressure (in the presence of AF, the threshold is >40 mL/m^2)
E/e' ratio at rest[a]	>**9**	Sensitivity 78%, specificity 59% for the presence of HFpEF by invasive exercise testing, although reported accuracy has varied. A higher cut-off of 13 had lower sensitivity (46%) but higher specificity (86%).[71,259,274]
NT-proBNP **BNP**	>**125** (SR) or >**365** (AF) pg/mL >**35** (SR) or >**105** (AF) pg/mL	Up to 20% of patients with invasively proven HFpEF have NPs below diagnostic thresholds, particularly in the presence of obesity
PA systolic pressure **TR velocity at rest**[a]	>**35** mmHg >**2.8** m/s	Sensitivity 54%, specificity 85% for the presence of HFpEF by invasive exercise testing[259,261]

AF = atrial fibrillation; BNP = B-type natriuretic peptide; E/e'ratio = early filling velocity on transmitral Doppler/early relaxation velocity on tissue Doppler; HFpEF = heart failure with preserved ejection fraction; LA = left atrial; LV = left ventricular; NP = natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PA = pulmonary artery; SR = sinus rhythm; TR = tricuspid regurgitation.
Note: The greater the number of abnormalities present, the higher the likelihood of HFpEF.
[a]Only commonly used indices are listed in the table; for less commonly used indices refer to the consensus document of the ESC/HFA.[259]

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capacity or QOL in HFpEF, e.g. NEAT-HFpEF,[280] INDIE-HFpEF,[281] VITALITY-HFpEF,[282] and CAPACITY-HFpEF (praliciguat).[283]

Despite the lack of evidence for specific disease-modifying therapies in HFpEF, as the vast majority of HFpEF patients have underlying hypertension and/or CAD, many are already treated with ACE-I/ARB, beta-blockers, or MRAs. In the PARAGON-HF study at baseline, more than 86% of patients were on ACE-I/ARBs, 80% were on beta-blockers, and more than 24% were on MRAs.[13]

The Task Force acknowledge that the treatment options for HFpEF are being revised as this guideline is being published. We note that the Food and Drug Administration (FDA) has endorsed the use of sacubitril/valsartan and spironolactone in those with an LVEF 'less than normal'. These statements relate to patients within both the HFmrEF and HFpEF categories. For sacubitril/valsartan, this decision was based on the subgroup analysis from the PARAGON-HF study, which showed a reduction in HF hospitalizations in those with an LVEF <57%, and a meta-analysis of the PARADIGM-HF and PARAGON-HF studies, showing a reduction in CV death and HF hospitalization in those with an LVEF below the normal range.[247] Regarding spironolactone, the subgroup of individuals in the TOPCAT study recruited in the Americas had a significant reduction in the primary endpoint of CV death and HF hospitalization, and a subsequent post hoc analysis by EF showed a significant reduction in outcomes for those with an LVEF <55%.[9,247] There are also ongoing trials with SGLT2 inhibitors. These developments may well accelerate a redefinition of HFpEF in the future and have therapeutic implications.

In the absence of recommendations regarding disease-modifying therapies, treatment should be aimed at reducing symptoms of congestion with diuretics. Loop diuretics are preferred, although thiazide diuretics may be useful for managing hypertension. Reducing body weight in obese patients and increasing exercise may further improve symptoms and exercise capacity and should therefore be considered in appropriate patients.[284,285]

It is important to identify and treat the underlying risk factors, aetiology, and coexisting comorbidities in HFpEF (e.g. hypertension in section 12.4, CAD in section 12.2, amyloidosis in section 14.6, AF in section 12.1.1, and valvular heart disease in section 12.3). Undoubtably, treatment of some of the underlying phenotypes of the the HFpEF syndrome leads to improved outcomes.

Recommendations for the treatment of patients with heart failure with preserved ejection fraction

Recommendations	Class[a]	Level[b]
Screening for, and treatment of, aetiologies, and cardiovascular and non-cardiovascular comorbidities is recommended in patients with HFpEF (see relevant sections of this document).	I	C
Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs.[137]	I	C

HFpEF = heart failure with preserved ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.

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Table 10 Risk factors for the development of heart failure and potential corrective actions

Risk factors for heart failure	Preventive strategies
Sedentary habit	Regular physical activity
Cigarette smoking	Cigarette smoking cessation
Obesity	Physical activity and healthy diet
Excessive alcohol intake[286]	General population: no/light alcohol intake is beneficial Patients with alcohol-induced CMP should abstain from alcohol
Influenza	Influenza vaccination
Microbes (e.g. *Trypanosoma cruzi*, Streptococci)	Early diagnosis, specific antimicrobial therapy for either prevention and/or treatment
Cardiotoxic drugs (e.g., anthracyclines)	Cardiac function and side effect monitoring, dose adaptation, change of chemotherapy
Chest radiation	Cardiac function and side effect monitoring, dose adaptation
Hypertension	Lifestyle changes, antihypertensive therapy
Dyslipidaemia	Healthy diet, statins
Diabetes mellitus	Physical activity and healthy diet, SGLT2 inhibitors
CAD	Lifestyle changes, statin therapy

CAD = coronary artery disease; CMP = cardiomyopathy; SGLT2 = sodium-glucose co-transporter 2.

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Recommendations for the primary prevention of heart failure in patients with risk factors for its development

Recommendations	Class[a]	Level[b]
Treatment of hypertension is recommended to prevent or delay the onset of HF, and to prevent HF hospitalizations.[287–290]	I	A
Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations.[291,292]	I	A
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations.[293–297]	I	A
Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF.[298–302]	I	C

CV = cardiovascular; HF = heart failure; SGLT2 = sodium-glucose co-transporter 2.
[a]Class of recommendation.
[b]Level of evidence.

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

9.1 Prevention of heart failure

General advice about risk factors for the development of HF (see *Supplementary Figure 1*) and strategies to prevent HF early in the CV continuum are summarized in *Table 10*.

It is widely recognized that, in addition to optimizing medical and device therapies for HF, attention should also be given to how HF care is delivered. The HFA of the ESC has issued several position papers that cover non-pharmacological management, discharge planning, and standards for delivering HF care.[303–305] It has also underscored the need for specialist HF cardiologists and specialist HF nurses to help provide care. Detailed curricula, to aid training of these, are available to be adapted for national implementation.[306,307] This section focuses on areas where recommendations with an evidence level can be given: multidisciplinary team management, lifestyle advice, exercise training, follow-up, and monitoring.

9.2 Multidisciplinary management of chronic heart failure

9.2.1 Models of care

In order to reduce hospitalizations and mortality, earlier guidelines[1] recommended the use of multidisciplinary HF management programmes (HF-MPs), which enable patients to have the correct investigations, an accurate diagnosis, appropriate evidence-based therapy, education, and suitable follow-up. The optimal implementation of a HF-MP requires a multidisciplinary team that is active along the whole HF trajectory; from onset, through critical events, periods of apparent stability, and its terminal stages.[303] Since the 2016 guidelines, new studies have been published that underscore the need for HF-MPs and reveal more insights into how care can be delivered.

A network meta-analysis including 53 randomized trials published in 2017, concluded that both disease-management clinics and home visits by nurses reduced all-cause mortality compared to usual care; home visits being most effective.[308] An IPD meta-analysis of 20 studies, including 5624 patients, concluded that self-management interventions in HF patients improve outcomes despite heterogeneity in the intensity, content, and the personnel who deliver the interventions.[309]

HF-MPs vary in their components and can apply different service models, such as clinic-based approaches (in primary, secondary, or tertiary care), home-based programmes, case management, or hybrids of these. Components used in the services vary, e.g. some HF-MPs use telemonitoring that may be applied at a local, regional, or national level. No service model has been shown to be consistently superior to others.[310] While home visits and HF clinics do reduce all-cause admissions and mortality, educational programmes, used alone, do not.[308,309] HF-MPs should be patient-centred and take a holistic approach to the patient rather than focussing solely on HF; management of comorbid conditions, such as arrhythmias, hypertension, diabetes, renal dysfunction, and depression, improve patient well-being and self-management, leading to better outcomes.[309,311] The organization of a HF-MP should be adapted to the healthcare system, available resources (infrastructure, facilities, staff, and finances), administrative policies, and tailored to the patient's needs.

Many patients with HF would derive benefit from the early integration of a palliative and supportive approach within the care provided by all members of the HF multidisciplinary team.[312,313] Palliative and supportive care should be thought about for all patients with HF, regardless of stage of their illness. Patients in the advanced stages and those considered for mechanical circulatory support (MCS) or heart transplantation should receive a palliative care consultation before such interventions as a matter of protocol (see section 10.2.4).

9.2.2 Characteristics and components of a heart failure management programme

Clinical trials have included complex, bundled interventions, making it difficult to determine the efficiency and effectiveness of each specific component. *Table 11* presents an overview of characteristics and components that are important to consider in a HF-MP.

Multidisciplinary interventions recommended for the management of chronic heart failure

Recommendations	Class[a]	Level[b]
It is recommended that HF patients are enrolled in a multidisciplinary HF management programme to reduce the risk of HF hospitalization and mortality.[309,314,315,316]	I	A
Self-management strategies are recommended to reduce the risk of HF hospitalization and mortality.[309]	I	A
Either home-based and/or clinic-based programmes improve outcomes and are recommended to reduce the risk of HF hospitalization and mortality.[310,317]	I	A
Influenza and pneumococcal vaccinations should be considered in order to prevent HF hospitalizations.[315,316]	IIa	B

HF = heart failure.
[a]Class of recommendation.
[b]Level of evidence.

9.3 Patient education, self-care and lifestyle advice

Adequate patient self-care is essential in the effective management of HF and allows patients to understand what is beneficial, and to agree to self-monitoring and management plans.[319] HF patients who report more effective self-care have a better QOL, lower readmission rates, and reduced mortality.[309]

Misunderstandings, misconceptions, and lack of knowledge all contribute to insufficient self-care and therefore patient education is vital. Improving patients' knowledge of their condition is fundamental for the development of self-care skills.[304]

Education to improve self-care should be tailored to the individual patient and based on, where available, scientific evidence or expert opinion. There is little evidence that specific lifestyle advice improves

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Table 11 Important characteristics and components in a heart failure management programme

Characteristics
1. Patient/person-centred[318]
2. Multidisciplinary
3. The focus of the programme should be flexible and include:
• prevention of disease progression
• symptom control
• maintaining patients in their preferred place of care for end-stage heart failure
4. Competent and professionally educated staff
5. Encourage patient/carer engagement in the understanding and management of their condition
Components
1. Optimized management; lifestyle choices, pharmacological, and devices
2. Patient education, with special emphasis on self-care and symptom management
3. Provision of psychosocial support to patients and family caregivers
4. Follow-up after discharge (clinic; home visits; telephone support or telemonitoring)
5. Easy access to healthcare, especially to prevent and manage decompensation
6. Assessment of (and appropriate intervention in response to) an unexplained change in weight, nutritional and functional status, quality of life, sleep problems, psychosocial problems or other findings (e.g., laboratory values)
7. Access to advanced treatment options; supportive and palliative care

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Table 12 Patient education and self-care

Education topic	Goal for the patient and caregiver	Professional behaviour and educational tools
Explanation about HF	To understand the cause of their HF, symptoms and treatment choice.	Provide tailored information.
The HF trajectory	To understand prognosis and the different possible phases in the HF trajectory. To make joint treatment decisions that recognise the patient's position on the HF trajectory.	Sensitively communicate information on prognosis at time of diagnosis, during decision making about treatment options, when there is a change in the clinical condition and whenever the patient requests.
Medical treatment		
Medication	To be able to make joint decisions about medication. To understand the indications, benefits, the need for long-term adherence to certain drugs, and the dosing and side effects of medication. To be able to recognize the common side effects of medication and know what actions to take.	Provide written and oral information on indication, benefits, dosing, effects and side effects. Discuss practical issues such as optimal time-schedule, what to do in case of a missed dose etc. Discuss possible barriers for medication taking. Advise on support aids such as dosette box, electronic reminders etc. when appropriate.[320]
Implanted devices	To be able to make joint decisions on device implantation. To understand the indications, importance, expectations and check-up routine for implanted devices, and any exception management. To be able to recognize the common complications (including the risk of inappropriate defibrillator shocks), and know what actions to take.	Provide written and oral information about the importance and expectations of implanted devices, and possible ways of follow-up (remote monitoring). Discuss expectations and any possible impact on driving. Clearly identify situations where the device might be deactivated or explanted. Involve patient and caregiver in decision making.
Self-care aspects		
Activity and exercise	To undertake regular exercise and be physically active. To be able to adapt physical activity to symptom status and personal circumstances.	Advise on exercise that recognizes physical and functional limitations, such as frailty, comorbidities. Refer to exercise programme or other activity modes. Discuss possible barriers, side-effects and opportunities.
Sleep and breathing	To recognize the importance of sleep and rest for (CV) health. To be able to recognize problems with sleeping and how to optimize sleep.	Review sleep history. Advise and discuss the importance of good sleep and provide advice on 'sleep health' (including timing of diuretics).

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Table 12 *Continued*

Education topic	Goal for the patient and caregiver	Professional behaviour and educational tools
		Consider and carefully discuss the benefits and deleterious effects of sleep medication.
Fluids	To avoid large volumes of fluid intake. A fluid restriction of 1.5–2 L/day may be considered in patients with severe HF/hyponatraemia to relieve symptoms and congestion. To avoid dehydration: where fluids are restricted, increase intake during periods of high heat/humidity and/or nausea/vomiting.	Provide information and discuss the advantages and disadvantages of fluid restriction. Advise to adapt fluid intake to weight, and in times of high heat and humidity, nausea/vomiting. Adjust advice during periods of acute decompensation and consider altering this advice towards end-of-life.
Healthy diet	To be able to prevent malnutrition and know how to eat healthily, avoiding excessive salt intake (>5 g/day) and maintaining a healthy body weight.	Discuss current food intake, role of salt, role of micronutrients. Discuss the need for supplementing in case of nutrient deficiencies but there is no clear role for routine micronutrient supplementation.[321] Discuss maintaining a healthy body weight.
Alcohol	To be able to abstain from or avoid excessive alcohol intake, especially for alcohol-induced CMP. To restrict alcohol according to CV prevention guidelines.	Tailor alcohol advice to aetiology of HF; e.g. abstinence in alcoholic CMP. Inform and discuss alcohol intake according to CV prevention guidelines (2 units per day in men or 1 unit per day in women)[a].
Immunization	To be aware of the need for immunization for influenza and pneumococcal disease.	Discuss benefits and possible barriers. Advise on local immunization practice.
Smoking and recreational drugs	To be aware of the consequences for health of smoking and use of recreational drugs. Stop smoking (including e-cigarettes) and taking recreational drugs.	Inform, discuss and help in decision making. Refer for specialist advice for smoking cessation and drug withdrawal and replacement therapy. Consider referral for cognitive behavioural theory and psychological support if patient wishes to stop smoking or taking drugs.
Travel, leisure, driving	To be able to prepare travel and leisure activities according to physical capacity. To be able to take an informed decision about driving.	Inform and discuss practical issues related to long haul travel, staying abroad, exposure to sun (amiodarone effects), high humidity or heat (dehydration), and high altitude (oxygenation). Provide practical advice related to travel with medication/devices (keep medicines in hand luggage, have a list with medication, device name/card and treating centres). Inform about local/national/international regulation related to driving.
Sexual activity	To be able to resume or adapt sexual activity according to physical capacity. To recognize possible problems with sexual activity and their relationship with HF or its treatment.	Inform and discuss that sexual activity is safe for stable HF patients. Provide advice on eliminating factors predisposing to sexual problems. Discuss and provide available pharmacological treatment for sexual problems. Refer to specialist for sexual counselling when necessary.
Symptom monitoring and symptom self-management	Monitor and recognize change in signs and symptoms. Being able to react adequately to change in signs and symptoms. Know how and when to contact a healthcare professional.	Provide individualized information to support self-management such as: In the case of increasing dyspnoea or oedema or a sudden unexpected weight gain of >2 kg in 3 days, patients may increase their diuretic dose and/or alert their healthcare team.
Living with HF		
Psychological issues	To be able to live a good life with HF. To be able to seek help in case of psychological problems such as depressive symptoms, anxiety or low mood which may occur in the course of the HF trajectory.	Regularly communicate information on disease, treatment options and self-care. Regularly discuss the need for support. Treat or referral to specialist for psychological support when necessary.

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Table 12 *Continued*

Education topic	Goal for the patient and caregiver	Professional behaviour and educational tools
	To recognise that the carer or family members may be greatly affected and need to seek help.	
Family and informal caregivers	To be able to ask for support.	Discuss the preference of caregiver/family involvement. Involve patients and caregivers in a respectful way.

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CMP = cardiomyopathy; CV = cardiovascular; HF = heart failure.
[a]1 unit is 10 mL of pure alcohol (e.g., 1 glass of wine, ½ pint of beer, 1 measure of spirit).

QOL or prognosis; however, providing this information has become a key component of education for self-care.

General educational approaches include:

- Providing information in a variety of formats that take into account educational grade and health literacy. Consider approaches with active roles for patients and caregivers such as 'ask-tell-ask', 'teach back', or motivational interviewing. Reinforce messages at regular time intervals.
- Recognizing barriers to communication (language, social skills, cognition, anxiety/depression, hearing or visual challenges).
- Recommending 'HFmatters.org'. Offer help and guidance to use it and offer discussion of questions arising.
- Inviting patients to be accompanied by a family member or friend.

Key topics to include are recommended in *Table 12*.

9.4 Exercise rehabilitation

There is consistent evidence that physical conditioning by exercise training improves exercise tolerance, and health-related QOL in patients with HF. Clinical trials and meta-analyses in people with HFrEF show that exercise rehabilitation improves exercise capacity and QOL. Several meta-analyses also show that it reduces all-cause and HF hospitalizations, although uncertainty persists about its effects on mortality.[322–328] The effect on hospitalization is seen in those who are highly adherent to the exercise programme.[329] High-intensity interval training, in patients who are able and willing, may improve peak oxygen consumption (VO_2).[330,331] Supervised exercise-based rehabilitation should be considered in those who are frail, who have more severe disease or comorbidities.[95]

Physical conditioning also improves exercise capacity and QOL.[332–335] No data on HFmrEF are available, but benefits observed in the other groups of HF should also apply to this group.

Recommendations for exercise rehabilitation in patients with chronic heart failure

Recommendations	Class[a]	Level[b]
Exercise is recommended for all patients who are able in order to improve exercise capacity, QOL, and reduce HF hospitalization.[c 324–328,335–337]	I	A
A supervised, exercise-based, cardiac rehabilitation programme should be considered in patients with more severe disease, frailty, or with comorbidities.[95,324–327,338]	IIa	C

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HF = heart failure; QOL = quality of life.
[a]Class of recommendation.
[b]Level of evidence.
[c]In those who are able to adhere to the exercise programme.

9.5 Follow-up of chronic heart failure

9.5.1 General follow-up

This is a relatively understudied area. Patients with HF, even if symptoms are well controlled and stable, require follow-up to ensure continued optimization of therapy, to detect asymptomatic progression of HF or its comorbidities and to discuss any new advances in care. These guidelines recommend follow-up at intervals no longer than 6 months to check symptoms, heart rate and rhythm, BP, full blood count, electrolytes, and renal function. For patients recently discharged from hospital, or in those undergoing uptitration of medication, follow-up intervals should be more frequent. Whether such stable patients need to be followed-up by cardiologists is uncertain. Some studies suggest that follow-up in primary care may be appropriate.[303,339] However, uptake of evidence-based interventions is poor in many settings[340,104] and several studies suggest that care and follow-up provided by HF specialists, and use of quality improvement registries can lead to higher rates of optimal therapy and improved outcomes.[341–343]

An ECG should be done annually to detect QRS prolongation[344] as such patients may become candidates for CRT. Furthermore, it may identify conduction disturbances and AF.

Serial echocardiography is generally not necessary, although an echocardiogram should be repeated if there has been a deterioration in clinical status. An echocardiogram is also advised 3–6 months after optimization of standard therapies for HFrEF to determine the need for addition of newer pharmacological agents and implanted devices.

9.5.2 Monitoring with biomarkers

Trials investigating the use of biomarkers (particularly BNP and/or NT-proBNP) to guide pharmacotherapy for HFrEF have produced conflicting results.[345–352] They are undoubtedly good prognostic markers.[72,353,354] Conceptually, it is not clear what a biomarker-supported strategy might offer in addition to assiduous application of guideline-recommended therapy. Current evidence, therefore, does not support the routine measurement of BNP or NT-proBNP to guide titration of therapy.

9.6 Telemonitoring

Telemonitoring enables patients to provide, remotely, digital health information to support and optimize their care. Data such as

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symptoms, weight, heart rate, and BP, can be collected frequently, stored in an electronic health record and used to guide patients (directly or through a healthcare professional), to adjust therapy or to seek further advice. Home telemonitoring (HTM) can help maintain quality of care, facilitate rapid access to care when needed, reduce patient travel costs, and minimize the frequency of clinic visits.[355] Enforced cessation of face-to-face consultations in many countries during the recent COVID-19 pandemic have highlighted some of the potential advantages of HTM.[356]

Trials of HTM are diverse. Patients are usually required to make measurements and, as for many other aspects of HF management, adherence may be incomplete. HTM may be provided as a local, regional, or national service. Systems that focus on optimizing management rather than detecting and managing medical emergencies need only to be staffed during standard working hours. Some systems are designed also to offer support at any time requested by the patient. The comparative effectiveness and cost effectiveness of each strategy is uncertain. Systems that focus on continuous optimization of care (a health maintenance approach) rather than trying to anticipate and manage episodes of worsening (a strategy that is plagued by a large number of false-positive alerts), appear more successful.[357] HTM is an efficient method for providing patient education and motivation and aiding delivery of care, but it should be adapted to work in synergy with existing healthcare provision.[358]

A Cochrane systematic review conducted in 2017 identified 39 relevant trials of HTM, largely based on assessments of symptoms, weight, heart rate and rhythm, and BP and found that HTM was associated with a reduction in all-cause mortality of 20% and HF hospitalization of 37%.[359] Since then, several neutral trials and at least one positive trial have been published.[357,360–364] These are unlikely to change the positive results of the systematic review. Importantly, if social distancing and the 'green' agenda are important, HTM only needs to show that it is not inferior to contemporary methods of delivering care to be an appropriate means of supporting care.[356]

Whether wearable technologies for monitoring heart rate and rhythm or lung congestion (bio-impedance or lung radar) offer additional benefits to conventional HTM described above is uncertain.[365–367]

Many implanted therapeutic devices can provide, wirelessly and remotely, information either on the device itself (generator and lead function), arrhythmias, or on patient physiology (heart rate, activity, heart sounds, bio-impedance). There is strong evidence that monitoring can detect device malfunction earlier than by conventional monitoring and that it may be useful for detecting arrhythmias such as AF. However, there is little evidence that device monitoring reduces admissions for HF or mortality.[368–370,371]

Devices that only provide a monitoring function are also available. Implantable loop-recorders can be injected subcutaneously and used to monitor heart rate and rhythm, activity, and bio-impedance. Monitoring devices can also be placed in the pulmonary artery to monitor pressure wirelessly, although the external reader required to detect the device signal is rather bulky and requires patient co-operation. A rise in diastolic pulmonary artery pressure may be one of the earliest signs of congestion. A preliminary, but fairly substantial, trial showed a reduction in the risk of recurrent HF hospitalization.[372] A much larger trial has completed recruitment (GUIDE-HF).[373]

Thus, non-invasive HTM may be considered for patients with HF in order to reduce the risk of recurrent CV and HF hospitalizations and CV death; further evidence on management guided by implanted systems is awaited.[374]

Recommendations for telemonitoring

Recommendations	Class[a]	Level[b]
Non-invasive HTM may be considered for patients with HF in order to reduce the risk of recurrent CV and HF hospitalizations and CV death.[374]	IIb	B
Monitoring of pulmonary artery pressure using a wireless haemodynamic monitoring system may be considered in symptomatic patients with HFrEF (LVEF ≤35%) in order to improve clinical outcomes.[372]	IIb	B

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CV = cardiovascular; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HTM = home telemonitoring; LVEF = left ventricular ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.

10 Advanced heart failure

10.1 Epidemiology, diagnosis, and prognosis

Many patients with HF progress into a phase of advanced HF, characterized by persistent symptoms despite maximal therapy.[375–377] The prevalence of advanced HF is increasing due to the growing number of patients with HF, ageing of the population, and better treatment and survival of HF. Prognosis remains poor, with a 1-year mortality ranging from 25% to 75%.[378–380]

The updated HFA-ESC 2018 criteria for the definition of advanced HF are reported in *Table 13*.[376] A severely reduced LVEF is common but not required for a diagnosis of advanced HF as it may develop in patients with HFpEF as well. In addition to the reported criteria, extra-cardiac organ dysfunction due to HF (e.g. cardiac cachexia, liver or kidney dysfunction) or type II pulmonary hypertension may be present, but are not required for the definition of advanced HF.[376]

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles, developed to classify patients with a potential indication for durable MCS devices, describes clinical parameters and characteristics consistent with a need for advanced therapies (*Table 14*).[381] This classification has also been shown to be useful in estimating the prognosis of patients undergoing urgent heart transplantation[382] or LV assist device (LVAD) implantation,[383] and for risk assessment in ambulatory advanced HF patients.[384]

Prognostic stratification is important to identify the ideal time for referral to an appropriate centre (i.e. one capable of providing advanced HF therapies), to properly convey expectations to patients and families, and to plan treatment and follow-up strategies

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Table 13 Criteria for definition of advanced heart failure

All the following criteria must be present despite optimal medical treatment:
1. Severe and persistent symptoms of heart failure [NYHA class III (advanced) or IV].
2. Severe cardiac dysfunction defined by at least one of the following: • LVEF ≤30% • Isolated RV failure (e.g., ARVC) • Non-operable severe valve abnormalities • Non-operable severe congenital abnormalities • Persistently high (or increasing) BNP or NT-proBNP values and severe LV diastolic dysfunction or structural abnormalities (according to the definitions of HFpEF).
3. Episodes of pulmonary or systemic congestion requiring high-dose i.v. diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing >1 unplanned visit or hospitalization in the last 12 months.
4. Severe impairment of exercise capacity with inability to exercise or low 6MWT distance (<300 m) or pVO_2 <12 mL/kg/min or <50% predicted value, estimated to be of cardiac origin.

6MWT = 6-minute walk test; ARVC = arrhythmogenic right ventricular cardiomyopathy; BNP = B-type natriuretic peptide; HFpEF = heart failure with preserved ejection fraction; i.v. = intravenous; LV = left ventricular; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; pVO_2 = peak oxygen consumption; RV = right ventricular. Modified from [376].

Table 14 Interagency Registry for Mechanically Assisted Circulatory Support profile descriptions of patients with advanced heart failure

Profile	Time frame for intervention
Profile 1. Critical cardiogenic shock Patient with life-threatening hypotension despite rapidly escalating inotropic support, critical organ hypoperfusion, often confirmed by worsening acidosis and/or lactate levels. "Crash and burn."	Definitive intervention needed within hours.
Profile 2. Progressive decline Patient with declining function despite i.v. inotropic support, may be manifest by worsening renal function, nutritional depletion, inability to restore volume balance. "Sliding on inotropes." Also describes declining status in patients unable to tolerate inotropic therapy.	Definitive intervention needed within few days.
Profile 3. Stable on inotrope or inotrope-dependent Patient with stable blood pressure, organ function, nutrition, and symptoms on continuous i.v. inotropic support (or a temporary circulatory support device or both) but demonstrating repeated failure to wean from support due to recurrent symptomatic hypotension or renal dysfunction. "Dependent stability."	Definitive intervention elective over a period of weeks to few months.
Profile 4. Frequent Flyer Patient can be stabilized close to normal volume status but experiences daily symptoms of congestion at rest or during activities of daily living. Doses of diuretics generally fluctuate at very high levels. More intensive management and surveillance strategies should be considered, which may in some cases reveal poor compliance that would compromise outcomes with any therapy. Some patients may shuttle between 4 and 5.	Definitive intervention elective over a period of weeks to few months.
Profile 5. Housebound Comfortable at rest and with activities of daily living but unable to engage in any other activity, living predominantly within the house. Patients are comfortable at rest without congestive symptoms, but may have underlying refractory elevated volume status, often with renal dysfunction. If underlying nutritional status and organ function are marginal, patients may be more at risk than INTERMACS 4, and require definitive intervention.	Variable urgency, depends upon maintenance of nutrition, organ function, and activity.
Profile 6. Exertion limited Patient without evidence of fluid overload, comfortable at rest and with activities of daily living and minor activities outside the home but fatigues after the first few minutes of any meaningful activity. Attribution to cardiac limitation requires careful measurement of peak oxygen consumption, in some cases with haemodynamic monitoring, to confirm severity of cardiac impairment. "Walking wounded."	Variable, depends upon maintenance of nutrition, organ function, and activity level.

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Table 14 *Continued*

Profile	Time frame for intervention
Profile 7. Advanced NYHA class III symptoms Patient without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion.	Heart transplantation or MCS may not be currently indicated.
Modifiers for profiles	**Possible profiles that can be modified**
Temporary MCS can modify profile only in hospitalized patients. They include IABP, ECMO, TandemHeart, LVAD, Impella.	1, 2, 3
Arrhythmia can modify any profile. They include recurrent ventricular tachyarrhythmias that have recently contributed substantially to clinical compromise, frequent ICD shocks or requirement for external defibrillation, usually more than twice weekly.	1–7
Frequent episodes of HF decompensation characterize patients requiring frequent emergency visits or hospitalizations for diuretics, ultrafiltration, or temporary i.v. vaso-active therapy. Frequent episodes may be considered as at least two emergency visits/ admissions in the past 3 months or three in the past 6 months.	3 if at home, 4, 5, 6. Rarely for profile 7.

ECMO = extracorporeal membrane oxygenation; HF = heart failure; IABP = intra-aortic balloon pump; ICD = implantable cardioverter-defibrillator; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; i.v. = intravenous; LVAD = left ventricular assist device; MCS = mechanical circulatory support; NYHA = New York Heart Association. Modified from [381].

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(*Figure 4*).[376] Patients with contraindications to MCS or heart transplantation should be considered for palliative care (see section 10.2.4).

Despite many prognostic parameters *(Supplementary Table 13)*, predicting outcomes remains difficult and patients are often referred to advanced HF centres too late. Identifying warning signs in patients with non-advanced symptoms may allow early referral so that MCS and heart transplantation may be offered before the development of end-organ failure (*Figure 5*; *Supplementary Table 14*).[376,386] An organizational model between centres with different levels of care complexity, based on a 'Hub and Spoke' network is the key to good patient management.[376]

10.2 Management

In patients with advanced HF, pharmacological therapy and short-term MCS may be needed until the implantation of long-term MCS or heart transplantation becomes available.

10.2.1 Pharmacological therapy and renal replacement

Inotropes may improve haemodynamic parameters, reducing congestion, augmenting cardiac output, and aiding peripheral perfusion. Although not proven, this may help to prevent worsening end-organ function. Conversely, traditional inotropes may favor myocardial ischaemia and/or tachyarrhythmias and worsen the clinical course.[387,388] They can be used as palliative therapy for the relief of symptoms in patients without other treatment options. Intermittent long-term use of inotropes may be considered in outpatients to improve functional class and QOL.[389,390]

Kidney dysfunction and loop diuretic resistance often characterize the clinical course of patients with advanced HF. Doubling of the loop diuretic dose is proposed, in the first instance, followed by concomitant administration of thiazides or metolazone (see section 11.3.3).[145] In patients who fail to respond to diuretic-based strategies, renal replacement therapies should be considered. Ultrafiltration is one of the most common approaches. It may be considered in those with diuretic resistance even if data about its effects on outcomes are unsettled.[391,392]

10.2.2 Mechanical circulatory support

MCS can improve survival and symptoms of patients with advanced HF.[376,393] The use of MCS should be considered for the different scenarios listed in *Table 15*. Indications for short- and long-term MCS should be based on the INTERMACS profiles *(Table 14*, *Figure 4)*.

Short-term mechanical circulatory support

Short-term MCS devices are indicated to reverse critical end-organ hypoperfusion and hypoxia in the setting of cardiogenic shock. They can be used for a short, limited, period of time, from a few days up to several weeks. The aim is to support the central nervous system and organ perfusion, to reverse acidosis and multi-organ failure until the patient's outcome becomes clearer be that of cardiac recovery, transition to durable MCS or heart transplantation, or, in some cases, towards a more palliative approach. The care of patients on short-term MCS is complex and requires dedicated expertise including having specific plans for stopping support when neither cardiac nor brain injury recovers. Short-term MCS should be used in patients with INTERMACS profiles 1 or 2 as a bridge to decision (BTD), bridge to recovery (BTR), bridge to bridge (BTB) for either long-term MCS or urgent heart transplantation (*Figure 4*).[394] Further details about short-term MCS are reported in the *Supplementary text 11.4*.

Long-term mechanical circulatory support

Long-term MCS is indicated in selected patients when MT is insufficient or when short-term MCS has not led to cardiac recovery or clinical improvement, to prolong life and improve QOL, or to keep the patient alive until transplantation (bridge to transplantation, BTT) or to reverse contraindications to heart transplantation (bridge to candidacy, BTC), or as destination therapy (DT) (*Table 15*).

Long-term MCS should be considered in patients with INTERMACS profiles 2 to 4 and also in patients with INTERMACS

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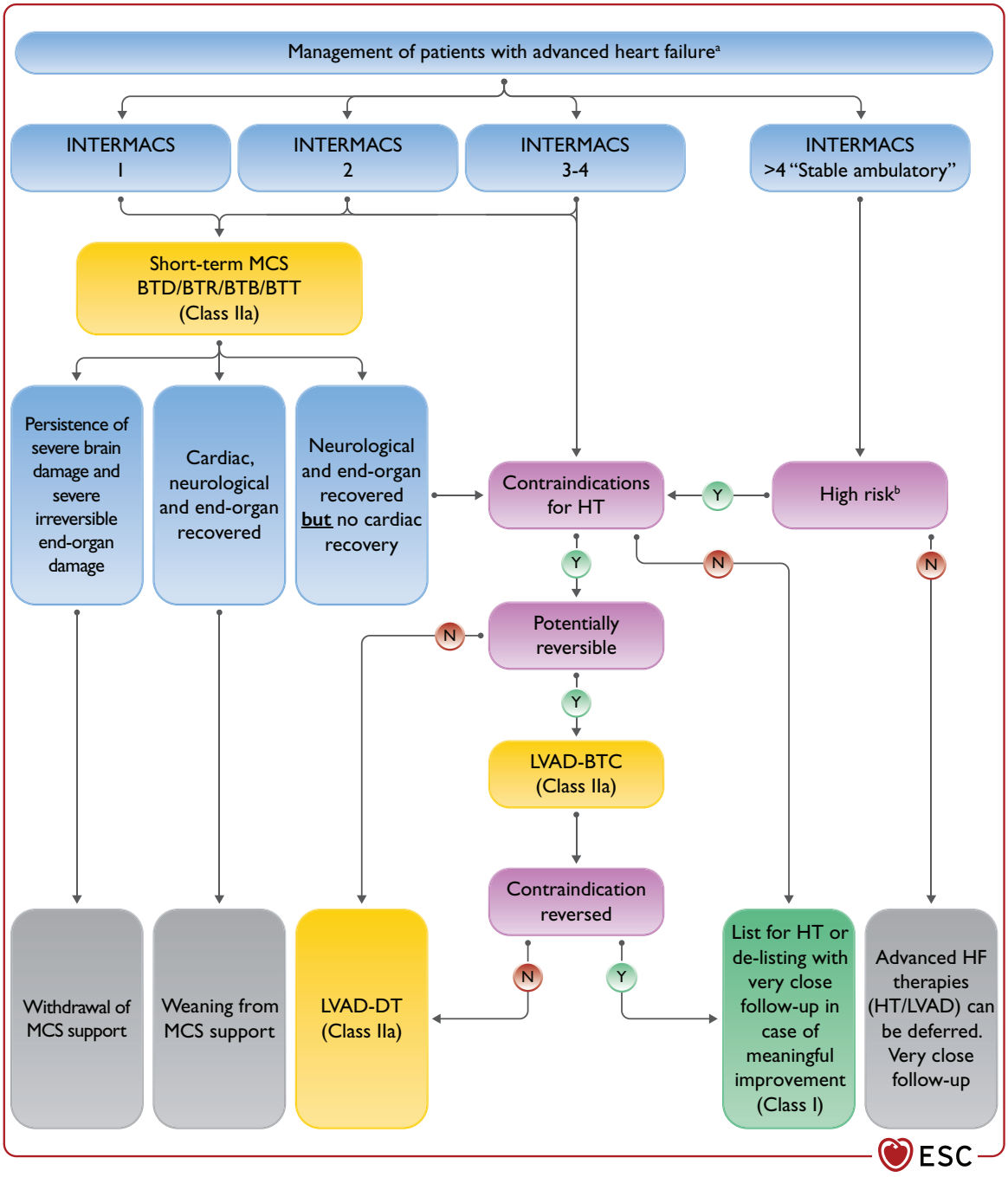

Figure 4 Algorithm for the treatment of patients with advanced heart failure. BTB = bridge to bridge; BTC = bridge to candidacy; BTD = bridge to decision; BTR = bridge to recovery; BTT = bridge to transplantation; CA = cardiac amyloidosis; DT = destination therapy; ESC = European Society of Cardiology; HCM = hypertrophic cardiomyopathy; HF = heart failure; HFA = Heart Failure Association; HT = heart transplantation; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; LVAD = left ventricular assist device; LVAD-BTC = left ventricular assist device – bridge to candidacy; LVAD-DT = left ventricular assist device – destination therapy; MCS = mechanical circulatory support. [a]This algorithm can be applied to all patients with advanced HF defined according to the ESC/HFA criteria,[376] with exception of HCM, CA, arrhythmic storm, adult congenital heart disease, refractory angina. [b]Recurrent hospitalization, progressive end-organ failure, refractory congestion, inability to perform cardiopulmonary exercise test or peak oxygen consumption <12 mL/min/kg or <50% of expected value.[385] Colour code for classes of recommendation: Green for Class of recommendation I and Yellow for Class of recommendation IIa (see *Table 1* for further details on classes of recommendation).

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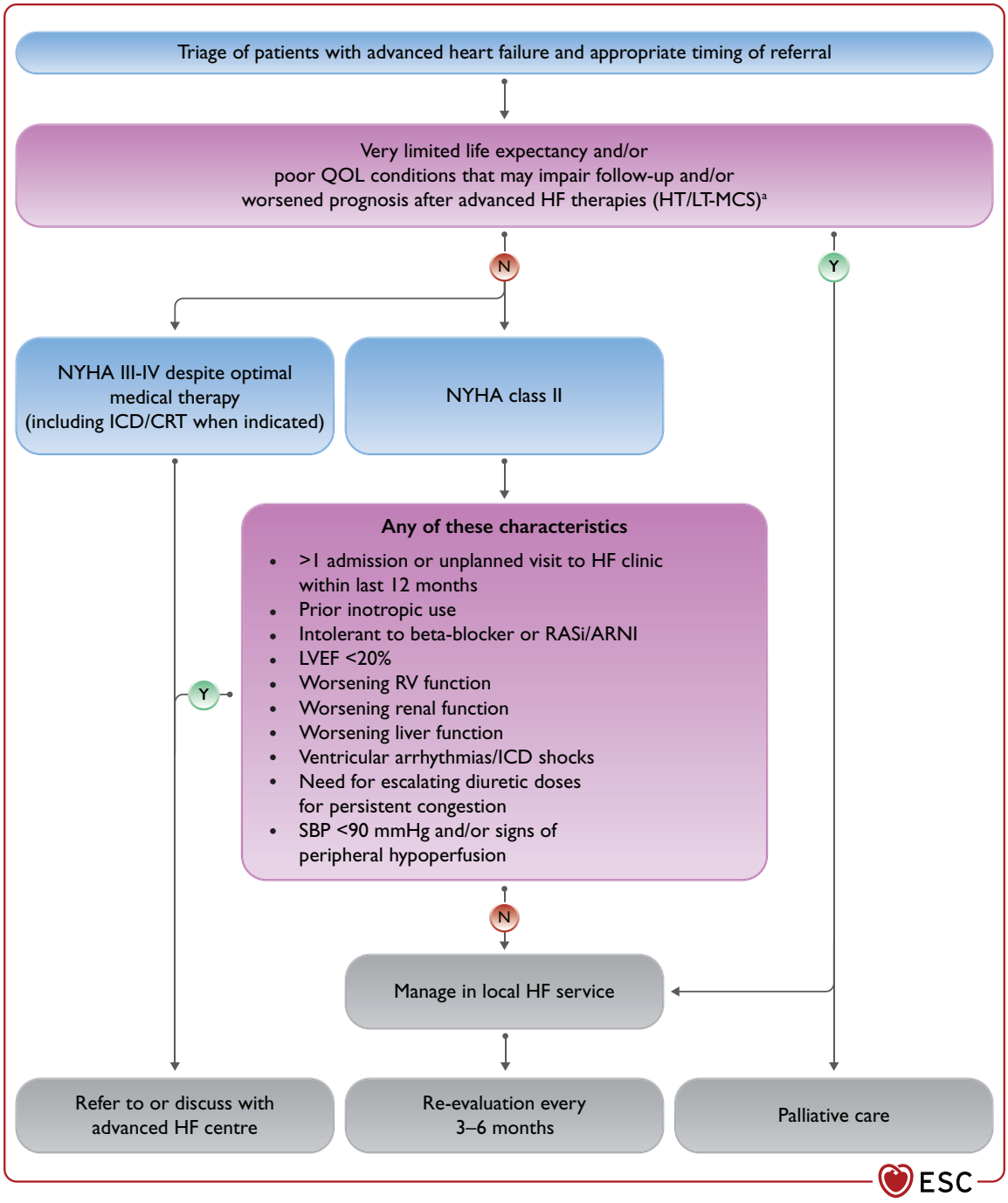

Figure 5 Triage of patients with advanced heart failure and appropriate timing of referral.[376] ARNI = angiotensin receptor-neprilysin inhibitor; CRT = cardiac resynchronization therapy; HF = heart failure; HT = heart transplantation; ICD = implantable cardioverter-defibrillator; LT-MCS = long-term mechanical circulatory support; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RASi = renin-angiotensin system inhibitor; RV = right ventricular; SBP = systolic blood pressure; QOL = quality of life. [a]Limited life expectancy may be due by major comorbidities such as cancer, dementia, end-stage organ dysfunction; other conditions that may impair follow-up or worsen post-treatment prognosis include frailty, irreversible cognitive dysfunction, psychiatric disorder, or psychosocial issues.

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Table 15 Terms describing various indications for mechanical circulatory support

Bridge to decision (BTD)/ Bridge to bridge (BTB)	Use of short-term MCS (ECMO or Impella) in patients with cardiogenic shock until haemodynamics and end-organ perfusion are stabilized, contraindications for long-term MCS are excluded (brain damage after resuscitation) and additional therapeutic options including long-term VAD therapy or heart transplant can be evaluated.
Bridge to candidacy (BTC)	Use of MCS (usually LVAD) to improve end-organ function and/or to make an ineligible patient eligible for heart transplantation.
Bridge to transplantation (BTT)	Use of MCS (LVAD, BiVAD or TAH) to keep a patient alive who is otherwise at high risk of death before transplantation until a donor organ becomes available.
Bridge to recovery (BTR)	Use of MCS (short-term or long-term) to keep a patient alive until cardiac function recovers sufficiently to remove MCS.
Destination therapy (DT)	Long-term use of MCS (LVAD) as an alternative to transplantation in patients with end-stage HF ineligible for transplantation.

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BiVAD = biventricular assist device; ECMO = extracorporeal membrane oxygenation; HF = heart failure; LVAD = left ventricular assist device; MCS = mechanical circulatory support; TAH = total artificial heart; VAD = ventricular assist device.

Table 16 Patients potentially eligible for implantation of a left ventricular assist device

Patients with persistence of severe symptoms despite optimal medical and device therapy, without severe right ventricular dysfunction and/or severe TR, with a stable psychosocial background and absence of major contraindications*, and who have at least one of the following:
• LVEF <25% and unable to exercise for HF or, if able to perform cardiopulmonary exercise testing, with peak VO_2 <12 mL/kg/min and/or <50% predicted value.
• ≥3 HF hospitalizations in previous 12 months without an obvious precipitating cause.
• Dependence on i.v. inotropic therapy or temporary MCS.
• Progressive end-organ dysfunction (worsening renal and/or hepatic function, type II pulmonary hypertension, cardiac cachexia) due to reduced perfusion and not to inadequately low ventricular filling pressure (PCWP ≥20 mmHg and SBP ≤90 mmHg or cardiac index ≤2 L/min/m^2).

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HF = heart failure; i.v. = intravenous; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MCS = mechanical circulatory support; PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure; TR = tricuspid regurgitation; VO_2 = oxygen consumption.
*Stable psychosocial background includes demonstrated understanding of the technology and patient living in the same household with a caregiver that will help the patient (i.e. living alone and poor psychosocial background is LVAD contraindication). Major contraindications include contraindication to long-term oral anticoagulation, infection, severe renal dysfunction, ventricular arrhythmias.

profile 5–6, when they have high-risk characteristics. Patients with no irreversible end-organ failure other than cardiac, recovering from INTERMACS level 1 while on short-term MCS, may also qualify for long-term MCS (*Figure 4*).[376,378,383,395–402] The characteristics of patients potentially eligible for implantation of an LVAD are reported in *Table 16*.

The details of the devices and studies on long-term MCS are summarized in *Supplementary Table 15*.

Current 2-year survival rates in patients receiving the latest continuous-flow LVADs are comparable to those after heart transplantation, although adverse events negatively affect QOL. Among patients with continuous flow LVADs, actuarial survival was reported of 80% at 1 year and 70% at 2 years.[403,404] Two-year survival was 84.5% and survival free of disabling stroke or need of reoperation for LVAD malfunction was 76.9% with a centrifugal-flow LVAD in MOMENTUM 3.[405] The fully magnetically levitated centrifugal-flow LVAD has significantly reduced pump thrombosis. In MOMENTUM 3, the need for reoperation to replace a malfunctioning device was 2.3% per 24 months, with only 0.6% per 24 months risk of pump replacement because of pump thrombosis. Stroke (namely, disabling stroke), major bleeding, and gastrointestinal haemorrhage were also lower in the centrifugal-flow pump group than in the axial-flow pump group. However, the incidence of all bleeding events, thromboembolism and driveline infection remained similar to that with older devices.[402]

Data on fully magnetically centrifugal-flow LVAD use in real-world studies with the 2-year outcomes from the ELEVATE registry showed an overall survival of 74.5%, with gastrointestinal bleeding in 9.7%, stroke in 10.2%, and pump thrombosis in 1.5% of patients.[406] According to the IMACS Registry, a new composite endpoint including QOL and adverse events beyond survival was proposed to help in guiding decision making. In this sense 'living well at one year' defined as freedom from death, stroke, bleeding requiring operation, RV assist device, pump replacement, or device-related infection within the first year, was 56.8% after isolated, centrifugal flow-LVAD.[383]

Although now outdated, REMATCH was the only RCT comparing an LVAD as DT with OMT in patients with advanced HF, NYHA class IV and a contraindication to transplantation. REMATCH showed lower all-cause mortality with LVAD therapy when compared with medical treatment (primary endpoint). However, there were high mortality rates at 2 years in both arms.[378] Other studies were not randomized (INTrEPID, ROADMAP)[396,407,408] or compared different devices (ADVANCE, ENDURANCE, MOMENTUM 3).[399,402,409] The two strategies of early LVAD implantation vs. medical treatment with LVAD implantation only after serious deterioration of the patient's condition are currently being compared in a

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prospective trial, Early-VAD (ClinicalTrials.gov Identifier: NCT02387112). Also, the Swedish evaluation of LVAD (SweVAD) study is comparing the survival of patients with advanced HF ineligible for heart transplantation prospectively randomized to LVAD as DT vs. MT (ClinicalTrials.gov Identifier: NCT02592499).[410]

10.2.3 Heart transplantation

Heart transplantation remains the gold standard for the treatment of advanced HF in the absence of contraindications. Post-transplant 1-year survival is around 90% with a median survival of 12.5 years.[385,411,412] Transplantation significantly improves QOL and functional status, although, for unclear reasons, the percentage of patients returning to work is lower than expected.[412] Apart from primary graft dysfunction, the main challenges after heart transplantation relate to either the efficacy or side effects of immunosuppression (e.g. rejection, infection, cardiac allograft vasculopathy, late graft dysfunction, malignancy, renal failure, hypertension, diabetes mellitus).

Organ donor shortage remains the main limitation to heart transplantation. Thus, the donor heart criteria have now been extended to allow an increased upper limit of the donor age, particularly in Europe. Moreover, careful recipient selection is needed, based on pre-transplant and post-transplant life expectancy (both are influenced by pre-operative status and comorbidities).

The main indications and contraindications for heart transplantation are listed in *Table 17*.[376,385]

Active infection is a relative contraindication to transplant but in some cases of infected LVADs it may actually be an indication. Elderly age is not an absolute contraindication. Although patients aged <65 years might be more appropriate candidates due to their overall life expectancy, most programmes accept patients up to 70 years of age, and biological age as well as chronological age must be taken into account. Surgical complexity [previous sternotomies, mediastinal radiation, adult congenital heart disease (ACHD)] should also be considered.

The decision pathway to transplantation or LVAD is never straightforward and is unique to each patient. Eligibility for each option may change according to the particular conditions of each patient, which may also change over time. Other factors, not related to the patient, such as time on the heart transplant waiting list, the

Table 17 Heart transplantation: indications and contraindications

Indications
Advanced HF[376]
No other therapeutic option, except for LVAD as BTT
Contraindications
Active infection[a]
Severe peripheral arterial or cerebrovascular disease
Pharmacologic irreversible pulmonary hypertension (LVAD should be considered to reverse elevated pulmonary vascular resistance with subsequent re-evaluation to establish candidacy)
Malignancy with poor prognosis (a collaboration with oncology specialists should occur to stratify each patient as regards their risk of tumour progression or recurrence which increases with the use of immunosuppression)
Irreversible liver dysfunction (cirrhosis) or irreversible renal dysfunction (e.g. creatinine clearance <30 mL/min/1.73 m^2). Combined heart-liver or heart-kidney transplant may be considered
Systemic disease with multiorgan involvement
Other serious comorbidity with poor prognosis
Pre-transplant BMI >35 kg/m^2 (weight loss is recommended to achieve a BMI <35 kg/m^2)
Current alcohol or drug abuse
Psychological instability that jeopardizes proper follow-up and intensive therapeutic regime after heart transplantation
Insufficient social supports to achieve compliant care in the outpatient setting

BMI = body mass index; BTT = bridge to transplantation; HF = heart failure; LVAD = left ventricular assist device.
[a]Active infection is a relative contraindication to transplant although in some cases of infected LVADs it may actually be an indication.
Adapted from Crespo-Leiro et al.[376]

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Recommendations for the treatment of patients with advanced heart failure

Recommendations	Class[a]	Level[b]
Patients being considered for long-term MCS must have good compliance, appropriate capacity for device handling and psychosocial support.[414–416]	I	C
Heart transplantation is recommended for patients with advanced HF, refractory to medical/device therapy and who do not have absolute contraindications.	I	C
Long-term MCS should be considered in patients with advanced HFrEF despite optimal medical and device therapy, not eligible for heart transplantation or other surgical options, and without severe right ventricular dysfunction, to reduce the risk of death and improve symptoms.[378,396,397,401,402,404,417]	IIa	A
Long-term MCS should be considered in patients with advanced HFrEF refractory to optimal medical and device therapy as a bridge to cardiac transplantation in order to improve symptoms, reduce the risk of HF hospitalization and the risk of premature death.[398–400,402,404]	IIa	B
Renal replacement therapy should be considered in patients with refractory volume overload and end-stage kidney failure.	IIa	C
Continuous inotropes and/or vasopressors may be considered in patients with low cardiac output and evidence of organ hypoperfusion as bridge to MCS or heart transplantation.[389,390]	IIb	C
Ultrafiltration may be considered in refractory volume overload unresponsive to diuretic treatment.[391,392]	IIb	C

HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MCS = mechanical circulatory support.
[a]Class of recommendation.
[b]Level of evidence.

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centre's surgical experience, and resources, can also influence decision making.[413]

10.2.4 Symptom control and end-of-life care

While the disease trajectory of each patient with HF is unique, there is a generalizable pattern of gradual decline, punctuated by episodes of acute deterioration leading either to sudden death or death due to progressive HF. Communication about the disease trajectory and anticipatory planning should start when a patient is diagnosed with advanced HF. Indications for and key components of a palliative care service are reported in *Tables 18* and *19*.[312,418]

A team-based approach to palliative and end-of-life care for patients with HF has been proposed.[419] Specific models of palliative care for patients with advanced HF have been also reported. They reduce hospitalizations, without a clear effect on survival, and have some effects on QOL and symptom burden.[420,421]

Symptom assessment should be performed on a regular basis. In addition to clinical assessment, symptoms can be assessed using the Numeric Rating Scale, the Edmonton Symptom Assessment Scale (ESAS) or ESAS-HF, or the Integrated Palliative care Outcome Scale.

Table 18 Patients with heart failure in whom end-of-life care should be considered

Progressive functional decline (physical and mental) and dependence in most activities of daily living.
Severe heart failure symptoms with poor QOL despite optimal pharmacological and non-pharmacological therapies.
Frequent admissions to hospital or other serious episodes of decompensation despite optimal treatment.
Heart transplantation and MCS ruled out.
Cardiac cachexia.
Clinically judged to be close to end of life.

MCS = mechanical circulatory support; QOL = quality of life.

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Table 19 Key components of palliative care service in patients with advanced heart failure

Focus on improving or maintaining the QOL of a patient and his/her family as well as possible until he/she dies.
Frequent assessment of symptoms (including dyspnoea and pain) resulting from advanced heart failure and other comorbidities and focus on symptom relief.
Access for the patient and his/her family to psychological support and spiritual care according to need.
Advanced care planning, taking into account preferences for place of death and resuscitation (which may include deactivating devices, such as ICD or long-term MCS that may require a multidisciplinary team decision).

ICD = implantable cardioverter-defibrillator; MCS = mechanical circulatory support; QOL = quality of life.

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Treatment for symptoms needs to be considered and might include additional intervention on top of OMT:

- Breathlessness: repeat doses of opioids may be considered for the relief of dyspnoea; however, their effectiveness is not demonstrated.[422,423] While using opioids, all patients should be guided about opioid side effects such as constipation and nausea, urinary retention, and mental status changes. Benzodiazepines may be considered as a second- or third-line treatment, when opioids and non-pharmacological measures have failed to control breathlessness. Increasing the inspired oxygen concentration may provide relief of dyspnoea.
- Pain: non-pharmacologic management can be helpful. In addition, opioid, oxycodone, hydromorphone, and fentanyl are generally viewed as safe options and can be provided orally, intravenously, and transdermally, especially in the hospital or in patient palliative care or hospice setting.[424]
- Anxiety and depression: adequate conventional treatment should be offered.

Proactive decisions and advanced planning with regard to palliative and end-of-life care discussions should be documented, regularly reviewed, and routinely communicated to all those involved in the patient's care. Healthcare providers should make sure that patients' and carer preferences are followed, wherever possible. They should also take into account that patients may choose not to, or may not be in a position to, express preferences (e.g. due to symptoms of depression or cognitive impairment).

11 Acute heart failure

11.1 Epidemiology, diagnosis and prognosis

AHF refers to rapid or gradual onset of symptoms and/or signs of HF, severe enough for the patient to seek urgent medical attention, leading to an unplanned hospital admission or an emergency department visit. Patients with AHF require urgent evaluation with subsequent initiation or intensification of treatment, including i.v. therapies or procedures. AHF is a leading cause of hospitalizations in subjects aged >65 years and is associated with high mortality and rehospitalization rates. In-hospital mortality ranges from 4% to 10%.[425–428] Post-discharge 1-year mortality can be 25–30% with up to more than 45% deaths or readmission rates.[104,426,427,429,430]

AHF may be the first manifestation of HF (new onset) or, more frequently, be due to an acute decompensation of chronic HF. Compared to patients with acutely decompensated CHF, those with new onset HF may have a higher in-hospital mortality[425] but have lower post-discharge mortality and rehospitalization rates.[425,428,431,432] Specific extrinsic factors may precipitate, but not cause, AHF in patients with pre-existing cardiac dysfunction (*Supplementary Table 16*). Clinical severity and in-hospital trajectory are determined by the complex interplay between precipitants, the underlying cardiac substrate, and the patient's comorbidities.

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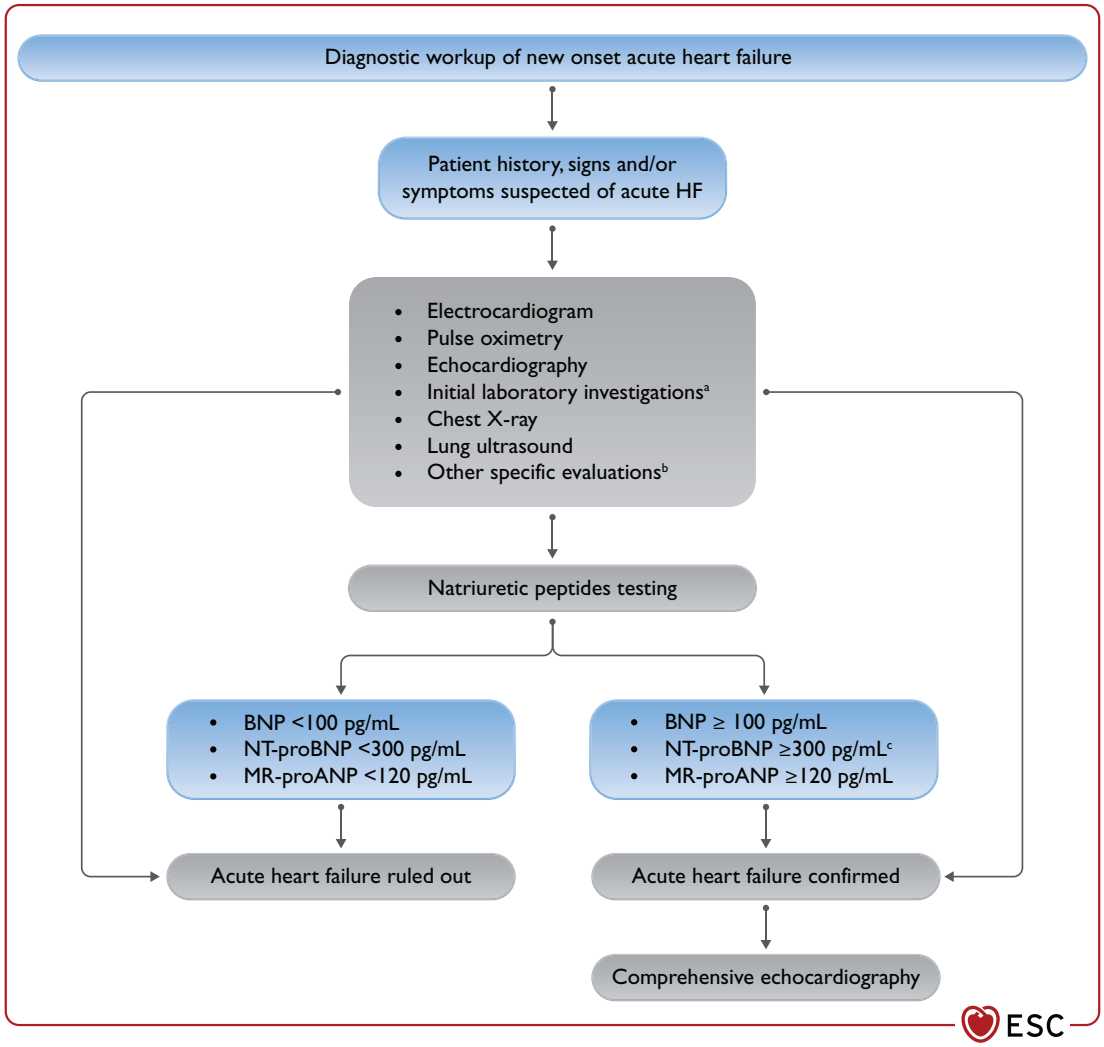

Figure 6 Diagnostic workup of new onset acute heart failure. ACS = acute coronary syndrome; BNP = B-type natriuretic peptide; CT = computed tomography; HF = heart failure; MR-proANP = mid-regional pro-atrial natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TSH = thyroid-stimulating hormone. [a]Initial laboratory exams include troponin, serum creatinine, electrolytes, blood urea nitrogen or urea, TSH, liver function tests as well as D-dimer and procalcitonin when pulmonary embolism or infection are suspected, arterial blood gas analysis in case of respiratory distress, and lactate in case of hypoperfusion. [b]Specific evaluation includes coronary angiography, in case of suspected ACS, and CT in case of suspected pulmonary embolism. [c]Rule-in values for the diagnosis of acute HF: >450 pg/mL if aged <55 years, >900 pg/mL if aged between 55 and 75 years and >1800 pg/mL if aged >75 years.[433,434]

The diagnostic workup of AHF starts at the time of the first medical contact, and is continued throughout the initial patient pathway, aiming to identify the clinical presentation and to diagnose and manage any potentially reversible causes/precipitants/coexisting life-threatening conditions in a timely manner (*Figure 6*). Diagnostic tests are outlined at *Table 20*. In addition to clinical signs and symptoms, diagnostic workup includes ECG and echocardiography, if possible. Additional investigations, i.e. chest X-ray and lung ultrasound may be used to confirm AHF diagnosis, especially when NP testing is not available. Plasma NP levels (BNP or NT-proBNP or MR-proANP) should be measured if the diagnosis is uncertain and a point-of-care assay is available. Normal concentrations of NPs make the diagnosis of AHF unlikely. Cut-offs for acute HF are: BNP <100 pg/mL, NT-proBNP <300 pg/mL and MR-proANP <120 pg/mL.[74,433–435] However, elevated NP values are associated with a wide range of cardiac and non-cardiac conditions *(Table 6)*. Low concentrations can be detected in some patients with advanced decompensated end-stage HF, obesity, flash pulmonary oedema or right-sided AHF. Higher levels can be found in the patients with concomitant AF and/or reduced renal function.[74]

Among other laboratory tests, troponin is useful for the detection of acute coronary syndrome (ACS) although elevated levels are detected in the vast majority of patients with AHF.[436–438] Blood urea nitrogen or urea, serum creatinine, electrolytes (sodium, potassium, chloride), and antigen carbohydrate 125 may help tailor treatment.[439,440] Detection of abnormal liver function identifies patients

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Table 20 Diagnostic tests in patients with acute heart failure

Exam	Time of measurement	Possible findings	Diagnostic value for AHF	Indication
ECG	Admission, during hospitalization,[a,b] pre-discharge	Arrhythmias, myocardial ischaemia	Exclusion of ACS or arrhythmias	Recommended
Chest-X ray	Admission, during hospitalization[a]	Congestion, lung infection	Confirmatory	May be considered
LUS	Admission, during hospitalization[a] pre-discharge	Congestion	Confirmatory	May be considered
Echocardiography	Admission, during hospitalization,[a] pre-discharge	Congestion, cardiac dysfunction, mechanical causes	Major	Recommended
Natriuretic peptides (BNP, NT-proBNP, MR-proANP)	Admission, pre-discharge	Congestion	High negative predictive value	Should be considered
Serum troponin	Admission	Myocardial injury	Exclusion of ACS	Recommended
Serum creatinine	Admission, during hospitalization,[a] pre-discharge	Renal dysfunction	None	Recommended for prognostic assessment
Serum electrolytes (sodium, potassium, chloride)	Admission, during hospitalization,[a] pre-discharge	Electrolyte disorders	None	Recommended for prognostic assessment and treatment
Iron status (transferrin, ferritin)	Pre-discharge	Iron depletion	None	Recommended for prognostic assessment and treatment
TSH	Admission	Hypo- hyperthyroidism	None	Recommended when hypo-hyperthyroidism is suspected
D-dimer	Admission	Pulmonary embolism	Useful to exclude pulmonary embolism	Recommended when pulmonary embolism is suspected
Procalcitonin	Admission	Pneumonia	Useful for diagnosis of pneumonia	May be done when pneumonia is suspected
Lactate	Admission, during hospitalization[a]	Lactic acidosis	Useful to assess perfusion status	Recommended when peripheral hypoperfusion is suspected
Pulse oximetry and arterial blood gas analysis	Admission, during hospitalization[a]	Respiratory failure	Useful to assess respiratory function	Recommended when respiratory failure is suspected

ACS = acute coronary syndrome; AHF = acute heart failure; BNP = B-type natriuretic peptide; ECG = electrocardiogram; LUS = lung ultrasound; MR-proANP = mid-regional pro-atrial natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TSH = thyroid-stimulating hormone.
[a]Based on clinical conditions.
[b]Continuous ECG monitoring can be considered based on clinical conditions.

with a poor prognosis.[441] Since both hypothyroidism and hyperthyroidism may precipitate AHF, thyroid-stimulating hormone (TSH) should be assessed in those with newly diagnosed AHF. Arterial blood gas analysis should be performed when a precise measurement of O_2 and CO_2 partial pressure is needed (i.e. patients with respiratory distress). Lactate and pH levels should be measured in patients with cardiogenic shock. D-dimer should be measured when acute pulmonary embolism is suspected. Procalcitonin may be used for the diagnosis of pneumonia and antibiotic therapy may have an indication when plasma levels are >0.2 µg/L. However, no impact of a strategy based on routine procalcitonin measurements on outcomes was shown in a prospective, controlled, trial.[442] Pulse oximetry should be measured routinely at the time of first presentation of patients with AHF and continuous monitoring may be needed in the first hours or days.[443,444]

11.2 Clinical presentations

Four major clinical presentations can be described with possible overlaps between them (*Table 21*).[1,425,445] Clinical presentations are mainly based on the presence of signs of congestion and/or peripheral hypoperfusion and require different treatments (*Table 21*).[1,425–427,432,446,447]

11.2.1 Acutely decompensated heart failure

Acutely decompensated heart failure (ADHF) is the most common form of AHF, accounting for 50–70% of presentations.[426,427,432] It

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Table 21 Clinical presentations of acute heart failure

	Acutely decompensated heart failure	Acute pulmonary oedema	Isolated right ventricular failure	Cardiogenic shock
Main mechanisms	LV dysfunction Sodium and water renal retention	Increased afterload and/or predominant LV diastolic dysfunction Valvular heart disease	RV dysfunction and/or pre-capillary pulmonary hypertension	Severe cardiac dysfunction
Main cause of symptoms	Fluid accumulation, increased intraventricular pressure	Fluid redistribution to the lungs and acute respiratory failure	Increased central venous pressure and often systemic hypoperfusion	Systemic hypoperfusion
Onset	Gradual (days)	Rapid (hours)	Gradual or rapid	Gradual or rapid
Main haemodynamic abnormalities	Increased LVEDP and PCWP[a] Low or normal cardiac output Normal to low SBP	Increased LVEDP and PCWP[a] Normal cardiac output Normal to high SBP	Increased RVEDP Low cardiac output Low SBP	Increased LVEDP and PCWP[a] Low cardiac output Low SBP
Main clinical presentations[1,446]	Wet and warm OR Wet and cold	Wet and warm[b]	Wet and cold	Wet and cold
Main treatment	Diuretics Inotropic agents/vasopressors (if peripheral hypoperfusion/hypotension) Short-term MCS or RRT if needed	Diuretics Vasodilators[b]	Diuretics for peripheral congestion Inotropic agents/vasopressors (if peripheral hypoperfusion/hypotension) Short-term MCS or RRT if needed	Inotropic agents/vasopressors Short-term MCS RRT

LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; MCS = mechanical circulatory support; PCWP = pulmonary capillary wedge pressure; RV = right ventricular; RVEDP = right ventricular end-diastolic pressure; RRT = renal replacement therapy; SBP = systolic blood pressure.
[a]May be normal with low cardiac output.
[b]Wet and cold profile with need of inotropes and/or vasopressors may rarely occur.

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usually occurs in patients with history of HF and previous cardiac dysfunction across the spectrum of LVEF and may include RV dysfunction. Distinct from the acute pulmonary oedema phenotype, it has a more gradual onset, and the main alteration is progressive fluid retention responsible for systemic congestion. Sometimes, congestion is associated with hypoperfusion.[426] The objectives of treatment are identification of precipitants, decongestion, and in rare instances, correction of hypoperfusion (*Figure 7*).

11.2.2 Acute pulmonary oedema

Acute pulmonary oedema is related to lung congestion. Clinical criteria for acute pulmonary oedema diagnosis include dyspnoea with orthopnoea, respiratory failure (hypoxaemia-hypercapnia), tachypnoea, >25 breaths/min, and increased work of breathing.[448]

Three therapies should be commenced, if indicated. First, oxygen, given as continuous positive airway pressure, non-invasive positive-pressure-ventilation and/or high-flow nasal cannula, should be started. Second, i.v. diuretics should be administered, and third, i.v. vasodilators may be given if systolic BP (SBP) is high, to reduce LV afterload (*Figure 8*). In a few cases of advanced HF, acute pulmonary oedema may be associated with low cardiac output and, in this case, inotropes, vasopressors, and/or MCS are indicated to restore organ perfusion.

11.2.3 Isolated right ventricular failure

RV failure is associated with increased RV and atrial pressure and systemic congestion. RV failure may also impair LV filling, and ultimately reduce systemic cardiac output, through ventricular interdependence.[449]

Diuretics are often the first option of therapy for venous congestion. Noradrenaline and/or inotropes are indicated for low cardiac output and haemodynamic instability. Inotropes reducing cardiac filling pressures may be preferred (i.e. levosimendan, phosphodiesterase type III inhibitors). Since inotropic agents may aggravate arterial hypotension, they may be combined with norepinephrine if needed (*Figure 9*).[449]

11.2.4 Cardiogenic shock

Cardiogenic shock is a syndrome due to primary cardiac dysfunction resulting in an inadequate cardiac output, comprising a life-threatening state of tissue hypoperfusion, which can result in multi-organ failure and death.[450–452] Cardiac insult causing severe impairment of cardiac performance may be acute, as a result of the acute loss of myocardial tissue (acute MI, myocarditis) or may be progressive as seen in patients with chronic decompensated HF who may experience a decline in disease stability as a result of the natural progression of advanced HF and/or specific precipitants.[426]

Diagnosis of cardiogenic shock mandates the presence of clinical signs of hypoperfusion, such as cold sweated extremities, oliguria, mental confusion, dizziness, narrow pulse pressure. In addition, biochemical manifestations of hypoperfusion, elevated serum creatinine, metabolic acidosis and elevated serum lactate are present and reflect tissue hypoxia and alterations of cellular

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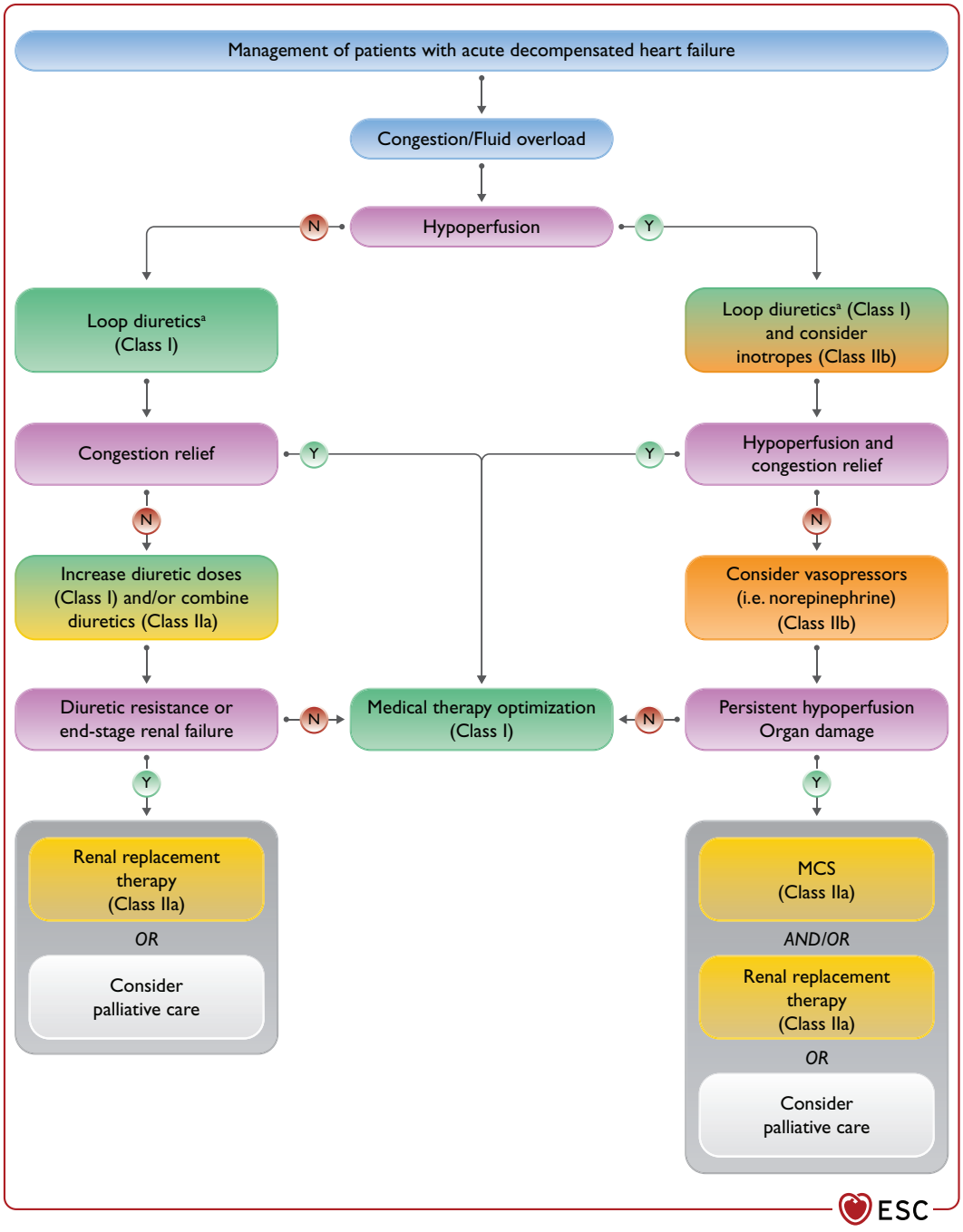

Figure 7 Management of acute decompensated heart failure. MCS = mechanical circulatory support. [a]Adequate diuretic doses to relieve congestion and close monitoring of diuresis is recommended (see *Figure 13*) regardless of perfusion status.

metabolism leading to organ dysfunction.[437,453] Of note, hypoperfusion is not always accompanied by hypotension, as BP may be preserved by compensatory vasoconstriction (with/without pressor agents), albeit at the cost of impaired tissue perfusion and oxygenation.[426,427,450,454]

Management of cardiogenic shock should start as early as possible. Early identification and treatment of the underlying cause, concomitant with haemodynamic stabilization and management of organ dysfunction, are key components of its management (*Figure 10*, *Supplementary text 11.1*; *Supplementary Figure 2*).

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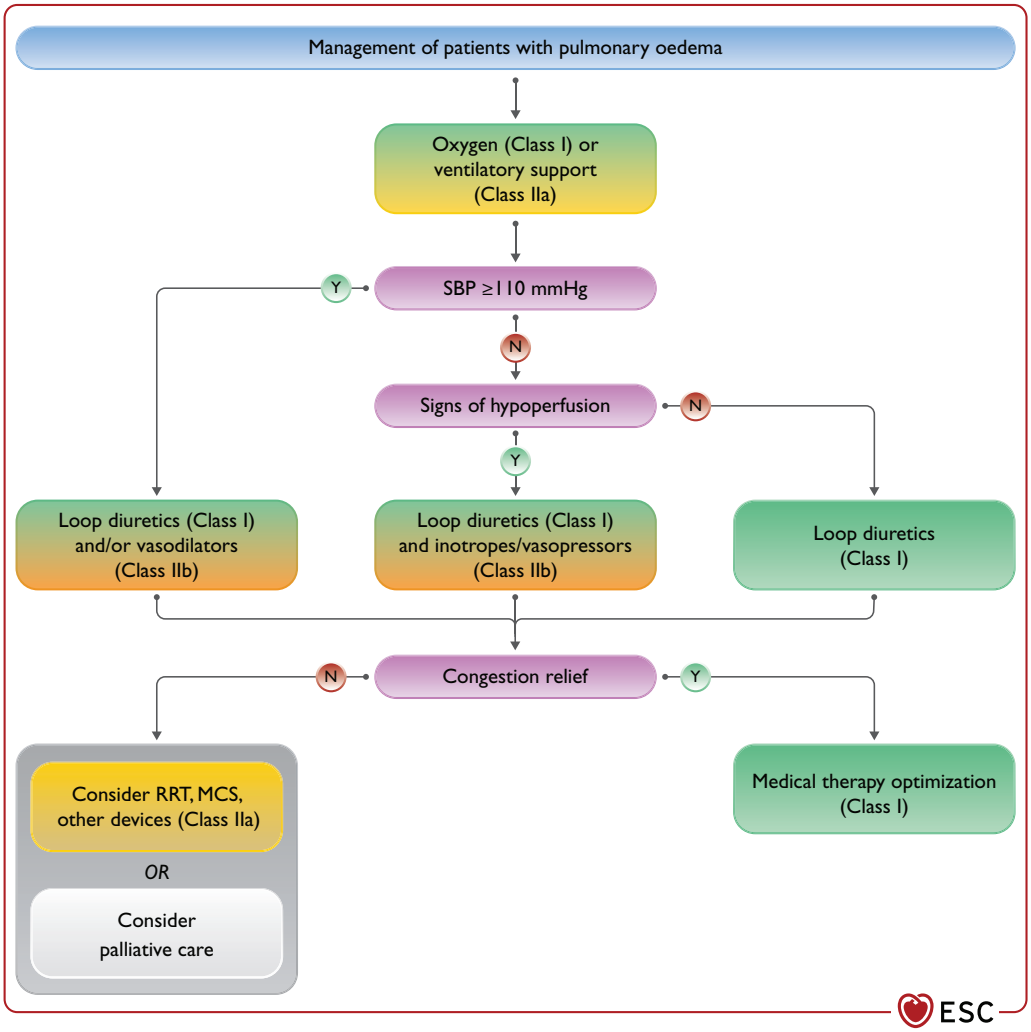

Figure 8 Management of pulmonary oedema. MCS = mechanical circulatory support; RRT = renal replacement therapy; SBP = systolic blood pressure.

11.3 Management

11.3.1 General aspects

Management can be subdivided in three stages (pre-hospital, in-hospital, and pre-discharge), having different goals and requiring different approaches (*Figure 11*).

Pre-hospital phase

In the pre-hospital setting, AHF patients should benefit from non-invasive monitoring, including pulse oximetry, BP, heart rate respiratory rate, and a continuous ECG, instituted within minutes of patient contact and in the ambulance if possible.[305] Oxygen therapy may be given based on clinical judgment unless oxygen saturation is <90% in which case it should be administered. In patients with respiratory distress, respiratory rate >25 breaths/min, oxygen saturation <90%, non-invasive ventilation should be initiated.[444,448] Although therapeutic tools may be available in the prehospital setting, whether more effective pre-hospital care would alter the clinical outcome remains to be proven in randomized clinical trials.[455] Furthermore, pre-hospital management should not delay the rapid transfer of AHF patients to the most appropriate medical setting.[455,456]

In-hospital management

Diagnostic workup and appropriate pharmacological and non-pharmacological treatment must be started promptly and in parallel (*Figure 12*). AHF patients are triaged to the appropriate level of care according to the degree of haemodynamic instability and severity of the critical illness. Disposition decisions are important components of the initial phase of management (see *Supplementary text 11.2* and *Supplementary Tables 17–19*).

The type and intensity of in-hospital monitoring depends on clinical severity, settings of care and in-hospital course (see *Supplementary text 11.3*). As AHF is a heterogeneous condition, management may differ according to the main clinical presentation. Management starts with the search for specific causes of AHF.[1,305,430] These include

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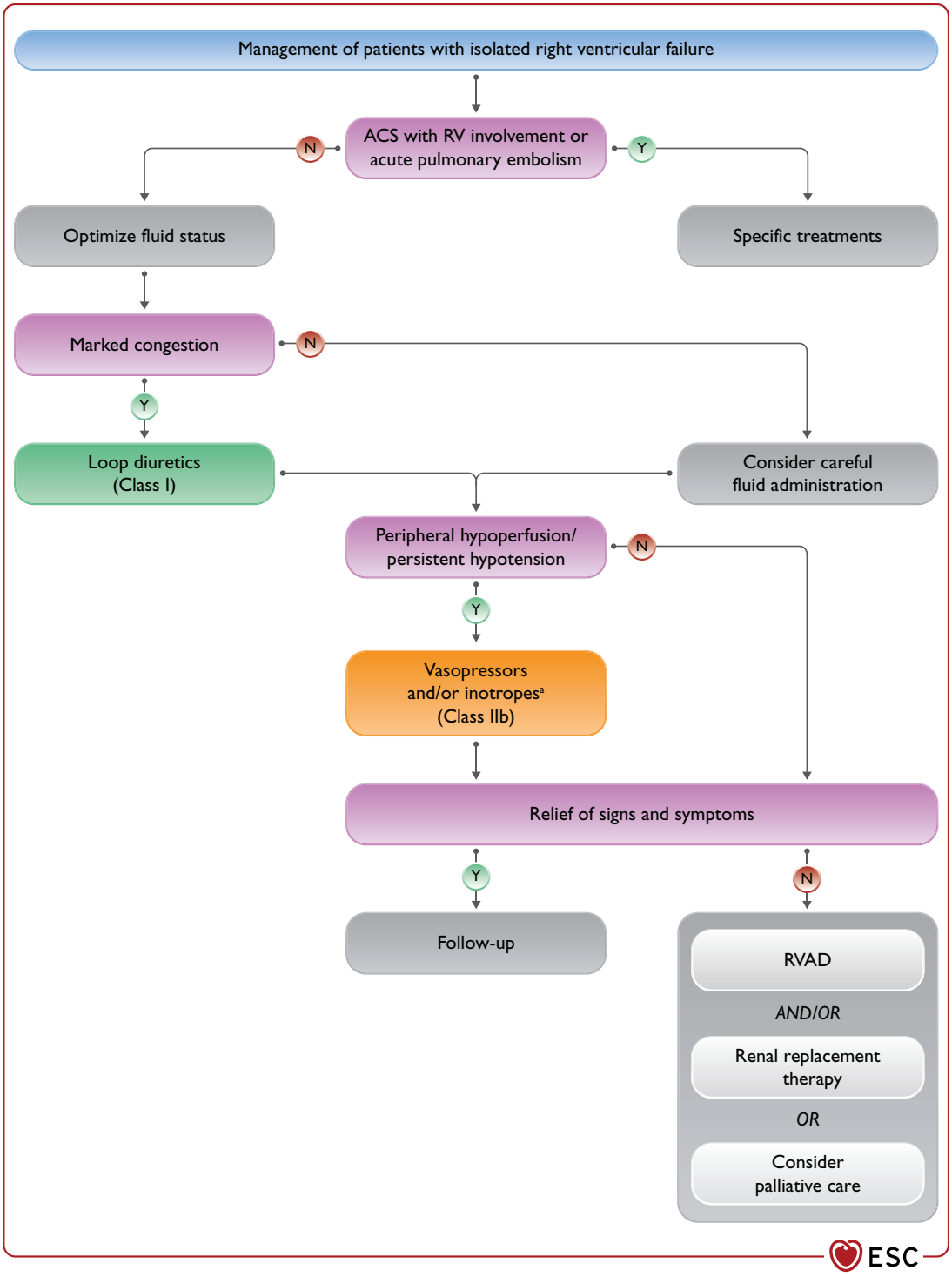

Figure 9 Management of right ventricular failure. ACS = acute coronary syndrome; RV = right ventricular; RVAD = right ventricular assist device. [a]Inotropes alone in case of hypoperfusion without hypotension.

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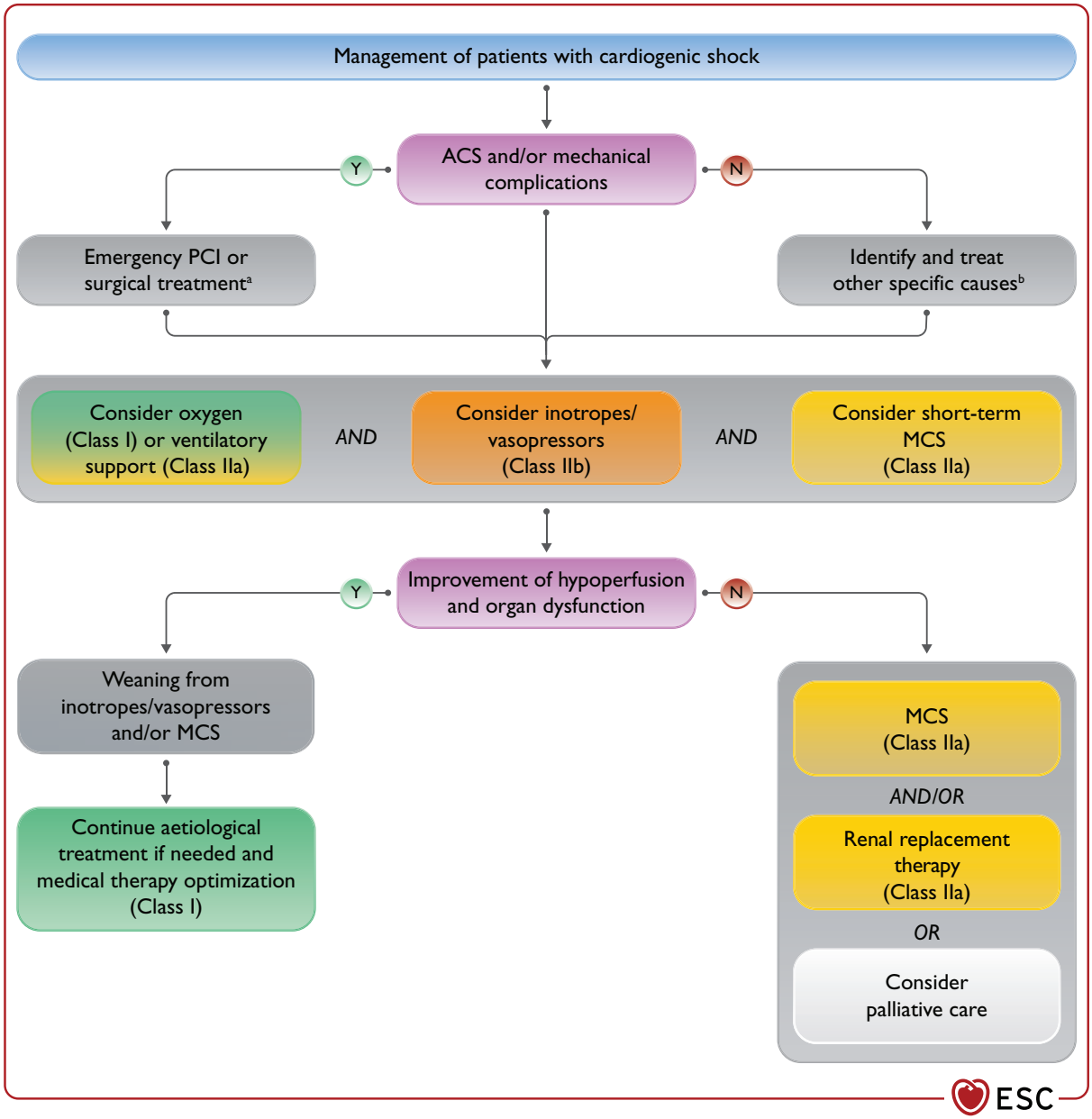

Figure 10 Management of cardiogenic shock. ACS = acute coronary syndrome; BTT = bridge to transplantation; MCS = mechanical circulatory support; PCI = percutaneous coronary intervention. [a]PCI in ACS, pericardiocentesis in tamponade, mitral valve surgery in papillary muscle rupture. In case of interventricular septum rupture, MCS as BTT should be considered. [b]Other causes include acute valve regurgitation, pulmonary embolism, infection, acute myocarditis, arrhythmia (see *Figure 12*).

ACS, a hypertensive emergency, rapid arrhythmias or severe bradycardia/conduction disturbance, acute mechanical causes such as acute valve regurgitation or acute pulmonary embolism, infection, including myocarditis, and tamponade (CHAMPIT) (*Figure 12*). After exclusion of these conditions, which need to be treated/corrected urgently, management of AHF differs according to the clinical presentations (*Figures 7–10*).

Pre-discharge phase

Details on this phase are shown in section 11.3.11.

11.3.2 Oxygen therapy and/or ventilatory support

In AHF, oxygen should not be used routinely in non-hypoxaemic patients, as it causes vasoconstriction and a reduction in cardiac output.[457] Oxygen therapy is recommended in patients with AHF and

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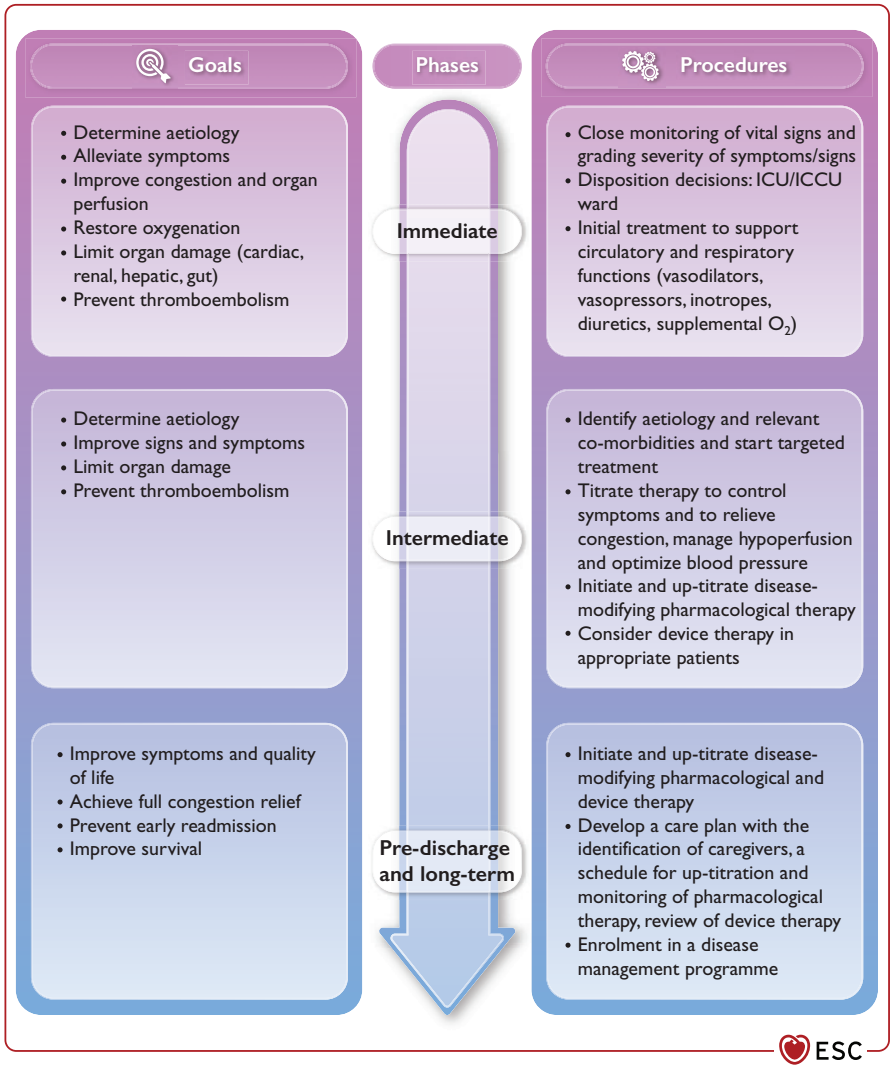

Figure 11 Stages of management of patients with acute heart failure. ICCU = intensive coronary care unit; ICU = intensive care unit.

SpO_2 <90% or PaO_2 <60 mmHg to correct hypoxaemia. In chronic obstructive pulmonary disease (COPD), hyper-oxygenation may increase ventilation–perfusion mismatch, suppress ventilation and lead to hypercapnia. During oxygen therapy, acid-base balance and SpO_2 should be monitored.

Non-invasive positive pressure ventilation, either continuous positive airway pressure and pressure support, improves respiratory failure, increases oxygenation and pH, and decreases the partial pressure of carbon dioxide (pCO_2) and work of breathing. Although a large randomized trial had neutral results, meta-analyses suggest it may improve dyspnoea and reduce the need for intubation and mortality, compared with traditional oxygen therapy.[1,458,459] Non-invasive positive pressure ventilation should be started as soon as possible in patients with respiratory distress (respiratory rate >25 breaths/min, SpO_2 <90%) to improve gas exchange and reduce the rate of endotracheal intubation.[448,459] The fraction of inspired oxygen (FiO_2) should be increased up to 100%, if necessary, according to oxygen saturation level.

Blood pressure should be monitored regularly during non-invasive positive pressure ventilation. The increase in intrathoracic pressure with non-invasive positive pressure ventilation decreases venous return and right and left ventricular preload. It may also decrease cardiac output and BP and should therefore be used with caution in patients with reduced preload reserve and hypotension. The increase in pulmonary vascular resistance and RV afterload may also be detrimental in RV dysfunction.[448]

Intubation is recommended for progressive respiratory failure in spite of oxygen administration or non-invasive ventilation (*Supplementary Table 20*).[448]

11.3.3 Diuretics

Intravenous diuretics are the cornerstone of AHF treatment. They increase renal excretion of salt and water and are indicated for the treatment of fluid overload and congestion in the vast majority of AHF patients.

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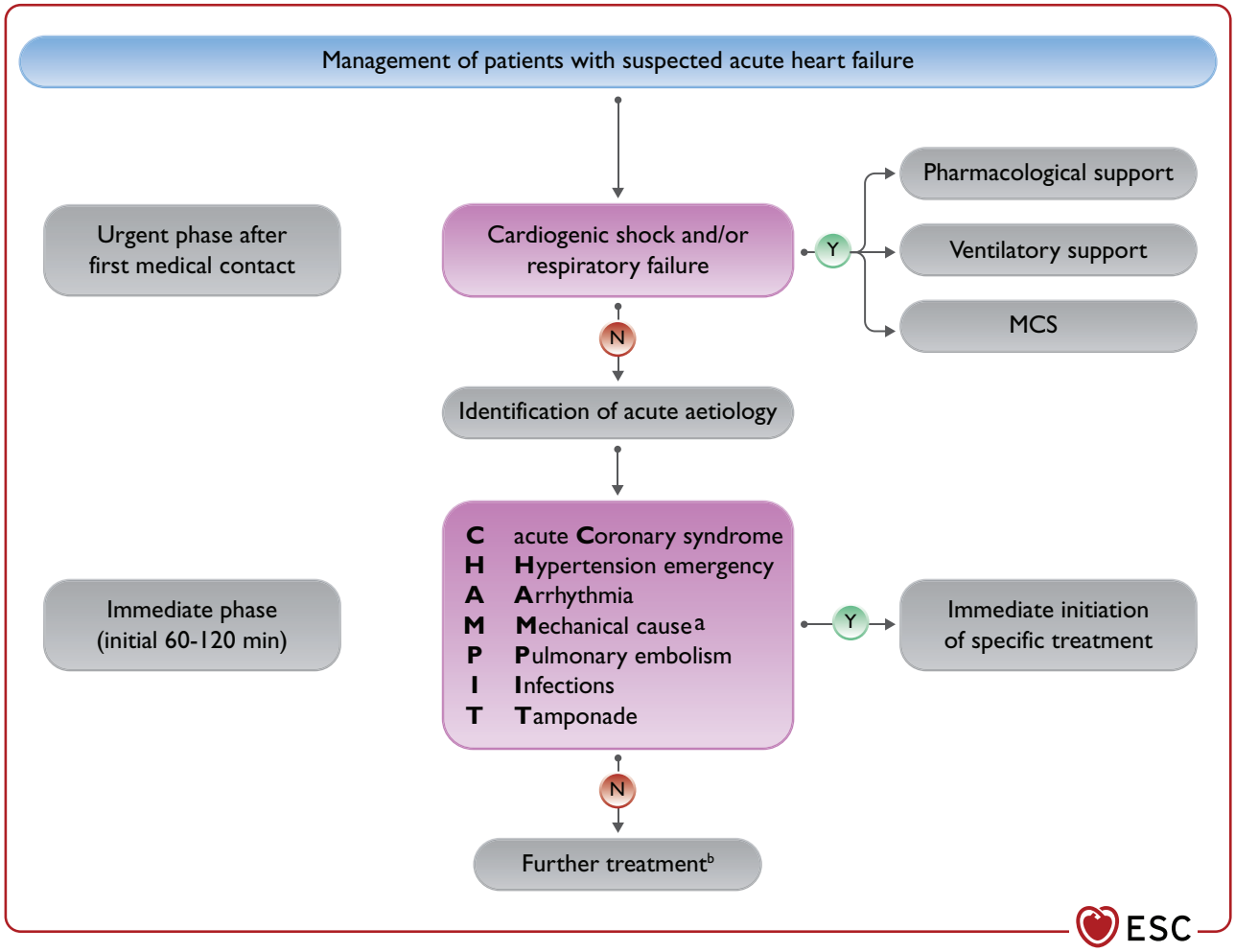

Figure 12 Initial management of acute heart failure. MCS = mechanical circulatory support. [a]Acute mechanical cause: myocardial rupture complicating acute coronary syndrome (free wall rupture, ventricular septal defect, acute mitral regurgitation), chest trauma or cardiac intervention, acute native or prosthetic valve incompetence secondary to endocarditis, aortic dissection or thrombosis. [b]See *Figures 7–10* for specific treatments according to different clinical presentations.

Loop diuretics are commonly used due to their rapid onset of action and efficacy. Data defining their optimal dosing, timing, and method of administration are limited. No difference in the primary efficacy outcome of patients' symptoms global assessment was shown with a high-dose regimen, compared with a low-dose regimen, in the DOSE trial. However, there was a greater relief of dyspnoea, change in weight and net fluid loss (with no prognostic role for increases in serum creatinine) in the higher-dose regimen.[460–462] High diuretic doses may cause greater neurohormonal activation and electrolyte abnormalities and are often associated with poorer outcomes, although a cause and effect relation cannot be proven by these retrospective analyses.[463–466] Based on these observations, it may be appropriate, when starting i.v. diuretic treatment, to use low doses, to assess the diuretic response and increase the dose when that is insufficient.

Diuretic treatment should be started with an initial i.v. dose of furosemide, or equivalent dose of bumetanide or torasemide, corresponding to 1–2 times the daily oral dose taken by the patient before admission. If the patient was not on oral diuretics, a starting dose of 20–40 mg of furosemide, or a bolus of 10–20 mg i.v. torasemide, can be used.[145,467] Furosemide can be given as 2–3 daily boluses or as a continuous infusion. Daily single bolus administrations are discouraged because of the possibility of post-dosing sodium retention.[145,461] With continuous infusion, a loading dose may be used to achieve steady state earlier. Diuretic response should be evaluated shortly after start of diuretic therapy and may be assessed by performing a spot urine sodium content measurement after 2 or 6 h and/or by measuring the hourly urine output. A satisfactory diuretic response can be defined as a urine sodium content >50–70 mEq/L at 2 h and/or by a urine output >100–150 mL/h during the first 6 h.[145,468] If there is an insufficient diuretic response, the loop diuretic i.v. dose can be doubled, with a further assessment of diuretic response.[145] If the diuretic response remains inadequate, e.g. <100 mL hourly diuresis despite doubling loop diuretic dose,

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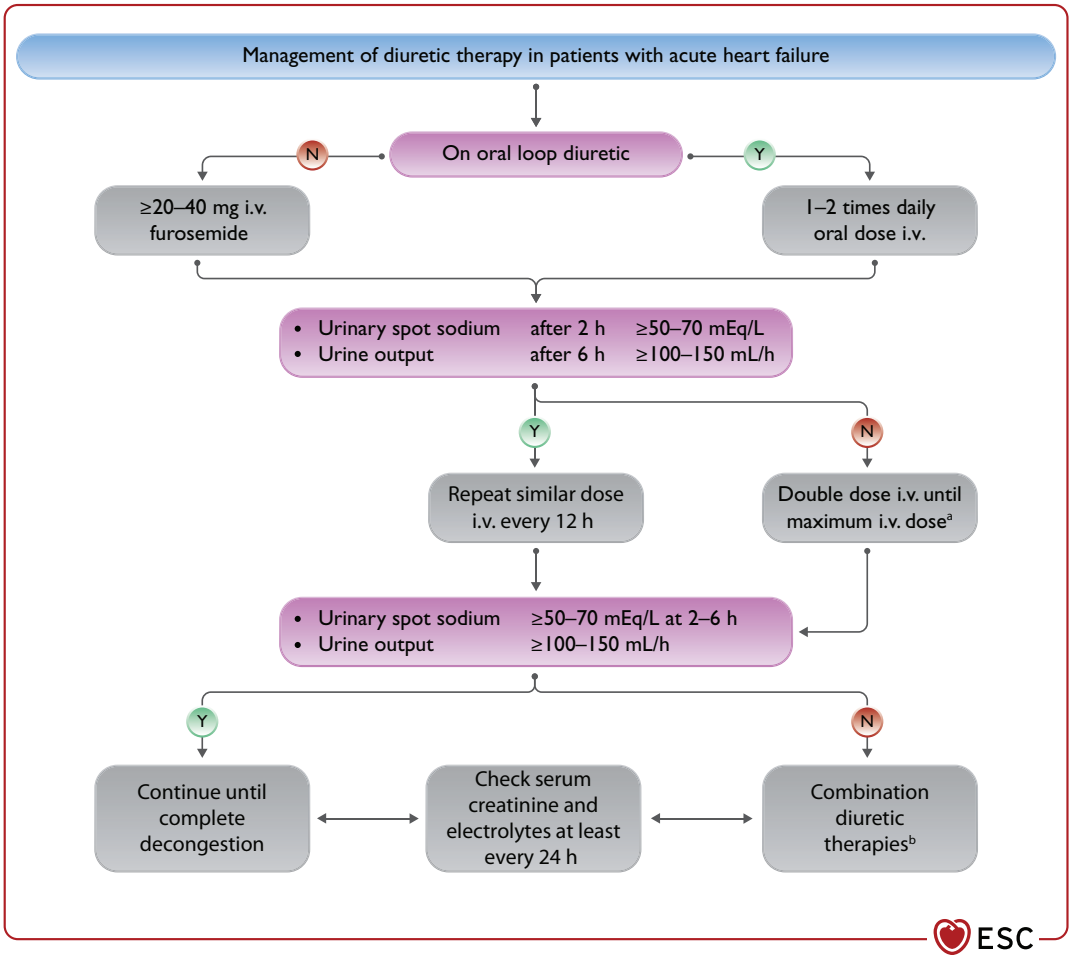

Figure 13 Diuretic therapy (furosemide) in acute heart failure. i.v. = intravenous. [a]The maximal daily dose for i.v. loop diuretics is generally considered furosemide 400–600 mg though up to 1000 mg may be considered in patients with severely impaired kidney function. [b]Combination therapy is the addition to the loop diuretic of a diuretic with a different site of action, e.g. thiazides or metolazone or acetazolamide. Modified from [145].

concomitant administration of other diuretics acting at different sites, namely thiazides or metolazone or acetazolamide, may be considered. However, this combination requires careful monitoring of serum electrolytes and renal function (*Figure 13*).[145,469,470] This strategy, based on early and frequent assessment of diuretic response, allows starting treatment with relatively low doses of loop diuretics, with frequent dose adjustments that may be less likely to cause dehydration and increase in serum creatinine. The loop diuretic dose should be progressively decreased when a significant negative fluid balance has been obtained. However, it should be pointed out that this algorithm is entirely based on expert opinion, to date.[145,461]

Transition to oral treatment should be commenced when the patient's clinical condition is stable. It is recommended that, after achievement of congestion relief, oral loop diuretics are continued at the lowest dose possible to avoid congestion.[463,471] Care must also be taken to avoid patients being discharged from hospital with persistent congestion, as this is a major predictor of increased deaths and rehospitalizations.[462,472] Hence, care should be taken to achieve adequate decongestion and establish an appropriate long-term diuretic dose before discharge.[427,473]

11.3.4 Vasodilators

Intravenous vasodilators, namely nitrates or nitroprusside (*Supplementary Table 21*), dilate venous and arterial vessels leading to a reduction in venous return to the heart, less congestion, lower afterload, increased stroke volume and consequent relief of symptoms. Nitrates act mainly on peripheral veins whereas nitroprusside is more a balanced arterial and venous dilator.[474,475] Because of their mechanisms of action, i.v. vasodilators may be more effective than diuretics in those patients whose acute pulmonary oedema is caused by increased afterload and fluid redistribution to the lungs in the absence or with minimal fluid accumulation.[427,476–478] However, two recent randomized trials comparing usual care with early intensive and sustained vasodilation failed to show a beneficial effect of i.v. vasodilators vs. high-dose diuretics.[479,480] No recommendation favouring a regimen based on vasodilator treatment vs. usual care can thus be given, to date.

Intravenous vasodilators may be considered to relieve AHF symptoms when SBP is >110 mmHg. They may be started at low doses and uptitrated to achieve clinical improvement and BP control. Nitrates are generally administered with an initial bolus followed by

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Table 22 Inotropes and/or vasopressors used to treat acute heart failure

Drug	Infusion rate
Dobutamine	2–20 μg/kg/min (beta+)
Dopamine	3–5 μg/kg/min; inotropic (beta+) >5 μg/kg/min: inotropic (beta+), vasopressor (alpha+)
Milrinone	0.375–0.75 μg/kg/min
Enoximone	5–20 μg/kg/min
Levosimendan	0.1 μg/kg/min, which can be decreased to 0.05 or increased to 0.2 μg/kg/min
Norepinephrine	0.2–1.0 μg/kg/min
Epinephrine	0.05–0.5 μg/kg/min

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continuous infusion. However, they may also be given as repeated boluses. Nitroglycerine can be given as 1–2 mg boluses in severely hypertensive patients with acute pulmonary oedema.[477] Care should be taken to avoid hypotension due to an excessive decrease in preload and afterload. For this reason, they should be used with extreme caution in patients with LVH and/or severe aortic stenosis. However, favorable effects were described in patients with LV systolic dysfunction and aortic stenosis when vasodilators were given with careful monitoring of haemodynamic parameters.[481]

11.3.5 Inotropes

Inotropes are still needed for treatment of patients with low cardiac output and hypotension (*Table 22*). They should be reserved for patients with LV systolic dysfunction, low cardiac output and low SBP (e.g. <90 mmHg) resulting in poor vital organ perfusion. However, they must be used with caution starting at low doses and uptitrating them with close monitoring.[387,388]

Inotropes, especially those with adrenergic mechanisms, can cause sinus tachycardia, increase ventricular rate in patients with AF, may induce myocardial ischaemia and arrhythmias, and increase mortality.[387,388,430,478] Levosimendan or type-3-phosphodiesterase inhibitors may be preferred over dobutamine for patients on beta-blockers as they act through independent mechanisms.[482,483] Excessive peripheral vasodilation and hypotension can be major limitations of type-3-phosphodiestaerase inhibitors or levosimendan, especially when administered at high doses and/or when commenced with a bolus dose.[482,484]

11.3.6 Vasopressors

Vasopressors used for the treatment of AHF are reported in *Table 22*.

Among drugs with a prominent peripheral arterial vasoconstrictor action, norepinephrine may be preferred in patients with severe hypotension. The aim is to increase perfusion to the vital organs. However, this is at the expense of an increase in LV afterload. Therefore, a combination of norepinephrine and inotropic agents may be considered, especially in patients with advanced HF and cardiogenic shock.

Some studies, though with limitations, support the use of norepinephrine as first choice, compared with dopamine or epinephrine. Dopamine was compared with norepinephrine as a first-line vasopressor therapy in patients with shock and was associated with more arrhythmic events and with a greater mortality in patients with cardiogenic shock but not in those with hypovolaemic or septic shock. Although the trial included 1679 patients, significance was seen only in a subgroup analysis of the 280 patients with cardiogenic shock and <10% of the patients had MI. As there were no data regarding revascularization, this limits the generalizability of the results.[485] In another prospective randomized trial epinephrine was compared with norepinephrine in patients with cardiogenic shock due to acute MI.[486] The trial was stopped prematurely due to a higher incidence of refractory shock with epinephrine. Epinephrine was also associated with higher heart rate and lactic acidosis. Despite limitations related to its relatively small sample size, short time of follow-up and lack of data regarding the maximum reached dose, the study suggests superior efficacy and safety with norepinephrine. These data are consistent with a meta-analysis including 2583 patients with cardiogenic shock showing a three-fold increase in the risk of death with epinephrine, compared with norepinephrine, in patients with cardiogenic shock.[487] However, the lack of information about dose, duration of treatment, and aetiology, makes these results partially explorative.

11.3.7 Opiates

Opiates relieve dyspnoea and anxiety. They may be used as sedative agents during non-invasive positive pressure ventilation to improve patient adaptation. Dose-dependent side effects include nausea, hypotension, bradycardia, and respiratory depression. Retrospective

Recommendations for the initial treatment of acute heart failure

Recommendations	Class[a]	Level[b]
Oxygen and ventilatory support		
Oxygen is recommended in patients with SpO_2 <90% or PaO_2 <60 mmHg to correct hypoxaemia.	I	C
Intubation is recommended for progressive respiratory failure persisting in spite of oxygen administration or non-invasive ventilation.[448]	I	C
Non-invasive positive pressure ventilation should be considered in patients with respiratory distress (respiratory rate >25 breaths/min, SpO_2 <90%) and started as soon as possible in order to decrease respiratory distress and reduce the rate of mechanical endotracheal intubation.[448]	IIa	B
Diuretics		
Intravenous loop diuretics are recommended for all patients with AHF admitted with signs/symptoms of fluid overload to improve symptoms.[145]	I	C
Combination of a loop diuretic with thiazide-type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses.[145]	IIa	B
Vasodilators		
In patients with AHF and SBP >110 mmHg, i.v. vasodilators may be considered as initial therapy to improve symptoms and reduce congestion.[475–477,479,480]	IIb	B

Continued

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Inotropic agents		
Inotropic agents may be considered in patients with SBP <90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function.[387]	IIb	C
Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion.[387,467,478]	III	C
Vasopressors		
A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion.[485–487]	IIb	B
Other drugs		
Thromboembolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism.[494,495]	I	A
Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety.[488,489]	III	C

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AHF = acute heart failure; i.v. = intravenous; LMWH = low-molecular-weight heparin; PaO_2 = partial pressure of oxygen; SBP = systolic blood pressure; SpO_2 = transcutaneous oxygen saturation.
[a]Class of recommendation.
[b]Level of evidence.

analyses suggest that morphine administration is associated with a greater frequency of mechanical ventilation, prolonged hospitalization, more intensive care unit admissions, and increased mortality.[488–491] Thus, routine use of opiates in AHF is not recommended although they may be considered in selected patients, particularly in case of severe/intractable pain or anxiety or in the setting of palliation.

11.3.8 Digoxin

Digoxin should be considered in patients with AF with a rapid ventricular rate (>110 b.p.m.) despite beta-blockers (see also section 12.1.1).[151,492,493] It can be given in boluses of 0.25–0.5 mg i.v., if not used previously. However, in patients with comorbidities (i.e. CKD) or other factors affecting digoxin metabolism (including other drugs) and/or the elderly, the maintenance dose may be difficult to estimate theoretically and measurements of serum digoxin concentrations should be performed. Digitoxin is a potential alternative to digoxin and is currently being evaluated in a randomized placebo-controlled trial (ClinicalTrials.gov Identifier: NCT03783429).[158]

11.3.9 Thromboembolism prophylaxis

Thromboembolism prophylaxis with heparin (e.g. low-molecular-weight heparin) or another anticoagulant is recommended, unless contraindicated or unnecessary (because of existing treatment with oral anticoagulants).[494,495]

11.3.10 Short-term mechanical circulatory support

In patients presenting with cardiogenic shock, short-term MCS may be necessary to augment cardiac output and support end-organ perfusion. Short-term MCS can be used as a BTR, BTD or BTB.[450-452] The initial improvements in cardiac output, BP and arterial lactate may be counterbalanced by significant complications. High-quality evidence regarding outcomes remains scarce. Hence, the unselected use of MCS in patients with cardiogenic shock is not supported and they require specialist multidisciplinary expertise for implantation and management, similar to that outlined for advanced HF centres (*Supplementary text 11.4; Supplementary Table 22*, see also section 10.2.2).[376,496] Recent studies show that a 'standardized team-based approach' using predefined algorithms for early MCS implant coupled with close monitoring (invasive haemodynamics, lactate, markers of end-organ damage) may potentially translate into improved survival.[497–499]

The Intra-aortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK-II) trial showed no difference in 30-day, as well as in long-term, mortality between intra-aortic balloon pump (IABP) and OMT in patients with cardiogenic shock following acute MI who underwent early revascularization.[500–502] According to these results, IABP is not routinely recommended in cardiogenic shock post-MI. However, it may still be considered in cardiogenic shock, especially if not due to ACS, and refractory to drug therapy, as a BTD, BTR, or BTB.

Other short-term MCS were compared with IABP in small, randomized trials and propensity-matched analyses with inconclusive results.[503–507] Similarly, RCTs comparing extracorporeal membrane oxygenation (ECMO) with IABP or MT are lacking. A meta-analysis including only observational studies showed favourable outcomes in patients with cardiogenic shock or cardiac arrest treated with veno-arterial (VA)-ECMO compared to controls.[508] VA-ECMO may also be considered in fulminant myocarditis and other conditions causing severe cardiogenic shock.[509] Depending on the severity of myocardial dysfunction and/or concomitant mitral or aortic regurgitation, VA-ECMO may increase LV afterload with an increase in LV end-

Recommendations for the use of short-term mechanical circulatory support in patients with cardiogenic shock

Recommendations	Class[a]	Level[b]
Short-term MCS should be considered in patients with cardiogenic shock as a BTR, BTD, BTB. Further indications include treatment of the cause of cardiogenic shock or long-term MCS or transplantation.	IIa	C
IABP may be considered in patients with cardiogenic shock as a BTR, BTD, BTB, including treatment of the cause of cardiogenic shock (i.e. mechanical complication of acute MI) or long-term MCS or transplantation.[450]	IIb	C
IABP is not routinely recommended in post-MI cardiogenic shock.[500–502]	III	B

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BTB = bridge to bridge; BTD = bridge to decision; BTR = bridge to recovery; IABP = intra-aortic balloon pump; MCS = mechanical circulatory support; MI = myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.

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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.[510,511]

11.3.11 Pre-discharge assessment and post-discharge management planning

A significant proportion of patients with AHF are discharged with minimal or no weight loss and, more importantly, persistent congestion.[427,472] Persistent congestion before discharge is associated with a higher risk of readmission and mortality.[426,472] Treatment, including diuretic dose, should therefore be optimized in order to keep the patient free of congestion.

In those admitted with ADHF, oral OMT should be continued, except for possible dose reduction or withdrawal if there is haemodynamic instability (symptomatic hypotension), severely impaired renal function or hyperkalaemia. Once haemodynamic stabilization is achieved with i.v. therapy, treatment should be optimized before discharge.[467] Treatment optimization has three major aims. First, to relieve congestion. Second, to treat comorbidities, such as iron deficiency, that have an impact on post-discharge outcome.[512] Third, to initiate, or restart oral, OMT with beneficial effects on outcome. Doses may be uptitrated before discharge and/or in the early post-discharge phase.

Studies have shown that such optimization of medical treatment is associated with a lower risk of 30-day readmission, although prospective randomized trials have not been performed, to date.[103,467,513] Retrospective analyses show that discontinuation or dose reduction of beta-blocker therapy during an AHF hospitalization is associated with worse outcomes.[514] Initiation of ARNI in recently hospitalized stable patients with HFrEF, including those who are ACE-I/ARB naïve, is safe and may be considered in this setting.[106,107] Safety and better outcome have also been recently shown in a prospective randomized trial with sotagliflozin in diabetic patients hospitalized for HF, irrespective of their LVEF.[136]

It is recommended to have one follow-up visit within 1 to 2 weeks after discharge.[515,516] Components of this follow-up visit should include monitoring of signs and symptoms of HF, assessment of volume status, BP, heart rate, and laboratory measurements including renal function, electrolytes, and possibly NPs. Iron status and hepatic function should also be assessed when not done before discharge. Based on clinical evaluation and laboratory exams, further optimization and/or initiation of disease-modifying treatment for HFrEF should occur. Retrospective studies show that such an approach is associated with lower 30-day readmission rates although prospective randomized trials have not been performed, to date.[513,516–518]

Recommendations for pre-discharge and early post-discharge follow-up of patients hospitalized for acute heart failure

Recommendations	Class[a]	Level[b]
It is recommended that patients hospitalized for HF be carefully evaluated to exclude persistent signs of congestion before discharge and to optimize oral treatment.[427,472]	I	C
It is recommended that evidence-based oral medical treatment be administered before discharge.[103,513]	I	C
An early follow-up visit is recommended at 1–2 weeks after discharge to assess signs of congestion, drug tolerance and start and/or uptitrate evidence-based therapy.[517,518]	I	C
Ferric carboxymaltose should be considered for iron deficiency, defined as serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with TSAT <20%, to improve symptoms and reduce rehospitalizations.[512]	IIa	B

HR = heart failure; TSAT = transferrin saturation.
[a]Class of recommendation.
[b]Level of evidence.

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12 Cardiovascular comorbidities

12.1 Arrhythmias and conduction disturbances

12.1.1 Atrial fibrillation

AF and HF frequently coexist.[519,520] They can cause or exacerbate each other through mechanisms such as structural cardiac remodelling, activation of neurohormonal systems, and rate-related LV impairment.[519–523] The proportion of patients with HF who develop AF increases with age and HF severity. When AF causes HF the clinical course seems more favourable than with other causes of HF (so called tachycardiomyopathy).[524] In contrast, development of AF in patients with chronic HF is associated with worse prognosis, including stroke and increased mortality.[525,526]

The management of patients with concomitant HF and AF is summarized in *Figure 14*.[7,521] It includes:

(1) Identification and treatment of possible causes or triggers of AF
(2) Management of HF
(3) Prevention of embolic events
(4) Rate control
(5) Rhythm control

Identification of triggers and management of heart failure

Potential causes or precipitating factors such as hyperthyroidism, electrolyte disorders, uncontrolled hypertension, mitral valve disease, and infection should be identified and corrected.

Worsening congestion due to AF should be managed with diuretics. Congestion relief may reduce sympathetic drive and ventricular rate and increase the chance of spontaneous return to SR. The presence of AF may reduce or abolish the prognostic benefits of beta-blockers and renders ivabradine ineffective.[12,125] Some treatments for HF decrease the risk of developing AF, including ACE-I, slightly, and CRT, probably.[7,527]

Prevention of embolic events

Unless contraindicated, an oral, long-term anticoagulant is recommended in all patients with HF and paroxysmal, persistent, or permanent AF. Direct-acting oral anticoagulants (DOACs) are preferred

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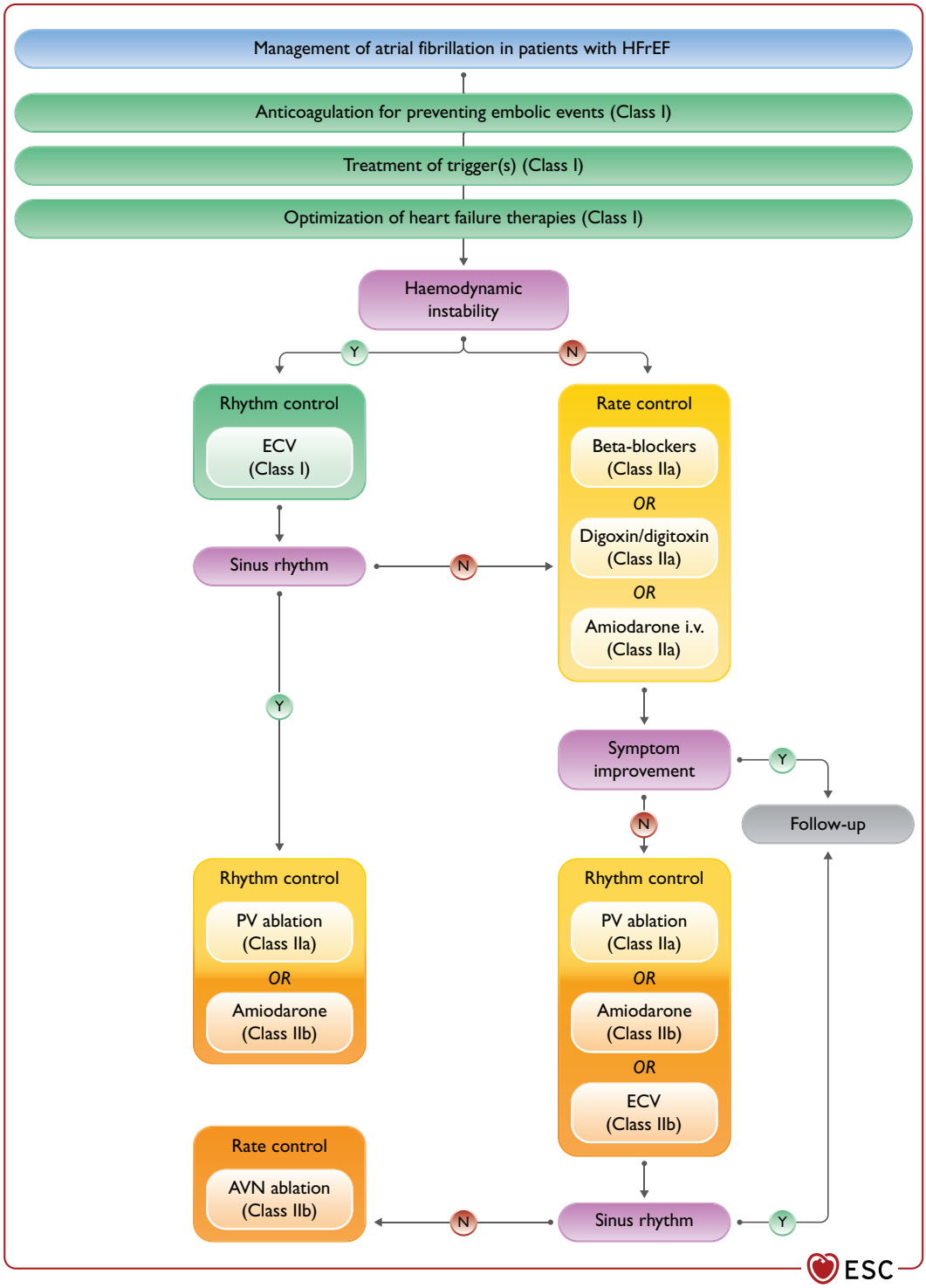

Figure 14 Management of atrial fibrillation in patients with heart failure. AF = atrial fibrillation; AVN = atrioventricular node; ECV = electrical cardioversion; HF = heart failure; i.v. = intravenous; PV = pulmonary vein. Colour code for classes of recommendation: Green for Class of recommendation I; Yellow for Class of recommendation IIa; Orange for Class of recommendation IIb; Red for Class of recommendation III (see *Table 1* for further details on classes of recommendation).

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for the prevention of thromboembolic events in patients with AF and without severe mitral stenosis and/or mechanical valve prosthesis, as they have similar efficacy to vitamin K antagonists (VKAs) but a lower risk of intracranial haemorrhage.[528]

LA appendage closure can be considered in patients with HF and AF who have a contraindication to oral anticoagulation though data from randomized trials have not included patients with contraindications to oral anticoagulants.[529,530]

Rate control

Data regarding rate control are not conclusive for the patients with AF and HF. A strategy of lenient rate control, defined by a resting heart rate <110 b.p.m., was compared to a strategy of strict rate control, defined by a heart rate <80 b.p.m. at rest and <110 b.p.m. during moderate exercise, in RACE II and in a pooled analysis of RACE and AFFIRM.[152,531] The studies showed no differences in outcome between the two strategies. However, only 10% of the patients in RACE II and 17% of those in the pooled analysis had a history of HF hospitalization or NYHA class II–III, respectively.[152,531] Higher heart rates are associated with worse outcomes in observational studies.[532,533] Thus, a lenient rate control is an acceptable initial approach with, however, treatment targeting a lower heart rate in case of persistent symptoms or cardiac dysfunction likely related to tachycardia (e.g. tachycardia-induced cardiomyopathy).[7,534]

Beta-blockers can be used for rate control in patients with HFrEF or HFmrEF because of their established safety in these patients (see section 5.3.2).[7,534,535] Digoxin or digitoxin can be considered when the ventricular rate remains high, despite beta-blockers, or when beta-blockers are contraindicated or not tolerated.[151,493,536] It may therefore be considered also an alternative to beta-blockers. For patients with NYHA class IV and/or haemodynamic instability, i.v. amiodarone can be considered to reduce ventricular rate.[537] For HFpEF, there is a paucity of evidence to demonstrate efficacy of any agent. The RATE-AF trial compared digoxin with bisoprolol in patients with persistent AF and NYHA class II–IV symptoms. Compared with bisoprolol, digoxin had the same effect on QOL at 6 months (primary endpoint) and a better effect on EHRA and NYHA functional class.[536] Only 19% of the patients had LVEF <50% so that most of the patients can be considered as having HFmrEF or HFpEF.[536]

AV node ablation can be considered in patients with poor ventricular rate control despite medical treatment not eligible for rhythm control by catheter ablation or in patients with biventricular pacing.[7,538–540]

Rhythm control

Urgent electrical cardioversion is recommended in the setting of acute worsening HF in patients presenting with rapid ventricular rates and haemodynamic instability, after consideration of the thromboembolic risk. Cardioversion should be considered also to improve symptoms in patients who have persistent and symptomatic AF, despite optimal pharmacological management. In patients who do not receive chronic therapy with oral anticoagulant and with AF onset >48 h, at least 3 weeks of therapeutic anticoagulation or a transoesophageal echocardiography is needed before cardioversion.[7] When pharmacological cardioversion is preferred, amiodarone is the drug of choice as other antiarrhythmic drugs (i.e. propafenone, flecainide, dronedarone) are associated with worse outcomes in HFrEF.[186,534,541–544] Amiodarone can help maintain HF patients in SR after cardioversion.[545,546]

Trials including patients with HF and comparing rate control and rhythm control strategies with the latter based on antiarrhythmic drugs failed to show any benefit of one strategy over the other.[547–550] More recently, EAST-AFNET 4, enrolling patients with early AF, 28.6% with HF, was stopped early after a median follow-up of 5.1 years for a lower occurrence of the primary outcome of death, stroke, or hospitalization for worsening HF or ACS in the patients assigned to early rhythm control vs. those assigned to usual care.[551] However, the patients assigned to the rhythm control strategy had a closer follow-up, which may have influenced their better outcome. Catheter ablation was performed in a minority of the patients in the rhythm control arm (19.4%).[551]

LA catheter ablation was compared with MT, rate or rhythm control strategy, in 363 patients with persistent or paroxysmal AF, LVEF <35% and an implanted device (ICD or CRT-D) enrolled in the CASTLE-AF trial.[552] The primary endpoint of all-cause death or HF hospitalizations occurred in fewer patients in the ablation group vs. the MT group, 51 patients (28.5%) vs. 82 (44.6%) [hazard ratio (HR); 95% confidence interval (CI), 0.62; 0.43–0.87; $P = 0.007$]. Also, other endpoints, all-cause or CV death or worsening HF, were reduced by catheter ablation.[552] This trial suggests that catheter ablation can improve the prognosis of patients with HFrEF. However, it enrolled a highly selected population, 363 of 3013 patients, was not blinded, had crossovers between the two treatment strategies and the number of events observed was low: 24 (13.4%) vs. 46 (25.0%) all-cause deaths and 37 (20.7%) vs. 66 (35.9%) HF hospitalizations in the ablation and MT groups, respectively.[552]

The CABANA trial was an investigator-initiated, open-label, multicentre, randomized trial enrolling 2204 patients with symptomatic AF. The trial failed to show a benefit of AF ablation strategy over medical care on the primary composite endpoint of death, disabling stroke, serious bleeding, or cardiac arrest in the overall population.[553] In an analysis of the 778 patients (35%) with NYHA class symptoms >II, the primary outcome occurred in 34 patients (9.0%) in the catheter ablation group vs. 49 (12.3%) in the drug therapy group (HR; 95% CI, 0.64; 0.41–0.99).[554] However, also in this trial, the number of events was small and HF was defined based only on symptoms with LVEF available in 73% of the patients and >50% and 40–49% in 79% and 11.7% of the cases, respectively.[554] Both CASTLE-AF and CABANA showed a highly significant effect of catheter ablation on patients' symptoms.[552–554]

Two other prospective trials enrolled patients with HFrEF and persistent AF, who were randomized to catheter ablation or MT in one trial (AMICA trial, $n = 140$), and to catheter ablation or amiodarone in the other one (AATAC trial, $n = 203$).[555,556] The first trial failed to show any difference in the LVEF increase between the two groups.[555] The second trial showed superiority of catheter ablation with respect of AF recurrence, the primary endpoint, with also a reduction in unplanned hospitalizations and mortality.[556] In contrast with the AMICA trial,[555] but in accordance with CASTLE-AF,[552] AATAC also showed a benefit of catheter ablation on LVEF.[556]

In conclusion, there is insufficient evidence in favour of a strategy of rhythm control with antiarrhythmic drugs vs. rate control in patients with HF and AF.[547–551] The results of randomized trials with

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Recommendations for the treatment of atrial fibrillation in patients with heart failure

Recommendations	Class[a]	Level[b]
Anticoagulation		
Long-term treatment with an oral anticoagulant is recommended in all patients with AF, HF, and CHA_2DS_2-VASc score ≥2 in men or ≥3 in women.[7]	I	A
DOACs are recommended in preference to VKAs in patients with HF, except in those with moderate or severe mitral stenosis or mechanical prosthetic heart valves.[528,558]	I	A
Long-term treatment with an oral anticoagulant should be considered for stroke prevention in AF patients with a CHA_2DS_2-VASc score of 1 in men or 2 in women.[7,559]	IIa	B
Rate control		
Beta-blockers should be considered for short- and long-term rate control in patients with HF and AF.[535]	IIa	B
Digoxin should be considered when the ventricular rate remains high, despite beta-blockers, or when beta-blockers are contraindicated or not tolerated.[536]	IIa	C
Cardioversion		
Urgent ECV is recommended in the setting of acute worsening of HF in patients presenting with rapid ventricular rates and haemodynamic instability.	I	C
Cardioversion may be considered in patients in whom there is an association between AF and worsening of HF symptoms despite optimal medical treatment.[7,541]	IIb	B
AF catheter ablation		
In cases of a clear association between paroxysmal or persistent AF and worsening of HF symptoms, which persist despite MT, catheter ablation should be considered for the prevention or treatment of AF.[552–554,557]	IIa	B

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AF = atrial fibrillation; CHA_2DS_2-VASc = congestive heart failure or left ventricular dysfunction, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74, Sex category (female) (score); DOAC = direct-acting oral anticoagulant; ECV = electrical cardioversion; HF = heart failure; MT = medical therapy; VKA = vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.

catheter ablation vs. MT showed a consistent improvement in symptoms whereas the results on mortality and hospitalization were obtained with a relatively small number of events not permitting to draw definitive conclusions.[152,548–550,552–554,557]

12.1.2 Ventricular arrhythmias

Ventricular arrhythmias may be a complication, and in some instances, a cause of HF. Frequent ventricular premature beats (VPBs) may lead to reversible systolic dysfunction. Possible factors may include dyssynchrony and abnormal calcium handling.[560]

Initial management of ventricular arrhythmias in HF should include correction of potential precipitants (including electrolyte abnormalities, particularly hypo/hyperkalaemia, and pro-arrhythmic drugs) as well as the optimization of HF drug therapy. Although ischaemia may be a triggering factor, revascularization has not been shown to reduce risk of ventricular arrhythmias.[561]

Amiodarone is effective also for suppression of ventricular arrhythmias. However, it does not reduce the incidence of sudden cardiac death or overall mortality.[161] For patients with premature ventricular contraction (PVC)-induced CMP, amiodarone administration may be considered to reduce recurrent arrhythmias and improve symptoms and LV function, although its side effects should be taken into consideration. Other drugs are discussed in *Supplementary text 12.1*.

Radiofrequency ablation of VPBs may improve LV function and, possibly, outcomes in patients with tachycardiomyopathy when VPBs contribute to LV dysfunction.[562] A sustained reduction in the baseline PVC burden has been associated with a lower risk of cardiac mortality, cardiac transplantation, or hospitalization for HF during follow-up.[563,564]

12.1.3 Symptomatic bradycardia, pauses and atrioventricular block

Indications for pacemaker therapy do not differ in patients with HF from those with other CV disease. There is ample evidence that RV pacing may have an adverse effect on LV systolic function leading, in the long term, to HF.[565] Patients with HFrEF requiring frequent ventricular pacing, e.g. with AV block or slow AF, and who have systolic dysfunction, should be implanted with CRT rather than a standard pacemaker to avoid adverse outcomes, as shown in the BLOCK-HF (Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block) trial.[216] In the quest for a more physiological alternative to RV pacing, physiological pacing is being increasingly adopted.[566] In a non-randomized comparison of 304 consecutive patients with His bundle pacing and 433 consecutive patients with RV pacing, the former group had less HF hospitalization and a trend in reduced mortality.[567] Although the technique is promising, more data are needed to confirm its role.

12.2 Chronic coronary syndromes

CAD is the most common cause of HF in industrialized, middle-income, and increasingly in low-income, countries. It should be considered as possible cause of HF in all patients presenting with new onset HF.

The diagnostic workup of patients with HF and chronic coronary syndromes (CCS) is reported in the recent 2019 ESC Guidelines on CCS.[5] Patients with HF should be carefully evaluated to assess signs and/or symptoms of CCS. Clinical and family histories, physical examination, ECG and imaging tests are recommended.[5] Documentation of ischaemia using non-invasive and invasive tests can be difficult in patients with HF because of the possible exercise intolerance and the effects of increased end-diastolic LV pressures. Coronary angiography or CTCA can be performed to establish the

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presence and extent of CAD and evaluate the potential indication for revascularization (see section 4.3).[5]

12.2.1 Medical therapy

Beta-blockers are the mainstay of therapy in patients with HFrEF and CAD because of their prognostic benefit.[116–120,568] Ivabradine should be considered as an alternative to beta-blockers (when contraindicated) or as additional anti-anginal therapy in patients in SR whose heart rate is ≥70 b.p.m.[139,569] Other anti-anginal drugs (e.g. amlodipine, felodipine, nicorandil, ranolazine, and oral or transdermal nitrates) are effective for treating symptoms, although data about their effects on outcomes are neutral or lacking.[5,570–574] Trimetazidine seems to have additive effects, such as improvement of LV function and exercise capacity, in patients with HFrEF and CCS already on beta-blockers.[575–577] Trimetazidine and other anti-anginal drugs may be considered in patients with HF and angina despite beta-blocker and/or ivabradine. Short-acting nitrates should be used with caution in patients with HF as they cause hypotension. Diltiazem and verapamil increase HF-related events in patients with HFrEF and are contraindicated.[578]

An algorithm for the use of anti-anginal medications in patients with HFrEF is reported in *Figure 15*.

Beta-blockers, long-acting nitrates, calcium channel blockers (CCBs), ivabradine, ranolazine, trimetazidine, nicorandil and their combinations should be considered in HFpEF for angina relief but without a foreseen benefit on HF and coronary end points.

Low-dose of rivaroxaban [2.5 mg twice daily (b.i.d.)] did not add prognostic benefit in patients with HFrEF and CCS in the COMMANDER-HF trial, a study to assess the effectiveness and safety of rivaroxaban in reducing the risk of death, MI or stroke in participants with HF and CAD following an episode of decompensated HF.[579] This trial included patients with HFrEF and a recent episode of worsening HF occurring within 21 days from the time of enrolment. These patients are at high risk of HF-related events and these were the main cause of deaths and hospitalizations in the trial. Rivaroxaban had no effect on these events. In contrast, in a non-pre-specified subgroup analysis of the COMPASS trial, low dose of rivaroxaban, on top of aspirin, was associated with a reduction in ischaemic events in patients with HF, mainly HFmrEF or HFpEF.[580] Based on these data, low-dose rivaroxaban may be considered in patients with CAD (or peripheral artery disease) and

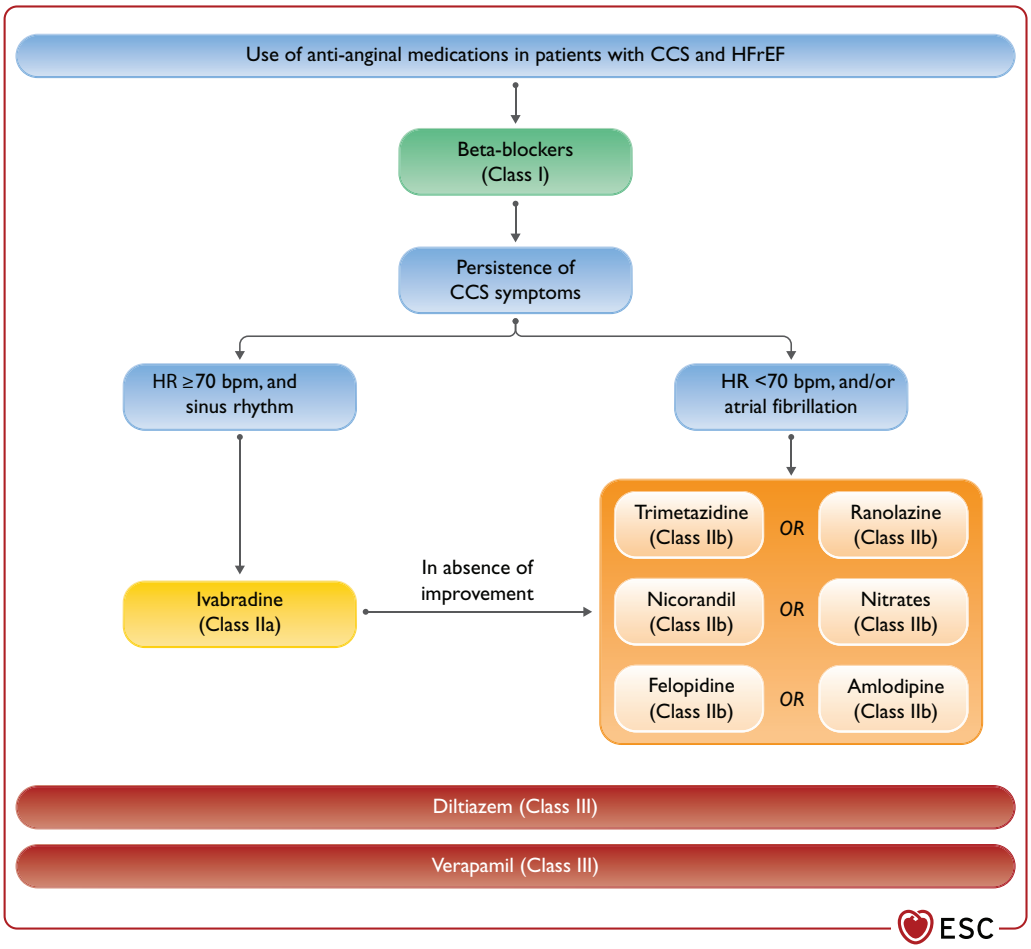

Figure 15 Algorithm for the medical treatment of chronic coronary syndrome in patients with heart failure with reduced ejection fraction. CCS = chronic coronary syndrome; HFrEF = heart failure with reduced ejection fraction; HR = heart rate. Colour code for classes of recommendation: Green for Class of recommendation I; Yellow for Class of recommendation IIa; Orange for Class of recommendation IIb; Red for Class of recommendation III (see *Table 1* for further details on classes of recommendation).

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HF, LVEF >40% and SR, when at high risk of stroke and with a low haemorrhagic risk.

12.2.2 Myocardial revascularization

Data on the benefit of myocardial revascularization in patients with HF are limited.

STICH compared coronary artery bypass grafting (CABG) with MT in patients with CAD, amenable by CABG, and with reduced LV function (EF ≤35%). At a median follow-up of 56 months, there was no significant difference between the CABG group and the MT group in the rate of death from any cause, primary outcome of the trial.[89] The extended follow-up report showed a significant reduction of death in the CABG group vs. the control group (58.9% vs. 66.1%; HR 0.84; 95% CI, 0.73−0.97; $P = 0.02$) over 10 years.[581] CV death and the combined endpoint of all-cause death or hospitalization for CV causes were also significantly reduced after CABG at 10 years of follow-up.[581] Post hoc analyses of the STICH trial suggested that neither myocardial viability, angina, nor ischaemia were related with outcomes after revascularization.[92,93,582] The Heart Failure Revascularisation Trial (HEART) was under-powered, with only 138 of the planned 800 patients to be enrolled, and failed to show differences in outcomes between HF patients receiving CABG or MT.[583]

There are currently no reported RCTs comparing percutaneous coronary intervention (PCI) with MT in patients with HFrEF. However, the REVIVED-BCIS2 trial has finished recruitment (ClinicalTrials.gov Identifier: NCT01920048).[584] There are also no randomized studies comparing PCI with CABG as such randomized trials excluded patients with HFrEF. In one prospective registry, including 4616 patients with multivessel disease and HFrEF, propensity-score matched comparisons showed similar survival (mean follow-up 2.9 years) in PCI vs. CABG group with PCIs associated with a higher risk of MI, particularly in patients with incomplete revascularization, and CABG associated with a higher risk of stroke.[585] A propensity-matched analysis showed a significantly lower risk of death or major CV events in diabetic patients with LV dysfunction and multivessel disease treated with CABG compared with PCI.[586] CABG was associated with better outcome than PCI also in patients with moderate or severe LV dysfunction and left main or complex coronary disease.[587,588] Two meta-analyses confirmed that CABG is associated with better outcomes, including mortality, MI, and repeated revascularization, compared with PCI and/or MT.[589,590]

12.3 Valvular heart disease

12.3.1 Aortic stenosis

Aortic stenosis may cause or worsen HF by increasing LV afterload and causing LV hypertrophy and remodelling.[591] When HF symptoms occur in patients with severe aortic stenosis, prognosis is extremely poor. No MT for aortic stenosis can improve outcomes. HF medical treatment should be given to all HF patients with symptomatic severe aortic stenosis. Care must be taken using vasodilators to avoid hypotension. Importantly, possible improvement of symptoms after MT should not delay intervention.

In the presence of suspected symptomatic and severe high-gradient aortic stenosis (valve area ≤1 cm^2, mean gradient ≥40 mmHg), other causes of high flow status must be excluded and corrected (i.e. anaemia, hyperthyroidism, arteriovenous shunts) before proceeding to aortic valve intervention.[592] An aortic valve intervention is recommended in patients with HF symptoms and severe, high-gradient aortic stenosis, regardless of LVEF. Management of patients with low-flow low-gradient aortic stenosis is reported in *Figure 16*.[592]

Intervention is recommended in patients with a life expectancy >1 year, avoiding futility. Transcatheter aortic valve implantation (TAVI) has been shown to be non-inferior to surgical aortic valve replacement (SAVR) in reducing clinical events (including mortality and disabling stroke) in patients at high and intermediate risk for surgery.[593−600] In low-risk patients, mean age in the RCTs comparing TAVI and SAVR was >70 years and follow-up was restricted to 2 years. Therefore, SAVR is recommended in patients aged <75 years and at low surgical risk (STS-PROM score or EuroSCORE II <4%), whereas TAVI is recommended in those aged >75 years or at high/prohibitive surgical risk (STS-PROM score or EuroSCORE II >8%). In all the other cases, the choice between TAVI and SAVR should be made by the Heart Team, weighing the pros and cons of each procedure, according to age, life expectancy, individual patient preference and other features including clinical and anatomical aspects. Aortic

Recommendations for myocardial revascularization in patients with heart failure with reduced ejection fraction

Recommendations	Class[a]	Level[b]
CABG should be considered as the first-choice revascularization strategy, in patients suitable for surgery, especially if they have diabetes and for those with multivessel disease.[581,587,588,590]	IIa	B
Coronary revascularization should be considered to relieve persistent symptoms of angina (or an angina-equivalent) in patients with HFrEF, CCS, and coronary anatomy suitable for revascularization, despite OMT including anti-anginal drugs.	IIa	C
In LVAD candidates needing coronary revascularization, CABG should be avoided, if possible.	IIa	C
Coronary revascularization may be considered to improve outcomes in patients with HFrEF, CCS, and coronary anatomy suitable for revascularization, after careful evaluation of the individual risk to benefit ratio, including coronary anatomy (i.e. proximal stenosis >90% of large vessels, stenosis of left main or proximal LAD), comorbidities, life expectancy, and patient's perspectives.	IIb	C
PCI may be considered as an alternative to CABG, based on Heart Team evaluation, considering coronary anatomy, comorbidities, and surgical risk.	IIb	C

CABG = coronary artery bypass graft; CCS = chronic coronary syndrome; HFrEF = heart failure with reduced ejection fraction; LAD = left anterior descending artery; LVAD = left ventricular assist device; OMT = optimal medical therapy; PCI = percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.

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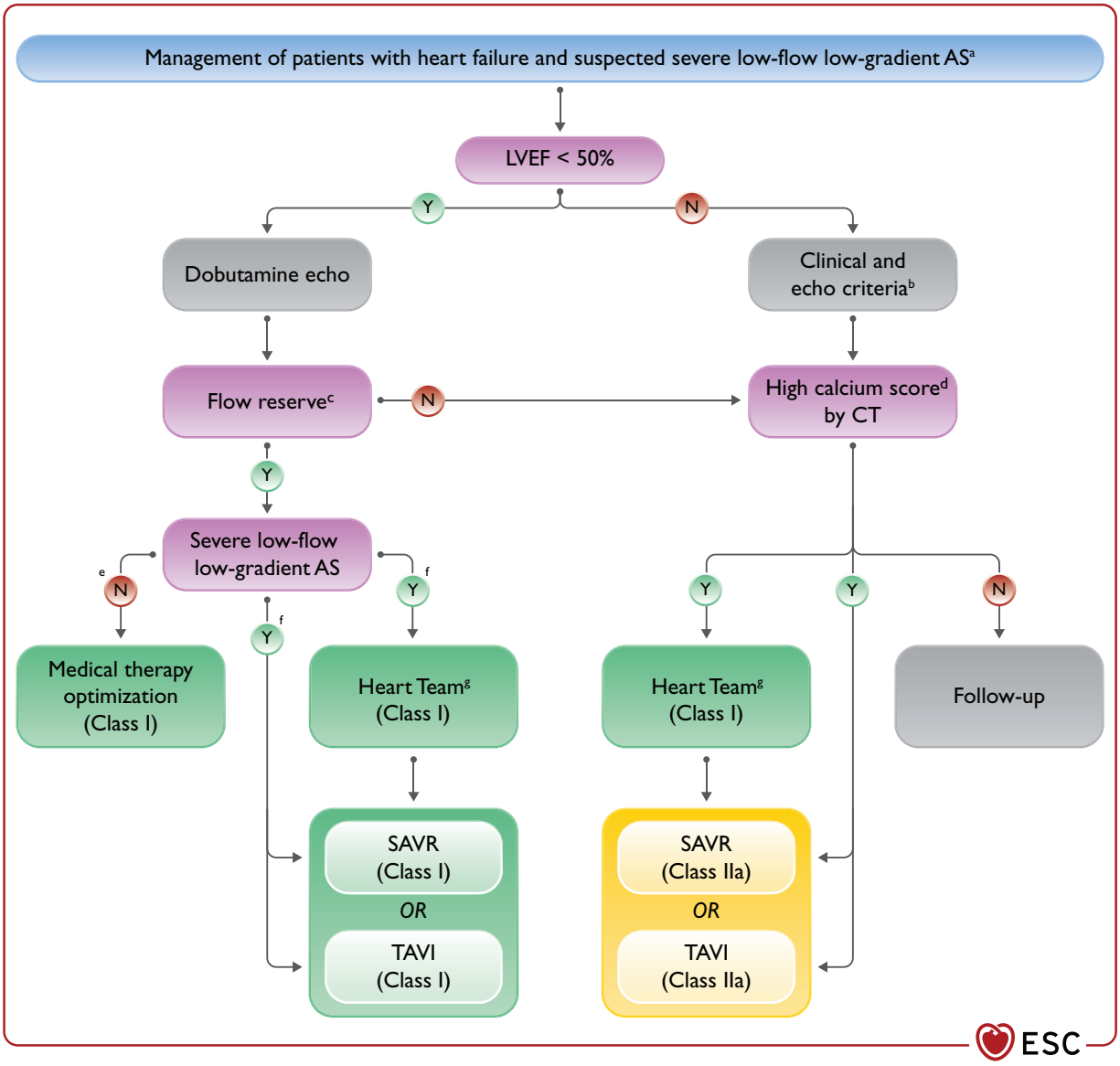

Figure 16 Management of patients with severe low-flow low-gradient aortic stenosis and heart failure. AS = aortic stenosis; CT = computed tomography; EuroSCORE II = European System for Cardiac Operative Risk Evaluation II; LVEF = left ventricular ejection fraction; OMT = optimal medical therapy; SAVR = surgical aortic valve replacement; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality; TAVI = transcatheter aortic valve implantation. [a]Valve area ≤1 cm^2, peak velocity <4.0 m/s, mean gradient <40; stroke volume index ≤35 mL/m^2. [b]Age >70 years, typical symptoms without other explanations, left ventricular hypertrophy or reduced left ventricular longitudinal function, mean gradient 30–40 mmHg, valve area ≤0.8 cm^2, stroke volume index ≤35 mL/m^2 assessed by techniques other than standard Doppler. [c]Flow reserve is defined as stroke volume index increase >20%. [d]AS is very likely if calcium score is ≥3000 in men and ≥1600 in women. AS is likely if calcium score is ≥2000 in men and ≥1200 in women. AS is unlikely if calcium score is <1600 in men and <800 in women. [e]Increase in valve area to >1.0 cm^2 in response to flow increase (flow reserve) during dobutamine echo. [f]Increase in mean gradient to at least 40 mmHg without significant change in valve area in response to flow increase (flow reserve) during dobutamine echo. [g]SAVR is recommended in patients aged <75 years and low surgical risk (STS-PROM score or EuroSCORE II <4%), whereas TAVI in those aged >75 years or at high/prohibitive surgical risk (STS-PROM score or EuroSCORE II >8%). In all the other cases, the choice between TAVI and SAVR is recommended to be decided by the Heart Team, weighing the pros and cons of each procedure, according to age, life expectancy, individual patient preference and features including clinical and anatomical aspects. Colour code for classes of recommendation: Green for Class of recommendation I; Yellow for Class of recommendation IIa (see *Table 1* for further details on classes of recommendation).

valve interventions should be performed only in centres having both interventional cardiology and cardiac surgery services on site and a structured collaborative Heart Team approach.

Balloon aortic valvuloplasty may be considered in highly symptomatic patients with AHF (i.e. cardiogenic shock) as bridge to TAVI or SAVR, or in advanced HF as BTR or DT.

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12.3.2 Aortic regurgitation

Severe aortic regurgitation can lead to progressive LV dilation with subsequent dysfunction, HF, and poor prognosis.

MT can improve HF symptoms in patients with severe aortic regurgitation. In particular, inhibitors of the RAAS can be useful.[601] Beta-blockers should be cautiously used as they prolong diastole and may worsen aortic regurgitation.

Aortic valve surgery is recommended in patients with severe aortic regurgitation and HF symptoms regardless of LVEF.[592,602,603] In case of high or prohibitive surgical risk, TAVI has been used to treat also aortic regurgitation.[604]

12.3.3 Mitral regurgitation

Primary (organic) mitral regurgitation

Primary mitral regurgitation (MR) is caused by abnormalities of the valve apparatus and can cause HF.

Surgery, preferably repair, is recommended in patients with severe primary MR and HF symptoms. If surgery is contraindicated

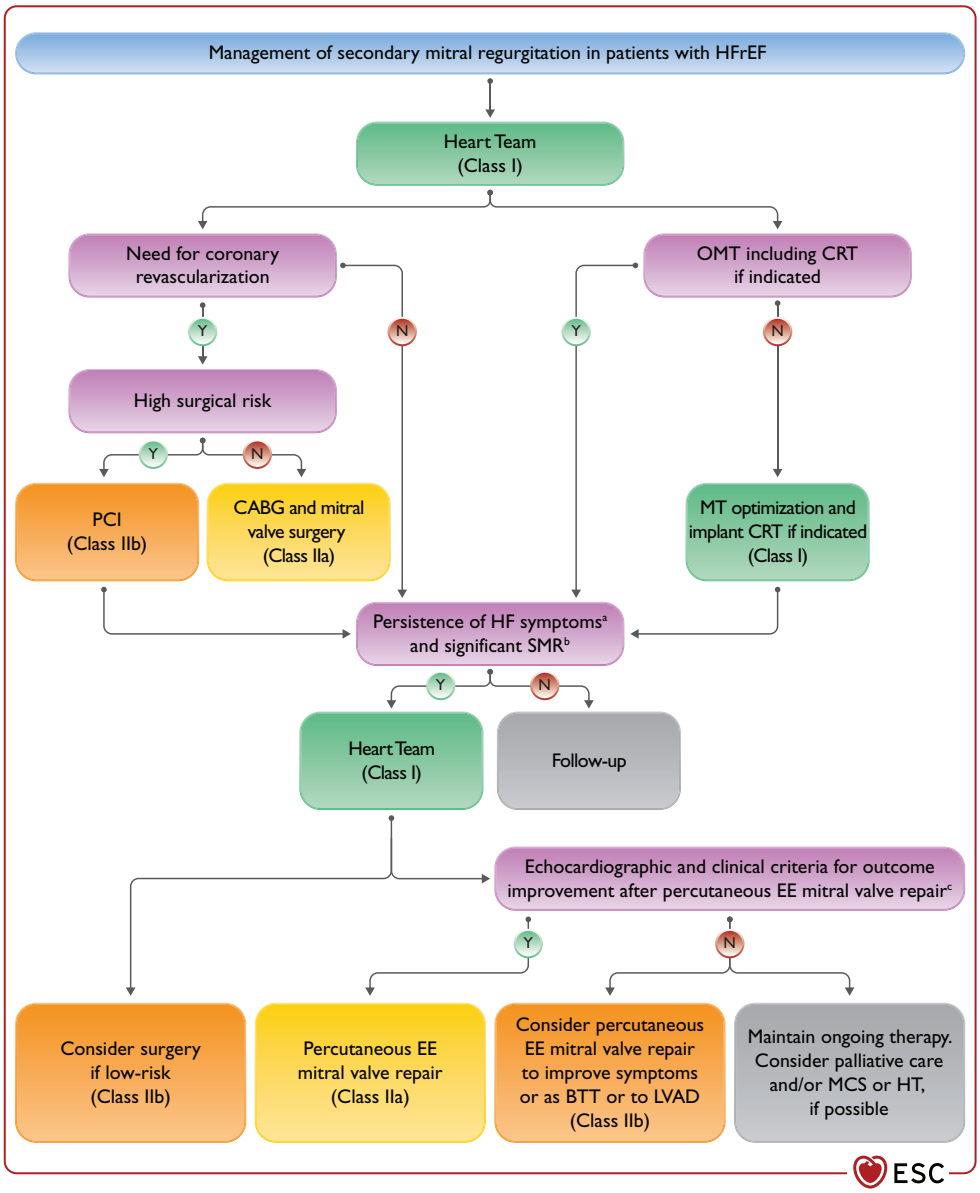

Figure 17 Management of secondary mitral regurgitation in patients with heart failure and reduced ejection fraction. BTT = bridge to transplantation; CABG = coronary artery bypass graft; CRT = cardiac resynchronization therapy; EE = edge-to edge; EROA = effective regurgitant orifice area; HF = heart failure; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; MCS = mechanical circulatory support; MT = medical therapy; NYHA = New York Heart Association; OMT = optimal medical therapy; PCI = percutaneous coronary intervention; SMR = secondary mitral regurgitation; TR = tricuspid regurgitation. [a]NYHA class II–IV. [b]Moderate-to-severe or severe (EROA ≥30 mm^2). [c]All of the following criteria must be fulfilled: LVEF 20–50%, LVESD <70 mm, systolic pulmonary pressure <70 mmHg, absence of moderate or severe right ventricular dysfunction or severe TR, absence of haemodynamic instability.[612] Colour code for classes of recommendation: Green for Class of recommendation I; Yellow for Class of recommendation IIa; Orange for Class of recommendation IIb (see *Table 1* for further details on classes of recommendation).

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or considered at high risk, then percutaneous repair may be considered.[592,605]

Secondary (functional) mitral regurgitation

Secondary mitral regurgitation (SMR) is mostly a disease of the left ventricle. It can also be caused by mitral annulus enlargement due to LA dilation.[606] Moderate or severe SMR is associated with an extremely poor prognosis in patients with HF.[607,608] The assessment of MR aetiology and severity should be performed by an experienced echocardiographer applying a multi-parametric approach, and ideally in stable patient conditions, after optimization of medical and resynchronization therapies. Being SMR a dynamic condition, echocardiographic quantification during exercise may be helpful in patients with moderate SMR at rest and symptoms during physical activity.[609] Early referral of patients with HF and moderate or severe MR to a multidisciplinary Heart Team, including HF specialists, is recommended for assessment and treatment planning. The Heart Team has to verify, first of all, that the patient is on optimal therapy, including CRT, when indicated (*Figure 17*).

In patients with severe SMR and HFrEF requiring revascularization, mitral valve surgery and CABG should be considered. Isolated mitral valve surgery may be considered in symptomatic patients with severe SMR despite optimal therapy and low surgical risk.[592]

Two randomized trials, MITRA-FR and COAPT, evaluated the effectiveness of percutaneous edge-to-edge mitral valve repair plus OMT compared to OMT alone, in symptomatic patients with reduced LVEF (15–40% in MITRA-FR and 20–50% in COAPT) and moderate-to-severe or severe SMR [effective regurgitant orifice area (EROA) ≥ 20 mm^2 in MITRA-FR and EROA ≥ 30 mm^2 in COAPT].[610–612] MITRA-FR failed to show any benefit from the intervention on all-cause mortality or HF hospitalization at 12 months (primary endpoint; HR 1.16, 95% CI 0.73–1.84) and at 24 months.[610,611] In contrast, COAPT showed a significant reduction in hospitalization for HF at 24 months (primary endpoint; HR 0.53, 95% CI 0.40–0.70) and mortality (secondary endpoint; HR 0.62, 95% CI 0.46–0.82).[612] Differences in patient selection, concomitant MT, echocardiographic assessment, procedural issues and severity of SMR in relation to the degree of LV dilatation may be responsible for the diverging results of the MITRA-FR and COAPT trials.[613–615] Thus, percutaneous edge-to-edge mitral valve repair should be considered for outcome improvement only in carefully selected patients who remain symptomatic (NYHA class II–IV) despite OMT, with moderate-to-severe or severe SMR (EROA ≥30 mm^2), favourable anatomical conditions, and fulfilling the inclusion criteria of the COAPT study (i.e. LVEF 20–50%, LV end-systolic diameter <70 mm, systolic pulmonary pressure <70 mmHg, absence of moderate or severe RV dysfunction, absence of severe TR, absence of haemodynamic instability) (*Figure 17*).[615,616]

Percutaneous edge-to-to edge mitral valve repair may also be considered to improve symptoms in patients with advanced HF, severe SMR and severe symptoms despite OMT. In these patients, cardiac transplantation or LVAD implantation must also be considered.[376,617]

Other percutaneous mitral valve repair systems, such as indirect annuloplasty, are available for treatment of SMR. This approach has a shorter learning curve and lesser technical requirements than percutaneous edge-to-to edge mitral valve repair and does not preclude different procedures once it is performed. A sham-controlled randomized trial testing a transcatheter indirect mitral annuloplasty device met its primary endpoint of mitral regurgitant volume reduction with reverse LV and LA remodelling at 12 months.[618] Further studies confirmed favourable results on LA volumes and LV remodelling with trends towards improvement in mean 6MWT distance and symptoms and a reduction in HF hospitalizations in an IPD meta-analysis.[619–622] Transcatheter mitral valve replacement is also emerging as a possible alternative option, but randomized trials are still lacking.[623]

Mitral valve interventions are not recommended in patients with a life expectancy of <1 year due to extra-cardiac conditions.[592]

Recommendations for the management of valvular heart disease in patients with heart failure

Recommendations	Class[a]	Level[b]
Aortic stenosis		
Aortic valve intervention, TAVI or SAVR, is recommended in patients with HF and severe high-gradient aortic stenosis to reduce mortality and improve symptoms.[594]	I	B
It is recommended that the choice between TAVI and SAVR be made by the Heart Team, according to individual patient preference and features including age, surgical risk, clinical, anatomical and procedural aspects, weighing the risks and benefits of each approach.[592]	I	C
Secondary mitral regurgitation		
Percutaneous edge-to-edge mitral valve repair should be considered in carefully selected patients with secondary mitral regurgitation, not eligible for surgery and not needing coronary revascularization, who are symptomatic[c] despite OMT and who fulfil criteria[d] for achieving a reduction in HF hospitalizations.[612]	IIa	B
In patients with HF, severe secondary mitral regurgitation and CAD who need revascularization, CABG and mitral valve surgery should be considered.	IIa	C
Percutaneous edge-to-edge mitral valve repair may be considered to improve symptoms in carefully selected patients with secondary mitral regurgitation, not eligible for surgery and not needing coronary revascularization, highly symptomatic despite OMT and who do not fulfil criteria for reducing HF hospitalization.[617]	IIb	C

CABG = coronary artery bypass graft; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; NYHA = New York Heart Association; OMT = optimal medical therapy; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation; TR = tricuspid regurgitation.
[a]Class of recommendation.
[b]Level of evidence.
[c]NYHA class II–IV.
[d]All of the following criteria must be fulfilled: LVEF 20–50%, LVESD <70 mm, systolic pulmonary pressure <70 mmHg, absence of moderate or severe right ventricular dysfunction or severe TR, absence of haemodynamic instability.[612]

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12.3.4 Tricuspid regurgitation

Tricuspid regurgitation (TR) can be caused by or be a consequence of RV dysfunction and HF. The management of HF with TR includes MT (i.e. diuretics, neurohormonal antagonists). Transcatheter therapy and surgery may be considered in selected cases.[592] A multidisciplinary Heart Team, including HF specialists, should be considered for assessment and treatment planning.

Tricuspid valve surgery is recommended in patients with severe TR requiring left-sided cardiac surgery. It should be also considered in patients with moderate TR and tricuspid annulus dilatation requiring left-sided cardiac surgery and in symptomatic patients with isolated severe TR.[592] However, surgery in isolated TR is burdened by high in-hospital mortality (8.8%) although the advanced stage of HF may have influenced these data.[624] Transcatheter techniques have recently emerged as potential treatment options of TR. Preliminary results show improvement in TR severity and symptoms with low complication rates.[625] Further prospective studies are needed to show the prognostic impact of these treatments in HF patients.

12.4 Hypertension

Arterial hypertension is a leading risk factor for the development of HF. Almost two-thirds of HF patients have a past history of hypertension.[104,626] Clinical trials evaluating antihypertensive strategies and BP targets in patients with HF and hypertension have not been performed.

Treatment of HFrEF is similar in hypertensive and normotensive patients. Recommended medications, including neurohormonal antagonists and diuretics, lower also BP. Lifestyle modifications, such as weight loss, reduced sodium intake, and increased physical activity, are useful adjunctive measures.[4] Uncontrolled hypertension in patients with HFrEF is rare, provided the patient is receiving OMT at recommended doses for HF. If further BP lowering is required, in absence of signs of fluid overload, amlodipine and felodipine have been shown to be safe in HFrEF and may be considered.[570,571] Non-dihydropyridine CCBs (diltiazem and verapamil) and centrally acting agents, such as moxonidine, are contraindicated as they are associated with worse outcomes.[627] Alpha-blockers have no effects on survival and are therefore not indicated.[143] They can be used for the treatment of concomitant prostatic hyperplasia but should be withdrawn in cases of hypotension.

Hypertension is the most important cause of HFpEF, with a prevalence of 60% to 89%.[39] Patients with HFpEF also frequently have an exaggerated hypertensive response to exercise and may present with hypertensive acute pulmonary oedema.[628,629] Antihypertensive agents, including ACE-I, ARBs, beta-blockers, CCB, and diuretics reduce the incidence of HF.[630,631] Reducing BP leads also to LVH regression, the degree of which depends on the class of drug used.[4] ARBs, ACE-I, and CCBs cause more effective LVH regression than beta-blockers or diuretics.[632] Poorly controlled hypertension may precipitate episodes of decompensation. Causes of secondary hypertension, such as renal vascular or parenchymal disease, primary aldosteronism and obstructive sleep apnoea (OSA), should be ruled out or, if confirmed, considered for treatment. Treatment of hypertension is an important issue in patients with HFpEF, but the optimal treatment strategy is uncertain. The treatment strategy used in HFrEF should also be considered in HFpEF.[4]

BP targets are uncertain in both HFrEF and HFpEF. However, evaluation of patient's age and comorbidities (i.e. diabetes, CKD, CAD, valvular heart disease and stroke) can be helpful to personalize the BP target.[4] Every effort should be made to reach target doses of evidence-based medications in HFrEF patients, despite slight hypotension.[4,633] Conversely, in HFpEF patients with LVH and limited preload reserve, hypotension should be avoided.

12.5 Stroke

HF and stroke frequently coexist because of an overlap of shared risk factors and subsequent mechanisms.[519,634] A higher risk of stroke is present also in HF patients in SR.[39,426,635–637] AF confers an additional risk and patients with HF and AF have a five-fold increased risk compared to the control population.[519,634,638]

As a temporal trend, the incidence of stroke is higher in the first 30 days after HF diagnosis or an episode of HF decompensation and decreases in the first 6 months following the acute event.[637,639] Patients with stroke and HF have higher mortality, more severe neurological deficits and longer hospital stays than those without HF.[637,640] Similarly, patients with HF and stroke have a higher mortality than patients without stroke.[640] In COMMANDER-HF, 47.5% of strokes were either disabling, 16.5%, or fatal, 31%.[637]

Patients with HF and concomitant AF, including paroxysmal AF, have a CHA_2DS_2-VASc score of at least 1 and have therefore an indication to anticoagulation. The indication to antithrombotic strategies in patients with HF and SR is controversial. In the Warfarin and Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial, warfarin reduced ischaemic stroke as compared with aspirin, but increased major haemorrhages and did not influence the primary endpoint of ischaemic stroke, intracerebral haemorrhage, or death.[641] Meta-analyses confirm an increased risk of bleeding outweighing ischaemic stroke prevention in placebo-controlled trials in patients with HFrEF and SR.[642] In COMMANDER-HF, rivaroxaban 2.5 mg b.i.d. did not improve the composite outcome of all-cause mortality, MI or stroke, nor did it favourably influence HF-related deaths or HF hospitalizations.[579] There are no data to support a routine strategy of anticoagulation in patients with HFrEF in SR who do not have history of paroxysmal AF. However, low-dose rivaroxaban may be considered in patients with concomitant CCS or peripheral artery disease, a high risk of stroke and no major haemorrhagic risk (see section 12.2).

Patients with visible intraventricular thrombus or at high thrombotic risk, such as those with history of peripheral embolism or some patients with PPCM or LV non-compaction (LVNC), should be considered for anticoagulation.[3,643–645]

13 Non-cardiovascular comorbidities

13.1 Diabetes

Treatment of HF is similar in patients with and without diabetes.[6,646] Conversely, antidiabetic drugs differ in their effects in patients with HF and preference must be given to drugs that are both safe and reduce HF-related events.[6,646,647]

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The SGLT2 inhibitors canagliflozin, dapagliflozin, empagliflozin, ertugliflozin and sotagliflozin were studied in patients with established CV disease in the EMPA-REG OUTCOME and VERTIS-CV trials, with established CV disease or CV risk factors in the CANVAS and DECLARE-TIMI 58 trials, and with CKD and CV risk in the SCORED trial, respectively.[293–297] A small proportion of patients had a history of HF. Empagliflozin and canagliflozin reduced the primary composite endpoint of major CV adverse events, including CV death or non-fatal MI or non-fatal stroke, and HF hospitalizations in EMPA-REG OUTCOME and CANVAS, respectively.[293,294] Empagliflozin also reduced all-cause death or CV death alone.[293] The effects on the primary endpoint were driven by the reduction in HF-related events.[293,294] In DECLARE-TIMI 58, dapagliflozin did not reduce major CV events but reduced the co-primary efficacy endpoint of CV death or HF hospitalization and HF hospitalization alone.[295] In VERTIS-CV, neither the primary major CV event endpoint nor the key secondary outcome of CV death or HF hospitalization were reduced significantly by ertugliflozin, although there was a statistically significant reduction in HF hospitalization and repeated hospitalizations.[297,648] In SCORED, sotagliflozin reduced CV deaths and HF hospitalizations.[296] In a meta-analysis of these trials and one further trial in patients with CKD (CREDENCE), overall SGLT2 inhibitors reduced HF and CV hospitalization by 22%.[649] SGLT2 inhibitors were well tolerated, although they may cause genital fungal skin infections and, rarely, diabetic ketoacidosis.[293–295] Trial results with dapagliflozin and empagliflozin in patients with HFrEF, with or without diabetes, and with the SGLT1/2 inhibitor sotagliflozin in patients with type 2 diabetes stabilized after hospitalization for acute HF or within 3 days after discharge, further support the administration of these agents (see section 5.3.5 and section 11.3.11).[108,109,136]

EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, and VERTIS-CV also showed a reduction in worsening renal function, end-stage renal disease or death from renal causes, with SGLT2 inhibitors.

Based on these results, the SGLT inhibitors canagliflozin, dapagliflozin, empagliflozin, ertugliflozin or sotagliflozin are recommended to prevent HF and CV death and worsening kidney function in patients with type 2 diabetes and CV disease and/or CV risk factors, or CKD. Dapagliflozin and empagliflozin are also indicated for the treatment of patients with type 2 diabetes and HFrEF (see section 5.3.5 and section 11.2.4) and sotagliflozin was shown to reduce CV deaths and HF rehospitalizations in patients recently hospitalized for HF.[6,296,646,647,650]

Metformin is thought to be safe in patients with HF, compared with insulin and sulfonylureas, based on observational studies.[651,652] However, it is not recommended in patients with an eGFR <30 mL/min/1.73 m^2 or hepatic impairment because of the risk of lactic acidosis. It has not been studied in controlled outcome trials, to date.[6,646]

Regarding dipeptidyl peptidase-4 (DPP-4) inhibitors, HF hospitalizations were increased by 27% in one trial with saxagliptin in patients with diabetes.[653] However, no difference over placebo for HF events was found with alogliptin, sitagliptin, and linagliptin.[654–656] Vidagliptin was associated with an increase in LV volumes and a numerically greater number of deaths and CV events in a small trial in patients with diabetes and HF.[657] Overall, the effects on mortality or CV events were neutral in the DPP-4 inhibitor trials and meta-analyses.[658,659] These drugs are therefore not recommended to reduce CV events in diabetic patients with HF.

Glucagon-like peptide-1 (GLP-1) receptor agonists reduce the risk of MI, stroke, and CV death in patients with diabetes, although probably do not reduce incident HF.[6,660] Liraglutide had no effect on LVEF, increased heart rate, and increased serious cardiac events in a randomized placebo-controlled trial in 241 patients with HFrEF with and without diabetes.[661] Neutral results on the primary endpoint were found in another trial in 300 patients with a numerical increase in deaths and HF hospitalizations, compared with placebo.[662] GLP-1 receptor agonists are therefore not recommended for the prevention of HF events.

Insulin is needed in patients with type 1 diabetes and to control hyperglycaemia in some patients with type 2 diabetes, especially when beta-cell function is exhausted. It is a sodium-retaining hormone and concern has been raised that it may exacerbate fluid retention in patients with HF. However, in a RCT that included patients with type 2 diabetes, impaired glucose tolerance, or impaired fasting glucose, insulin did not increase the risk of incident HF.[663] Use of insulin was associated with poorer outcomes in retrospective analyses of randomized trials and administrative databases.[664,665] If insulin is needed in a patient with HF, the patient should be monitored for evidence of worsening of HF after treatment initiation.

Sulfonylureas were associated with a higher risk of HF events in some analyses.[666,667] Therefore, they are not a preferred treatment in patients with HF and, if needed, patients should be monitored for evidence of worsening of HF after treatment initiation.[6,646] Thiazolidinediones (glitazones) cause sodium and water retention and an increased risk of worsening HF and hospitalization.[668] They are contraindicated in patients with HF.

Recommendations for the treatment of diabetes in heart failure

Recommendation	Class[a]	Level[b]
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with T2DM at risk of CV events to reduce hospitalizations for HF, major CV events, end-stage renal dysfunction, and CV death.[293–297]	I	A
SGLT2 inhibitors (dapagliflozin, empagliflozin, and sotagliflozin) are recommended in patients with T2DM and HFrEF to reduce hospitalizations for HF and CV death.[108,109,136]	I	A

CV = cardiovascular; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; SGLT2 = sodium-glucose co-transporter 2; T2DM = type 2 diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.

13.2 Thyroid disorders

Assessment of thyroid function is recommended in all patients with HF as both hypo- and hyperthyroidism may cause or precipitate HF.[669] Subclinical hypothyroidism and isolated low triiodothyronine levels

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were associated with poorer outcomes in observational studies in patients with HF.[670,671] Treatment of thyroid disorders should be guided by general endocrine guidelines. There are no randomized trials evaluating the efficacy of thyroid replacement therapy in subclinical hypothyroidism, but there is a general agreement to correct it when the TSH is >10 mIU/L, particularly in patients <70 years. Correction may also be considered at lower TSH levels (7–10 mIU/L).[672–674]

13.3 Obesity

Obesity is a risk factor for hypertension and CAD and is also associated with an increased risk of HF. There is possibly a stronger association with HFpEF.[258,675–677] Once obese patients have HF, an obesity paradox has been described such that overweight or mildly/moderately obese patients have a better prognosis than leaner patients, particularly compared with those who are underweight.[678,679] However, other variables may influence this relationship and the obesity paradox is not observed in patients with diabetes.[680,681] Second, BMI does not take into account body composition, e.g. the relation between lean skeletal muscle mass and fat mass. Obese patients who are fit and have a preserved skeletal muscle mass have better prognosis than obese sarcopenic patients.[682] Waist circumference or the waist-to-hip ratio, measuring visceral obesity, is less influenced by muscle mass and may have a stronger relationship with outcomes than BMI, especially in female patients.[683,684]

Body fat has a major impact on the diagnostic and prognostic value of multiple parameters. Obese patients with HF have lower NP concentrations due to increased expression of clearance receptors and augmented peptide degradation by the adipose tissue.[74] Peak oxygen consumption adjusted for body weight underestimates exercise capacity in obese patients and an adjustment for lean body mass should be used for risk stratification.[96]

Obesity may be a major cause of HFpEF and obese HFpEF patients display several pathophysiologic mechanisms that differ from non-obese patients with HFpEF.[258,675–677,685] Caloric restriction and exercise training had additive beneficial effects on exercise capacity and QOL of patients with obesity and HFpEF in a randomized trial.[337]

13.4 Frailty, cachexia, sarcopenia

Frailty is a multidimensional dynamic state, independent of age, that makes the individual more vulnerable to the effect of stressors.[686] HF and frailty are two distinct yet commonly associated conditions. The assessment of frailty in patients with HF is crucial as it is associated with both unfavourable outcomes and reduced access to, and tolerance of, treatments. Several tools have been proposed for frailty screening and assessment in different chronic conditions, including HF. The HFA of ESC has developed a HF-specific tool based on four major domains, clinical, psycho-cognitive, functional, and social.[686]

Frailty is more prevalent in patients with HF than in the general population and may occur in up to 45% of the patients, according to a recent meta-analysis.[687,688] Patients with HF are up to six times more likely to be frail, and frail people have a significantly increased risk of developing HF.[689,690] Frailty is associated with a higher risk of death, hospitalizations, and functional decline as well as with a longer duration of hospital stay.[691–693] The treatment of frailty in HF should be multifactorial and targeted to its main components and may include physical rehabilitation with exercise training, nutritional supplementation as well as an individualized approach to treating comorbidities.[686]

Cachexia is defined as a 'complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass'.[694] Its major clinical feature is a >5% oedema-free body weight loss during the previous 12 months or less.[694,695] Cachexia is a generalized wasting process that may coexist with frailty and may occur in 5–15% of patients with HF, especially those with HFrEF and more advanced disease status. It is associated with reduced functional capacity and decreased survival.[695–698] As it is associated with other chronic diseases, such as cancer, alternative, non-cardiac causes for cachexia should always be investigated.[699]

Sarcopenia is defined by the presence of low muscle mass together with low muscle function, strength, or performance.[698] It is usually identified by an appendicular skeletal muscle mass, defined as the sum of the muscle mass of the four limbs, 2 standard deviation below the mean of a healthy reference group aged 18–40 years with a cut-off value of 7.26 kg/m^2 for men.[688,700,701] It occurs physiologically with aging. However, it is accelerated by chronic diseases, such as cancer and HF. Sarcopenia can be found in 20–50% of patients with HFrEF and is often associated with frailty and increased morbidity and mortality. It is a major determinant of outcomes outweighing the effect of body weight and BMI.[684,698,701,702] So far, the most effective strategy for sarcopenia treatment is resistance exercise training, possibly combined with a protein intake of 1–1.5 g/kg/day.[698,703] Drug treatments, including anabolic compounds like testosterone, growth hormone, ghrelin receptor agonists, were tested in small studies, showing favourable results mostly in terms of exercise capacity and muscle strength.[697,703–705] There are no data showing a favourable impact of sarcopenia treatment on outcomes. However, exercise training has favourable effects in patients with HF (see section 9.4).[95,323–329]

13.5 Iron deficiency and anaemia

Iron deficiency and anaemia are common in patients with HF, being independently associated with reduced exercise capacity, recurrent HF hospitalizations, and high CV and all-cause mortality.[706,707] According to the World Health Organization criteria, anaemia is defined as a haemoglobin concentration <12 g/dL in women and <13 g/dL in men. In patients with HF, iron deficiency is defined as either a serum ferritin concentration <100 ng/mL or 100–299 ng/mL with transferrin saturation (TSAT) <20%.[708–710] Ferritin tissue expression and concentration in the peripheral blood is increased by inflammation and several disorders such as infection, cancer, liver disease, and HF itself. Hence, higher cut-off values have been applied for the definition of iron deficiency in patients with HF.[709–711] Another marker reflecting depleted intracellular iron can be high serum soluble transferrin receptors, which derives from proteolysis of the membrane transferrin receptor. Its synthesis is increased in case of iron deficiency and is not affected by inflammation. High serum soluble transferrin receptors identify patients at high risk of death beyond standard prognostic variables.[711,712] However, its applicability for iron supplementation therapy has not been demonstrated yet.

Iron deficiency, which can be present independently of anaemia, is present in up to 55% of chronic HF patients and in up to 80% of those with AHF.[713–716] It may be caused by increased loss, reduced intake or absorption (i.e. malnutrition, gut congestion) and/or impaired iron metabolism caused by the chronic inflammatory activation of HF, although the exact cause of iron deficiency in HF remains unknown. Iron deficiency may impair functional capacity, precipitate circulatory

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decompensation, promote skeletal muscle dysfunction, and is associated with frailty, irrespective of anaemia.[716–718]

It is recommended that all patients with HF are regularly screened for anaemia and iron deficiency with full blood count, serum ferritin concentration, and TSAT. The detection of anaemia and/or iron deficiency should prompt appropriate investigation to define their cause.

Darbepoetin-alpha failed to reduce all-cause death or HF hospitalization and increased the risk of thromboembolic events in the only large-scale randomized trial in patients with HFrEF and mild to moderate anaemia.[719] As a result, erythropoietin stimulating agents are not indicated for the treatment of anaemia in HF.

Recommendations for the management of anaemia and iron deficiency in patients with heart failure

Recommendations	Class[a]	Level[b]
It is recommended that all patients with HF be periodically screened for anaemia and iron deficiency with a full blood count, serum ferritin concentration, and TSAT.	I	C
Intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic patients with LVEF <45% and iron deficiency, defined as serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with TSAT <20%, to alleviate HF symptoms, improve exercise capacity and QOL.[720,722,724]	IIa	A
Intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic HF patients recently hospitalized for HF and with LVEF <50% and iron deficiency, defined as serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with TSAT <20%, to reduce the risk of HF hospitalization.[512]	IIa	B

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HF = heart failure; LVEF = left ventricular ejection fraction; QOL = quality of life; TSAT = transferrin saturation.
[a]Class of recommendation.
[b]Level of evidence.

RCTs have shown that iron supplementation with i.v. ferric carboxymaltose is safe and improves symptoms, exercise capacity, and QOL of patients with HFrEF and iron deficiency.[720–723] Meta-analyses of RCTs showed also a reduction in the risk of the combined endpoints of all-cause death or CV hospitalization, CV death or HF hospitalization, CV death or recurrent CV or HF hospitalizations.[724,725] The favourable effects of iron supplementation were independent from anaemia coexistence.[726] In AFFIRM-AHF, patients hospitalized for HF with LVEF <50% and concomitant iron deficiency were randomized to i.v. ferric carboxymaltose or placebo, repeated at 6- and then 12-week intervals if indicated according to repeat iron studies.[512] Administration of ferric carboxymaltose did not significantly reduce the primary composite outcome of total HF hospitalizations and CV death at 52 weeks (rate ratio 0.79, 95% CI 0.62–1.01, $P = 0.059$). However, it reduced the composite endpoint of first HF hospitalization or CV death (HR 0.80, 95% CI 0.66–0.98, $P = 0.030$) and total HF hospitalizations (rate ratio 0.74, 95% CI 0.58–0.94, $P = 0.013$).[512] Therefore, iron supplementation with i.v. ferric carboxymaltose should be considered for the improvement of symptoms, exercise capacity, and QOL in patients with HF and LVEF <45%. It should also be considered for the reduction of HF rehospitalizations in patients with LVEF <50% recently hospitalized for worsening HF. Ongoing trials are expected to provide more evidence on the effects of ferric carboxymaltose in patients with HFpEF. In addition, large outcomes trials with other iron formulations are ongoing in HFrEF, HFpEF, and AHF.[727] Oral iron therapy is not effective in iron repletion and did not improve exercise capacity in patients with HFrEF and iron deficiency.[728] It is therefore not recommended for the treatment of iron deficiency in the patients with HF.

13.6 Kidney dysfunction

CKD and HF frequently coexist.[471,707,729] They share common risk factors, such as diabetes or hypertension. CKD may worsen CV function causing hypertension and vascular calcification. HF may worsen renal function, through the effects of neurohormonal and inflammatory activation, increased venous pressure and hypoperfusion. Oxidative stress and fibrosis likely play a major role as pathogenic mechanisms in HF with CKD.[730,731]

While CKD and worsening renal function both appear more common in HFpEF as compared to in HFmrEF and HFrEF, perhaps due to shared pathophysiological mechanisms, they appear to be less associated with worse outcomes in HFpEF than in HFmrEF and HFrEF.[732,733]

CKD is a major independent determinant of increased mortality and morbidity in HF.[471,734–736] However, there are settings in which changes in serum creatinine are not associated with worse outcomes. When RAAS inhibitors, ARNI or SGLT2 inhibitors are started, the initial decrease in the glomerular filtration pressure may decrease GFR and increase serum creatinine. However, these changes are generally transient and occur despite improvement in patient outcomes and slower worsening of renal function in the long term. For instance, in EMPEROR-Reduced, the placebo-corrected eGFR dip induced by empagliflozin at week 4 was of 2.4 mL/min/1.73 m^2 for patients with CKD and 2.7 mL/min/1.73 m^2 for those without CKD, corresponding to a decrease from baseline of 5.2% and 3.8%, respectively. This was followed by a slower slope of eGFR decline and by a reduced rate of the composite kidney outcome with empagliflozin vs. placebo, with no difference between patients with or without CKD at baseline.[109,737]

Thus, with respect to the initiation of RAAS inhibitors, ARNI or SGLT2 inhibitors, a transient decrease in renal function should not prompt their interruption. An increase in serum creatinine of <50% above baseline, as long as it is <266 µmol/L (3 mg/dL), or a decrease in eGFR of <10% from baseline, as long as eGFR is >25 mL/min/1.73 m^2, can be considered as acceptable (see section 5.3 and *Supplementary Table 8*). Also, with respect to diuretic therapy, small and transient rises in serum creatinine during treatment of acute HF are not associated with poorer outcomes when the patient is free of congestion.[108,109,460–462,471,729,737–740]

Randomized trials have shown that patients with HF and concomitant CKD are at higher risk of events but the beneficial effects of MT

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are similar, if not greater, than in the patients with normal renal function.[206,471,741,742] Beta-blockers reduce mortality in HFrEF patients with moderate (eGFR 45–59 mL/min/1.73 m^2) and moderately severe (eGFR 30–44 mL/min/1.73 m^2) renal dysfunction, whereas limited evidence is available regarding patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2).[743] Sacubitril/valsartan, compared with enalapril, led to a slower decline in renal function, despite a slight increase in the urinary albumin/creatinine ratio, and improved CV outcomes to a similar extent in patients with CKD vs. the others in PARADIGM-HF.[127] SGLT2 inhibitors lead to a slower decline in renal function, compared with placebo, both in patients with HFrEF and in those with CKD.[108,109,737,738,744] The improvement in cardiac output after CRT or LVAD implantation may be associated with, at least, a transient improvement in renal function.[471,745,746] The benefits of ICDs may be reduced in patients with severe renal dysfunction because of the competing risk of non-arrhythmic causes of death.[747–749]

There is little direct evidence to support any recommendations for treatment of HF patients with severe CKD as to date, RCTs excluded patients with advanced stages of CKD, i.e. eGFR <30 mL/min/1.73 m^2 (*Supplementary Table 23*). Cut-off values for inclusion were lower in recent trials: 25 mL/min/1.73 m^2 in DAPA-CKD, 20 mL/min/1.73 m^2 in EMPEROR-Reduced and GALACTIC-HF, and 15 mL/min/1.73 m^2 in VICTORIA, respectively.[109,141,737,738,750] Despite differences in baseline characteristics between patients with severely impaired renal function and the others, no interaction between drug effects and renal function was noted in subgroup analysis of these trials.[109,141,738,750]

13.7 Electrolyte disorders: hypokalaemia, hyperkalaemia, hyponatraemia, hypochloraemia

Electrolyte disturbances are frequent in patients with HF and may often be iatrogenic.[751] Serum potassium levels have a U-shaped relation with mortality with the lowest risk of death within a relatively narrow range of 4 to 5 mmol/L.[752–758]

Hypokalaemia is defined as serum potassium <3.5 mmol/L and may occur in up to 50% of patients with HF.[759] Hypokalaemia is often induced by loop and thiazide diuretic administration. It may cause lethal ventricular arrhythmias and increase CV mortality. Its treatment includes the use of RAAS inhibitors, potassium-sparing diuretics, and prescription of oral potassium supplements (i.e. potassium chloride tablets). When oral administration is not possible, potassium supplementation by infusion may be necessary (20 to 40 mmol of potassium in 250–1000 mL of normal saline). Potassium-rich solution should be infused at slow rate through a large vein using a venous catheter.

Hyperkalaemia is defined as serum potassium >5 mmol/L and can be classified as mild (>5.0 to <5.5 mmol/L), moderate (5.5 to 6.0 mmol/L), or severe (>6.0 mmol/L).[760] It is associated with an increased risk of hospitalization and death.[752,753,755,756,761,762] Hyperkalaemia can be associated with the administration of RAAS inhibitors, CKD and increased absorption.[760] Among patients with HF, the prevalence of hyperkalaemia at any given time among patients with HF appears to be less than 5%,[757] but the incidence is much higher, at up to 40% in chronic HF and 73% in CKD over follow-up durations of approximately 1 year.[753,756,757,763–765] In PARADIGM-HF, treatment with sacubitril/valsartan was associated with lower risk of severe hyperkalaemia, compared with enalapril.[128] Life-threatening hyperkalaemia requires immediate treatment with a combination of calcium carbonate and/or sodium bicarbonate, insulin, with or without glucose, and beta adrenoceptor agonists [e.g. salbutamol, off-label use in some European Union (EU) countries]. These agents favour potassium entry into the cells and do not increase potassium excretion. Thus, they only provide temporary benefit and rebound hyperkalaemia can occur after few hours. Loop diuretics can be administered to facilitate potassium loss.

Potassium binders bind to potassium in the gastrointestinal tract reducing its absorption. They can be used for acute and chronic potassium lowering. They include sodium polystyrene sulfonate, calcium polystyrene sulfonate, and the much better tolerated patiromer sorbitex calcium and sodium zirconium cyclosilicate (SZC). Sodium polystyrene sulfonate is still indicated in anuric or severely oliguric patients, but it should not be used in the medium or long term as it may cause severe gastrointestinal side effects, including bowel necrosis.[760] Patiromer or SZC increase faecal potassium excretion and act mainly in the colon. Both compounds are effective in normalizing elevated potassium levels, maintaining normokalaemia over time and preventing the recurrence of hyperkalaemia and can be considered for treatment of hyperkalaemia[766–768] (see *Supplementary Table 24*).

Renal dysfunction and hyperkalaemia are the major causes of underuse of RAAS inhibitors, particularly MRA, in clinical practice.[342,753,758,769–771] Administration of the potassium-lowering agents, patiromer or SZC, may allow their initiation or uptitration in a larger proportion of patients. This hypothesis was tested in double-blind, placebo-controlled, randomized trials with patiromer or placebo administration to patients with CKD and hyperkalaemia, or discontinuation of RAAS inhibitors for hyperkalaemia, and with an indication for spironolactone for HF and/or resistant hypertension. Patiromer was more likely to lower serum potassium and decreased episodes of hyperkalaemia than spironolactone initiation and uptitration.[772–775] The ongoing RCT DIAMOND (NCT03888066) is testing the impact on clinical outcomes of a strategy based on patiromer administration, compared with placebo, in patients with HFrEF who are hyperkalaemic while on RAAS inhibitors or with a history of hyperkalaemia with subsequent reduction or discontinuation of a RAAS inhibitor[776,777] (see *Supplementary text 13.1*).

Hyponatraemia is defined as a serum sodium concentration lower than 136 mmol/L. It is common in HF and may be present in up to 30% of patients admitted to hospital with HF. It reflects neurohormonal activation and is a powerful independent marker of poor outcomes in patients with acute or chronic HF.[778,779]

Severe hyponatraemia may cause neurologic symptoms (seizures, obtundation, delirium) due to cerebral oedema and may require immediate treatment with hypertonic saline with serum sodium increases by 1–2 mmol/L per hour, though less than 8 mmol/L in 24 h as a more rapid correction increases the risk of myelinolysis. Intravenous treatment is not required when hyponatraemia is less

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severe, e.g. >124 mmol/L, and in the absence of symptoms. As the pathogenesis of hyponatraemia in HF is dilutional, e.g. caused by water retention induced by increased vasopressin secretion, treatment is based on water restriction or vasopressin antagonists. Fluid restrictions to less than 800–1000 mL/day may be indicated to achieve a negative water balance and treat hyponatraemia. Water restriction was associated with improved QOL in a small, randomized study but with only slight increases in serum sodium in an observational registry.[780,781] Tolvaptan, an orally active selective arginine vasopressin V2 receptor antagonist, can be considered to increase serum sodium and diuresis in patients with persistent hyponatraemia and congestion. However, no effects on outcomes have been shown in RCTs[782–785] (see *Supplementary text 13.1*). The infusion of hypertonic saline combined with loop diuretics was associated with an increase in serum sodium levels and greater diuretic efficacy in small trials and observational studies.[786–788]

Hypochloraemia (<96 mmol/L) is a powerful independent predictor of mortality in patients with acute and chronic HF.[439,789–792] Serum chloride may have a direct role in the control of renin secretion and the response to loop or thiazide diuretics.[439,793] The carbonic anhydrase inhibitor acetazolamide increases chloride reabsorption causing a greater bicarbonate and sodium excretion in the proximal tubule of the nephron. It can increase serum chloride levels and diuresis in patients with severe HF at risk of diuretic resistance.[145,794] It is currently being tested in a multicentre randomized study in decompensated HF.[469]

13.8 Lung disease, sleep-disordered breathing

Overall, COPD affects about 20% of patients with HF and has a major impact on symptoms and outcomes.[795–797] Due to the overlap in symptoms and signs, the differentiation between HF and COPD may be difficult. Pulmonary function testing with spirometry is recommended as the first diagnostic tool and should be considered in patients with suspected COPD. For adequate interpretation, it should be performed in stable and euvolaemic patients to avoid congestion related to obstructive pulmonary function patterns. If there is uncertainty about the reversibility of airflow obstruction, pneumology referral for more sophisticated tests (bronchodilatatory test, bronchial provocation tests, diffusion capacity) is warranted.[798,799]

Treatment of HF is generally well tolerated in COPD.[800] Beta-blockers can worsen pulmonary function in individual patients but are not contraindicated in either COPD or asthma, as stated in the Global initiative for chronic Obstructive Lung Disease (GOLD) and the Global INitiative for Asthma (GINA), respectively.[801,802] GINA states that asthma should not be regarded as an absolute contraindication to the use of cardioselective beta-blockers (bisoprolol, metoprolol succinate, or nebivolol) with consideration of relative risks and benefits. In clinical practice, starting with low doses of cardioselective beta-blockers combined with close monitoring for signs of airway obstruction (wheezing, shortness of breath with lengthening of the expiration) should be encouraged. Although not tested in HF patients, inhaled corticosteroids and beta-adrenergic agonists do not seem to increase CV events, including HF, in patients at high risk.[803,804] Moreover, optimal COPD management can improve cardiac function.[805]

Sleep-disordered breathing occurs in more than one third of patients with HF and is even more prevalent in patients with AHF. The most common types are: central sleep apnoea (CSA, similar to Cheyne-Stokes respiration), OSA, and a mixed pattern of the two. CSA and OSA have been shown to be associated with a worse prognosis in HF. OSA is associated with an increased risk of incident HF in men. CSA is the most common form of sleep-disordered breathing in HFrEF and HFmrEF is the most common cause of CSA.[806,807]

Patients with HF can be investigated for sleep-disordered breathing. History taking should involve partners. Questionnaires are instrumental in identifying patients at risk. Home monitoring can usually identify and distinguish the type of sleep apnoea. However, overnight polysomnography remains the definitive investigation.[807] The use of adaptive servo-ventilation in patients with HFrEF and predominantly CSA is not recommended, based on the results of SERVE-HF, which was neutral regarding the composite primary endpoint of death from any cause or lifesaving CV intervention, but showed an increase in both all-cause mortality and CV mortality with adaptive servo-ventilation.[808] Transvenous phrenic nerve stimulation was tested in a prospective, multicentre, randomized trial involving 151 patients with CSA.[809] The primary efficacy endpoint was the reduction of the apnoea-hypopnoea index from baseline to 6 months and was achieved by a larger percentage of patients with the active treatment. Other measurements of sleep quality and QOL were improved and no difference in any safety endpoint was found between active treatment and control.[809] Similar results were observed in the 96 patients with HF.[810]

Patients with HFrEF being considered for a sleep-disordered breathing treatment with positive pressure airway mask must undergo formal sleep study to document the predominant type of sleep apnoea (central vs. obstructive). When sleep-disordered breathing is caused by OSA, nocturnal hypoxaemia can be treated with nocturnal oxygen supplementation, continuous positive airway pressure, bi-level positive airway pressure, and adaptive servo-ventilation. However, none of these interventions has been shown to have beneficial effects on outcomes in HF.[807] When sleep-disordered breathing is caused by CSA, positive pressure airway masks are contraindicated in HFrEF patients.[808] In these patients, implantable phrenic nerve stimulation can be considered for symptomatic relief.

13.9 Hyperlipidaemia and lipid-modifying therapy

Two large RCTs, including mainly patients with HFrEF, as well as a meta-analysis of 24 RCTs, showed no benefit of statin treatment on CV mortality or stroke in patients with HFrEF.[811,812] A reduction in HF hospitalizations as well as a small reduction in MI was observed in a meta-analysis of the CORONA and GISSI-HF trials.[813–815] Based on current evidence, routine administration of statins in patients with HF without other indications for their use (e.g. CAD) is not

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recommended. Because there is no evidence of harm in patients on statin treatment after the occurrence of HF, there is no need for statin discontinuation for patients already treated.

13.10 Gout and arthritis

Hyperuricemia is a common finding in patients with CHF with a prevalence up to 50%.[816,817] Hyperuricemia may be caused or aggravated by diuretic treatment and it is related to symptoms, exercise capacity, severity of diastolic dysfunction and long-term prognosis.[817,818] For every 1 mg/dL increase in serum uric acid levels the risk of all-cause mortality and of HF hospitalization increases by 4% and 28%, respectively.[819] Both febuxostat and allopurinol reduce uric acid levels. However, allopurinol was associated with a lower rate of all-cause death and CV death, compared with febuxostat, in a prospective, multicentre, double-blind, non-inferiority trial enrolling 6190 patients with gout and CV disease, 20% with HF, with a median follow-up of 32 months.[820] Allopurinol is therefore recommended as the first-choice urate-lowering drug in HF patients with no contraindication. There is no evidence that uric acid-lowering treatment has beneficial effects on LV function, symptoms or outcomes of patients with HF.[821–823]

With respect to treatment of acute gout attacks, non-steroidal anti-inflammatory drugs (NSAIDs) can worsen renal function and precipitate acute HF decompensation. Colchicine should be preferred as it is associated with less side effects.[824] However, it, too, should be used with caution in patients with severe renal dysfunction and is contraindicated in patients on dialysis. An increase in ventricular vulnerability was shown in experimental models.[825]

Arthritis is a common comorbidity and is a common cause of both self-taken and prescribed NSAIDs. These agents are relatively contraindicated as they may precipitate acute decompensation in patients with HF.[826] Rheumatoid arthritis is associated with a two- to three-fold increase in the risk of HF and this increased risk is independent of ischaemic heart disease, suggesting a direct role in HF pathophysiology.[827,828] The safety of disease-modifying drugs used for the treatment of rheumatoid arthritis has not been established in HF. High doses of anti-tumour necrosis factor alpha agents were associated with worsening HF in initial trials and should be used with caution. No adverse effects were noted with lower doses.[829–831]

13.11 Erectile dysfunction

Erectile dysfunction is a serious problem in HF patients due to its association with CV risk factors, comorbidities (e.g. diabetes), lifestyle (e.g. inactivity), and treatment (e.g. drugs).[832] In the general population, the prevalence of erectile dysfunction is estimated to be 50% in men aged ≥60, but erectile dysfunction can be present in up to 81% of cardiac patients across different cultures and ethnic groups.[833] Optimal assessment should include both questions assessing the presence of erectile dysfunction and factors that can be related to erectile dysfunction. Numerous classes of CV drugs, particularly diuretics and beta-blockers, have been implicated causing erectile dysfunction. However, the relationships between many contemporary CV drugs and erectile dysfunction is not clear.[834] For the treatment of erectile dysfunction, phosphodiesterase type 5 inhibitors are generally safe and effective in patients with compensated HF.[834,835] No studies have shown one agent to be more effective or safer than the others. However, phosphodiesterase type 5 inhibitors should not be used in patients receiving nitrates and nitrates should not be administered to patients within 24 h of sildenafil or vardenafil administration or within 48 h of tadalafil administration.[834]

13.12 Depression

Depression affects 20% of patients with HF and is severe in half of them. Its occurrence is higher in women and it is associated with worse clinical status and a poor prognosis.[836–838] Screening using a validated questionnaire is recommended when there is a clinical suspicion of depression. The Beck Depression Inventory and Cardiac Depression Scale are the tools formally validated for the assessment of depression in patients with HF. Other questionnaires (e.g. Geriatric Depression Scale, Hamilton Depression Scale, Hospital Anxiety and Depression Scale) can also be used.[837,838]

There is still no consensus on the best therapy for HF patients with depression. Psychosocial intervention may improve depressive symptoms but has no effect on prognosis of depressed patients with HF.[839] Depressive symptoms may improve with selective serotonin reuptake inhibitors but trials specifically designed to assess the effect of these drugs in patients with HF and depression have failed to show any significant benefit over placebo on both symptoms and outcomes.[840,841] Interestingly, patients improved also in the placebo arm showing the importance of better care in these patients. Both trials showed the safety of sertraline and escitalopram, respectively.[840,841] Tricyclic antidepressants should be avoided for the treatment of depression in HF as they may cause hypotension, worsening HF, and arrhythmias.[837,838]

13.13 Cancer

HF occurs in patients with cancer as a result of the interaction among anticancer therapy, cancer itself, and patients' CV background (risk factors and coexisting CV disease).[842–846] Several anticancer therapies may cause HF directly, thorough their cardiotoxic effects (*Table 23*), or, indirectly, through other mechanisms, such as myocarditis, ischaemia, systemic or pulmonary hypertension, arrhythmias or valve disease.[844,845,847–852] HF, in turn, may affect cancer outcomes by depriving patients of effective anticancer therapies.[699] Some epidemiological and experimental evidence suggests a further reciprocal interaction between cancer and HF with some, though not all, studies showing a higher incidence rate of cancer in patients with HF.[853–858]

The prevention of HF in patients with cancer undergoing potential cardiotoxic therapies requires careful patient's assessment and management before, during, and after cancer therapy, preferably in the context of an integrated Cardio-Oncology service (*Figure 18*).[845,859,860] A CV baseline risk assessment for all patients scheduled to receive potentially cardiotoxic cancer therapies using the HFA-ICOS risk assessment is advisable.[846] Baseline CV risk assessment forms have been developed for different potentially cardiotoxic cancer therapies. History of HF or CMP characterizes patients as being at very high risk or at high risk for all cancer therapies, except anti-androgen treatments for prostate cancer. An LVEF <50% is an additional factor for high-risk patients and elevated levels

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Table 23 Cancer drugs causing heart failure

Cancer therapy	Indication
Anthracycline chemotherapy (doxorubicin, epirubicin, daunorubicin, idarubicin)	Breast cancer, lymphoma, acute leukaemia, sarcoma
HER2-targeted therapies (trastuzumab, pertuzumab, trastuzumab emtansine T-DM1, lapatinib, neratinib, tucatinib)	HER2+ breast cancer HER2+ gastric cancer
VEGF inhibitors TKIs (sunitinib, pazopanib, sorafenib, axitinib, tivozanib, cabozantinib, regorafenib, lenvatinib, vandetinib) and antibodies (bevacizumab, ramucirumab)	VEGF TKIs: renal cancer, hepatocellular cancer, thyroid cancer, colon cancer, sarcoma, GIST Antibodies: breast cancer, ovarian cancer, gastric cancer, gastro-oesophageal cancer, colon cancer
Multi-targeted kinase inhibitors: second and third generation BCR-ABL TKIs (ponatinib, nilotinib, dasatinib, bosutinib)	Chronic myeloid leukaemia
Proteasome inhibitors (carfilzomib, bortezomib, ixazomib) **Immunomodulatory drugs** (lenalidomide, pomalidomide)	Multiple myeloma
Combination RAF and MEK inhibitors (dabrafenib+trametinib, vemurafenib+cobimetinib, encorafenib+ binimetinib)	RAF mutant melanoma
Androgen deprivation therapies GnRH agonists (goserelin, leuprorelin) Antiandrogrens (abiraterone)	Prostate cancer, breast cancer
Immune checkpoint inhibitors: anti-programmed cell death 1 inhibitors (nivolumab, pembrolizumab) anti-cytotoxic T-lymphocyte-associated protein 4 inhibitor (ipilimumab) anti-programmed death-ligand 1 inhibitors (avelumab, atezolizumab, durvalumab)	Melanoma (metastatic and adjuvant) Metastatic renal cancer, non-small cell lung cancer, small cell lung cancer, refractory Hodgkin's lymphoma, metastatic triple negative breast cancer, metastatic urothelial cancer, liver cancer, MMR-deficient cancer

GIST = gastrointestinal stromal tumour; GnRH = gonadotropin-releasing hormone; HER2 = human epidermal growth factor receptor 2; MEK = mitogen-activated protein kinase; MMR = mismatch repair; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.

of NPs or troponin at baseline are additional criteria of medium risk for most of the cancer treatments.[846]

During cancer treatment with potential cardiotoxic therapies, LV systolic function can be monitored through echocardiography. Chemotherapy should be reconsidered and treatment with an ACE-I and a beta-blocker (preferably carvedilol) should be started in patients who develop LV systolic dysfunction, defined as 10% or more absolute reduction in LVEF to a value below 50%.[844,861–864] Global longitudinal strain can detect cardiac dysfunction at an earlier stage.[865,866] A ≥12% relative reduction in global longitudinal strain was compared with an LVEF decline in a prospective randomized trial in high-risk patients undergoing potentially cardiotoxic chemotherapy. Compared to treatment based on LVEF, treatment based on changes in global longitudinal strain led to the same decrease in LVEF (primary endpoint) but with fewer patients who developed cardiac dysfunction at the end of the study, thus suggesting usefulness of global longitudinal strain for the early detection of cardiotoxicity.[867]

Promising results for the early detection of cardiac dysfunction have also been obtained through monitoring of biomarkers, such as NPs and troponin.[868,869] Patients on immunotherapy with immune checkpoint inhibitors are at increased risk of myocarditis and should be monitored for related symptoms and signs and by weekly assessment of cardiac troponin during at least the first 6 weeks of therapy and managed accordingly.[870]

Timing of the imaging procedures and biomarkers assessment depend on the anticancer treatment and patient's risk profile (*Figure 18*).[865] In general, all patients scheduled for potential cardiotoxic therapies must undergo a baseline evaluation that would define the level of risk for cardiotoxicity (low, medium, or high) and the intensity of monitoring and follow-up during and after cancer treatment.[865] Cancer survivors exposed to potentially cardiotoxic therapies should be periodically monitored in the long term as HF may develop several years after cancer therapy.[865,871]

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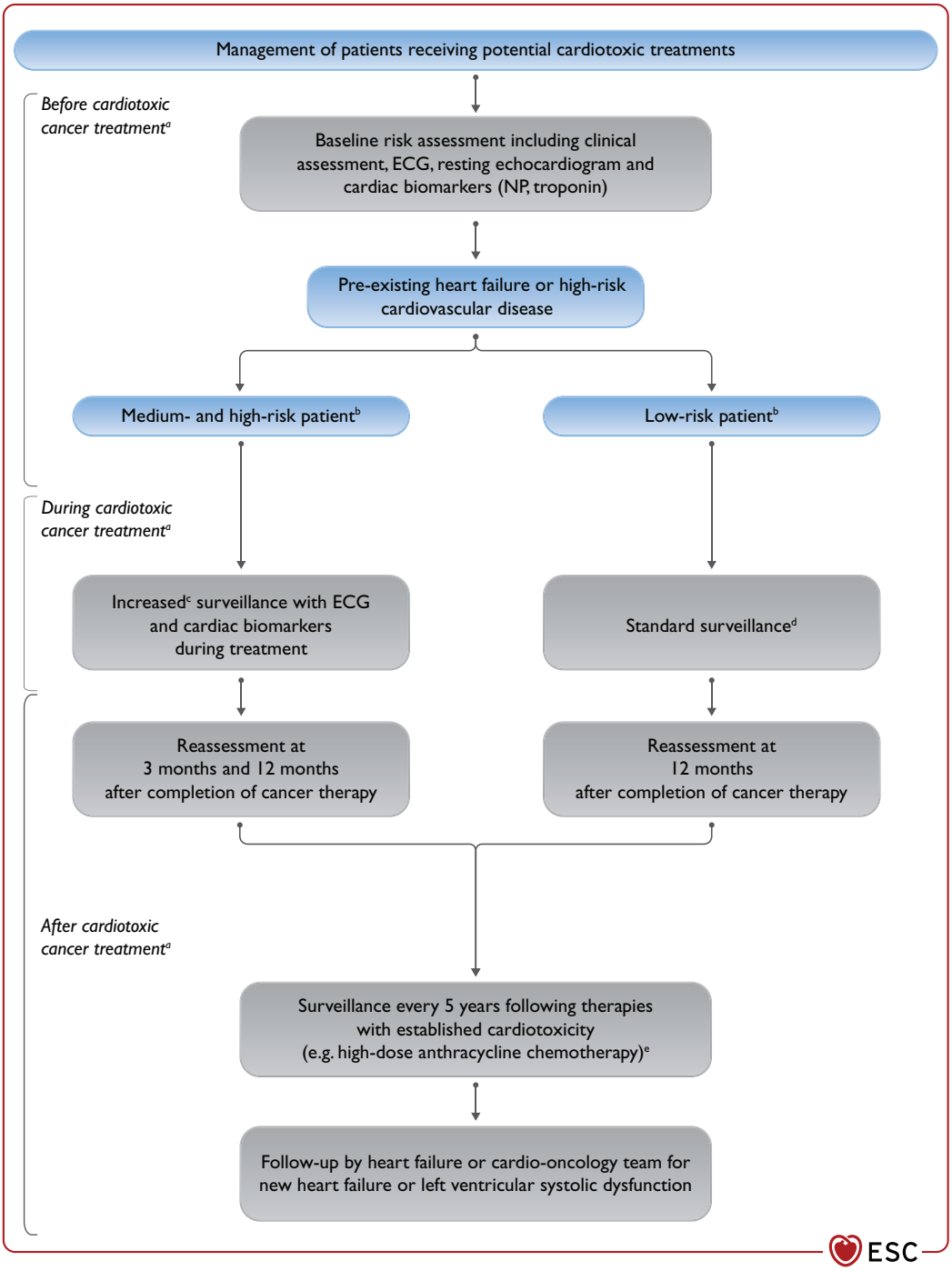

Figure 18 Management of patients with cancer and heart failure. ECG = electrocardiogram; HER2 = human epidermal growth factor receptor 2; HF = heart failure; HFA = Heart Failure Association; ICOS = International Cardio-Oncology Society; MEK = mitogen-activated protein kinase; NP = natriuretic peptide; VEGF = vascular endothelial growth factor. [a]Anthracycline chemotherapy, trastuzumab and HER2 targeted therapies, VEGF inhibitors, proteasome inhibitors, combination RAF+MEK inhibitors. [b]Low, medium and high risk may be calculated using the HFA-ICOS baseline cardiovascular risk proformas.[846] [c]Increased surveillance is intended between 1 and 4 weeks. [d]Standard surveillance is intended every 3 months. [e]5 yearly surveillance at follow-up = clinical review every 5 years with history, examination, NPs and troponin levels, and echocardiogram.[865]

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Recommendations for the management of patients with cancer and heart failure

Recommendation	Class[a]	Level[b]
It is recommended that cancer patients at increased risk for cardiotoxicity, defined by a history or risk factors of CV disease, previous cardiotoxicity or exposure to cardiotoxic agents, undergo CV evaluation before scheduled anticancer therapy, preferably by a cardiologist with experience/interest in Cardio-Oncology.	I	C
Treatment with an ACE-I and a beta-blocker (preferably carvedilol) should be considered in cancer patients developing LV systolic dysfunction, defined as a 10% or more decrease in LVEF and to a value lower than 50%, during anthracycline chemotherapy.[861,862]	IIa	B
A baseline CV risk assessment should be considered in all cancer patients scheduled to receive a cancer treatment with the potential to cause heart failure.[846,865]	IIa	C

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ACE-I = angiotensin-converting enzyme inhibitor; CV = cardiovascular; LV = left ventricular; LVEF = left ventricular ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.

13.14 Infection

Infective disorders may worsen HF symptoms and be a precipitant factor for AHF.[872,873] Severe sepsis and pneumonia can cause myocardial injury and depress cardiac function leading to cardiac dysfunction and HF and this risk is greater in patients with a history of HF.[873–875] More recently, the coronavirus disease 2019 (COVID-19) pandemic has emerged as a major cause of morbidity and mortality as well as of HF decompensation.[873,876–878] Specific guidance is available.[879] General recommendations related to infections are given in *Table 24*.

Influenza vaccination is associated with a reduced risk of all-cause death in patients with HF in observational studies and retrospective analyses.[880–882] Influenza and pneumococcal vaccination, as well as COVID-19 vaccination, when available, should be considered in patients with HF.[879,883]

Table 24 Infections in patients with heart failure

Patients with HF are at increased risk of infections and have poorer outcomes once infected.
Telemonitoring avoids the risks of infections caused by close contact. It is useful during pandemic conditions.
Telemonitoring may be implemented for patients' follow-up in pandemic conditions.
During pandemics, HF patients should be screened for infection at the time of hospitalization, in case of urgent admissions, or before elective hospitalizations.
Careful assessment of fluid status, in addition to clinical signs of HF, is mandatory during hospitalization in patients with concomitant sepsis. Repeated measures of inferior vena cava diameter and collapsibility by echocardiography may be used to assess fluid status.
OMT (including beta-blocker, ACE-I, ARB or ARNI, MRA and SGLT2 inhibitors), should be continued in chronic HF patients whenever BP and haemodynamic conditions permit and considering drug interaction with infection related therapies and side effect profile.

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ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BP = blood pressure; HF = heart failure; MRA = mineralocorticoid receptor antagonist; OMT = optimal medical therapy; SGLT2 = sodium-glucose co-transporter 2.

14 Special conditions

14.1 Pregnancy

14.1.1 Pregnancy in pre-existing heart failure

Women with pre-existing HF have a higher risk of pregnancy-related CV complications including HF decompensation. Moderate- and high-risk patients according to the modified World Health Organization (mWHO) class III–IV should be referred to a specialist centre with a multidisciplinary Pregnancy Heart Team.[884] An algorithm for the management of HF patients before and during pregnancy is reported in *Figure 19*.

Pre-pregnancy management includes the modification of existing HF medications to avoid foetal harm. ACE-Is, ARBs, ARNI, MRAs, ivabradine, and SGLT2 inhibitors are contraindicated and should be stopped prior to conception with close clinical and echocardiographic monitoring. Beta-blockers should be continued and switched to beta-1-selective blockers (bisoprolol, metoprolol succinate). Hydralazine, oral nitrates and methyldopa can be started if required. Therapeutic anticoagulation with low-molecular-weight heparin (LMWH), in the first and last trimesters, and VKAs, with the usual target international normalized ratios (INRs) or LMWH for the second trimester, is recommended for patients with HF and AF. DOACs should be avoided.[884]

Assessment of patients with HF in pre-pregnancy or at presentation with a new pregnancy should include a clinical assessment (symptoms, clinical examination, BP, SaO_2), ECG and resting echocardiography. The modalities of delivery should be planned by cardiologists, obstetricians, and anaesthesiologists around 35 weeks in a multidisciplinary Pregnancy Heart Team. Bimonthly assessments for women in mWHO II–III, and monthly assessments for women with pre-existing HF in mWHO III, must be performed. Women with advanced HF (LVEF <30%, NYHA class III–IV) in mWHO IV who are pregnant can be referred to a specialist centre for counselling regarding any consideration of termination of pregnancy. The decision regarding modalities of delivery can be planned by cardiologists, obstetricians, and anaesthesiologists around 35 weeks in a multidisciplinary Pregnancy Heart Team and discussed with the patient.[884]

14.1.2 New heart failure presenting during pregnancy

The increased demands on ventricular function due to the increased circulating volume and cardiac output of pregnancy can unmask pre-

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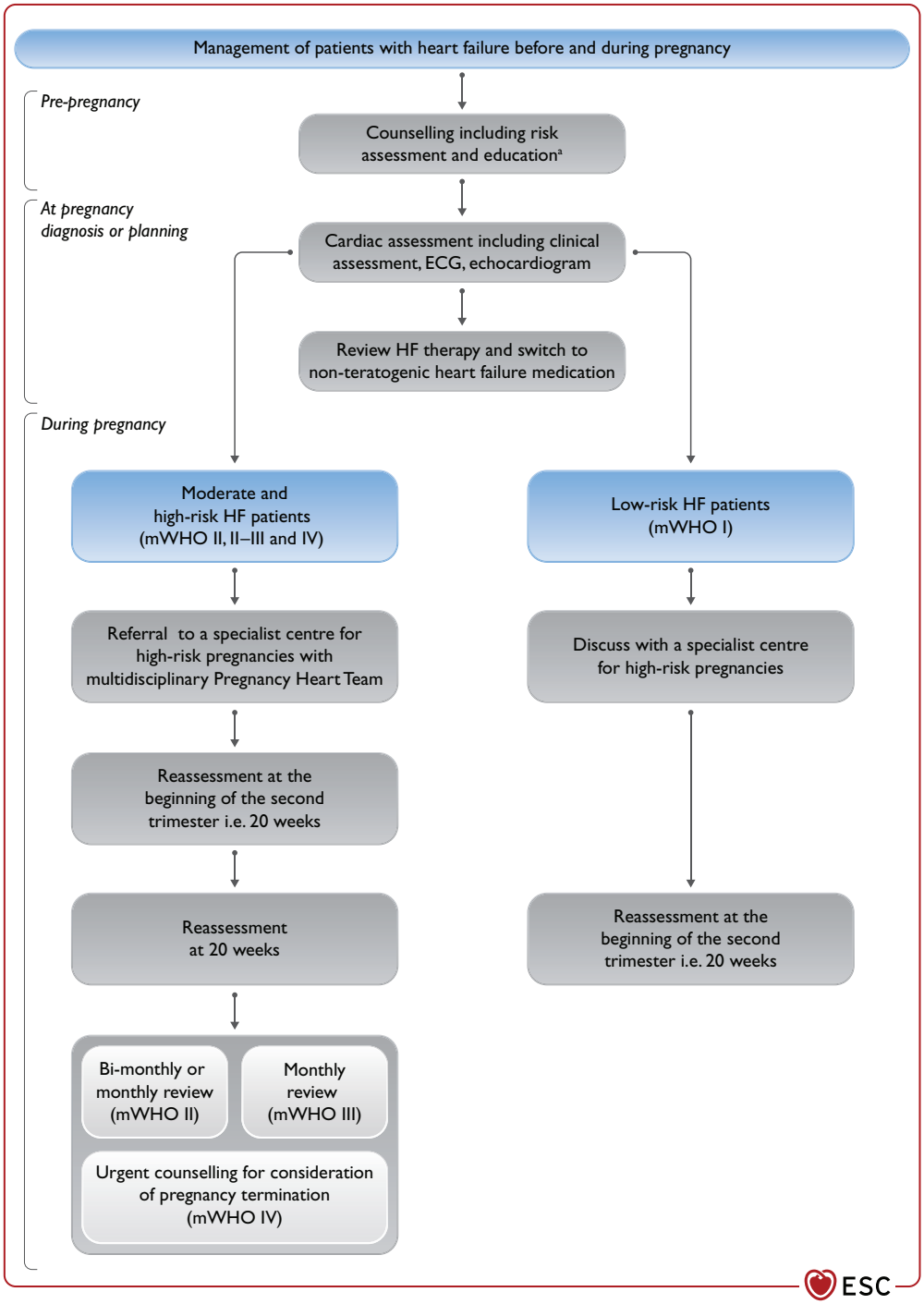

Figure 19 Management of patients with heart failure before and during pregnancy. ECG = electrocardiogram; HF = heart failure; mWHO = modified World Health Organization. [a]Advice regarding contraception, HF medication, to contact HF specialist when planning pregnancy.

existing, but previously undiagnosed, causes of HF such as CMPs and valve diseases.[885] Symptoms are more likely to occur in the second trimester when the demand for an increased cardiac output is the highest. Severe emotionally stressful episodes during pregnancy and delivery can also cause Takotsubo syndrome.[884,885]

PPCM presents as HF secondary to LV systolic dysfunction, usually shown by an LVEF <45%, occurring towards the end of pregnancy (third trimester) or in the months following delivery without any other identifiable cause. The majority of PPCM cases are diagnosed in post-partum. The prevalence ranges from 1:100 in Nigeria to 1:1000

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in South Africa and 1:1500 in Germany.[643] Prospective large cohort studies report a 6-month mortality ranging from 2.0% in Germany to 12.6% in a 206 PPCM patient cohort from South Africa.[643]

PPCM frequently presents with acute HF but may also present with ventricular arrhythmias and/or cardiac arrest. An LVEF <30%, marked LV dilatation, LV end-diastolic diameter >6.0 cm, and RV involvement are associated with adverse outcomes.[643] Cardiac recovery may occur in the first 3–6 months though it may be delayed to up to 2 years. Recovery rates vary among regions, from 75% to less than 50%.[886–888]

Assessment and management of pregnant patients presenting with HF depends upon the clinical setting and severity of presentation. Detailed cardiac assessment with echocardiography, NP levels, foetal ultrasound and foetal monitoring is recommended. In cases of new HF or if there is diagnostic uncertainty non-contrast CMR may be considered.

Milder cases can be treated with oral diuretics, beta-blockers, hydralazine and oral nitrates. Pregnant women presenting with signs of acute HF require urgent hospital admission. In case of PPCM presenting with severe HF and cardiogenic shock requiring inotropic or vasopressor support, transfer to an advanced HF centre, where ECMO, LVAD and/or cardiac transplantation can be performed, is recommended. Urgent delivery by caesarean section (irrespective of gestation) should be considered with MCS immediately available.

Adrenergic agents (dobutamine, adrenaline) may have detrimental effects.[889] When a PPCM patient is haemodynamically unstable, levosimendan or MCS may be considered. LVAD implantation as a BTT or BTR should be considered in refractory cases of cardiogenic shock.[643] Bromocriptine has been proposed for patients with acute PPCM to reduce the production of a cleaved 16 kDa prolactin fragment, which may contribute to the pathophysiology of PPCM. Bromocriptine was tested in a randomized trial in 63 patients comparing its long-term, 8 weeks, with its short-term, 1-week, treatment. It was associated with recovery of LV function, with no difference between the two regimens and in line with the results of a previous international PPCM registry.[890,891] Bromocriptine may be considered for treatment of PPCM. Untoward effects of treatment, including deep venous thrombosis and cessation of lactation, must be considered if it is initiated. It should therefore be accompanied by prophylactic (or therapeutic) anticoagulation.

14.2 Cardiomyopathies

14.2.1 Epidemiology and diagnosis

CMPs can be either inherited (genetic/familial) and/or acquired. They can also be accelerated by disease modifiers.[892–894] They are a heterogeneous group of diseases and are major causes of HF.[895] DCM has an estimated prevalence of 1 in 250 to 1 in 500 of the general population, HCM ranges between 1 in 500 to 1 in 5000, and AC is estimated to be present in around 1 in 1000 to 1 in 5000 persons.[895,896]

Direct causes of CMPs include pathogenic gene variants (mutations), toxins, auto-immunity, storage diseases, infections, and tachyarrhythmias. Disease modifiers, conditions that may aggravate or trigger a CMP, include epigenetic factors and acquired modifiers, such as pregnancy and most CV comorbidities. It is important to consider this key interaction between genetic and acquired causes during the diagnostic workup.[897] Identification of an acquired cause of the CMP does not exclude an underlying pathogenic gene variant, whereas the latter may require an additional acquired cause and/or disease modifier to become manifest clinically. The commonest causes and disease modifiers are shown in *Table 25*.

The key elements of the diagnostic workup for all patients with HF and CMP are reported in *Table 26*.[892,894,895,898,899] Specifics aspects of diagnosis and treatment are summarized in *Tables 27–29*. Clinical history, laboratory tests, and imaging are the first-line investigations. Echocardiography is central for the diagnosis and monitoring of HCM, DCM, and AC. CMR imaging provides more detailed morphological and prognostic information and should be performed at baseline. The prevalence of gene mutations may vary according to the morphological phenotype or the underlying acquired cause. Gene mutations occur in up to 40% of DCM, 60% of HCM, and 15% in chemotherapy-induced, alcoholic or peripartum CMPs.[895,898,900–905] The prevalence of genetic mutations is over 10% also in non-familial DCM.[898,906] Finding a pathogenic gene variant in a patient with CMP allows better prediction of the disease outcome and progression, may contribute to the indications for device implantation and inform genetic counselling for families.

Endomyocardial biopsy (EMB) with immunohistochemical quantification of inflammatory cells remains the gold standard investigation for the identification of cardiac inflammation. It may confirm the diagnosis of auto-immune disease in patients with DCM and suspected giant cell myocarditis, eosinophilic myocarditis, vasculitis and sarcoidosis.[893,907] It may also help for the diagnosis of storage diseases, including amyloid or Fabry disease, if imaging or genetic testing does not provide a definitive diagnosis (see also section 14.6). EMB might be considered also in HCM if genetic or acquired causes cannot be identified. The risks and benefits of EBM should be evaluated and this procedure should be reserved for specific situations where its results may affect treatment.

14.2.2 Treatment

The current pharmacological treatment of HF in DCM, HCM, or AC patients does not differ from general HF management, except for peculiar aspects reported in *Tables 27–29*. A pilot randomized study, TRED-HF, investigated the possibility of withdrawing medical treatment in those patients with non-ischaemic DCM who had had partial to complete recovery of LVEF (>40%). However, relapse of DCM within 6 months was observed in 44% of patients, and rapid LV remodelling with early tissue and functional changes, even amongst patients who did not relapse, was found.[271,908]

In a phase 3, randomized, double-blind, placebo-controlled trial (EXPLORER-HCM), treatment with mavacamten improved exercise capacity, LVOT obstruction, NYHA functional class, and health status in patients with obstructive HCM. This offers the possibility of disease-specific treatment for inherited CMPs. [909]

ICD implantation should be considered for patients with DCM, HCM, or AC (see section 6).[895,910–912] The strength of the indication varies according to the clinical risk factors for sudden cardiac death with higher priority being given to those patients with significant LGE

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Table 25 Possible causes and disease modifiers of most frequent cardiomyopathies

	Cause	Disease modifier	Phenotype
Genetic mutations			
LMNA	x		DCM
TTN	x	x	DCM, (HCM)
RBM20	x		DCM
MYH7	x		DCM, HCM
MYPC	x		DCM, HCM
TNNT	x		DCM, HCM
PLN	x		DCM, HCM, AC
DSP	x	x	AC, DCM, myocarditis
SCN5a	x	x	AC, (DCM)
Tropomyosin-1	x		DCM
Haemochromatosis (HFE gene, C282Y)	x		HCM, DCM
Galactosidase-A (Fabry disease)	x		HCM
Neuromuscular disorders			
Duchenne muscular dystrophy, Becker muscular dystrophy, myotonic dystrophy	x		DCM
Syndromic disorders			
Mitochondrial X-linked mutations	x		DCM
Acquired diseases			
Infection (viruses)	x	x	Myocarditis, DCM
Immuno-mediated diseases (rheumathoid arthritis, systemic lupus erythematosus, dermatomyositis)	x	x	Myocarditis, DCM
Toxic (alcohol, amphetamines, cocaine)	x	x	DCM, myocarditis
Drugs (anthracyclines, trastuzumab, immune checkpoint inhibitors)	x	x	DCM, myocarditis
Overload (haemochromoatosis)	x	x	HCM, DCM
Peripartum (pregnancy)	x	x	DCM
Comorbidities with possible interactions with the gene mutations and an effect on phenotype and outcome			
Tachy-arrhythmias	x	x	DCM
Diabetes mellitus	x	x	DCM, HCM
Hypertension	x	x	DCM, HCM
Hypo- and hyperthyroidism		x	DCM, HCM, myocarditis

AC = arrhythmogenic cardiomyopathy; DCM = dilated cardiomyopathy; DSP = desmoplakin; HCM = hypertrophic cardiomyopathy; LMNA = lamin A/C; MYH7 (gene) = myosin heavy chain 7; MYPC = myosin-binding protein C; PLN = phospholamban; RBM20 = ribonucleic acid binding motif 20; SCN5a = sodium channel alpha unit 5; TTN = titin; TNNT = troponin-T.

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Table 26 Initial diagnostic assessment in patients with suspected cardiomyopathy

History including detailed questions on any systemic disease, toxic agents (chemotherapy, alcohol, drugs), and familial history of cardiac or neuromuscular disease, or sudden cardiac death in family members at young age (<50 years).
Laboratory exams including cardiac and muscular enzymes, liver and renal function, haemoglobin, white blood cell count (including differential white blood cell count to detect eosinophilia), natriuretic peptides, thyroid function tests, iron status, and markers of systemic auto-immune disease (hsCRP, anti-nuclear antibodies, soluble IL-2 receptor).
Standard 12-lead ECG and echocardiography to detect arrhythmias and assess cardiac structure and function and concomitant abnormalities.
Invasive coronary angiography or CTCA to rule out significant CAD in patients with cardiac dysfunction.
CMR imaging with T1 and T2 sequencing and LGE to visualize structural changes, storage, infiltration, inflammation, fibrosis and scarring.
Genetic counselling and genetic testing should be performed depending on age, family history, cardiac phenotype.
24 or 48-hour ambulatory ECG monitoring to detect atrial and ventricular arrhythmias.

CAD = coronary artery disease; CMR = cardiac magnetic resonance; CTCA = computed tomography coronary angiography; ECG = electrocardiogram; hsCRP = high-sensitivity C-reactive protein; IL-2 = interleukin-2; LGE = late gadolinium enhancement.

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Table 27 Dilated cardiomyopathy or hypokinetic non-dilated cardiomyopathy: specific aspects of diagnosis and treatment

Diagnostic criteria and definitions[894,895]
DCM is characterized by LV dilatation and systolic dysfunction in the absence of known abnormal loading conditions or significant CAD. HNDC is characterized by LV or biventricular global systolic dysfunction (LVEF <45%) without dilatation in the absence of known abnormal loading conditions or significant CAD. DCM and HNDC can be considered "familial" if two or more first- or second-degree relatives have DCM or HNDC, or a first-degree relative has autopsy proven DCM and sudden death at <50 years of age.
Genetic counselling and testing[892,894,898,916]
Indication. All patients with a diagnosis of DCM or HNDC and all first-degree adult relatives of patients with DCM or HNDC and a definite disease-causing mutation, regardless of their phenotype, in order to identify genetically affected individuals at a preclinical phase. **Aim.** First-degree adult relatives should have their evaluation repeated every 5 years or less when aged <50 years or non-diagnostic abnormalities are found. Clinical evaluation, ECG, echocardiography and possibly CMR, must be performed in first-degree relatives of patients. **Aims.** Can identify patients with DCM or HNDC at highest risk of arrhythmia and/or deserving other specific treatments. Early identification of asymptomatic relatives may lead to early treatment and prevention of progression to HF and proper genetic counseling. **Minimal set of genes**[a]: TTN, LMNA, MHC, TNNT, troponin-C, MYPC, RBM20, PLN, sodium channel alpha unit, BAG3, actin alpha cardiac muscle, nexilin, tropomyosin-1, vinculin. The use of additional sequencing for the analysis of very large panel of genes may be considered when there is a clear familial history or structural phenotype, by preference combined with family segregation.
Endomyocardial biopsy[97,907,917–919]
Indication. In suspected phenotypes requiring specific treatments (i.e. giant cell myocarditis, eosinophilic myocarditis, sarcoidosis, vasculitis, SLE, other systemic, auto-immune inflammatory conditions, or storage diseases). **Number of samples**. A minimum of 5 but possibly at least 7 samples: 3 for pathology, 2 for infection (DNA, PCR) and 2 for RNA viruses/viral replication.[918,919] **Aetiology.** Search for common cardiotrophic viruses (parvovirus B19, HHV4, HHV6, enteroviruses, adenovirus and coxsackie) by quantitative rtPCR. Viral mRNA for active viral replication must be assessed, if possible. Further assessment if indicated: CMV, HIV, *Borrelia burgdorferi* (Lyme disease), *Coxiella burnetii* (Q-fever), *Trypanosoma cruzi* (Chagas disease) and SARS-CoV-2. **Immunohistochemistry**. Quantification of CD3-, CD4-, CD8- or CD45- staining lymphocytes and CD68 macrophages per mm^2; anti-HLA-DR. **Histology**. Haematoxylin and eosin staining, fibrosis assessment with Masson's Trichrome and Picrosirius Red, amyloid fibrils detection with Congo Red.
Therapeutic options[895,917]
HF treatment for HFrEF (see sections 5 and 6)
LMNA, RBM20, PLN and FLN mutation. Higher risk of sudden cardiac death: early indication for primary prevention by ICD implantation should be considered (guided by risk factors as detailed).[920]
TTN mutation. Higher rate of LV reverse remodeling (in up to 70%), but a higher risk of atrial and ventricular tachyarrhythmias.
Lyme disease (*Borrelia*). Treatment with doxycycline.
Chagas disease (*Trypanosoma cruzi*). Specific treatment according to current recommendations.[921,922]
Auto-immune/inflammatory. Consider immunosuppressive therapy in giant cell myocarditis, eosinophilic myocarditis, sarcoidosis or vasculitis, and in highly selected patients with increased cardiac inflammation of unknown origin based upon multidisciplinary counselling (cardiology and immunology).

BAG3 = Bcl2-associated athanogene 3; CAD = coronary artery disease; CMR = cardiac magnetic resonance; CMV = cytomegalovirus; DCM = dilated cardiomyopathy; DNA = deoxyribonucleic acid; ECG = electrocardiogram; FLN = filamin; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HHV = human herpes virus; HIV = human immunodeficiency virus; HLA-DR = human leukocyte antigen-DR isotype; HNDC = hypokinetic non-dilated cardiomyopathy; ICD = implantable cardioverter-defibrillator; LMNA = lamin A/C; LV = left ventricular; LVEF = left ventricular ejection fraction; MHC = myosin heavy chain; MYPC = myosin-binding protein C; mRNA = messenger ribonucleic acid; NSVT = non-sustained ventricular tachycardia; PCR = polymerase chain reaction; PLN = phospholamban; RBM20 = ribonucleic acid binding motif 20; RNA = ribonucleic acid; rtPCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SLE = systemic lupus erythematosus; TNNT = troponin-T; TTN = titin.

[a]This list of genes is not exhaustive, and will change over time, with increasing knowledge of the pathogenicity. Contact the genetic department to ask which core panel of genes they are using.

[b]Risk factors in patients with a confirmed LMNA mutation: NSVT during ambulatory ECG monitoring, LVEF <45% at first evaluation, male sex and non-missense mutations (insertion, deletion, truncations, or mutations affecting splicing).

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Table 28 Hypertrophic cardiomyopathy: specific aspects of diagnosis and treatment

Definition[895,896,923]
Wall thickness >14 mm in one or more LV myocardial segments not sufficiently explained solely by abnormal loading conditions. LVOTO ≥30 mmHg at rest or exercise, asymmetric hypertrophy, or increased LGE in a patchy mid-wall pattern in the most hypertrophied segment, further suggest the presence of HCM. It can be considered familial when two or more first- or second-degree relatives with HCM or a first-degree relative with autopsy proven HCM and sudden death at <50 years of age are detected.
Differential diagnosis
It might be difficult with physiological hypertrophy induced by intense athletic training, severe hypertension or aortic stenosis and with isolated septal hypertrophy. Consider a genetic HCM if the degree of LV hypertrophy is disproportionate with respect to the acquired trigger. Consider amyloidosis as a cause when increased thickness of the interatrial septum, AV valve and/or RV free wall are detected (see section 14.6).
Genetic counselling and testing
Indication. Must be offered to all patients with a diagnosis of HCM to identify a possible underlying genetic cause and to all first-degree adult relatives of patients with HCM and a definite disease-causing mutation, regardless of their phenotype, in order to identify genetically affected individuals at a preclinical phase. Clinical evaluation, ECG and echocardiography, must be performed in first-degree relatives who have the same definite disease-causing mutation as the index patient. When no definite genetic mutation is identified in the index patient or genetic testing is not performed, clinical evaluation with ECG and echocardiography should be considered in first-degree adult relatives and repeated every 2–5 years or less if non-diagnostic abnormalities are present. **Minimal set of genes**[a] (sarcomeric gene mutation in up to 60% of cases): TTN, LMNA, MHC, TNNT, Troponin-C, MYPC, RMB20, PLN, Sodium channel alpha unit, BAG3, Actin Alpha Cardiac Muscle, Nexilin, Tropomyosin-1, Vinculin.[898,924–926] The use of additional sequencing for the analysis of very large panel of genes may be considered if there is a clear familial history or structural phenotype, by preference combined with family segregation. **Specific conditions.** Muscular weakness: consider mitochondrial X-linked mutations, glycogen storage disorders, FHLI mutations, Friedreich's ataxia. Syndromic conditions (cognitive, visual impairment, drooping eyelid): consider mitochondrial X-linked mutations, Noonan syndrome, Danon disease. Café au lait spots (lentigines): consider Leopard/Noonan syndrome
Endomyocardial biopsy
Indication. It may be considered when the baseline clinical assessment suggests cardiac inflammation or storage disease which cannot be diagnosed by other means[896] (see also Section 14.6).
Therapeutic options[895,896,923]
With LVOTO Avoid hypovolaemia (dehydration), arterial and venous dilators (nitrates and phosphodiesterase type 5 inhibitors), and digoxin. Use non-vasodilating beta-blockers or use verapamil if beta-blockers non-tolerated or ineffective. Low-dose loop or thiazide diuretics must be used with caution to improve dyspnoea associated with LVOTO, but avoiding hypovolaemia. Invasive treatment (septal reduction therapy by alcohol ablation or myomectomy), in experienced centres, may be considered in those patients with a resting or maximum provoked LVOT ≥50 mmHg and/or who remain symptomatic (NYHA class III or IV, syncope) despite OMT. Novel drugs or devices may be considered once available.[909,927]
Symptomatic without LVOTO Cautious use of low-dose loop or thiazide diuretics avoiding hypovolaemia. Verapamil/diltiazem if LVEF >50% and beta-blockers are not tolerated or ineffective.
Indication to ICD Based on sudden cardiac death risk models.[928–930] Consider ICD implantation if: - family history of sudden cardiac death in one or more first degree relatives under 40 years of age or sudden cardiac death in a first degree relative with confirmed HCM at any age; - NSVT; - unexplained syncope.[931]
Fabry disease Enzyme replacement therapy (alpha-galactosidase A deficiency).[895]
Amyloidosis. See section 14.6 and *Figure 21*.

AV = atrio-ventricular; BAG3 = Bcl2-associated athanogene 3; ECG = electrocardiogram; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LMNA = lamin A/C; LV = left ventricular; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; LVOTO = left ventricular outflow tract obstruction; MHC = myosin heavy chain; MYPC = myosin-binding protein C; NSVT = non-sustained ventricular tachycardia; NYHA = New York Heart Association; OMT = optimal medical therapy; PLN = phospholamban; RMB20 = ribonucleic acid binding motif 20; RV = right ventricular; TNNT = troponin-T; TTN = titin.

[a]The list of genes is not exhaustive, and will change over time, with increasing knowledge of the pathogenicity. Contact the genetic department to ask which core panel of genes they are using.

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Table 29 Arrhythmogenic cardiomyopathy: specific aspects of diagnosis and treatment[912,915,932]

Definition
Inherited heart muscle disease characterized by progressive fibrofatty replacement of the RV myocardium which may act as a substrate for ventricular arrhythmias, unexplained syncope and/or sudden cardiac death. LV involvement and systolic dysfunction occurs in >30% of AC patients, therefore its phenotype may overlap with DCM.
Diagnosis[933]
Based upon the evaluation of a combination of the genetic factors (most cases autosomal dominant desmosomal mutations), documentation of ventricular arrhythmias and imaging criteria (echocardiography and MRI) of RV dysplasia with the fibrofatty replacement either or not confirmed by EMB. Specific ECG abnormalities can be present or absent.
Genetic counselling/testing[898,912]
Indication. Must be offered to all patients with a suspected AC and has to be offered to all first-degree adult relatives of patients with AC and a definite disease-causing mutation, regardless of their phenotype in order to identify genetically affected individuals at a preclinical phase. Genetic family screening can be also indicated for arrhythmic risk stratification purposes. Clinical evaluation, ECG, echocardiography and possibly CMR have to be performed in first-degree relatives who have the same definite disease-causing mutation as the index patient. When no definite genetic mutation is identified in the index patient or genetic testing is not performed, clinical evaluation with ECG and echocardiography should be considered in first-degree adult relatives and repeated every 2–5 years or less if non-diagnostic abnormalities are present. **Minimal set of genes:** Desmosomal, mostly with isolated RV involvement: plakoglobin, DSP, PKP2, DSG2 and DSC2[a] With frequent LV involvement/DCM: DSP, FLNC, SCN5A, TMEM43, FLN, LDB3, desmin, α-actinin, BAG3, NKX2-5, RBM20, SCN5A, KCNQ1, KCNH2, TRPM4 or PLN variants in particular. If mild LV hypertrophy: consider TNNT variants. Cutaneous abnormalities, palmar and plantar hyperkeratosis: consider rare recessive mutations leading to Carvajal syndrome and Naxos disease. Plakoglobin (JUP). With CMR presentation of myocarditis along AC: consider *DSP* gene variants.[934,935]
Endomyocardial biopsy
It should be reserved to highly selected cases after all non-invasive studies have been assessed. Fibrofatty replacement with or without replacement type fibrosis at RV septal biopsies are the characteristic findings. EMB has low sensitivity for the diagnosis of AC in cases of focal distribution.
Therapeutic options
HF treatment for HFrEF (see sections 5 and 6). Competitive sports should be avoided, limit activities to leisure-time activities.[936] In patients with ventricular arrhythmias: beta-blockers must be titrated to the maximally tolerated dose as first-line therapy. Amiodarone can be considered in addition to beta-blockers or if beta-blockers contraindicated or not tolerated; ICD implantation is indicated if history of aborted sudden cardiac death or sustained and/or haemodynamically poorly tolerated ventricular tachycardia.[910–912] In patients with no ventricular arrhythmias: ICD can be considered (see section 6.1) even in patients with LMNA or FLNC gene mutations and LVEF <45%.[912]

AC = arrhythmogenic cardiomyopathy; BAG3 = Bcl2-associated athanogene 3; CMR = cardiac magnetic resonance; DCM = dilated cardiomyopathy; DSC2 = desmocollin 2; DSG2 = desmoglein 2; DSP = desmoplakin; ECG = electrocardiogram; EMB = endomyocardial biopsy; FLN = filamin; FLNC = filamin C; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; JUP = junction plakoglobin; KCNH2 = potassium voltage-gated channel subfamily H member 2; KCNQ1 = potassium voltage-gated channel subfamily Q member 1; LDB3 = LIM domain binding 3; LMNA = lamin A/C; LV = left ventricular; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; NKX2-5 = NK2 transcription factor related, locus 5; PLN = phospholamban; PKP2 = plakophilin 2; RMB20 = ribonucleic acid binding motif 20; RV = right ventricular; SCN5A = sodium channel alpha subunit 5; TMEM43 = transmembrane protein 43; TNNT = troponin-T; TRPM4 = transient receptor potential cation channel subfamily M member 4.

on CMR, younger age, or with a specific familial/genetic phenotype (*Tables 27–29*). Risk models for the prediction of ICD benefits were applied to the patients enrolled in DANISH and may help for the indication to ICD implantation in DCM.[166,913] Treatment of HCM and AC, including indications for ICD, are detailed in previous documents.[895,896,899,912,914,915]

14.3 Left ventricular non-compaction

LVNC is a very rare congenital CMP characterized by endomyocardial trabeculations that increase in number and prominence. In most cases, including when the condition is caused by mutations in the MYH7 or MYBPC3 gene, LVNC is inherited in an autosomal dominant pattern.[644,937,938] A clear overlap exists in families with

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DCM and HCM phenotypes. Quite commonly individuals with features of LVNC are found in families where other affected relatives have typical HCM or DCM. Therefore, LVNC is not treated as a separate disease entity, but as a separate rare presentation of a genetic susceptibility to either HCM or DCM.[939]

14.4 Atrial disease

14.4.1 Definition

Atrial disease, also termed atrial failure or myopathy, can be defined as a complex of subclinical structural, electrophysiological, and functional changes that affect the atria with the potential to produce clinical consequences.[606,940,941] It has been suggested that atrial disease links the pathophysiology of HF, especially HFpEF, with AF, as they often coexist, are closely inter-related and share common risk factors.[606,685,942,943]

14.4.2 Diagnosis

Atrial size and function can be evaluated by multimodality imaging including two- and three-dimensional echocardiography, myocardial deformation, computed tomography (CT) and CMR.[944] Cardiac biomarkers, including high-sensitivity cardiac troponins and NPs, may assess pathophysiological aspects of atrial disease.[945–947] The increased levels of NPs in AF may also be an indicator of an underlying atrial disease.[942,948] A comprehensive characterization of atrial disease combining clinical, imaging, biochemical and molecular features is, however, still lacking.

14.4.3 Management

Atrial disease is an emerging therapeutic target in the prevention of AF, systemic thromboembolism, and perhaps HFpEF.[949] As atrial disease appears to result from the intersection of shared risk factors and comorbidities predisposing to both AF and HF, diabetes mellitus, hypertension, obesity, smoking, and physical inactivity may be of paramount importance for its development.[7,950] Effective management of HF and AF (see section 12.1.1), as well as treatment of mitral regurgitation (see section 12.3.3), may also be important to counteract atrial disease progression.

Table 30 Aetiologies to be considered triggering acute myocarditis[917]

Infectious	
Viral	Parvovirus B19, human herpes virus-6, Epstein-Barr virus, enteroviruses, (coxsackievirus, adenovirus), CMV, HIV, SARS-CoV-2
Others	*Borrelia, Coxiella burnetii* (Q-fever)
Systemic disease	
Auto-immune and others	Sarcoidosis, giant cell myocarditis, eosinophilic myocarditis, SLE, ANCA-positive vasculitis, rheumatoid arthritis, any other auto-immune disease
Toxic	
Medications	Immune check point inhibitors, anthracyclines, clozapine, adrenergic drugs, 5-fluorouracil
Other agents	Alcohol, amphetamines, cocaine

ANCA = antineutrophil cytoplasmic antibody; CMV = cytomegalovirus; HIV = human immunodeficiency virus; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SLE = systemic lupus erythematosus.

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14.5 Myocarditis

14.5.1 Epidemiology and diagnosis

The incidence of acute myocarditis is estimated to be 1.5 million cases per year globally.[951] The contribution of myocarditis as a cause of HF varies by age and region from approximately 0.5% to 4.0%.[918,952] Chronic, EMB proven, inflammation can be found in 9% to 30% of adult patients with a DCM.[918,953] The most frequent potential aetiologies triggering acute myocarditis in Europe are reported in *Table 30*.

The clinical presentation of acute myocarditis may vary from mild symptoms to cardiogenic shock. Workup for the diagnosis of acute myocarditis in patients with HF is reported in *Table 31* and *Figure 20*. Specific criteria about biopsies and CMR are reported in *Tables 32* and *33*.

14.5.2 Treatment

Hospitalization for at least 48 h may be useful for patients with acute myocarditis and HF, especially when troponins are elevated and when cardiac dysfunction, and/or arrhythmias are present at initial presentation.

Despite the lack of evidence in the specific setting of acute myocarditis, treatment of HFrEF is recommended in the presence of systolic LV dysfunction. Immunosuppression is only indicated in selected cases of acute myocarditis (*Table 34*). Once cardiac enzymes decrease, arrhythmias are absent, and cardiac systolic dysfunction is stabilized, standard HF therapy should be continued for at least 6 months (see also *Figure 20*).

Immunosuppression has been considered for treatment of patients with chronic cardiac inflammation at EMB and no evidence of active viral infection.[918,919] This was associated with an improvement in cardiac function in small studies and with better outcomes in a retrospective observational study.[953,963,964] Prospective trials with old or newer immunosuppressive/immunomodulatory drugs are needed. A placebo-controlled trial testing the effects of immunoadsorption with i.v. immunoglobulins on LV function is ongoing and other treatment options are being tested.[919]

14.6 Amyloidosis

14.6.1 Epidemiology and diagnosis

CA or amyloid cardiomyopathy is still an underdiagnosed cause of HF.[895,965,966] The two most prevalent forms of CA are light chain immunoglobulin (AL) and transthyretin (ATTR) amyloidosis. ATTR includes the wild-type (>90% of cases), and the hereditary or variant type (<10% of cases). It is estimated that 6% to 16% of all patients

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Table 31 Diagnostic workup in suspected acute myocarditis

Definition of suspected acute myocarditis			
Clinical presentation + ≥1 mandatory diagnostic test being positive (by preference CMR) in the absence of significant coronary artery, valvular or congenital heart disease, or other causes.			
		Sensitivity	**Specificity**
Clinical presentation			
Acute/new onset chest pain, dyspnoea, signs of left and/or right HF, and/or unexplained arrhythmias or aborted sudden death.		Low	Low
Mandatory diagnostic tests			
ECG	New and dynamic ST-T abnormalities, including pseudo-infarct ST segment elevation, atrial or ventricular arrhythmias, AV blocks, QRS abnormalities.	High	Low
Laboratory tests	Elevated troponins with dynamic changes consistent with myocardial necrosis. Standard tests including white blood cells count to exclude eosinophilia.[919,954]	Intermediate	Low
Echocardiography	New structural or function abnormalities, regional wall motion abnormalities or global ventricular dysfunction without ventricular dilatation or with, generally mild, dilatation, increased wall thickness due to myocardial oedema, pericardial effusion, intracardiac thrombi, not explained by other conditions (e.g., CAD, ACS or valvular heart disease).	High	Low
CMR	Oedema, inflammation and fibrosis detection, quantification and localization through T1 and T2 mapping, extracellular volume assessment and LGE (see *Table 33*).[955,956]	High	Intermediate
Additional diagnostic tests			
Coronary angiography or CTCA	Excludes significant CAD or ACS in clinically suspected myocarditis.	High	High
Endomyocardial biopsy	For diagnosis and indication to specific treatment (see *Table 32*).	Intermediate	High
Cardiac PET	May be useful in patients who cannot undergo CMR or with suspected systemic autoimmune disease or cardiac sarcoidosis.[919,957]	Low	Low
Additional laboratory test	Skeletal muscle enzymes, liver and renal function, natriuretic peptides, thyroid function tests, iron status, markers of systemic autoimmune disease.	Low	Low
	CRP elevated in 80–90% patients.[919,954]	Intermediate	Low
	PCR testing of common cardiotrophic viruses. It can detect systemic infection but does not prove cardiac infection and cannot substitute viral genome analysis on EMB samples.[917] Circulating IgG antibodies to cardiotrophic viruses are common in the absence of viral myocarditis. Very limited diagnostic usefulness.[917,918] Specific test for SARS-CoV-2, Borrelia, HIV or CMV if clinical suspicion.	Low	Low

ACS = acute coronary syndrome; AV = atrio-ventricular; CAD = coronary artery disease; CMR = cardiac magnetic resonance; CMV = cytomegalovirus; CRP = C-reactive protein; CTCA = computed tomography coronary angiography; ECG = electrocardiogram; EMB = endomyocardial biopsy; HF = heart failure; HIV = human immunodeficiency virus; IgG = immunoglobulin G; LGE = late gadolinium enhancement; PCR = polymerase chain reaction; PET = positron emission tomography; QRS = Q, R and S waves (combination of three of the graphical deflections); SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; ST = ST segment of the electrocardiogram; ST-T = ST segment and T wave of the electrocardiogram.

with unexplained LVH or HFpEF at hospitalization or severe aortic stenosis undergoing aortic valve replacement, aged above 65 years, may have wtTTR-CA.[967–972]

Diagnosis and treatment of CA were recently reviewed.[973] Age >65 years and HF along with a LV wall thickness >12 mm at echocardiography are major criteria for the suspicion of CA.[973] Criteria for a suspicion of CA and to confirm diagnosis are reported in *Table 35*, *Supplementary Table 25*, and *Figure 21*.[973,974] Cardiac imaging and EMB or extra-cardiac biopsy are needed for the diagnosis of AL-CA in patients with abnormal haematological tests (*Figure 21*). Technetium-labelled ^{99m}Tc-PYP or DPD or HMDP scintigraphy with planar and SPECT imaging has a specificity and positive predictive value for TTR-CA of up to 100%.[975] In contrast, CMR has a sensitivity and specificity of 85% and 92%, respectively.[966,976] The hereditary form should be excluded by genetic testing. EMB is the gold standard for the diagnosis of TTR-CA with nearly 100% sensitivity and specificity if specimens are collected from >4 multiple sites and tested for amyloid deposits by Congo red staining.[966] However, a biopsy is not

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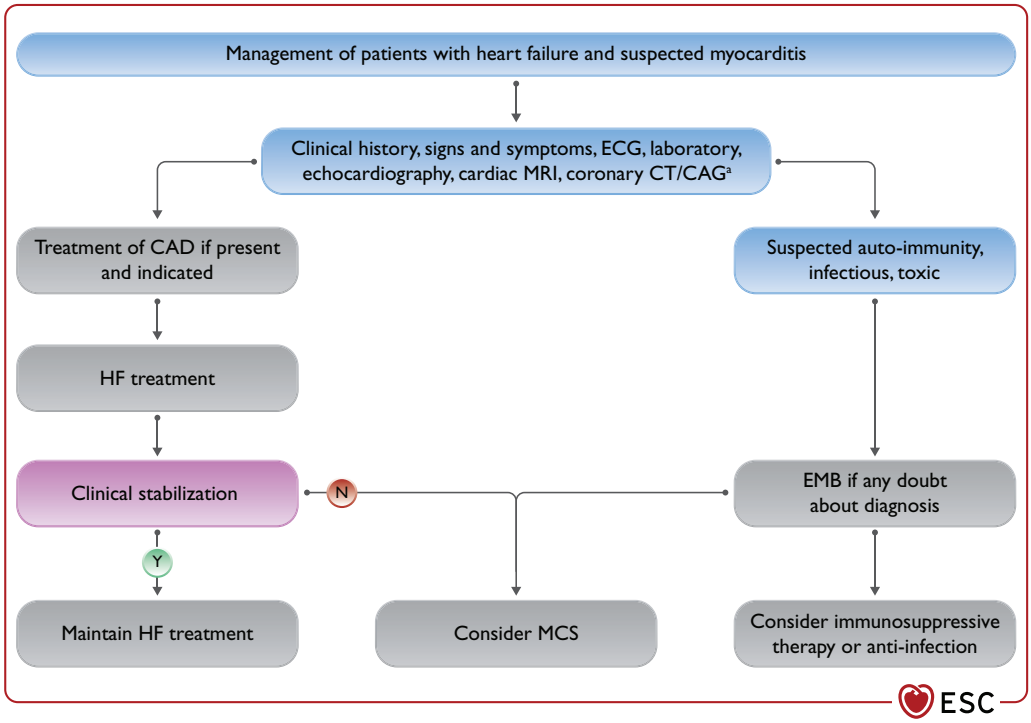

Figure 20 Management of patients with heart failure and acute myocarditis. ACS = acute coronary syndrome; CAD = coronary artery disease; CAG = coronary artery angiogram; CMR = cardiac magnetic resonance; CT = computed tomography; ECG = electrocardiogram; EMB = endomyocardial biopsy; HF = heart failure; MCS = mechanical circulatory support. [a]To exclude CAD/ACS.

Table 32 Endomyocardial biopsy in patients with suspected myocarditis

Indication (see also Section 4.3). Progressive or persistent severe cardiac dysfunction and/or life-threatening ventricular arrhythmias and/or Mobitz type 2 second-degree or higher AV block with lack of short-term (<1-2 weeks) expected response to usual medical treatment. The aim is to identify aetiology and to indicate specific treatment (e.g. giant cell myocarditis, eosinophilic myocarditis, cardiac sarcoidosis, systemic inflammatory disorders).[97,98,917,918,958]
Number and sites of the samples A minimum of 5 but possibly at least 7 samples, 3 for pathology, 2 for infections (DNA, PCR) and 2 for RNA viruses/viral replication. Left and/or right ventricle. CMR or PET guided sampling may be considered.[919]
Aetiology Quantitative PCR viral genome analysis for common cardiotrophic viruses (parvovirus B19, HHV4, HHV6, enteroviruses, adenovirus and coxsackievirus) by rtPCR. Viral mRNA for active viral replication may be assessed although it has low sensitivity. On indication, search for CMV, HIV, *Borrelia, Coxiella burnetii* (Q-fever) and SARS-CoV-2.
Diagnosis of inflammation Immunohistochemistry with staining for anti-CD3-, CD4-, CD8- or CD45 antibodies for lymphocytes and anti-CD68 antibodies for macrophages and anti-HLA-DR antibodies.[907,917,918,959]
Therapeutic implications **Immunosuppressive therapy** may be indicated based on the results of EMB as in giant cell myocarditis or eosinophilic myocarditis and, possibly, also in sarcoidosis, vasculitis or selected patients with increased cardiac inflammation of unknown origin based upon multidisciplinary counselling.[98,917–919,954] **Antibiotics:** *Borrelia* (Lyme disease). **Antiviral therapy:** HIV, CMV, HHV6 pending on load and viral replication (mRNA).

CMR = cardiac magnetic resonance; CMV = cytomegalovirus; DNA = deoxyribonucleic acid; EMB = endomyocardial biopsy; HHV = human herpes virus; HIV = human immunodeficiency virus; HLA-DR = human leucocyte antigen-DR isotype; mRNA = messenger ribonucleic acid; PCR = polymerase chain reaction; PET = positron emission tomography; RNA = ribonucleic acid; rtPCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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Table 33 Cardiac magnetic resonance in patients with suspected myocarditis[955,956]

Indication
Indicated at baseline, in all patients with clinical history + ECG, elevated troponin or echocardiographic abnormalities, and significant CAD excluded or unlikely.
Advised at follow-up in patients with persistent dysfunction at echocardiography, arrhythmias or ECG abnormalities.[a]
Main findings
At baseline: T1-weighted (inflammation, injury) and T2-weighted (oedema) sequences, extracellular volume and LGE within 2 weeks after symptom onset.[956,960]
At follow up: LGE to evaluate the degree of scarring, T1 and T2 to identify persistent inflammation.[a]
Diagnostic significance
At least one T2-based criterion (global or regional increase of myocardial T2 relaxation time or an increased signal intensity in T2-weighted images), with at least one T1-based criterion (increased myocardial T1, extracellular volume, or LGE) in the acute phase.
Only one (i.e., T2-based or T1-based) marker may still support a diagnosis of acute myocardial inflammation in an appropriate clinical scenario, albeit with less specificity in the acute phase.
A negative T1/T2 scan does not exclude a still ongoing inflammatory process in the chronic phase.[a]

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CAD = coronary artery disease; CMR = cardiac magnetic resonance; ECG = electrocardiogram; LGE = late gadolinium enhancement.
[a]It takes at least 3 months before CMR signs of oedema (secondary to inflammation in the acute phase/baseline) disappear. At 6 months, T1 or T2 signs of oedema should have disappeared if inflammation would be completely absent. Still, the absence of T1 or T2 oedema does not exclude chronic low-grade inflammation.

needed with a grade 2–3 positivity of scintigraphy with SPECT (*Figure 21*).[973]

14.6.2 Therapy of amyloidosis and heart failure

Maintenance of euvolaemia is central to management but is challenging due to the markedly reduced ventricular capacitance.[977] If HF symptoms are present, a loop diuretic, possibly with an MRA, may be given, but orthostatic hypotension may cause intolerance. Beta-blockers, digitalis, ACE-I, ARBs, or ARNI may not be well tolerated because of hypotension, and their place in CA treatment is unsettled. Their withdrawal must be often considered due to hypotension and/or bradycardia.[973,974] CCB should be avoided as they may cause severe hypotension and fatigue, or form complexes with amyloid.[966]

Amyloid infiltration of the atrial wall leads to atrial myopathy and electromechanical dissociation with high embolic risk. Patients with CA and history of AF should receive anticoagulation. There is no evidence to support anticoagulation for patients in SR, yet.[7,978] Amiodarone is the preferred antiarrhythmic agent.[973]

Table 34 Treatment and follow-up of acute myocarditis

HF therapy should be started if LV systolic dysfunction is present at presentation and should be continued for at least 6 months upon complete functional recovery (EF >50%).[918,919]
Immunosuppression for at least 6–12 months is required in acute myocarditis with clinical or EMB evidence of auto-immune disease, including giant cell myocarditis, vasculitis or sarcoidosis.[98,917–919,953,954,961]
Immunosuppression is not advised on a routine basis in acute myocarditis without clinical or EMB-based evidence of auto-immune disease.[917] Initial empirical administration of i.v. corticosteroids may be taken into consideration in cases of high suspicion of immune-mediated myocarditis especially if complicated by acute HF, malignant arrhythmias and/or high degree AV block.[954,962]
Intense sporting activities should be avoided as long as symptoms, cardiac enzymes elevated or ECG/imaging abnormalities are present and last for at least 6 months since complete recovery.[936]
Yearly follow-up for at least 4 years, with an ECG and echocardiography, is needed as acute myocarditis may lead to DCM in up to 20% of cases.

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AV = atrio-ventricular; DCM = dilated cardiomyopathy; ECG = electrocardiogram; EF = ejection fraction; EMB = endomyocardial biopsy; HF = heart failure; i.v. = intravenous; LV = left ventricular.

Therapy of AL-CA is based on treatment of the underlying haematological problem with chemotherapy or autologous stem-cell transplant.

TTR stabilization and reduction of its production are the basis of TTR-CA treatment. Liver and/or cardiac transplantation can be considered only in end-stage disease of familial TTR-CA. Tafamidis reduced all-cause mortality and CV hospitalizations in cardiac or non-cardiac biopsy-proven hereditary and wtTTR-CA, mainly in those patients with NYHA class I and II at baseline. Functional improvement occurred within 6 months, whereas the decrease in mortality took nearly 2 years to occur.[979,980] Intravenous patisiran, a small RNA interfering molecule, or subcutaneous inotersen, antisense oligonucleotide against TTR, may be considered in those patients with combined hTTR-polyneuropathy and CA (*Figure 21*).[981,982] Off-label use of diflunisal may be considered in wtTTR-CA in combination with a proton pump inhibitor.[983]

14.7 Iron overload cardiomyopathy

Iron overload results either from genetically determined increased intestinal iron absorption in the context of hereditary haemochromatosis (primary iron overload) or from multiple blood transfusions required for the management of haematological conditions such as beta-thalassaemia (secondary iron overload).[984] In iron overload, the iron binding capacity of transferrin is saturated and non-transferrin-bound iron enters cardiomyocytes through L-type calcium channels, causing oxidative myocardial damage.[985]

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Table 35 "Red flags" for most common forms of cardiac amyloidosis

Type	Red Flag	TTR	AL
Extracardiac	Polyneuropathy	X	X
	Dysautonomia	X	X
	Skin bruising		X
	Macroglossia		X
	Deafness	X	
	Bilateral carpal tunnel syndrome	X	
	Ruptured biceps tendon	X	
	Lumbar spinal stenosis	X	
	Vitreous deposits	X[a]	
	Family history	X[a]	
	Renal insufficiency		X
	Proteinuria		X
Cardiac	**Clinical**		
	Hypotension or normotensive if previously hypertensive	X	X
	ECG		
	Pseudo-infarct ECG pattern	X	X
	Low/decreased QRS voltage to degree of LV thickness	X	X
	AV conduction disease	X	X
	Laboratory		
	Disproportionally elevated NT-proBNP to degree of HF	X	X
	Persisting elevated troponin levels	X	X
	Echocardiography		
	Granular sparkling of myocardium	X	X
	Increased right ventricular wall thickness	X	X
	Increased AV valve thickness	X	X
	Pericardial effusion	X	X
	Reduced longitudinal strain with apical sparing pattern	X	X
	CMR		
	Subendocardial LGE	X	X
	Elevated native T1 values	X	X
	Increased extracellular volume	X	X
	Abnormal gadolinium kinetics	X	X

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AL = light chain immunoglobulin; AV = atrio-ventricular; CA = cardiac amyloidosis; CMR = cardiac magnetic resonance; ECG = electrocardiogram; HF = heart failure; LGE = late gadolinium enhancement; LV = left ventricular; NT-proBNP = N-terminal pro-B-type natriuretic peptide; QRS = Q, R and S waves (combination of three of the graphical deflections); TTR = transthyretin.
Modified from[973].
[a]Hereditary TTR-CA.

Additional iron-induced complications, such as liver disease and endocrine abnormalities, further contribute to cardiac deterioration.[986,987] The end result is the development of iron overload cardiomyopathy (IOCM), which may have either a restrictive or a dilated phenotype, the former potentially evolving to the latter as the disease advances. Myocardial iron deposition can be accurately estimated by the CMRT2* technique; T2* values are correlated with left and right ventricular systolic function and predict the development of iron-induced HF or arrhythmias.[984] Prevention of IOCM is successfully accomplished with iron chelators, including deferoxamine, deferiprone, and deferasirox, while established IOCM may be completely reversed by intensified and combined iron chelation therapy.[985]

Recommendations for the treatment of transthyretin amyloidosis-cardiac amyloidosis

Recommendations	Class[a]	Level[b]
Tafamidis is recommended in patients with genetic testing proven hereditary hTTR-CMP and NYHA class I or II symptoms to reduce symptoms, CV hospitalization and mortality.[979]	I	B
Tafamidis is recommended in patients with wtTTR-CA and NYHA class I or II symptoms to reduce symptoms, CV hospitalization and mortality.[979]	I	B

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CA = cardiac amyloidosis; CMP = cardiomyopathy; CV = cardiovascular; hTTR = hereditary transthyretin; NYHA = New York Heart Association; wtTTR = wild-type transthyretin.
[a]Class of recommendation.
[b]Level of evidence.

14.8 Adult congenital heart disease

The management of ACHD has been reviewed in detail in a recent ESC guideline.[988] HF is a common problem affecting 20–50% of the ACHD population, and an important cause of death.[989] The pathophysiology of cardiac dysfunction in ACHD is often different from non-congenital (acquired) heart disease, in particular in those with: a systemic right ventricle (RV), a failing subpulmonary ventricle, a single ventricle,[988] surgery-related injury, chronic pressure/volume overload in systemic and sub-pulmonary ventricles, and those with hypertrophy or non-compaction induced by gene mutations. Therefore, extrapolation of current HF treatment guidelines to ACHD patients is not always appropriate. In addition, the few available data on HF treatments in ACHD patients are often inconclusive and are derived from small patient cohorts. As a consequence, ACHD specific recommendations are mostly based on clinical experience or position statements.[990]

Importantly, ACHD patients with HF should be referred to expert centres. The general principles of management, while awaiting transfer to specialist centres, is summarized in *Table 36*.

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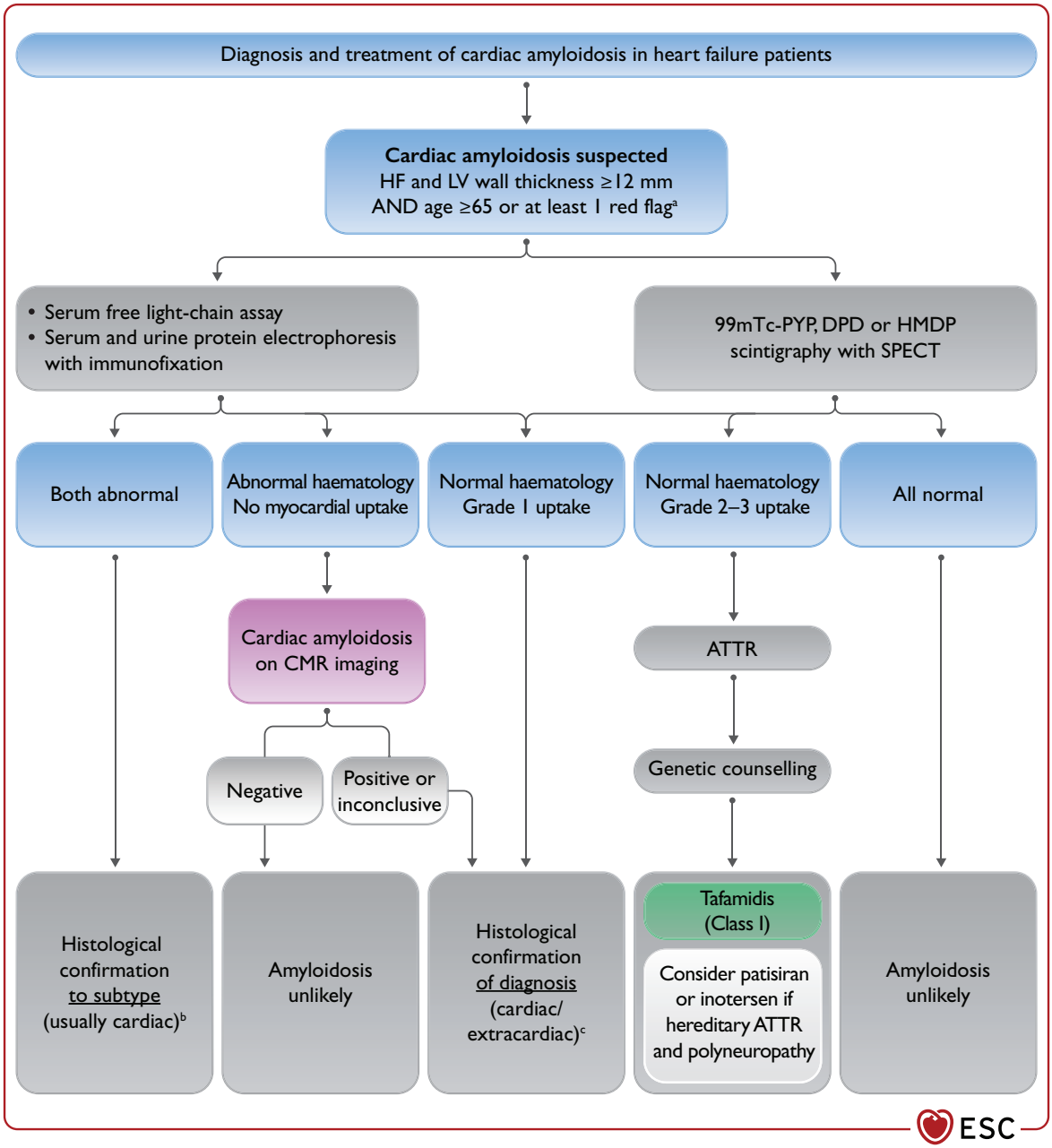

Figure 21 Diagnosis and treatment of cardiac amyloidosis in heart failure patients. Based on.[973] ATTR = transthyretin amyloidosis; CMR = cardiac magnetic resonance; DPD = 3,3-diphosphono1,2-propanodicarboxylic acid; HF = heart failure; HMDP = hydroxymethylene diphosphonate; LV = left ventricular; SPECT = single-photon emission computed tomography; 99mTc-PYP = technetium-labelled ^{99m}Tc-pyrophosphate. [a]Red flags are listed in *Table 35*. [b]Generally requires endomyocardial biopsy for a diagnosis of the cardiac subtype. [c]Requires biopsy that may be cardiac or abdominal.

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Table 36 Treatment of adult congenital heart disease and heart failure in specialized centres

ACHD patients with chronic HF should be referred to specialized centres.
Specific guidelines for medical treatment of chronic HF in ACHD are lacking, and practitioners should follow the current guidelines for medical treatment of HF. It remains unknown whether the long-term use of neurohormonal modulators affects clinical outcomes and prognosis in ACHD.
Sacubitril/valsartan may decrease morbidity,[991–993] however, no recommendation can be made at this moment based on the retrospective or anecdotical nature of these observations.
Co-morbidities in HF such as diabetes mellitus, AF, CSA, iron deficiency, and cachexia should be treated according to specific recommendations reported in this document.
In a biventricular circulation, patients with an impaired systemic LV should be treated with conventional HF therapy; this may also be considered in symptomatic patients with a failing systemic right ventricle.
Diuretics are recommended to control symptoms of fluid retention.
Treatment of symptomatic patients with a failing single ventricle in a Fontan circulation, or in the case of a persistent right-to-left shunt, should always be carefully initiated, taking the labile balance of ventricular preload and systemic afterload into account.
CRT may be a therapeutic option in ACHD patients with HF, but evidence in this specific setting is still lacking. Efficacy of CRT will depend on the underlying structural and functional substrate, such as anatomy of the systemic ventricle (left, right, or functionally single), presence and degree of structural systemic AV valve regurgitation, primary myocardial disease or scarring, and type of electrical conduction delay.[988]
Treatment of acute HF in ACHD patients should be in an expert centre, with proper knowledge of inotropes, the availability of extracorporeal membrane oxygenation, and advanced bridging techniques.[988,994]
Timely evaluation for transplantation by ACHD HF specialists in a transplant centre with ACHD expertise is recommended.
Ventricular assist devices can bridge patients to transplantation, or in a subgroup of patients, may be an option as destination therapy.

ACHD = adult congenital heart disease; AF = atrial fibrillation; AV = atrioventricular; CRT = cardiac resynchronization therapy; CSA = central sleep apnoea; HF = heart failure; LV = left ventricular.

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15 Key messages

(1) Patients with HF are classified based on their LVEF. Those with a LVEF between 41% and 49% are defined as 'mildly reduced LVEF' (HFmrEF).

(2) Measurement of NPs and echocardiography have key roles in the diagnosis of HF.

(3) ACE-I or ARNI, beta-blockers, MRA, and SGLT2 inhibitors are recommended as cornerstone therapies for patients with HFrEF.

(4) ICDs are recommended in selected patients with HFrEF of an ischaemic aetiology and should be considered in those with a non-ischaemic aetiology.

(5) CRT-P/D is recommended in those patients with HFrEF, in sinus rhythm, with a LBBB ≥150 ms and should be considered in those with a LBBB ≥130–149 ms or non-LBBB ≥150 ms.

(6) Advanced HF strategies (heart transplantation/MCS) may be appropriate in selected patients.

(7) ACE-I/ARNI, beta-blockers, and MRA may be considered in patients with HFmrEF.

(8) The diagnosis of HFpEF requires objective evidence of cardiac structural, or functional abnormalities as well as elevated plasma NP concentrations consistent with the presence of LV diastolic dysfunction and raised LV filling pressures. A diastolic stress test is recommended when these markers are equivocal.

(9) To date, no treatment has been shown to reduce mortality and morbidity in patients with HFpEF.

(10) It is recommended that all patients with HF be enrolled in a multidisciplinary HF-MP.

(11) Exercise is recommended for all patients who are able, to improve exercise capacity and QOL, and reduce HF hospitalization.

(12) Patients with advanced HF refractory to medical/device therapy and who do not have absolute contraindications should be referred for consideration of heart transplantation. MCS should also be considered as BTT or DT in selected patients.

(13) Four major clinical presentations of acute HF may occur: ADHF, acute pulmonary oedema, RV failure, and cardiogenic shock.

(14) Treatment of acute HF is based on diuretics for congestion, inotropes, and short- term MCS for peripheral hypoperfusion.

(15) Patients hospitalized for HF should be carefully evaluated to exclude persistent signs of congestion. Oral treatment should be optimized before discharge.

(16) In addition to oral anticoagulation, a strategy of rhythm control including catheter ablation should be considered in patients whose symptoms and/or cardiac dysfunction are associated with AF.

(17) SAVR or TAVI, as advised by the Heart Team, are recommended in patients with symptomatic severe aortic valve stenosis.

(18) Patients with isolated significant SMR and COAPT criteria should be considered for percutaneous edge-to-edge repair, whereas those with SMR and CAD, who need revascularization, should be considered for surgery.

(19) It is recommended that patients with type II diabetes are treated with SGLT2 inhibitors.

(20) Patients should be periodically screened for anaemia and iron deficiency and i.v. iron supplementation with ferric carboxymaltose should be considered in symptomatic patients with LVEF <45% and iron deficiency, and in patients recently hospitalized for HF and with LVEF ≤50% and iron deficiency.

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16 Gaps in evidence

Major advances in the diagnosis and treatment of patients with HF have occurred over recent years. Strong evidence for new treatment options have been given by recent RCTs and HF management may undergo major changes in the next years. New discoveries, however, pose new challenges and many areas with lack of evidence still remain. The following is a short list of selected, common issues that deserve to be addressed in future clinical research.

(1) **Definition and epidemiology**
   i. Further research into the underlying characteristics, pathophysiology, and diagnosis of HFmrEF and HFpEF
   ii. Consensus about normal values/ranges of EF
   iii. Better phenotyping of HFpEF
   iv. More information on the incidence and prevalence of 'recovered LV' systolic function

(2) **Diagnosis**
   i. Definitive studies on the role of biomarkers, focusing on their additive value in the diagnosis of HF
   ii. More randomized studies on screening for HF in asymptomatic subjects that may translate into improved outcomes
   iii. Studies on biomarkers showing the impact on outcome of their measurements for the identification of subjects at risk of developing HF as well as to guide treatment in patients with HF
   iv. Validated diagnostic protocols for the diagnosis of HFmrEF and HFpEF

(3) **Pharmacotherapy of CHF**
   i. Pragmatic studies on the order of adding disease-modifying drugs for HFrEF
   ii. Specific therapies for HFmrEF and HFpEF and, likely, their different phenotypes
   iii. More data and prospective clinical trials of HFrEF therapies in patients with eGFR <30 mL/min/1.73 m^2
   iv. Further evidence from prospective RCTs for the treatment of specific HF phenotypes: myocarditis, cardiotoxicity, inherited CMPs, PPCM, amyloidosis
   v. Management strategies and therapies for 'recovered LV' systolic function
   vi. More evidence on the effects of fluid restriction, dietary salt restriction, and nutrition

(4) **Devices and interventions**
   i. Indications for ICDs in specific subgroups of HFmrEF/HFpEF and optimal selection of ICD candidates in HFrEF, including patients with ischaemic and non-ischaemic cardiomyopathy
   ii. More research on CRT efficacy in AF
   iii. Further prospective randomized studies showing the impact on outcomes of AF ablation strategies compared to OMT in HF patients
   iv. Further research on the percutaneous treatment of valve heart disease and its impact on patients' outcomes and QOL
   v. Larger RCTs on CCM and baroreceptor stimulation in HFrEF

(5) **Disease management**
   i. The role of remote monitoring strategies in HF in the post COVID-19 era
   ii. Studies on optimal models for follow-up of stable HF patients
   iii. Studies to determine specific options for palliative care

(6) **Advanced HF**
   i. Better definition of risk profiles according to INTERMACS and other classifications
   ii. RCTs to establish the effects on outcomes of long-term MCS in hospitalized patients as well as in ambulatory outpatients (for instance INTERMACS 4–6 profiles)
   iii. Advances in long-term MCS, including strategies to reduce the risk of bleeding, thromboembolic events, and infection
   iv. Advances in medical treatment for the many patients who cannot undergo MCS or heart transplantation including development of treatment strategies, novel inotropes or myotropes for patients with advanced HF

(7) **AHF**
   i. Better definition and classification of patient phenotypes to facilitate improved treatment
   ii. Evidence-based use of imaging techniques and biomarkers that have an impact on patients' clinical course
   iii. Development of better strategies for congestion relief, including monitoring of diuretic administration, and/or to improve organ perfusion
   iv. Identification of treatments with an impact on post-discharge outcomes
   v. New devices for short-term MCS
   vi. Definition of evidence-based treatment options and therapeutic algorithms for patients with cardiogenic shock

(8) **CV comorbidities**
   i. RCTs showing best strategies for the treatment of ventricular arrhythmias
   ii. RCTs to establish the role of coronary revascularization procedures in different patient subsets
   iii. RCTs to establish the impact on patients' outcomes and/or QOL of percutaneous treatment of mitral or tricuspid valve disease in patients with HF

(9) **Non-CV comorbidities**
   i. RCTs addressing cachexia and/or sarcopenia and/or frailty and showing the impact of treatment on QOL and/or outcome
   ii. RCTs of medical therapies or devices in patients with severe CKD and HF
   iii. RCTs showing the effects on outcomes of medical treatment of electrolyte abnormalities
   iv. RCTs showing the effects on outcomes of treatment of CSA
   v. Prospective studies showing the impact on outcomes and/or QOL of early diagnosis, better prevention and treatment of cardiotoxicity of cancer therapies
   vi. Better treatment of infections and prevention of cardiac injury with infection

(10) **Special conditions**
   i. RCTs of treatment for PPCM
   ii. Better phenotyping of CMPs through genetic testing, biomarkers and imaging modalities, and tailoring of therapy
   iii. RCTs of treatment of different types of myocarditis, including immunosuppressive therapies
   iv. RCTs of new treatments of different forms of cardiac amyloid
   v. Better definition and treatment of LA myopathy.

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17 'What to do' and 'what not to do' messages from the guidelines

Recommendations	Class[a]	Level[b]
Recommendations for the diagnosis of chronic HF		
BNP/NT-proBNP.[c]	I	B
12-lead ECG.	I	C
Transthoracic echocardiography.	I	C
Chest radiography (X-ray).	I	C
Routine blood tests for comorbidities (including full blood count, urea and electrolytes, thyroid function, fasting glucose and HbA1c, lipids. Iron studies (TSAT and ferritin).	I	C
CMR is recommended for the assessment of myocardial structure and function in those with poor echocardiogram acoustic windows.	I	C
CMR is recommended for the characterization of myocardial tissue in suspected infiltrative disease, Fabry disease, inflammatory disease (myocarditis), LV non-compaction, amyloid, sarcoidosis, iron overload/haemochromatosis.	I	C
Invasive coronary angiography is recommended in patients with angina despite pharmacological therapy or symptomatic ventricular arrhythmias.	I	B
Cardiopulmonary exercise testing is recommended as a part of the evaluation for heart transplantation and/or MCS.	I	C
Right heart catheterization is recommended in patients with severe HF being evaluated for heart transplantation or MCS.	I	C
Recommendations for the treatment of HFrEF		
ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.	I	A
MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.	I	B
Diuretics are recommended in patients with HFrEF with signs and/or symptoms of congestion to alleviate HF symptoms, improve exercise capacity and reduce HF hospitalizations.	I	C
An ARB[c] is recommended to reduce the risk of HF hospitalization and CV death in symptomatic patients unable to tolerate an ACE-I or ARNI (patients should also receive a beta-blocker and an MRA).	I	B
The addition of an ARB (or renin inhibitor) to the combination of an ACE-I and an MRA is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalaemia.	III	C
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing haemodynamic instability, and who are expected to survive for >1 year with good functional status, in the absence of reversible causes or unless the ventricular arrhythmia has occurred <48 h after a MI.	I	A
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II–III) of an ischaemic aetiology (unless they have had an MI in the prior 40 days—see below), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status.	I	A
ICD implantation is not recommended within 40 days of an MI as implantation at this time does not improve prognosis.	III	A
ICD therapy is not recommended in patients in NYHA class IV with severe symptoms refractory to pharmacological therapy unless they are candidates for CRT, a VAD, or cardiac transplantation.	III	C
CRT is recommended for symptomatic patients with HF in SR with a QRS duration ≥150 ms and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	A
CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class or QRS width who have an indication for ventricular pacing for high degree AV block in order to reduce morbidity. This includes patients with AF.	I	A
CRT is not recommended in patients with a QRS duration <130 ms who do not have an indication for pacing due to high-degree AV block.	III	A
Recommendations for the treatment of HFmrEF and HFpEF		
Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs.	I	C

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Screening for, and treatment of, aetiologies, and CV and non-CV comorbidities is recommended in patients with HFpEF (see relevant sections of this document).	I	C
Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs.	I	C
Recommendations for the prevention of chronic HF		
Treatment of hypertension is recommended to prevent or delay the onset of HF, and to prevent HF hospitalizations.	I	A
Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations.	I	A
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations.	I	A
Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF.	I	C
Other recommendations for the management of chronic HF		
It is recommended that HF patients are enrolled in a multidisciplinary HF management programme to reduce the risk of HF hospitalization and mortality.	I	A
Self-management strategies are recommended to reduce the risk of HF hospitalization and mortality.	I	A
Either home-based and/or clinic-based programmes improve outcomes and are recommended to reduce the risk of HF hospitalization and mortality.	I	A
Exercise is recommended for all patients who are able in order to improve exercise capacity and QOL, and reduce HF hospitalization.[d]	I	A
Recommendations for treatment of patients with advanced HF		
Patients being considered for long-term MCS must have good compliance, appropriate capacity for device handling and psychosocial support.	I	C
Heart transplantation is recommended for patients with advanced HF, refractory to medical/device therapy and who do not have absolute contraindications.	I	C
Recommendations for treatment of patients with acute HF		
Oxygen is recommended in patients with SpO_2 <90% or PaO_2 <60 mmHg to correct hypoxaemia.	I	C
Intubation is recommended for progressive respiratory failure persisting in spite of oxygen administration or non-invasive ventilation.	I	C
Intravenous loop diuretics are recommended for all patients with AHF admitted with signs/symptoms of fluid overload to improve symptoms.	I	C
Thromboembolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism.	I	A
Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion.	III	C
Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety.	III	C
IABP is not routinely recommended in post-MI cardiogenic shock.	III	B
Recommendations for management of patients after HF hospitalization		
It is recommended that patients hospitalized for HF be carefully evaluated to exclude persistent signs of congestion before discharge and to optimize oral treatment.	I	C
It is recommended that evidence-based oral medical treatment be administered before discharge.	I	C
An early follow-up visit is recommended at 1–2 weeks after discharge to assess signs of congestion, drug tolerance, and start and/or uptitrate evidence-based therapy.	I	C
Recommendations for treatment of patients with HF and AF		
Long-term treatment with an oral anticoagulant is recommended in all patients with AF, HF, and CHA_2DS_2-VASc score >2 in men or >3 in women.	I	A
DOACs are recommended in preference to VKAs in patients with HF, except in those with moderate or severe mitral stenosis or mechanical prosthetic heart valves.	I	A
Urgent ECV is recommended in the setting of acute worsening of HF in patients presenting with rapid ventricular rates and haemodynamic instability.	I	C
Treatment with the anti-arrhythmic agents flecainide, encainide, disopyramide, dronedarone, and D-sotalol is not recommended due to safety concerns.	III	A

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Diltiazem or verapamil are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization.	III	C
Recommendations for treatment of patients with HF and aortic stenosis		
Aortic valve intervention, TAVI or SAVR, is recommended in patients with HF and severe high-gradient aortic stenosis to reduce mortality and improve symptoms.	I	B
It is recommended that the choice between TAVI and SAVR be made by the Heart Team, according to individual patient preference and features including age, surgical risk, clinical, anatomical and procedural aspects, weighing the risks and benefits of each approach.	I	C
Recommendations for treatment of patients with HF and diabetes		
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with T2DM at risk of CV events to reduce hospitalizations for HF, major CV events, end-stage renal dysfunction, and CV death.	I	A
SGLT2 inhibitors (dapagliflozin, empagliflozin, and sotagliflozin) are recommended in patients with T2DM and HFrEF to reduce hospitalizations for HF and CV death.	I	A
Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	A
The DPP-4 inhibitor saxagliptin is not recommended in patients with HF.	III	B
Recommendations for treatment of patients with HF and iron deficiency		
It is recommended that all patients with HF be periodically screened for anaemia and iron deficiency with a full blood count, serum ferritin concentration, and TSAT.	I	C
Treatment of anaemia in HF with erythropoietin-stimulating agents is not recommended in the absence of other indications for this therapy.	III	B
Recommendation for treatment of patients with HF and sleep apnoea		
Adaptive servo-ventilation is not recommended in patients with HFrEF and a predominant CSA because of an increased all-cause and CV mortality.	III	A
Recommendation for treatment of patients with HF and arthritis		
NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	B
Recommendation for treatment of patients with HF and cancer		
It is recommended that cancer patients at increased risk for cardiotoxicity, defined by a history or risk factors of CV disease, previous cardiotoxicity or exposure to cardiotoxic agents, undergo CV evaluation before scheduled anticancer therapy, preferably by a cardiologist with experience/interest in Cardio-Oncology.	I	C
Recommendations for treatment of patients with HF and amyloidosis		
Tafamidis is recommended in patients with genetic testing proven hereditary hTTR-CMP and NYHA class I or II symptoms to reduce symptoms, CV hospitalization and mortality.	I	B
Tafamidis is recommended in patients with wtTTR-CA and NYHA class I or II symptoms to reduce symptoms, CV hospitalization and mortality.	I	B

ACE-I = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; AHF = acute heart failure; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; AV = atrio-ventricular; BNP = B-type natriuretic peptide; CHA_2DS_2-VASc = congestive heart failure or left ventricular dysfunction, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74, Sex category (female) (score); CMP = cardiomyopathy; CMR = cardiac magnetic resonance; CRT = cardiac resynchronization therapy; CSA = central sleep apnoea; CV = cardiovascular; DOAC = direct-acting oral anticoagulant; DPP-4 = dipeptidyl peptidase-4; ECG = electrocardiogram; ECV = electrical cardioversion; HbA1c = glycated haemoglobin; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; hTTR = hereditary transthyretin; IABP = intra-aortic balloon pump; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LMWH = low-molecular-weight heparin; LV = left ventricular/ventricle; LVEF = left ventricular ejection fraction; MCS = mechanical circulatory support; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NSAID = non-steroidal anti-inflammatory drug; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OMT = optimal medical therapy; PaO_2 = partial pressure of oxygen; QOL = quality of life; QRS = Q, R, and S waves (on an ECG); RV = right ventricular; SAVR = surgical aortic valve replacement; SGLT2 = sodium-glucose co-transporter 2; SpO_2 = transcutaneous oxygen saturation; SR = sinus rhythm; T2DM = type 2 diabetes mellitus; TAVI = transcatheter aortic valve implantation; TSAT = transferrin saturation; VAD = ventricular assist device; VKA = vitamin K antagonist; wtTTR-CA = wild-type transthyretin cardiac amyloidosis.

[a]Class of recommendation.

[b]Level of evidence.

[c]References are listed in section 4.2 for this item.

[d]In those who are able to adhere to the exercise programme.

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18 Quality indicators

QIs are tools that may be used to evaluate care quality, including that of processes of care and clinical outcomes.[995] They may also serve as a mechanism for enhancing adherence to guideline recommendations, through quality assurance endeavours and benchmarking of care providers.[996] As such, the role of QIs in driving quality improvement is increasingly recognized and attracts interest from healthcare authorities, professional organizations, payers, and the public.[997]

The ESC recognizes the need for measuring and reporting quality and outcomes of CV care. The methodology by which the ESC QIs are developed has been published[997] and, to date, a suite of QIs for an initial tranche of CV conditions has been produced.[998,999] To facilitate quality improvement initiatives, the disease-specific ESC QIs are included in corresponding ESC Clinical Practice Guidelines.[7,1000] This is further enhanced by way of their integration in the ESC registries, such as the EURObservational Research Programme (EORP) and the European Unified Registries On Heart Care Evaluation and Randomized Trials (EuroHeart) project.[1001]

For patients with HF, QIs may help healthcare providers to simultaneously operationalize discrete guideline recommendations and enable the discrimination between missed opportunities and appropriate care. Furthermore, QIs allow the capture of patients'

Table 37 Main European Society of Cardiology quality indicators for the evaluation of care and outcomes for patient with heart failure (*a full list is published in a separate article*)

Domain 1. Structural QIs[a]
Main (1): Centre should have a dedicated multidisciplinary team to manage patients with HF
Numerator: Availability of a dedicated multidisciplinary team to manage patients with HF.
Domain 2. Patient assessment[b]
Main (1): Proportion of patients with HF who have a documentation of their HF clinical type (HFrEF, HFmrEF, HFpEF)
Numerator: Number of patients with HF who have a documentation of their HF clinical type (HFrEF, HFmrEF, HFpEF). **Denominator:** Number of patients with HF.
Main (2): Proportion of patients with HF who have a documentation of their ECG findings
Numerator: Number of patients with HF who have a documentation of their ECG findings. **Denominator:** Number of patients with HF.
Main (3): Proportion of patients with HF who have their NPs measured
Numerator: Number of patients with HF who have a documentation of their NPs levels. **Denominator:** Number of patients with HF.
Domain 3. Initial treatment
Main (1). Proportion of patients with HFrEF who are prescribed the beta-blocker bisoprolol, carvedilol, sustained-release metoprolol succinate, or nebivolol in the absence of any contraindications
Numerator: Number of patients with HFrEF who are prescribed **the beta-blocker** bisoprolol, carvedilol, sustained-release metoprolol succinate, or nebivolol. **Denominator:** Number of patients with HFrEF without any contraindications for **the beta-blocker** bisoprolol, carvedilol, sustained-release metoprolol succinate, and nebivolol.
Main (2). Proportion of patients with HFrEF who are prescribed ACE inhibitor, ARB or ARNI in the absence of any contraindications
Numerator: Number of patients with HFrEF who are prescribed an ACE inhibitor, ARB or ARNI. **Denominator:** Number of patients with HFrEF without any contraindications for ACE inhibitors, ARBs and ARNI.
Main (3). Proportion of patients with HF who are prescribed diuretic therapy if they have evidence of fluid retention
Numerator: Number of patients with HF, with evidence of fluid retention who are prescribed diuretic therapy. **Denominator:** Number of patients with HF who have evidence of fluid retention and no contraindications for diuretic therapy.
Main (4): Proportion of patients with HFrEF who are prescribed an MRA in the absence of any contraindications
Numerator: Number of patients with HFrEF who are prescribed an MRA. **Denominator:** Number of patients with HFrEF without any contraindications for MRA.
Main (5): Proportion of patients with HFrEF who are prescribed a SGLT2 inhibitor in the absence of any contraindications
Numerator: Number of patients with HFrEF who are prescribed a SGLT2 inhibitor. **Denominator:** Number of patients with HFrEF without any contraindications for SGLT2 inhibitor.

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; IHD = ischaemic heart disease; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NP = natriuretic peptide; NYHA = New York Heart Association; OMT = optimal medical therapy; QI = quality indicator; SGLT2 = sodium-glucose co-transporter 2.

[a]Structural QIs are binary measurements (Yes/No), and thus, have only numerator definitions.

[b]Blood tests include urea, creatinine, electrolytes, full blood count, glucose, glycated haemoglobin, thyroid-stimulating hormone, liver function test, lipids, and iron profile.

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experience. As such, and in parallel with the writing of these guidelines, a suite of QIs for the evaluation of care and outcomes for patients with HF was developed. These QIs, alongside their specifications and development process are published separately with a short summary shown in *Table 37*.

19 Supplementary data

Supplementary data with additional Supplementary Figures, Tables, and text complementing the full text are available on the *European Heart Journal* website and via the ESC website at www.escardio.org/guidelines.

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21 Appendix

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22 References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–2200.
2. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Lochen ML, Lollgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S, ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–2381.
3. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P, ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:119–177.
4. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I, ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;**39**:3021–3104.
5. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ, ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–477.
6. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Juni P, Lettino M, Marx N, Mellbin LG, Ostgren CJ, Rocca B, Roffi M, Sattar N, Seferovic PM, Sousa-Uva M, Valensi P, Wheeler DC, ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020;**41**:255–323.
7. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL, ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021;**42**:373–498.
8. Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, Swedberg K, Yusuf S, Granger CB, Pfeffer MA, McMurray JJV, Solomon SD. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. *Eur J Heart Fail* 2018;**20**:1230–1239.

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9. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, O'Meara E, Shah SJ, McKinlay S, Fleg JL, Sopko G, Pitt B, Pfeffer MA, TOPCAT Investigators. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur Heart J* 2016;**37**:455–462.
10. Abdul-Rahim AH, Shen L, Rush CJ, Jhund PS, Lees KR, McMurray JJV, VICCTA-Heart Failure Collaborators. Effect of digoxin in patients with heart failure and mid-range (borderline) left ventricular ejection fraction. *Eur J Heart Fail* 2018;**20**:1139–1145.
11. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J, PEP-CHF Investigators. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006;**27**:2338–2345.
12. Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, Manzano L, McMurray JJV, Ruschitzka F, van Veldhuisen DJ, von Lueder TG, Bohm M, Andersson B, Kjekshus J, Packer M, Rigby AS, Rosano G, Wedel H, Hjalmarson A, Wikstrand J, Kotecha D, Beta-blockers in Heart Failure Collaborative Group. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur Heart J* 2018;**39**:26–35.
13. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Dungen HD, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP, PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019;**381**:1609–1620.
14. Lam CSP, Voors AA, Piotr P, McMurray JJV, Solomon SD. Time to rename the middle child of heart failure: heart failure with mildly reduced ejection fraction. *Eur Heart J* 2020;**41**:2353–2355.
15. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, Anker SD, Atherton J, Bohm M, Butler J, Drazner MH, Michael Felker G, Filippatos G, Fiuzat M, Fonarow GC, Gomez-Mesa JE, Heidenreich P, Imamura T, Jankowska EA, Januzzi J, Khazanie P, Kinugawa K, Lam CSP, Matsue Y, Metra M, Ohtani T, Francesco Piepoli M, Ponikowski P, Rosano GMC, Sakata Y, Seferovic P, Starling RC, Teerlink JR, Vardeny O, Yamamoto K, Yancy C, Zhang J, Zieroth S. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail* 2021;**23**:352–380.
16. Galderisi M, Cosyns B, Edvardsen T, Cardim N, Delgado V, Di Salvo G, Donal E, Sade LE, Ernande L, Garbi M, Grapsa J, Hagendorff A, Kamp O, Magne J, Santoro C, Stefanidis A, Lancellotti P, Popescu B, Habib G, EACVI Scientific Documents Committee. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2017;**18**:1301–1310.
17. Arrigo M, Huber LC, Winnik S, Mikulicic F, Guidetti F, Frank M, Flammer AJ, Ruschitzka F. Right ventricular failure: pathophysiology, diagnosis and treatment. *Card Fail Rev* 2019;**5**:140–146.
18. Gorter TM, van Veldhuisen DJ, Bauersachs J, Borlaug BA, Celutkiene J, Coats AJS, Crespo-Leiro MG, Guazzi M, Harjola VP, Heymans S, Hill L, Lainscak M, Lam CSP, Lund LH, Lyon AR, Mebazaa A, Mueller C, Paulus WJ, Pieske B, Piepoli MF, Ruschitzka F, Rutten FH, Seferovic PM, Solomon SD, Shah SJ, Triposkiadis F, Wachter R, Tschope C, de Boer RA. Right heart dysfunction and failure in heart failure with preserved ejection fraction: mechanisms and management. Position statement on behalf of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018;**20**:16–37.
19. Caraballo C, Desai NR, Mulder H, Alhanti B, Wilson FP, Fiuzat M, Felker GM, Pina IL, O'Connor CM, Lindenfeld J, Januzzi JL, Cohen LS, Ahmad T. Clinical implications of the New York Heart Association classification. *J Am Heart Assoc* 2019;**8**:e014240.
20. Solomon SD, Claggett B, Packer M, Desai A, Zile MR, Swedberg K, Rouleau J, Shi V, Lefkowitz M, McMurray JJV. Efficacy of sacubitril/valsartan relative to a prior decompensation: the PARADIGM-HF trial. *JACC Heart Fail* 2016;**4**:816–822.
21. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, Allison M, Hemingway H, Cleland JG, McMurray JJV, Rahimi K. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet* 2018;**391**:572–580.
22. Dunlay SM, Roger VL. Understanding the epidemic of heart failure: past, present, and future. *Curr Heart Fail Rep* 2014;**11**:404–415.
23. Roth GA, Forouzanfar MH, Moran AE, Barber R, Nguyen G, Feigin VL, Naghavi M, Mensah GA, Murray CJ. Demographic and epidemiologic drivers of global cardiovascular mortality. *N Engl J Med* 2015;**372**:1333–1341.
24. Savarese G, Lund LH. Global public health burden of heart failure. *Card Fail Rev* 2017;**3**:7–11.
25. Meyer S, Brouwers FP, Voors AA, Hillege HL, de Boer RA, Gansevoort RT, van der Harst P, Rienstra M, van Gelder IC, van Veldhuisen DJ, van Gilst WH, van der Meer P. Sex differences in new-onset heart failure. *Clin Res Cardiol* 2015;**104**:342–350.
26. Brouwers FP, de Boer RA, van der Harst P, Voors AA, Gansevoort RT, Bakker SJ, Hillege HL, van Veldhuisen DJ, van Gilst WH. Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. *Eur Heart J* 2013;**34**:1424–1431.
27. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;**392**:1789–1858.
28. Roger VL. Epidemiology of heart failure. *Circ Res* 2013;**113**:646–659.
29. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart* 2007;**93**:1137–1146.
30. Smeets M, Vaes B, Mamouris P, Van Den Akker M, Van Pottelbergh G, Goderis G, Janssens S, Aertgeerts B, Henrard S. Burden of heart failure in Flemish general practices: a registry-based study in the Intego database. *BMJ Open* 2019;**9**:e022972.
31. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Shay CM, Spartano NL, Stokes A, Tirschwell DL, VanWagner LB, Tsao CW, American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. *Circulation* 2020;**141**:e139–e596.
32. van Riet EE, Hoes AW, Limburg A, Landman MA, van der Hoeven H, Rutten FH. Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion. *Eur J Heart Fail* 2014;**16**:772–777.
33. van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. *Eur J Heart Fail* 2016;**18**:242–252.
34. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD, Ferguson JF, Fornage M, Gillespie C, Isasi CR, Jimenez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Lutsey PL, Mackey JS, Matchar DB, Matsushita K, Mussolino ME, Nasir K, O'Flaherty M, Palaniappan LP, Pandey A, Pandey DK, Reeves MJ, Ritchey MD, Rodriguez CJ, Roth GA, Rosamond WD, Sampson UKA, Satou GM, Shah SH, Spartano NL, Tirschwell DL, Tsao CW, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P, American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. *Circulation* 2018;**137**:e67–e492.
35. Ceia F, Fonseca C, Mota T, Morais H, Matias F, de Sousa A, Oliveira A, EPICA Investigators. Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. *Eur J Heart Fail* 2002;**4**:531–539.
36. Bibbins-Domingo K, Pletcher MJ, Lin F, Vittinghoff E, Gardin JM, Arynchyn A, Lewis CE, Williams OD, Hulley SB. Racial differences in incident heart failure among young adults. *N Engl J Med* 2009;**360**:1179–1190.
37. Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, Witteman JC, Stricker BH. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. *Eur Heart J* 2004;**25**:1614–1619.
38. Koh AS, Tay WT, Teng THK, Vedin O, Benson L, Dahlstrom U, Savarese G, Lam CSP, Lund LH. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. *Eur J Heart Fail* 2017;**19**:1624–1634.
39. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, Parissis J, Laroche C, Piepoli MF, Fonseca C, Mebazaa A, Lund L, Ambrosio GA, Coats AJ, Ferrari R, Ruschitzka F, Maggioni AP, Filippatos G. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017;**19**:1574–1585.
40. Shah RU, Klein L, Lloyd-Jones DM. Heart failure in women: epidemiology, biology and treatment. *Womens Health (Lond)* 2009;**5**:517–527.

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41. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, Jacobsen SJ. Trends in heart failure incidence and survival in a community-based population. *JAMA* 2004;**292**:344–350.
42. Vedin O, Lam CSP, Koh AS, Benson L, Teng THK, Tay WT, Braun OO, Savarese G, Dahlstrom U, Lund LH. Significance of ischemic heart disease in patients with heart failure and preserved, midrange, and reduced ejection fraction: a nationwide cohort study. *Circ Heart Fail* 2017;**10**:e003875.
43. Kapoor JR, Kapoor R, Ju C, Heidenreich PA, Eapen ZJ, Hernandez AF, Butler J, Yancy CW, Fonarow GC. Precipitating clinical factors, heart failure characterization, and outcomes in patients hospitalized with heart failure with reduced, borderline, and preserved ejection fraction. *JACC Heart Fail* 2016;**4**:464–472.
44. Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med* 2002;**162**:1682–1688.
45. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, Killian JM, Roger VL. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med* 2015;**175**:996–1004.
46. Tsao CW, Lyass A, Enserro D, Larson MG, Ho JE, Kizer JR, Gottdiener JS, Psaty BM, Vasan RS. Temporal trends in the incidence of and mortality associated with heart failure with preserved and reduced ejection fraction. *JACC Heart Fail* 2018;**6**:678–685.
47. Motiejunaite J, Akiyama E, Cohen-Solal A, Maggioni AP, Mueller C, Choi DJ, Kavoliuniene A, Celutkiene J, Parenica J, Lassus J, Kajimoto K, Sato N, Miro O, Peacock WF, Matsue Y, Voors AA, Lam CSP, Ezekowitz JA, Ahmed A, Fonarow GC, Gayat E, Regitz-Zagrosek V, Mebazaa A. The association of long-term outcome and biological sex in patients with acute heart failure from different geographic regions. *Eur Heart J* 2020;**41**:1357–1364.
48. Dunlay SM, Roger VL, Weston SA, Jiang R, Redfield MM. Longitudinal changes in ejection fraction in heart failure patients with preserved and reduced ejection fraction. *Circ Heart Fail* 2012;**5**:720–726.
49. Clarke CL, Grunwald GK, Allen LA, Baron AE, Peterson PN, Brand DW, Magid DJ, Masoudi FA. Natural history of left ventricular ejection fraction in patients with heart failure. *Circ Cardiovasc Qual Outcomes* 2013;**6**:680–686.
50. Tsuji K, Sakata Y, Nochioka K, Miura M, Yamauchi T, Onose T, Abe R, Oikawa T, Kasahara S, Sato M, Shiroto T, Takahashi J, Miyata S, Shimokawa H, CHART-2 Investigators. Characterization of heart failure patients with mid-range left ventricular ejection fraction–a report from the CHART-2 Study. *Eur J Heart Fail* 2017;**19**:1258–1269.
51. Rastogi A, Novak E, Platts AE, Mann DL. Epidemiology, pathophysiology and clinical outcomes for heart failure patients with a mid-range ejection fraction. *Eur J Heart Fail* 2017;**19**:1597–1605.
52. Lupon J, Gavidia-Bovadilla G, Ferrer E, de Antonio M, Perera-Lluna A, Lopez-Ayerbe J, Domingo M, Nunez J, Zamora E, Moliner P, Diaz-Ruata P, Santesmases J, Bayes-Genis A. Dynamic trajectories of left ventricular ejection fraction in heart failure. *J Am Coll Cardiol* 2018;**72**:591–601.
53. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Kober L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN, Meta-Analysis Global Group in Chronic Heart Failure. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. *Eur Heart J* 2013;**34**:1404–1413.
54. Barasa A, Schaufelberger M, Lappas G, Swedberg K, Dellborg M, Rosengren A. Heart failure in young adults: 20-year trends in hospitalization, aetiology, and case fatality in Sweden. *Eur Heart J* 2014;**35**:25–32.
55. Jhund PS, Macintyre K, Simpson CR, Lewsey JD, Stewart S, Redpath A, Chalmers JW, Capewell S, McMurray JJ. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. *Circulation* 2009;**119**:515–523.
56. Dunlay SM, Redfield MM, Weston SA, Therneau TM, Hall Long K, Shah ND, Roger VL. Hospitalizations after heart failure diagnosis a community perspective. *J Am Coll Cardiol* 2009;**54**:1695–1702.
57. Taylor CJ, Ordonez-Mena JM, Roalfe AK, Lay-Flurrie S, Jones NR, Marshall T, Hobbs FDR. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population based cohort study. *BMJ* 2019;**364**:l223.
58. Lorenzoni G, Azzolina D, Lanera C, Brianti G, Gregori D, Vanuzzo D, Baldi I. Time trends in first hospitalization for heart failure in a community-based population. *Int J Cardiol* 2018;**271**:195–199.
59. Mosterd A, Reitsma JB, Grobbee DE. Angiotensin converting enzyme inhibition and hospitalisation rates for heart failure in the Netherlands, 1980 to 1999: the end of an epidemic? *Heart* 2002;**87**:75–76.
60. Chen J, Hsieh AF, Dharmarajan K, Masoudi FA, Krumholz HM. National trends in heart failure hospitalization after acute myocardial infarction for Medicare beneficiaries: 1998-2010. *Circulation* 2013;**128**:2577–2584.
61. Lawson CA, Zaccardi F, Squire I, Ling S, Davies MJ, Lam CSP, Mamas MA, Khunti K, Kadam UT. 20-year trends in cause-specific heart failure outcomes by sex, socioeconomic status, and place of diagnosis: a population-based study. *Lancet Public Health* 2019;**4**:e406–e420.
62. Al-Mohammad A, Mant J, Laramee P, Swain S, Chronic Heart Failure Guideline Development Group. Diagnosis and management of adults with chronic heart failure: summary of updated NICE guidance. *BMJ* 2010;**341**:c4130.
63. Mant J, Doust J, Roalfe A, Barton P, Cowie MR, Glasziou P, Mant D, McManus RJ, Holder R, Deeks J, Fletcher K, Qume M, Sohanpal S, Sanders S, Hobbs FD. Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care. *Health Technol Assess* 2009;**13**:1–207, iii.
64. Davie AP, Francis CM, Caruana L, Sutherland GR, McMurray JJ. Assessing diagnosis in heart failure: which features are any use? *QJM* 1997;**90**:335–339.
65. Oudejans I, Mosterd A, Bloemen JA, Valk MJ, van Velzen E, Wielders JP, Zuithoff NP, Rutten FH, Hoes AW. Clinical evaluation of geriatric outpatients with suspected heart failure: value of symptoms, signs, and additional tests. *Eur J Heart Fail* 2011;**13**:518–527.
66. Kelder JC, Cramer MJ, van Wijngaarden J, van Tooren R, Mosterd A, Moons KG, Lammers JW, Cowie MR, Grobbee DE, Hoes AW. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. *Circulation* 2011;**124**:2865–2873.
67. Thibodeau JT, Turer AT, Gualano SK, Ayers CR, Velez-Martinez M, Mishkin JD, Patel PC, Mammen PP, Markham DW, Levine BD, Drazner MH. Characterization of a novel symptom of advanced heart failure: bendopnea. *JACC Heart Fail* 2014;**2**:24–31.
68. Gohar A, Rutten FH, den Ruijter H, Kelder JC, von Haehling S, Anker SD, Mockel M, Hoes AW. Mid-regional pro-atrial natriuretic peptide for the early detection of non-acute heart failure. *Eur J Heart Fail* 2019;**21**:1219–1227.
69. Hildebrandt P, Collinson PO. Amino-terminal pro-B-type natriuretic peptide testing to assist the diagnostic evaluation of heart failure in symptomatic primary care patients. *Am J Cardiol* 2008;**101**:25–28.
70. Maisel A, Mueller C, Adams K, Jr., Anker SD, Aspromonte N, Cleland JG, Cohen-Solal A, Dahlstrom U, DeMaria A, Di Somma S, Filippatos GS, Fonarow GC, Jourdain P, Komajda M, Liu PP, McDonagh T, McDonald K, Mebazaa A, Nieminen MS, Peacock WF, Tubaro M, Valle R, Vanderhyden M, Yancy CW, Zannad F, Braunwald E. State of the art: using natriuretic peptide levels in clinical practice. *Eur J Heart Fail* 2008;**10**:824–839.
71. Lancellotti P, Galderisi M, Edvardsen T, Donal E, Goliasch G, Cardim N, Magne J, Laginha S, Hagendorff A, Haland TF, Aaberge L, Martinez C, Rapacciuolo A, Santoro C, Ilardi F, Postolache A, Dulgheru R, Mateescu AD, Beladan CC, Deleanu D, Marchetta S, Auffret V, Schwammenthal E, Habib G, Popescu BA. Echo-Doppler estimation of left ventricular filling pressure: results of the multicentre EACVI Euro-Filling study. *Eur Heart J Cardiovasc Imaging* 2017;**18**:961–968.
72. Gardner RS, Ozalp F, Murday AJ, Robb SD, McDonagh TA. N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. *Eur Heart J* 2003;**24**:1735–1743.
73. Roberts E, Ludman AJ, Dworzynski K, Al-Mohammad A, Cowie MR, McMurray JJ, Mant J, NICE Guideline Development Group for Acute Heart Failure. The diagnostic accuracy of the natriuretic peptides in heart failure: systematic review and diagnostic meta-analysis in the acute care setting. *BMJ* 2015;**350**:h910.
74. Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JGF, Kozhuharov N, Coats AJS, Metra M, Mebazaa A, Ruschitzka F, Lainscak M, Filippatos G, Seferovic PM, Meijers WC, Bayes-Genis A, Mueller T, Richards M, Januzzi JL Jr, Heart Failure Association of the European Society of Cardiology. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. *Eur J Heart Fail* 2019;**21**:715–731.
75. Madamanchi C, Alhosaini H, Sumida A, Runge MS. Obesity and natriuretic peptides, BNP and NT-proBNP: mechanisms and diagnostic implications for heart failure. *Int J Cardiol* 2014;**176**:611–617.
76. Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Sutton GC. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997;**350**:1349–1353.
77. Zaphiriou A, Robb S, Murray-Thomas T, Mendez G, Fox K, McDonagh T, Hardman SM, Dargie HJ, Cowie MR. The diagnostic accuracy of plasma BNP and NTproBNP in patients referred from primary care with suspected heart failure: results of the UK natriuretic peptide study. *Eur J Heart Fail* 2005;**7**:537–541.
78. Kelder JC, Cramer MJ, Verweij WM, Grobbee DE, Hoes AW. Clinical utility of three B-type natriuretic peptide assays for the initial diagnostic assessment of new slow-onset heart failure. *J Card Fail* 2011;**17**:729–734.
79. Verdu JM, Comin-Colet J, Domingo M, Lupon J, Gomez M, Molina L, Casacuberta JM, Munoz MA, Mena A, Bruguera-Cortada J. Rapid point-of-care NT-proBNP optimal cut-off point for heart failure diagnosis in primary care. *Rev Esp Cardiol (Engl Ed)* 2012;**65**:613–619.
80. Taylor CJ, Roalfe AK, Iles R, Hobbs FR, investigators R, Barton P, Deeks J, McCahon D, Cowie MR, Sutton G, Davis RC, Mant J, McDonagh T, Tait L. Primary care REFerral for EchocaRdiogram (REFER) in heart failure: a diagnostic accuracy study. *Br J Gen Pract* 2017;**67**:e94–e102.
81. Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D, Voigt JU, Zamorano JL, European Association of Echocardiography. Stress

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Echocardiography Expert Consensus Statement–Executive Summary: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur Heart J* 2009;**30**:278–289.
82. Lancellotti P, Pellikka PA, Budts W, Chaudhry FA, Donal E, Dulgheru R, Edvardsen T, Garbi M, Ha JW, Kane GC, Kreeger J, Mertens L, Pibarot P, Picano E, Ryan T, Tsutsui JM, Varga A. The clinical use of stress echocardiography in non-ischaemic heart disease: recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging* 2016;**17**:1191–1229.
83. Gonzalez JA, Kramer CM. Role of imaging techniques for diagnosis, prognosis and management of heart failure patients: cardiac magnetic resonance. *Curr Heart Fail Rep* 2015;**12**:276–283.
84. Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, Mascherbauer J, Nezafat R, Salerno M, Schelbert EB, Taylor AJ, Thompson R, Ugander M, van Heeswijk RB, Friedrich MG. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2 and extracellular volume: a consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). *J Cardiovasc Magn Reson* 2017;**19**:75.
85. Witteles RM, Bokhari S, Damy T, Elliott PM, Falk RH, Fine NM, Gospodinova M, Obici L, Rapezzi C, Garcia-Pavia P. Screening for transthyretin amyloid cardiomyopathy in everyday practice. *JACC Heart Fail* 2019;**7**:709–716.
86. Gupta DK, Wang TJ. Natriuretic peptides and cardiometabolic health. *Circ J* 2015;**79**:1647–1655.
87. Zois NE, Bartels ED, Hunter I, Kousholt BS, Olsen LH, Goetze JP. Natriuretic peptides in cardiometabolic regulation and disease. *Nat Rev Cardiol* 2014;**11**:403–412.
88. Nishikimi T, Kuwahara K, Nakao K. Current biochemistry, molecular biology, and clinical relevance of natriuretic peptides. *J Cardiol* 2011;**57**:131–140.
89. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A, Ali IS, Pohost G, Gradinac S, Abraham WT, Yii M, Prabhakaran D, Szwed H, Ferrazzi P, Petrie MC, O'Connor CM, Panchavinnin P, She L, Bonow RO, Rankin GR, Jones RH, Rouleau JL, STICH Investigators. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med* 2011;**364**:1607–1616.
90. Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. *J Am Coll Cardiol* 2002;**39**:1151–1158.
91. Ling LF, Marwick TH, Flores DR, Jaber WA, Brunken RC, Cerqueira MD, Hachamovitch R. Identification of therapeutic benefit from revascularization in patients with left ventricular systolic dysfunction: inducible ischemia versus hibernating myocardium. *Circ Cardiovasc Imaging* 2013;**6**:363–372.
92. Bonow RO, Maurer G, Lee KL, Holly TA, Binkley PF, Desvigne-Nickens P, Drozdz J, Farsky PS, Feldman AM, Doenst T, Michler RE, Berman DS, Nicolau JC, Pellikka PA, Wrobel K, Alotti N, Asch FM, Favaloro LE, She L, Velazquez EJ, Jones RH, Panza JA, STICH Trial Investigators. Myocardial viability and survival in ischemic left ventricular dysfunction. *N Engl J Med* 2011;**364**:1617–1625.
93. Panza JA, Ellis AM, Al-Khalidi HR, Holly TA, Berman DS, Oh JK, Pohost GM, Sopko G, Chrzanowski L, Mark DB, Kukulski T, Favaloro LE, Maurer G, Farsky PS, Tan RS, Asch FM, Velazquez EJ, Rouleau JL, Lee KL, Bonow RO. Myocardial viability and long-term outcomes in ischemic cardiomyopathy. *N Engl J Med* 2019;**381**:739–748.
94. Corra U, Piepoli MF, Adamopoulos S, Agostoni P, Coats AJ, Conraads V, Lambrinou E, Pieske B, Piotrowicz E, Schmid JP, Seferovic PM, Anker SD, Filippatos G, Ponikowski PP. Cardiopulmonary exercise testing in systolic heart failure in 2014: the evolving prognostic role: a position paper from the Committee on Exercise Physiology and Training of the Heart Failure Association of the ESC. *Eur J Heart Fail* 2014;**16**:929–941.
95. Piepoli MF, Conraads V, Corra U, Dickstein K, Francis DP, Jaarsma T, McMurray J, Pieske B, Piotrowicz E, Schmid JP, Anker SD, Solal AC, Filippatos GS, Hoes AW, Gielen S, Giannuzzi P, Ponikowski PP. Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. *Eur J Heart Fail* 2011;**13**:347–357.
96. Corra U, Agostoni PG, Anker SD, Coats AJS, Crespo Leiro MG, de Boer RA, Hairola VP, Hill L, Lainscak M, Lund LH, Metra M, Ponikowski P, Riley J, Seferovic PM, Piepoli MF. Role of cardiopulmonary exercise testing in clinical stratification in heart failure. A position paper from the Committee on Exercise Physiology and Training of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018;**20**:3–15.
97. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U, Levine GN, Narula J, Starling RC, Towbin J, Virmani R. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. *Eur Heart J* 2007;**28**:3076–3093.
98. Cooper LT Jr, Berry GJ, Shabetai R. Idiopathic giant-cell myocarditis–natural history and treatment. Multicenter Giant Cell Myocarditis Study Group Investigators. *N Engl J Med* 1997;**336**:1860–1866.
99. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:233–270.
100. Gheorghiade M, Shah AN, Vaduganathan M, Butler J, Bonow RO, Rosano GM, Taylor S, Kupfer S, Misselwitz F, Sharma A, Fonarow GC. Recognizing hospitalized heart failure as an entity and developing new therapies to improve outcomes: academics', clinicians', industry's, regulators', and payers' perspectives. *Heart Fail Clin* 2013;**9**:285–290, v-vi.
101. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lam CSP, Sato N, Shah AN, Gheorghiade M. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol* 2014;**63**:1123–1133.
102. Anker SD, Schroeder S, Atar D, Bax JJ, Ceconi C, Cowie MR, Crisp A, Dominjon F, Ford I, Ghofrani HA, Gropper S, Hindricks G, Hlatky MA, Holcomb R, Honarpour N, Jukema JW, Kim AM, Kunz M, Lefkowitz M, Le Floch C, Landmesser U, McDonagh TA, McMurray JJ, Merkely B, Packer M, Prasad K, Revkin J, Rosano GM, Somaratne R, Stough WG, Voors AA, Ruschitzka F. Traditional and new composite endpoints in heart failure clinical trials: facilitating comprehensive efficacy assessments and improving trial efficiency. *Eur J Heart Fail* 2016;**18**:482–489.
103. Gayat E, Arrigo M, Littnerova S, Sato N, Parenica J, Ishihara S, Spinar J, Muller C, Harjola VP, Lassus J, Miro O, Maggioni AP, AlHabib KF, Choi DJ, Park JJ, Zhang Y, Zhang J, Januzzi JL, Jr., Kajimoto K, Cohen-Solal A, Mebazaa A, Network G. Heart failure oral therapies at discharge are associated with better outcome in acute heart failure: a propensity-score matched study. *Eur J Heart Fail* 2018;**20**:345–354.
104. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, Ferrari R, Piepoli MF, Delgado Jimenez JF, Metra M, Fonseca C, Hradec J, Amir O, Logeart D, Dahlstrom U, Merkely B, Drozdz J, Goncalvesova E, Hassanein M, Chioncel O, Lainscak M, Seferovic PM, Tousoulis D, Kavoliuniene A, Fruhwald F, Fazlibegovic E, Temizhan A, Gatzov P, Erglis A, Laroche C, Mebazaa A, Heart Failure Association of the European Society of Cardiology. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail* 2016;**18**:613–625.
105. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993–1004.
106. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, Rocha R, Braunwald E, PIONEER-HF Investigators. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med* 2019;**380**:539–548.
107. Wachter R, Senni M, Belohlavek J, Straburzynska-Migaj E, Witte KK, Kobalava Z, Fonseca C, Goncalvesova E, Cavusoglu Y, Fernandez A, Chaaban S, Bohmer E, Pouleur AC, Mueller C, Tribouilloy C, Lonn E, Buraiki ALJ, Gniot J, Mozheiko M, Lelonek M, Noè A, Schwende H, Bao W, Butylin D, Pascual-Figal D, TRANSITION Investigators. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. *Eur J Heart Fail* 2019;**21**:998–1007.
108. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang C-E, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde AM, DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995–2008.
109. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Bohm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F, EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;**383**:1413–1424.
110. The CONSENSUS Trial Study Group. Enalapril for congestive heart failure. *N Engl J Med* 1987;**317**:1349–1351.

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111. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA* 1995;**273**:1450–1456.
112. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Ryden L, Thygesen K, Uretsky BF. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation* 1999;**100**:2312–2318.
113. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;**325**:293–302.
114. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;**353**:2001–2007.
115. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med* 1996;**334**:1349–1355.
116. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL, Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;**344**:1651–1658.
117. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, Wikstrand J, El Allaf D, Vitovec J, Aldershvile J, Halinen M, Dietz R, Neuhaus KL, Janosi A, Thorgeirsson G, Dunselman PH, Gullestad L, Kuch J, Herlitz J, Rickenbacher P, Ball S, Gottlieb S, Deedwania P. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA* 2000;**283**:1295–1302.
118. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Staiger C, Holcslaw TL, Amann-Zalan I, DeMets DL, Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation* 2002;**106**:2194–2199.
119. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, Cohen-Solal A, Dumitrascu D, Ferrari R, Lechat P, Soler-Soler J, Tavazzi L, Spinarova L, Toman J, Bohm M, Anker SD, Thompson SG, Poole-Wilson PA, SENIORS Investigators. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005;**26**:215–225.
120. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;**353**:9–13.
121. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;**341**:709–717.
122. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B, EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11–21.
123. Fowler MB. Effects of beta blockers on symptoms and functional capacity in heart failure. *Am J Cardiol* 1997;**80**:55L–58L.
124. Willenheimer R, van Veldhuisen DJ, Silke B, Erdmann E, Follath F, Krum H, Ponikowski P, Skene A, van de Ven L, Verkenne P, Lechat P, CIBIS III Investigators. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. *Circulation* 2005;**112**:2426–2435.
125. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, Lip GY, Coats AJ, Andersson B, Kirchhof P, von Lueder TG, Wedel H, Rosano G, Shibata MC, Rigby A, Flather MD, Beta-Blockers in Heart Failure Collaborative Group. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet* 2014;**384**:2235–2243.
126. Seferovic JP, Claggett B, Seidelmann SB, Seely EW, Packer M, Zile MR, Rouleau JL, Swedberg K, Lefkowitz M, Shi VC, Desai AS, McMurray JJV, Solomon SD. Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: a post-hoc analysis from the PARADIGM-HF trial. *Lancet Diabetes Endocrinol* 2017;**5**:333–340.
127. Damman K, Gori M, Claggett B, Jhund PS, Senni M, Lefkowitz MP, Prescott MF, Shi VC, Rouleau JL, Swedberg K, Zile MR, Packer M, Desai AS, Solomon SD, McMurray JJV. Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure. *JACC Heart Fail* 2018;**6**:489–498.
128. Desai AS, Vardeny O, Claggett B, McMurray JJ, Packer M, Swedberg K, Rouleau JL, Zile MR, Lefkowitz M, Shi V, Solomon SD. Reduced risk of hyperkalemia during treatment of heart failure with mineralocorticoid receptor antagonists by use of sacubitril/valsartan compared with enalapril: a secondary analysis of the PARADIGM-HF Trial. *JAMA Cardiol* 2017;**2**:79–85.
129. Vardeny O, Claggett B, Kachadourian J, Desai AS, Packer M, Rouleau J, Zile MR, Swedberg K, Lefkowitz M, Shi V, McMurray JJV, Solomon SD. Reduced loop diuretic use in patients taking sacubitril/valsartan compared with enalapril: the PARADIGM-HF trial. *Eur J Heart Fail* 2019;**21**:337–341.
130. Vardeny O, Claggett B, Kachadourian J, Pearson SM, Desai AS, Packer M, Rouleau J, Zile MR, Swedberg K, Lefkowitz M, Shi V, McMurray JJV, Solomon SD. Incidence, predictors, and outcomes associated with hypotensive episodes among heart failure patients receiving sacubitril/valsartan or enalapril: the PARADIGM-HF trial (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure). *Circ Heart Fail* 2018;**11**:e004745.
131. Morrow DA, Velazquez EJ, DeVore AD, Desai AS, Duffy CI, Ambrosy AP, Gurmu Y, McCague K, Rocha R, Braunwald E. Clinical outcomes in patients with acute decompensated heart failure randomly assigned to sacubitril/valsartan or enalapril in the PIONEER-HF trial. *Circulation* 2019;**139**:2285–2288.
132. Kosiborod MN, Jhund PS, Docherty KF, Diez M, Petrie MC, Verma S, Nicolau JC, Merkely B, Kitakaze M, DeMets DL, Inzucchi SE, Kober L, Martinez FA, Ponikowski P, Sabatine MS, Solomon SD, Bengtsson O, Lindholm D, Niklasson A, Sjostrand M, Langkilde AM, McMurray JJV. Effects of dapagliflozin on symptoms, function, and quality of life in patients with heart failure and reduced ejection fraction: results from the DAPA-HF trial. *Circulation* 2020;**141**:90–99.
133. Butler J, Anker SD, Filippatos G, Khan MS, Ferreira JP, Pocock SJ, Giannetti N, Januzzi JL, Pina IL, Lam CSP, Ponikowski P, Sattar N, Verma S, Brueckmann M, Jamal W, Vedin O, Peil B, Zeller C, Zannad F, Packer M, EMPEROR-Reduced Trial Committees and Investigators. Empagliflozin and health-related quality of life outcomes in patients with heart failure with reduced ejection fraction: the EMPEROR-Reduced trial. *Eur Heart J* 2021;**42**:1203–1212.
134. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, Brueckmann M, Ofstad AP, Pfarr E, Jamal W, Packer M. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet* 2020;**396**:819–829.
135. Jackson AM, Dewan P, Anand IS, Belohlavek J, Bengtsson O, de Boer RA, Bohm M, Boulton DW, Chopra VK, DeMets DL, Docherty KF, Dukat A, Greasley PJ, Howlett JG, Inzucchi SE, Katova T, Kober L, Kosiborod MN, Langkilde AM, Lindholm D, Ljungman CEA, Martinez FA, O'Meara E, Sabatine MS, Sjostrand M, Solomon SD, Tereshchenko S, Verma S, Jhund PS, McMurray JJV. Dapagliflozin and diuretic use in patients with heart failure and reduced ejection fraction in DAPA-HF. *Circulation* 2020;**142**:1040–1054.
136. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Voors AA, Metra M, Lund LH, Komajda M, Testani JM, Wilcox CS, Ponikowski P, Lopes RD, Verma S, Lapuerta P, Pitt B, SOLOIST-WHF Trial Investigators. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2021;**384**:117–128.
137. Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. *Int J Cardiol* 2002;**82**:149–158.
138. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K, CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;**362**:772–776.
139. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L, SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;**376**:875–885.
140. Swedberg K, Komajda M, Bohm M, Borer J, Robertson M, Tavazzi L, Ford I, SHIFT Investigators. Effects on outcomes of heart rate reduction by ivabradine in patients with congestive heart failure: is there an influence of beta-blocker dose?: findings from the SHIFT (Systolic Heart failure treatment with the I(f) inhibitor ivabradine Trial) study. *J Am Coll Cardiol* 2012;**59**:1938–1945.
141. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, Lam CSP, Ponikowski P, Voors AA, Jia G, McNulty SE, Patel MJ, Roessig L, Koglin J, O'Connor CM, VICTORIA Study Group. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2020;**382**:1883–1893.
142. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R, Jr., Ferdinand K, Taylor M, Adams K, Sabolinski M, Worcel M, Cohn JN, African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004;**351**:2049–2057.
143. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986;**314**:1547–1552.

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144. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;**336**:525–533.
145. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, Testani JM, Tang WHW, Orso F, Rossignol P, Metra M, Filippatos G, Seferovic PM, Ruschitzka F, Coats AJ. The use of diuretics in heart failure with congestion – a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:137–155.
146. Rohde LE, Rover MM, Figueiredo Neto JA, Danzmann LC, Bertoldi EG, Simoes MV, Silvestre OM, Ribeiro ALP, Moura LZ, Beck-da-Silva L, Prado D, Sant'Anna RT, Bridi LH, Zimerman A, Raupp da Rosa P, Biolo A. Short-term diuretic withdrawal in stable outpatients with mild heart failure and no fluid retention receiving optimal therapy: a double-blind, multicentre, randomized trial. *Eur Heart J* 2019;**40**:3605–3612.
147. Cohn JN, Tognoni G, Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;**345**:1667–1675.
148. Bohm M, Borer J, Ford I, Gonzalez-Juanatey JR, Komajda M, Lopez-Sendon J, Reil JC, Swedberg K, Tavazzi L. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. *Clin Res Cardiol* 2013;**102**:11–22.
149. Ouyang AJ, Lv YN, Zhong HL, Wen JH, Wei XH, Peng HW, Zhou J, Liu LL. Meta-analysis of digoxin use and risk of mortality in patients with atrial fibrillation. *Am J Cardiol* 2015;**115**:901–906.
150. Vamos M, Erath JW, Hohnloser SH. Digoxin-associated mortality: a systematic review and meta-analysis of the literature. *Eur Heart J* 2015;**36**:1831–1838.
151. Ziff OJ, Lane DA, Samra M, Griffith M, Kirchhof P, Lip GY, Steeds RP, Townend J, Kotecha D. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. *BMJ* 2015;**351**:h4451.
152. Van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, Hillege HL, Bergsma-Kadijk JA, Cornel JH, Kamp O, Tukkie R, Bosker HA, Van Veldhuisen DJ, Van den Berg MP, RACE II Investigators. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med* 2010;**362**:1363–1373.
153. Bavishi C, Khan AR, Ather S. Digoxin in patients with atrial fibrillation and heart failure: a meta-analysis. *Int J Cardiol* 2015;**188**:99–101.
154. Freeman JV, Reynolds K, Fang M, Udaltsova N, Steimle A, Pomernacki NK, Borowsky LH, Harrison TN, Singer DE, Go AS. Digoxin and risk of death in adults with atrial fibrillation: the ATRIA-CVRN study. *Circ Arrhythm Electrophysiol* 2015;**8**:49–58.
155. Washam JB, Stevens SR, Lokhnygina Y, Halperin JL, Breithardt G, Singer DE, Mahaffey KW, Hankey GJ, Berkowitz SD, Nessel CC, Fox KA, Califf RM, Piccini JP, Patel MR, ROCKET Steering Committee and Investigators. Digoxin use in patients with atrial fibrillation AF and adverse cardiovascular outcomes: retrospective analysis of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin a K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). *Lancet* 2015;**385**:2363–2370.
156. Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA* 2003;**289**:871–878.
157. Adams KF, Jr., Patterson JH, Gattis WA, O'Connor CM, Lee CR, Schwartz TA, Gheorghiade M. Relationship of serum digoxin concentration to mortality and morbidity in women in the Digitalis Investigation Group trial: a retrospective analysis. *J Am Coll Cardiol* 2005;**46**:497–504.
158. Bavendiek U, Berliner D, Davila LA, Schwab J, Maier L, Philipp SA, Rieth A, Westenfeld R, Piorkowski C, Weber K, Hanselmann A, Oldhafer M, Schallhorn S, von der Leyen H, Schroder C, Veltmann C, Stork S, Bohm M, Koch A, Bauersachs J, DIGIT-HF Investigators and Committees. Rationale and design of the DIGIT-HF trial (DIGitoxin to Improve ouTcomes in patients with advanced chronic Heart Failure): a randomized, double-blind, placebo-controlled study. *Eur J Heart Fail* 2019;**21**:676–684.
159. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, Adams KF, Anand I, Arias-Mendoza A, Biering-Sorensen T, Bohm M, Bonderman D, Cleland JGF, Corbalan R, Crespo-Leiro MG, Dahlstrom U, Echeverria LE, Fang JC, Filippatos G, Fonseca C, Goncalvesova E, Goudev AR, Howlett JG, Lanfear DE, Li J, Lund M, Macdonald P, Mareev V, Momomura SI, O'Meara E, Parkhomenko A, Ponikowski P, Ramires FJA, Serpytis P, Sliwa K, Spinar J, Suter TM, Tomcsanyi J, Vandekerckhove H, Vinereanu D, Voors AA, Yilmaz MB, Zannad F, Sharpsten L, Legg JC, Varin C, Honarpour N, Abbasi SA, Malik FI, Kurtz CE, GALACTIC-HF Investigators. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. *N Engl J Med* 2021;**384**:105–116.
160. Shen L, Jhund PS, Petrie MC, Claggett BL, Barlera S, Cleland JGF, Dargie HJ, Granger CB, Kjekshus J, Kû¡ber L, Latini R, Maggioni AP, Packer M, Pitt B, Solomon SD, Swedberg K, Tavazzi L, Wikstrand J, Zannad F, Zile MR, McMurray JJV. Declining risk of sudden death in heart failure. *N Engl J Med* 2017;**377**:41–51.
161. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH, Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;**352**:225–237.
162. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, Greene HL, Boczor S, Domanski M, Follmann D, Gent M, Roberts RS, investigators of the AVID, CASH and CIDS studies. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. *Eur Heart J* 2000;**21**:2071–2078.
163. Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;**337**:1576–1583.
164. Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000;**102**:748–754.
165. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML, Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;**346**:877–883.
166. Kober L, Thune JJ, Nielsen JC, Haarbo J, Videbaek L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjaer H, Brandes A, Thogersen AM, Gustafsson F, Egstrup K, Videbaek R, Hassager C, Svendsen JH, Hofsten DE, Torp-Pedersen C, Pehrson S, DANISH Investigators. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016;**375**:1221–1230.
167. Beggs SAS, Jhund PS, Jackson CE, McMurray JJV, Gardner RS. Non-ischaemic cardiomyopathy, sudden death and implantable defibrillators: a review and meta-analysis. *Heart* 2018;**104**:144–150.
168. Merchant FM, Jones P, Wehrenberg S, Lloyd MS, Saxon LA. Incidence of defibrillator shocks after elective generator exchange following uneventful first battery life. *J Am Heart Assoc* 2014;**3**:e001289.
169. Yap SC, Schaer BA, Bhagwandien RE, Kuhne M, Dabiri Abkenari L, Osswald S, Szili-Torok T, Sticherling C, Theuns DA. Evaluation of the need of elective implantable cardioverter-defibrillator generator replacement in primary prevention patients without prior appropriate ICD therapy. *Heart* 2014;**100**:1188–1192.
170. Kini V, Soufi MK, Deo R, Epstein AE, Bala R, Riley M, Groeneveld PW, Shalaby A, Dixit S. Appropriateness of primary prevention implantable cardioverter-defibrillators at the time of generator replacement: are indications still met? *J Am Coll Cardiol* 2014;**63**:2388–2394.
171. Erkapic D, Sperzel J, Stiller S, Meltendorf U, Mermi J, Wegscheider K, Hugl B, Investigators I. Long-term benefit of implantable cardioverter/defibrillator therapy after elective device replacement: results of the INcidence free SUrvival after ICD REplacement (INSURE) trial–a prospective multicentre study. *Eur Heart J* 2013;**34**:130–137.
172. Alsheikh-Ali AA, Homer M, Maddukuri PV, Kalsmith B, Estes NA, 3rd, Link MS. Time-dependence of appropriate implantable defibrillator therapy in patients with ischemic cardiomyopathy. *J Cardiovasc Electrophysiol* 2008;**19**:784–789.
173. Opreanu M, Wan C, Singh V, Salehi N, Ahmad J, Szymkiewicz SJ, Thakur RK. Wearable cardioverter-defibrillator as a bridge to cardiac transplantation: a national database analysis. *J Heart Lung Transplant* 2015;**34**:1305–1309.
174. Zishiri ET, Williams S, Cronin EM, Blackstone EH, Ellis SG, Roselli EE, Smedira NG, Gillinov AM, Glad JA, Tchou PJ, Szymkiewicz SJ, Chung MK. Early risk of mortality after coronary artery revascularization in patients with left ventricular dysfunction and potential role of the wearable cardioverter defibrillator. *Circ Arrhythm Electrophysiol* 2013;**6**:117–128.
175. Kutyifa V, Moss AJ, Klein H, Biton Y, McNitt S, MacKecknie B, Zareba W, Goldenberg I. Use of the wearable cardioverter defibrillator in high-risk cardiac patients: data from the Prospective Registry of Patients Using the Wearable Cardioverter Defibrillator (WEARIT-II Registry). *Circulation* 2015;**132**:1613–1619.
176. Kutyifa V, Moss AJ, Klein HU, McNitt S, Zareba W, Goldenberg I. One-year follow-up of the Prospective Registry of Patients Using the Wearable Defibrillator (WEARIT-II Registry). *Pacing Clin Electrophysiol* 2018;**41**:1307–1313.
177. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, Fain E, Gent M, Connolly SJ, DINAMIT Investigators. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004;**351**:2481–2488.
178. Steinbeck G, Andresen D, Seidl K, Brachmann J, Hoffmann E, Wojciechowski D, Kornacewicz-Jach Z, Sredniawa B, Lupkovics G, Hofgartner F, Lubinski A, Rosenqvist M, Habets A, Wegscheider K, Senges J, IRIS Investigators.

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Defibrillator implantation early after myocardial infarction. *N Engl J Med* 2009;**361**:1427–1436.
179. Sanders GD, Hlatky MA, Owens DK. Cost-effectiveness of implantable cardioverter-defibrillators. *N Engl J Med* 2005;**353**:1471–1480.
180. Steinberg BA, Al-Khatib SM, Edwards R, Han J, Bardy GH, Bigger JT, Buxton AE, Moss AJ, Lee KL, Steinman R, Dorian P, Hallstrom A, Cappato R, Kadish AH, Kudenchuk PJ, Mark DB, Inoue LY, Sanders GD. Outcomes of implantable cardioverter-defibrillator use in patients with comorbidities: results from a combined analysis of 4 randomized clinical trials. *JACC Heart Fail* 2014;**2**:623–629.
181. Raphael CE, Finegold JA, Barron AJ, Whinnett ZI, Mayet J, Linde C, Cleland JG, Levy WC, Francis DP. The effect of duration of follow-up and presence of competing risk on lifespan-gain from implantable cardioverter defibrillator therapy: who benefits the most? *Eur Heart J* 2015;**36**:1676–1688.
182. Miller RJ, Howlett JG, Exner DV, Campbell PM, Grant AD, Wilton SB. Baseline functional class and therapeutic efficacy of common heart failure interventions: a systematic review and meta-analysis. *Can J Cardiol* 2015;**31**:792–799.
183. Hess PL, Al-Khatib SM, Han JY, Edwards R, Bardy GH, Bigger JT, Buxton A, Cappato R, Dorian P, Hallstrom A, Kadish AH, Kudenchuk PJ, Lee KL, Mark DB, Moss AJ, Steinman R, Inoue LY, Sanders G. Survival benefit of the primary prevention implantable cardioverter-defibrillator among older patients: does age matter? An analysis of pooled data from 5 clinical trials. *Circ Cardiovasc Qual Outcomes* 2015;**8**:179–186.
184. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, Mitchell LB, Green MS, Klein GJ, O'Brien B. Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000;**101**:1297–1302.
185. Kober L, Torp-Pedersen C, McMurray JJ, Gotzsche O, Levy S, Crijns H, Amlie J, Carlsen J, Dronedarone Study Group. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008;**358**:2678–2687.
186. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, Arensberg D, Baker A, Friedman L, Greene HL. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991;**324**:781–788.
187. Theuns DA, Smith T, Hunink MG, Bardy GH, Jordaens L. Effectiveness of prophylactic implantation of cardioverter-defibrillators without cardiac resynchronization therapy in patients with ischaemic or non-ischaemic heart disease: a systematic review and meta-analysis. *Europace* 2010;**12**:1564–1570.
188. Elming MB, Nielsen JC, Haarbo J, Videbaek L, Korup E, Signorovitch J, Olesen LL, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjaer H, Brandes A, Thogersen AM, Gustafsson F, Egstrup K, Videbaek R, Hassager C, Svendsen JH, Hofsten DE, Torp-Pedersen C, Pehrson S, Kober L, Thune JJ. Age and outcomes of primary prevention implantable cardioverter-defibrillators in patients with nonischemic systolic heart failure. *Circulation* 2017;**136**:1772–1780.
189. Selvanayagam JB, Hartshorne T, Billot L, Grover S, Hillis GS, Jung W, Krum H, Prasad S, McGavigan AD. Cardiovascular magnetic resonance-GUIDEd management of mild to moderate left ventricular systolic dysfunction (CMR GUIDE): Study protocol for a randomized controlled trial. *Ann Noninvasive Electrocardiol* 2017;**22**:e12420.
190. Leyva F, Zegard A, Acquaye E, Gubran C, Taylor R, Foley PWX, Umar F, Patel K, Panting J, Marshall H, Qiu T. Outcomes of cardiac resynchronization therapy with or without defibrillation in patients with nonischemic cardiomyopathy. *J Am Coll Cardiol* 2017;**70**:1216–1227.
191. Di Marco A, Anguera I, Schmitt M, Klem I, Neilan TG, White JA, Sramko M, Masci PG, Barison A, McKenna P, Mordi I, Haugaa KH, Leyva F, Rodriguez Capitan J, Satoh H, Nabeta T, Dallaglio PD, Campbell NG, Sabate X, Cequier A. Late gadolinium enhancement and the risk for ventricular arrhythmias or sudden death in dilated cardiomyopathy: systematic review and meta-analysis. *JACC Heart Fail* 2017;**5**:28–38.
192. Gulati A, Jabbour A, Ismail TF, Guha K, Khwaja J, Raza S, Morarji K, Brown TD, Ismail NA, Dweck MR, Di Pietro E, Roughton M, Wage R, Daryani Y, O'Hanlon R, Sheppard MN, Alpendurada F, Lyon AR, Cook SA, Cowie MR, Assomull RG, Pennell DJ, Prasad SK. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. *JAMA* 2013;**309**:896–908.
193. Stewart GC, Weintraub JR, Pratibhu PP, Semigran MJ, Camuso JM, Brooks K, Tsang SW, Anello MS, Nguyen VT, Lewis EF, Nohria A, Desai AS, Givertz MM, Stevenson LW. Patient expectations from implantable defibrillators to prevent death in heart failure. *J Card Fail* 2010;**16**:106–113.
194. Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP, Estes NA, 3rd, Greenberg H, Hall WJ, Huang DT, Kautzner J, Klein H, McNitt S, Olshansky B, Shoda M, Wilber D, Zareba W, MADIT-RIT Trial Investigators. Reduction in inappropriate therapy and mortality through ICD programming. *N Engl J Med* 2012;**367**:2275–2283.
195. Healey JS, Hohnloser SH, Glikson M, Neuzner J, Mabo P, Vinolas X, Kautzner J, O'Hara G, VanErven L, Gadler F, Pogue J, Appl U, Gilkerson J, Pochet T, Stein KM, Merkely B, Chrolavicius S, Meeks B, Foldesi C, Thibault B, Connolly SJ, Shockless IMPLant Evaluation Investigators. Cardioverter defibrillator implantation without induction of ventricular fibrillation: a single-blind, non-inferiority, randomised controlled trial (SIMPLE). *Lancet* 2015;**385**:785–791.
196. Gasparini M, Proclemer A, Klersy C, Kloppe A, Lunati M, Ferrer JB, Hersi A, Gulaj M, Wijfels MC, Santi E, Manotta L, Arenal A. Effect of long-detection interval vs standard-detection interval for implantable cardioverter-defibrillators on antitachycardia pacing and shock delivery: the ADVANCE III randomized clinical trial. *JAMA* 2013;**309**:1903–1911.
197. Cleland JG, Buga L. Device therapy: defibrillators–a shocking therapy for cardiomyopathy? *Nat Rev Cardiol* 2010;**7**:69–70.
198. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, Kutalek SP, Sharma A, Dual Chamber and VVI Implantable Defibrillator Trial Investigators. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *JAMA* 2002;**288**:3115–3123.
199. Boersma L, Barr C, Knops R, Theuns D, Eckardt L, Neuzil P, Scholten M, Hood M, Kuschyk J, Jones P, Duffy E, Husby M, Stein K, Lambiase PD, Group EI. Implant and midterm outcomes of the subcutaneous implantable cardioverter-defibrillator registry: the EFFORTLESS study. *J Am Coll Cardiol* 2017;**70**:830–841.
200. Burke MC, Gold MR, Knight BP, Barr CS, Theuns D, Boersma LVA, Knops RE, Weiss R, Leon AR, Herre JM, Husby M, Stein KM, Lambiase PD. Safety and efficacy of the totally subcutaneous implantable defibrillator: 2-year results from a pooled analysis of the IDE study and EFFORTLESS registry. *J Am Coll Cardiol* 2015;**65**:1605–1615.
201. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ, ESC Scientific Document Group. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015;**36**:2793–2867.
202. Knops RE, Olde Nordkamp LRA, Delnoy PHM, Boersma LVA, Kuschyk J, El-Chami MF, Bonnemeier H, Behr ER, Brouwer TF, Kaab S, Mittal S, Quast ABE, Smeding L, van der Stuijt W, de Weger A, de Wilde KC, Bijsterveld NR, Richter S, Brouwer MA, de Groot JR, Kooiman KM, Lambiase PD, Neuzil P, Vernooy K, Alings M, Betts TR, Bracke F, Burke MC, de Jong J, Wright DJ, Tijssen JGP, Wilde AAM, PRAETORIAN Investigators. Subcutaneous or transvenous defibrillator therapy. *N Engl J Med* 2020;**383**:526–536.
203. Duncker D, Konig T, Hohmann S, Bauersachs J, Veltmann C. Avoiding untimely implantable cardioverter/defibrillator implantation by intensified heart failure therapy optimization supported by the wearable cardioverter/defibrillator–the PROLONG Study. *J Am Heart Assoc* 2017;**6**:e004512.
204. Olgin JE, Pletcher MJ, Vittinghoff E, Wranicz J, Malik R, Morin DP, Zweibel S, Buxton AE, Elayi CS, Chung EH, Rashba E, Borggrefe M, Hue TF, Maguire C, Lin F, Simon JA, Hulley S, Lee BK, VEST Investigators. Wearable cardioverter-defibrillator after myocardial infarction. *N Engl J Med* 2018;**379**:1205–1215.
205. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood GA, Santini M, Bailleul C, Daubert JC, Multisite Stimulation in Cardiomyopathies (MUSTIC) Study Investigators. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;**344**:873–880.
206. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L, Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–1549.
207. Daubert C, Gold MR, Abraham WT, Ghio S, Hassager C, Goode G, Szili-Torok T, Linde C, REVERSE Study Group. Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction: insights from the European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial. *J Am Coll Cardiol* 2009;**54**:1837–1846.
208. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. *Eur Heart J* 2006;**27**:1928–1932.
209. Cleland JG, Freemantle N, Erdmann E, Gras D, Kappenberger L, Tavazzi L, Daubert JC. Long-term mortality with cardiac resynchronization therapy in the Cardiac Resynchronization-Heart Failure (CARE-HF) trial. *Eur J Heart Fail* 2012;**14**:628–634.
210. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM, Comparison of Medical Therapy Pacing and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable

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defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–2150.
211. Cleland JG, Abraham WT, Linde C, Gold MR, Young JB, Claude Daubert J, Sherfesee L, Wells GA, Tang AS. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. *Eur Heart J* 2013;**34**:3547–3556.
212. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;**363**:2385–2395.
213. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA, 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W, MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;**361**:1329–1338.
214. Goldenberg I, Kutyifa V, Klein HU, Cannom DS, Brown MW, Dan A, Daubert JP, Estes NA, 3rd, Foster E, Greenberg H, Kautzner J, Klempfner R, Kuniss M, Merkely B, Pfeffer MA, Quesada A, Viskin S, McNitt S, Polonsky B, Ghanem A, Solomon SD, Wilber D, Zareba W, Moss AJ. Survival with cardiac-resynchronization therapy in mild heart failure. *N Engl J Med* 2014;**370**:1694–1701.
215. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C, REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction) Study Group. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol* 2008;**52**:1834–1843.
216. Curtis AB, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfesee L, Shinn T, Sutton MS, Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK AF) Trial Investigators. Biventricular pacing for atrioventricular block and systolic dysfunction. *N Engl J Med* 2013;**368**:1585–1593.
217. Brignole M, Botto G, Mont L, Iacopino S, De Marchi G, Oddone D, Luzi M, Tolosana JM, Navazio A, Menozzi C. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. *Eur Heart J* 2011;**32**:2420–2429.
218. Stavrakis S, Garabelli P, Reynolds DW. Cardiac resynchronization therapy after atrioventricular junction ablation for symptomatic atrial fibrillation: a meta-analysis. *Europace* 2012;**14**:1490–1497.
219. Leclercq C, Walker S, Linde C, Clementy J, Marshall AJ, Ritter P, Djiane P, Mabo P, Levy T, Gadler F, Bailleul C, Daubert JC. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. *Eur Heart J* 2002;**23**:1780–1787.
220. Woods B, Hawkins N, Mealing S, Sutton A, Abraham WT, Beshai JF, Klein H, Sculpher M, Plummer CJ, Cowie MR. Individual patient data network meta-analysis of mortality effects of implantable cardiac devices. *Heart* 2015;**101**:1800–1806.
221. Gage RM, Burns KV, Bank AJ. Echocardiographic and clinical response to cardiac resynchronization therapy in heart failure patients with and without previous right ventricular pacing. *Eur J Heart Fail* 2014;**16**:1199–1205.
222. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, Dickstein K, Ford I, Gorcsan J, 3rd, Gras D, Krum H, Sogaard P, Holzmeister J, EchoCRT Study Group. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *N Engl J Med* 2013;**369**:1395–1405.
223. Steffel J, Robertson M, Singh JP, Abraham WT, Bax JJ, Borer JS, Dickstein K, Ford I, Gorcsan J, 3rd, Gras D, Krum H, Sogaard P, Holzmeister J, Brugada J, Ruschitzka F. The effect of QRS duration on cardiac resynchronization therapy in patients with a narrow QRS complex: a subgroup analysis of the EchoCRT trial. *Eur Heart J* 2015;**36**:1983–1989.
224. Zusterzeel R, Selzman KA, Sanders WE, Canos DA, O'Callaghan KM, Carpenter JL, Pina IL, Strauss DG. Cardiac resynchronization therapy in women: US Food and Drug Administration meta-analysis of patient-level data. *JAMA Intern Med* 2014;**174**:1340–1348.
225. Sohaib SM, Finegold JA, Nijjer SS, Hossain R, Linde C, Levy WC, Sutton R, Kanagaratnam P, Francis DP, Whinnett ZI. Opportunity to increase life span in narrow QRS cardiac resynchronization therapy recipients by deactivating ventricular pacing: evidence from randomized controlled trials. *JACC Heart Fail* 2015;**3**:327–336.
226. Greenberg H, Case RB, Moss AJ, Brown MW, Carroll ER, Andrews ML, MADIT-II Investigators. Analysis of mortality events in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II). *J Am Coll Cardiol* 2004;**43**:1459–1465.
227. Linde C, Gold MR, Abraham WT, St John Sutton M, Ghio S, Cerkvenik J, Daubert C, REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction Study Group. Long-term impact of cardiac resynchronization therapy in mild heart failure: 5-year results from the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study. *Eur Heart J* 2013;**34**:2592–2599.
228. Cleland JG, Mareev Y, Linde C. Reflections on EchoCRT: sound guidance on QRS duration and morphology for CRT? *Eur Heart J* 2015;**36**:1948–1951.
229. Linde C, Stahlberg M, Benson L, Braunschweig F, Edner M, Dahlstrom U, Alehagen U, Lund LH. Gender, underutilization of cardiac resynchronization therapy, and prognostic impact of QRS prolongation and left bundle branch block in heart failure. *Europace* 2015;**17**:424–431.
230. Cunnington C, Kwok CS, Satchithananda DK, Patwala A, Khan MA, Zaidi A, Ahmed FZ, Mamas MA. Cardiac resynchronisation therapy is not associated with a reduction in mortality or heart failure hospitalisation in patients with non-left bundle branch block QRS morphology: meta-analysis of randomised controlled trials. *Heart* 2015;**101**:1456–1462.
231. Doshi RN, Daoud EG, Fellows C, Turk K, Duran A, Hamdan MH, Pires LA, PAVE Study Group. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). *J Cardiovasc Electrophysiol* 2005;**16**:1160–1165.
232. Koplan BA, Kaplan AJ, Weiner S, Jones PW, Seth M, Christman SA. Heart failure decompensation and all-cause mortality in relation to percent biventricular pacing in patients with heart failure: is a goal *of 100% biventricular pacing necessary? J Am Coll Cardiol* 2009;**53**:355–360.
233. Hawkins NM, Petrie MC, Burgess MI, McMurray JJ. Selecting patients for cardiac resynchronization therapy: the fallacy of echocardiographic dyssynchrony. *J Am Coll Cardiol* 2009;**53**:1944–1959.
234. Beela AS, Unlu S, Duchenne J, Ciarka A, Daraban AM, Kotrc M, Aarones M, Szulik M, Winter S, Penicka M, Neskovic AN, Kukulski T, Aakhus S, Willems R, Fehske W, Faber L, Stankovic I, Voigt JU. Assessment of mechanical dyssynchrony can improve the prognostic value of guideline-based patient selection for cardiac resynchronization therapy. *Eur Heart J Cardiovasc Imaging* 2019;**20**:66–74.
235. Khan FZ, Virdee MS, Palmer CR, Pugh PJ, O'Halloran D, Elsik M, Read PA, Begley D, Fynn SP, Dutka DP. Targeted left ventricular lead placement to guide cardiac resynchronization therapy: the TARGET study: a randomized, controlled trial. *J Am Coll Cardiol* 2012;**59**:1509–1518.
236. Saba S, Marek J, Schwartzman D, Jain S, Adelstein E, White P, Oyenuga OA, Onishi T, Soman P, Gorcsan J, 3rd. Echocardiography-guided left ventricular lead placement for cardiac resynchronization therapy: results of the Speckle Tracking Assisted Resynchronization Therapy for Electrode Region trial. *Circ Heart Fail* 2013;**6**:427–434.
237. Kosmala W, Marwick TH. Meta-analysis of effects of optimization of cardiac resynchronization therapy on left ventricular function, exercise capacity, and quality of life in patients with heart failure. *Am J Cardiol* 2014;**113**:988–994.
238. Whinnett ZI, Francis DP, Denis A, Willson K, Pascale P, van Geldorp I, De Guillebon M, Ploux S, Ellenbogen K, Haissaguerre M, Ritter P, Bordachar P. Comparison of different invasive hemodynamic methods for AV delay optimization in patients with cardiac resynchronization therapy: implications for clinical trial design and clinical practice. *Int J Cardiol* 2013;**168**:2228–2237.
239. Daubert C, Behar N, Martins RP, Mabo P, Leclercq C. Avoiding non-responders to cardiac resynchronization therapy: a practical guide. *Eur Heart J* 2017;**38**:1463–1472.
240. Mullens W, Auricchio A, Martens P, Witte K, Cowie MR, Delgado V, Dickstein K, Linde C, Vernooy K, Leyva F, Bauersachs J, Israel CW, Lund LH, Donal E, Boriani G, Jaarsma T, Berruezo A, Traykov V, Yousef Z, Kalarus Z, Cosedis Nielsen J, Steffel J, Vardas P, Coats A, Seferovic P, Edvardsen T, Heidbuchel H, Ruschitzka F, Leclercq C. Optimized implementation of cardiac resynchronization therapy: a call for action for referral and optimization of care: a joint position statement from the Heart Failure Association (HFA), European Heart Rhythm Association (EHRA), and European Association of Cardiovascular Imaging (EACVI) of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:2349–2369.
240a. Glikson M, Nielsen JC, Michowitz Y, Kronborg MB, Auricchio A, Barbash IM, Barrabés JA, Boriani G, Braunschweig F, Brignole M, Burri H, Coats AJS, Deharo JC, Delgado V, Diller GP, Israel CW, Keren A, Knops RE, Kotecha D, Leclercq C, Merkely B, Starck C, Thylén I, Tolosana JM; ESC Scientific Document Group. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J* 2021; doi: 10.1093/eurheartj/ehab364 [Epub ahead of print].
241. Abraham WT, Kuck KH, Goldsmith RL, Lindenfeld J, Reddy VY, Carson PE, Mann DL, Saville B, Parise H, Chan R, Wiegn P, Hastings JL, Kaplan AJ, Edelmann F, Luthje L, Kahwash R, Tomassoni GF, Gutterman DD, Stagg A, Burkhoff D, Hasenfuss G. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation. *JACC Heart Fail* 2018;**6**:874–883.
242. NICE: National Institute for Health and Care Excellence. Interventional procedures guidance. Cardiac contractility modulation device implantation for heart failure. www.nice.org.uk/guidance/ipg655 (28 May 2021).

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab368/6358045 by guest on 08 September 2021

243. Abraham WT, Zile MR, Weaver FA, Butter C, Ducharme A, Halbach M, Klug D, Lovett EG, Muller-Ehmsen J, Schafer JE, Senni M, Swarup V, Wachter R, Little WC. Baroreflex activation therapy for the treatment of heart failure with a reduced ejection fraction. *JACC Heart Fail* 2015;**3**:487–496.
244. Zile MR, Lindenfeld J, Weaver FA, Zannad F, Galle E, Rogers T, Abraham WT. Baroreflex activation therapy in patients with heart failure with reduced ejection fraction. *J Am Coll Cardiol* 2020;**76**:1–13.
245. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. *Lancet* 2003;**362**:777–781.
246. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM, TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014;**370**:1383–1392.
247. Solomon SD, Vaduganathan M, Claggett BL, Packer M, Zile M, Swedberg K, Rouleau J, Pfeffer MA, Desai A, Lund LH, Kober L, Anand I, Sweitzer N, Linssen G, Merkely B, Luis Arango J, Vinereanu D, Chen CH, Senni M, Sibulo A, Boytsov S, Shi V, Rizkala A, Lefkowitz M, McMurray JJV. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. *Circulation* 2020;**141**:352–361.
248. Rogers JK, Pocock SJ, McMurray JJ, Granger CB, Michelson EL, Ostergren J, Pfeffer MA, Solomon SD, Swedberg K, Yusuf S. Analysing recurrent hospitalizations in heart failure: a review of statistical methodology, with application to CHARM-Preserved. *Eur J Heart Fail* 2014;**16**:33–40.
249. van Veldhuisen DJ, Cohen-Solal A, Bohm M, Anker SD, Babalis D, Roughton M, Coats AJ, Poole-Wilson PA, Flather MD, SENIORS Investigators. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: data from SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). *J Am Coll Cardiol* 2009;**53**:2150–2158.
250. Hai OY, Mentz RJ, Zannad F, Gasparini M, De Ferrari GM, Daubert JC, Holzmeister J, Lam CS, Pochet T, Vincent A, Linde C. Cardiac resynchronization therapy in heart failure patients with less severe left ventricular dysfunction. *Eur J Heart Fail* 2015;**17**:135–143.
251. Shah SJ, Feldman T, Ricciardi MJ, Kahwash R, Lilly S, Litwin S, Nielsen CD, van der Harst P, Hoendermis E, Penicka M, Bartunek J, Fail PS, Kaye DM, Walton A, Petrie MC, Walker N, Basuray A, Yakubov S, Hummel SL, Chetcuti S, Forde-McLean R, Herrmann HC, Burkhoff D, Massaro JM, Cleland JGF, Mauri L. One-year safety and clinical outcomes of a transcatheter interatrial shunt device for the treatment of heart failure with preserved ejection fraction in the Reduce Elevated Left Atrial Pressure in Patients With Heart Failure (REDUCE LAP-HF I) Trial: a randomized clinical trial. *JAMA Cardiol* 2018;**3**:968–977.
252. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Yusuf S, Pocock S, CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003;**362**:759–766.
253. Dewan P, Jackson A, Lam CSP, Pfeffer MA, Zannad F, Pitt B, Solomon SD, McMurray JJV. Interactions between left ventricular ejection fraction, sex and effect of neurohumoral modulators in heart failure. *Eur J Heart Fail* 2020;**22**:898–901.
254. Campbell RT, Petrie MC, McMurray JJV. Redefining heart failure phenotypes based on ejection fraction. *Eur J Heart Fail* 2018;**20**:1634–1635.
255. Echocardiographic Normal Ranges Meta-Analysis of the Left Heart Collaboration. Ethnic-specific normative reference values for echocardiographic LA and LV size, LV mass, and systolic function: the EchoNoRMAL Study. *JACC Cardiovasc Imaging* 2015;**8**:656–665.
256. Wehner GJ, Jing L, Haggerty CM, Suever JD, Leader JB, Hartzel DN, Kirchner HL, Manus JNA, James N, Ayar Z, Gladding P, Good CW, Cleland JGF, Fornwalt BK. Routinely reported ejection fraction and mortality in clinical practice: where does the nadir of risk lie? *Eur Heart J* 2020;**41**:1249–1257.
257. Stewart S, Playford D, Scalia GM, Currie P, Celermajer DS, Prior D, Codde J, Strange G, NEDA Investigators. Ejection fraction and mortality: a nationwide register-based cohort study of 499 153 women and men. *Eur J Heart Fail* 2021;**23**:406–416.
258. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2020;**17**:559–573.
259. Pieske B, Tschope C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J* 2019;**40**:3297–3317.
260. Ho JE, Zern EK, Wooster L, Bailey CS, Cunningham T, Eisman AS, Hardin KM, Zampierollo GA, Jarolim P, Pappagianopoulos PP, Malhotra R, Nayor M, Lewis GD. Differential clinical profiles, exercise responses, and outcomes associated with existing HFpEF definitions. *Circulation* 2019;**140**:353–365.
261. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation* 2018;**138**:861–870.
262. Segar MW, Patel KV, Berry JD, Grodin JL, Pandey A. Generalizability and implications of the H2FPEF score in a cohort of patients with heart failure with preserved ejection fraction. *Circulation* 2019;**139**:1851–1853.
263. Myhre PL, Vaduganathan M, Claggett BL, Lam CSP, Desai AS, Anand IS, Sweitzer NK, Fang JC, O'Meara E, Shah SJ, Shah AM, Lewis EF, Rouleau J, Pitt B, Solomon SD. Application of the H2 FPEF score to a global clinical trial of patients with heart failure with preserved ejection fraction: the TOPCAT trial. *Eur J Heart Fail* 2019;**21**:1288–1291.
264. Sepehrvand N, Alemayehu W, Dyck GJB, Dyck JRB, Anderson T, Howlett J, Paterson I, McAlister FA, Ezekowitz JA. External validation of the H2F-PEF model in diagnosing patients with heart failure and preserved ejection fraction. *Circulation* 2019;**139**:2377–2379.
265. Sueta D, Yamamoto E, Nishihara T, Tokitsu T, Fujisue K, Oike F, Takae M, Usuku H, Takashio S, Arima Y, Suzuki S, Nakamura T, Ito M, Kanazawa H, Sakamoto K, Kaikita K, Tsujita K. H2FPEF score as a prognostic value in HFpEF patients. *Am J Hypertens* 2019;**32**:1082–1090.
266. Barandiaran Aizpurua A, Sanders-van Wijk S, Brunner-La Rocca HP, Henkens M, Heymans S, Beussink-Nelson L, Shah SJ, van Empel VPM. Validation of the HFA-PEFF score for the diagnosis of heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020;**22**:413–421.
267. Sanders-van Wijk S, Barandiaran Aizpurua A, Brunner-La Rocca HP, Henkens M, Weerts J, Knackstedt C, Uszko-Lencer N, Heymans S, van Empel V. The HFA-PEFF and H2 FPEF scores largely disagree in classifying patients with suspected heart failure with preserved ejection fraction. *Eur J Heart Fail* 2021;**23**:838–840.
268. Selvaraj S, Myhre PL, Vaduganathan M, Claggett BL, Matsushita K, Kitzman DW, Borlaug BA, Shah AM, Solomon SD. Application of diagnostic algorithms for heart failure with preserved ejection fraction to the community. *JACC Heart Fail* 2020;**8**:640–653.
269. Ouwerkerk W, Tromp J, Jin X, Jaufeerally F, Yeo PSD, Leong KTG, Ong HY, Ling LH, Loh SY, Sim D, Lee S, Soon D, Chin C, Richards AM, Lam CSP. Heart failure with preserved ejection fraction diagnostic scores in an Asian population. *Eur J Heart Fail* 2020;**22**:1737–1739.
270. Playford D, Strange G, Celermajer DS, Evans G, Scalia GM, Stewart S, Prior D, NEDA Investigators. Diastolic dysfunction and mortality in 436 360 men and women: the National Echo Database Australia (NEDA). *Eur Heart J Cardiovasc Imaging* 2021;**22**:505–515.
271. Halliday BP, Wassall R, Lota AS, Khalique Z, Gregson J, Newsome S, Jackson R, Rahneva T, Wage R, Smith G, Venneri L, Tayal U, Auger D, Midwinter W, Whiffin N, Rajani R, Dungu JN, Pantazis A, Cook SA, Ware JS, Baksi AJ, Pennell DJ, Rosen SD, Cowie MR, Cleland JGF, Prasad SK. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet* 2019;**393**:61–73.
272. Lupon J, Gavidia-Bovadilla G, Ferrer E, de Antonio M, Perera-Lluna A, Lopez-Ayerbe J, Domingo M, Nunez J, Zamora E, Moliner P, Santiago-Vacas E, Santesmases J, Bayes-Genis A. Heart failure with preserved ejection fraction infrequently evolves toward a reduced phenotype in long-term survivors. *Circ Heart Fail* 2019;**12**:e005652.
273. Savarese G, Vedin O, D'Amario D, Uijl A, Dahlstrom U, Rosano G, Lam CSP, Lund LH. Prevalence and prognostic implications of longitudinal ejection fraction change in heart failure. *JACC Heart Fail* 2019;**7**:306–317.
274. Nauta JF, Hummel YM, van der Meer P, Lam CSP, Voors AA, van Melle JP. Correlation with invasive left ventricular filling pressures and prognostic relevance of the echocardiographic diastolic parameters used in the 2016 ESC heart failure guidelines and in the 2016 ASE/EACVI recommendations: a systematic review in patients with heart failure with preserved ejection fraction. *Eur J Heart Fail* 2018;**20**:1303–1311.
275. Sharifov OF, Schiros CG, Aban I, Denney TS, Gupta H. Diagnostic accuracy of tissue Doppler index E/e' for evaluating left ventricular filling pressure and diastolic dysfunction/heart failure with preserved ejection fraction: a systematic review and meta-analysis. *J Am Heart Assoc* 2016;**5**:e002078.
276. Eisman AS, Shah RV, Dhakal BP, Pappagianopoulos PP, Wooster L, Bailey C, Cunningham TF, Hardin KM, Baggish AL, Ho JE, Malhotra R, Lewis GD. Pulmonary capillary wedge pressure patterns during exercise predict exercise capacity and incident heart failure. *Circ Heart Fail* 2018;**11**:e004750.

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277. Cleland JG, Tendera M, Adamus J, Freemantle N, Gray CS, Lye M, O'Mahony D, Polonski L, Taylor J. Perindopril for elderly people with chronic heart failure: the PEP-CHF study. The PEP Investigators. *Eur J Heart Fail* 1999;**1**:211–217.
278. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A, I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008;**359**:2456–2467.
279. Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, Love TE, Aronow WS, Adams KF Jr, Gheorghiade M. Effects of digoxin on morbidity and mortality in diastolic heart failure: the Ancillary Digitalis Investigation Group trial. *Circulation* 2006;**114**:397–403.
280. Redfield MM, Anstrom KJ, Levine JA, Koepp GA, Borlaug BA, Chen HH, LeWinter MM, Joseph SM, Shah SJ, Semigran MJ, Felker GM, Cole RT, Reeves GR, Tedford RJ, Tang WH, McNulty SE, Velazquez EJ, Shah MR, Braunwald E, NHLBI Heart Failure Clinical Research Network. Isosorbide mononitrate in heart failure with preserved ejection fraction. *N Engl J Med* 2015;**373**:2314–2324.
281. Borlaug BA, Anstrom KJ, Lewis GD, Shah SJ, Levine JA, Koepp GA, Givertz MM, Felker GM, LeWinter MM, Mann DL, Margulies KB, Smith AL, Tang WHW, Whellan DJ, Chen HH, Davila-Roman VG, McNulty S, Desvigne-Nickens P, Hernandez AF, Braunwald E, Redfield MM, National Heart, Lung, and Blood Institute Heart Failure Clinical Research Network. Effect of inorganic nitrite vs placebo on exercise capacity among patients with heart failure with preserved ejection fraction: the INDIE-HFpEF randomized clinical trial. *JAMA* 2018;**320**:1764–1773.
282. Armstrong PW, Lam CSP, Anstrom KJ, Ezekowitz J, Hernandez AF, O'Connor CM, Pieske B, Ponikowski P, Shah SJ, Solomon SD, Voors AA, She L, Vlajnic V, Carvalho F, Bamber L, Blaustein RO, Roessig L, Butler J, VITALITY-HFpEF Study Group. Effect of vericiguat vs placebo on quality of life in patients with heart failure and preserved ejection fraction: the VITALITY-HFpEF randomized clinical trial. *JAMA* 2020;**324**:1512–1521.
283. Udelson JE, Lewis GD, Shah SJ, Zile MR, Redfield MM, Burnett J, Jr., Parker J, Seferovic JP, Wilson P, Mittleman RS, Profy AT, Konstam MA. Effect of praliciguat on peak rate of oxygen consumption in patients with heart failure with preserved ejection fraction: the CAPACITY HFpEF randomized clinical trial. *JAMA* 2020;**324**:1522–1531.
284. Omar W, Pandey A, Haykowsky MJ, Berry JD, Lavie CJ. The evolving role of cardiorespiratory fitness and exercise in prevention and management of heart failure. *Curr Heart Fail Rep* 2018;**15**:75–80.
285. Kitzman DW, Upadhya B, Reeves G. Hospitalizations and prognosis in elderly patients with heart failure and preserved ejection fraction: time to treat the whole patient. *JACC Heart Fail* 2015;**3**:442–444.
286. Wood AM, Kaptoge S, Butterworth AS, Willeit P, Warnakula S, Bolton T, Paige E, Paul DS, Sweeting M, Burgess S, Bell S, Astle W, Stevens D, Koulman A, Selmer RM, Verschuren WMM, Sato S, Njolstad I, Woodward M, Salomaa V, Nordestgaard BG, Yeap BB, Fletcher A, Melander O, Kuller LH, Balkau B, Marmot M, Koenig W, Casiglia E, Cooper C, Arndt V, Franco OH, Wennberg P, Gallacher J, de la Camara AG, Volzke H, Dahm CC, Dale CE, Bergmann MM, Crespo CJ, van der Schouw YT, Kaaks R, Simons LA, Lagiou P, Schoufour JD, Boer JMA, Key TJ, Rodriguez B, Moreno-Iribas C, Davidson KW, Taylor JO, Sacerdote C, Wallace RB, Quiros JR, Tumino R, Blazer DG, 2nd, Linneberg A, Daimon M, Panico S, Howard B, Skeie G, Strandberg T, Weiderpass E, Nietert PJ, Psaty BM, Kromhout D, Salamanca-Fernandez E, Kiechl S, Krumholz HM, Grioni S, Palli D, Huerta JM, Price J, Sundstrom J, Arriola L, Arima H, Travis RC, Panagiotakos DB, Karakatsani A, Trichopoulou A, Kuhn T, Grobbee DE, Barrett-Connor E, van Schoor N, Boeing H, Overvad K, Kauhanen J, Wareham N, Langenberg C, Forouhi N, Wennberg M, Despres JP, Cushman M, Cooper JA, Rodriguez CJ, Sakurai M, Shaw JE, Knuiman M, Voortman T, Meisinger C, Tjonneland A, Brenner H, Palmieri L, Dallongeville J, Brunner EJ, Assmann G, Trevisan M, Gillum RF, Ford I, Sattar N, Lazo M, Thompson SG, Ferrari P, Leon DA, Smith GD, Peto R, Jackson R, Banks E, Di Angelantonio E, Danesh J, Emerging Risk Factors Collaboration/EPIC-CVD/UK Biobank Alcohol Study Group. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. *Lancet* 2018;**391**:1513–1523.
287. Kostis JB, Davis BR, Cutler J, Grimm RH, Jr., Berge KG, Cohen JD, Lacy CR, Perry HM, Jr., Blaufox MD, Wassertheil-Smoller S, Black HR, Schron E, Berkson DM, Curb JD, Smith WM, McDonald R, Applegate WB. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. SHEP Cooperative Research Group. *JAMA* 1997;**278**:212–216.
288. Group SR, Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC Jr, Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**:2103–2116.
289. Sciarretta S, Palano F, Tocci G, Baldini R, Volpe M. Antihypertensive treatment and development of heart failure in hypertension: a Bayesian network meta-analysis of studies in patients with hypertension and high cardiovascular risk. *Arch Intern Med* 2011;**171**:384–394.
290. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ, HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008;**358**:1887–1898.
291. Scirica BM, Morrow DA, Cannon CP, Ray KK, Sabatine MS, Jarolim P, Shui A, McCabe CH, Braunwald E, PROVE IT-TIMI Investigators. Intensive statin therapy and the risk of hospitalization for heart failure after an acute coronary syndrome in the PROVE IT-TIMI 22 study. *J Am Coll Cardiol* 2006;**47**:2326–2331.
292. Kjekshus J, Pedersen TR, Olsson AG, Faergeman O, Pyorala K. The effects of simvastatin on the incidence of heart failure in patients with coronary heart disease. *J Card Fail* 1997;**3**:249–254.
293. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE, EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117–2128.
294. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR, CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**:644–657.
295. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS, DECLARE-TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;**380**:347–357.
296. Bhatt DL, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Inzucchi SE, Kosiborod MN, Cherney DZI, Dwyer JP, Scirica BM, Bailey CJ, Diaz R, Ray KK, Udell JA, Lopes RD, Lapuerta P, Steg PG, SCORED Investigators. Sotagliflozin in patients with diabetes and chronic kidney disease. *N Engl J Med* 2020;**384**:129–139.
297. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, Charbonnel B, Frederich R, Gallo S, Cosentino F, Shih WJ, Gantz I, Terra SG, Cherney DZI, McGuire DK, VERTIS CV Investigators. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med* 2020;**383**:1425–1435.
298. Suskin N, Sheth T, Negassa A, Yusuf S. Relationship of current and past smoking to mortality and morbidity in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2001;**37**:1677–1682.
299. Dorans KS, Mostofsky E, Levitan EB, Hakansson N, Wolk A, Mittleman MA. Alcohol and incident heart failure among middle-aged and elderly men: cohort of Swedish men. *Circ Heart Fail* 2015;**8**:422–427.
300. Goncalves A, Claggett B, Jhund PS, Rosamond W, Deswal A, Aguilar D, Shah AM, Cheng S, Solomon SD. Alcohol consumption and risk of heart failure: the Atherosclerosis Risk in Communities Study. *Eur Heart J* 2015;**36**:939–945.
301. Pandey A, Garg S, Khunger M, Darden D, Ayers C, Kumbhani DJ, Mayo HG, de Lemos JA, Berry JD. Dose-response relationship between physical activity and risk of heart failure: a meta-analysis. *Circulation* 2015;**132**:1786–1794.
302. Padwal R, McAlister FA, McMurray JJ, Cowie MR, Rich M, Pocock S, Swedberg K, Maggioni A, Gamble G, Ariti C, Earle N, Whalley G, Poppe KK, Doughty RN, Bayes-Genis A, Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The obesity paradox in heart failure patients with preserved versus reduced ejection fraction: a meta-analysis of individual patient data. *Int J Obes (Lond)* 2014;**38**:1110–1114.
303. McDonagh TA, Blue L, Clark AL, Dahlstrom U, Ekman I, Lainscak M, McDonald K, Ryder M, Stromberg A, Jaarsma T, European Society of Cardiology Heart Failure Association Committee on Patient Care. European Society of Cardiology Heart Failure Association Standards for delivering heart failure care. *Eur J Heart Fail* 2011;**13**:235–241.
304. Lainscak M, Blue L, Clark AL, Dahlstrom U, Dickstein K, Ekman I, McDonagh T, McMurray JJ, Ryder M, Stewart S, Stromberg A, Jaarsma T. Self-care management of heart failure: practical recommendations from the Patient Care Committee of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2011;**13**:115–126.
305. Mebazaa A, Yilmaz MB, Levy P, Ponikowski P, Peacock WF, Laribi S, Ristic AD, Lambrinou E, Masip J, Riley JP, McDonagh T, Mueller C, deFilippi C, Harjola VP, Thiele H, Piepoli MF, Metra M, Maggioni A, McMurray JJ, Dickstein K, Damman K, Seferovic PM, Ruschitzka F, Leite-Moreira AF, Bellou A, Anker SD, Filippatos G. Recommendations on pre-hospital and early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine

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and the Society of Academic Emergency Medicine–short version. *Eur Heart J* 2015;**36**:1958–1966.
306. McDonagh TA, Gardner RS, Lainscak M, Nielsen OW, Parissis J, Filippatos G, Anker SD. Heart Failure Association of the European Society of Cardiology specialist heart failure curriculum. *Eur J Heart Fail* 2014;**16**:151–162.
307. Riley JP, Astin F, Crespo-Leiro MG, Deaton CM, Kienhorst J, Lambrinou E, McDonagh TA, Rushton CA, Stromberg A, Filippatos G, Anker SD. Heart Failure Association of the European Society of Cardiology heart failure nurse curriculum. *Eur J Heart Fail* 2016;**18**:736–743.
308. Van Spall HGC, Rahman T, Mytton O, Ramasundarahettige C, Ibrahim Q, Kabali C, Coppens M, Brian Haynes R, Connolly S. Comparative effectiveness of transitional care services in patients discharged from the hospital with heart failure: a systematic review and network meta-analysis. *Eur J Heart Fail* 2017;**19**:1427–1443.
309. Jonkman NH, Westland H, Groenwold RH, Agren S, Anguita M, Blue L, Bruggink-Andre de la Porte PW, DeWalt DA, Hebert PL, Heisler M, Jaarsma T, Kempen GI, Leventhal ME, Lok DJ, Martensson J, Muniz J, Otsu H, Peters-Klimm F, Rich MW, Riegel B, Stromberg A, Tsuyuki RT, Trappenburg JC, Schuurmans MJ, Hoes AW. What are effective program characteristics of self-management interventions in patients with heart failure? An individual patient data meta-analysis. *J Card Fail* 2016;**22**:861–871.
310. Takeda A, Martin N, Taylor RS, Taylor SJ. Disease management interventions for heart failure. *Cochrane Database Syst Rev* 2019;**1**:CD002752.
311. Kalogirou F, Forsyth F, Kyriakou M, Mantle R, Deaton C. Heart failure disease management: a systematic review of effectiveness in heart failure with preserved ejection fraction. *ESC Heart Fail* 2020;**7**:194–212.
312. Hill L, Prager Geller T, Baruah R, Beattie JM, Boyne J, de Stoutz N, Di Stolfo G, Lambrinou E, Skibelund AK, Uchmanowicz I, Rutten FH, Celutkiene J, Piepoli MF, Jankowska EA, Chioncel O, Ben Gal T, Seferovic PM, Ruschitzka F, Coats AJS, Stromberg A, Jaarsma T. Integration of a palliative approach into heart failure care: a European Society of Cardiology Heart Failure Association position paper. *Eur J Heart Fail* 2020;**22**:2327–2339.
313. Kyriakou M, Middleton N, Ktisti S, Philippou K, Lambrinou E. Supportive care interventions to promote health-related quality of life in patients living with heart failure: a systematic review and meta-analysis. *Heart Lung Circ* 2020;**29**:1633–1647.
314. Feltner C, Jones CD, Cene CW, Zheng ZJ, Sueta CA, Coker-Schwimmer EJ, Arvanitis M, Lohr KN, Middleton JC, Jonas DE. Transitional care interventions to prevent readmissions for persons with heart failure: a systematic review and meta-analysis. *Ann Intern Med* 2014;**160**:774–784.
315. Blue L, Lang E, McMurray JJ, Davie AP, McDonagh TA, Murdoch DR, Petrie MC, Connolly E, Norrie J, Round CE, Ford I, Morrison CE. Randomised controlled trial of specialist nurse intervention in heart failure. *BMJ* 2001;**323**:715–718.
316. Lambrinou E, Kalogirou F, Lamnisos D, Sourtzi P. Effectiveness of heart failure management programmes with nurse-led discharge planning in reducing re-admissions: a systematic review and meta-analysis. *Int J Nurs Stud* 2012;**49**:610–624.
317. Stewart S, Vandenbroek AJ, Pearson S, Horowitz JD. Prolonged beneficial effects of a home-based intervention on unplanned readmissions and mortality among patients with congestive heart failure. *Arch Intern Med* 1999;**159**:257–261.
318. Ekman I, Wolf A, Olsson LE, Taft C, Dudas K, Schaufelberger M, Swedberg K. Effects of person-centred care in patients with chronic heart failure: the PCC-HF study. *Eur Heart J* 2012;**33**:1112–1119.
319. Riegel B, Bennett JA, Davis A, Carlson B, Montague J, Robin H, Glaser D. Cognitive impairment in heart failure: issues of measurement and etiology. *Am J Crit Care* 2002;**11**:520–528.
320. Laufs U, Rettig-Ewen V, Bohm M. Strategies to improve drug adherence. *Eur Heart J* 2011;**32**:264–268.
321. Abraityte A, Aukrust P, Kou L, Anand IS, Young J, McMurray JJV, van Veldhuisen DJ, Gullestad L, Ueland T. T cell and monocyte/macrophage activation markers associate with adverse outcome, but give limited prognostic value in anemic patients with heart failure: results from RED-HF. *Clin Res Cardiol* 2019;**108**:133–141.
322. Flynn KE, Pina IL, Whellan DJ, Lin L, Blumenthal JA, Ellis SJ, Fine LJ, Howlett JG, Keteyian SJ, Kitzman DW, Kraus WE, Miller NH, Schulman KA, Spertus JA, O'Connor CM, Weinfurt KP, HF-ACTION Investigators. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;**301**:1451–1459.
323. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Pina IL, HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;**301**:1439–1450.
324. Taylor RS, Walker S, Smart NA, Piepoli MF, Warren FC, Ciani O, Whellan D, O'Connor C, Keteyian SJ, Coats A, Davos CH, Dalal HM, Dracup K, Evangelista LS, Jolly K, Myers J, Nilsson BB, Passino C, Witham MD, Yeh GY, ExTraMATCH II Collaboration. Impact of exercise rehabilitation on exercise capacity and quality-of-life in heart failure: individual participant meta-analysis. *J Am Coll Cardiol* 2019;**73**:1430–1443.
325. Taylor RS, Walker S, Smart NA, Piepoli MF, Warren FC, Ciani O, O'Connor C, Whellan D, Keteyian SJ, Coats A, Davos CH, Dalal HM, Dracup K, Evangelista L, Jolly K, Myers J, McKelvie RS, Nilsson BB, Passino C, Witham MD, Yeh GY, Zwisler AO, ExTraMATCH II Collaboration. Impact of exercise-based cardiac rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalisation: an individual patient data meta-analysis of randomised trials. *Eur J Heart Fail* 2018;**20**:1735–1743.
326. Pandey A, Parashar A, Kumbhani D, Agarwal S, Garg J, Kitzman D, Levine B, Drazner M, Berry J. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. *Circ Heart Fail* 2015;**8**:33–40.
327. Taylor RS, Long L, Mordi IR, Madsen MT, Davies EJ, Dalal H, Rees K, Singh SJ, Gluud C, Zwisler AD. Exercise-based rehabilitation for heart failure: Cochrane Systematic Review, meta-analysis, and trial sequential analysis. *JACC Heart Fail* 2019;**7**:691–705.
328. Taylor RS, Walker S, Ciani O, Warren F, Smart NA, Piepoli M, Davos CH. Exercise-based cardiac rehabilitation for chronic heart failure: the EXTRAMATCH II individual participant data meta-analysis. *Health Technol Assess* 2019;**23**:1–98.
329. Cooper LB, Mentz RJ, Sun JL, Schulte PJ, Fleg JL, Cooper LS, Pina IL, Leifer ES, Kraus WE, Whellan DJ, Keteyian SJ, O'Connor CM. Psychosocial factors, exercise adherence, and outcomes in heart failure patients: insights from Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION). *Circ Heart Fail* 2015;**8**:1044–1051.
330. Gomes Neto M, Duraes AR, Conceicao LSR, Saquetto MB, Ellingsen O, Carvalho VO. High intensity interval training versus moderate intensity continuous training on exercise capacity and quality of life in patients with heart failure with reduced ejection fraction: a systematic review and meta-analysis. *Int J Cardiol* 2018;**261**:134–141.
331. Ellingsen O, Halle M, Conraads V, Stoylen A, Dalen H, Delagardelle C, Larsen AI, Hole T, Mezzani A, Van Craenenbroeck EM, Videm V, Beckers P, Christle JW, Winzer E, Mangner N, Woitek F, Hollriegel R, Pressler A, Monk-Hansen T, Snoer M, Feiereisen P, Valborgland T, Kjekshus J, Hambrecht R, Gielen S, Karlsen T, Prescott E, Linke A, SMARTEX Heart Failure Study Group. High-intensity interval training in patients with heart failure with reduced ejection fraction. *Circulation* 2017;**135**:839–849.
332. Edelmann F, Gelbrich G, Dungen HD, Frohling S, Wachter R, Stahrenberg R, Binder L, Topper A, Lashki DJ, Schwarz S, Herrmann-Lingen C, Loffler M, Hasenfuss G, Halle M, Pieske B. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. *J Am Coll Cardiol* 2011;**58**:1780–1791.
333. Nolte K, Herrmann-Lingen C, Wachter R, Gelbrich G, Dungen HD, Duvinage A, Hoischen N, von Oehsen K, Schwarz S, Hasenfuss G, Halle M, Pieske B, Edelmann F. Effects of exercise training on different quality of life dimensions in heart failure with preserved ejection fraction: the Ex-DHF-P trial. *Eur J Prev Cardiol* 2015;**22**:582–593.
334. Ismail H, McFarlane JR, Nojoumian AH, Dieberg G, Smart NA. Clinical outcomes and cardiovascular responses to different exercise training intensities in patients with heart failure: a systematic review and meta-analysis. *JACC Heart Fail* 2013;**1**:514–522.
335. Kitzman DW, Brubaker PH, Herrington DM, Morgan TM, Stewart KP, Hundley WG, Abdelhamed A, Haykowsky MJ. Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. *J Am Coll Cardiol* 2013;**62**:584–592.
336. Ismail H, McFarlane J, Smart NA. Is exercise training beneficial for heart failure patients taking beta-adrenergic blockers? A systematic review and meta-analysis. *Congest Heart Fail* 2013;**19**:61–69.
337. Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, Kraus WE, Eggebeen J, Nicklas BJ. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* 2016;**315**:36–46.
338. Taylor RS, Sagar VA, Davies EJ, Briscoe S, Coats AJ, Dalal H, Lough F, Rees K, Singh S. Exercise-based rehabilitation for heart failure. *Cochrane Database Syst Rev* 2014:CD003331.
339. Schou M, Gustafsson F, Videbaek L, Tuxen C, Keller N, Handberg J, Sejr Knudsen A, Espersen G, Markenvard J, Egstrup K, Ulriksen H, Hildebrandt PR,

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the NorthStar Investigators, all members of The Danish Heart Failure Clinics Network. Extended heart failure clinic follow-up in low-risk patients: a randomized clinical trial (NorthStar). *Eur Heart J* 2013;**34**:432–442.
340. Thorvaldsen T, Benson L, Dahlstrom U, Edner M, Lund LH. Use of evidence-based therapy and survival in heart failure in Sweden 2003-2012. *Eur J Heart Fail* 2016;**18**:503–511.
341. Lund LH, Braunschweig F, Benson L, Stahlberg M, Dahlstrom U, Linde C. Association between demographic, organizational, clinical, and socio-economic characteristics and underutilization of cardiac resynchronization therapy: results from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2017;**19**:1270–1279.
342. Savarese G, Carrero JJ, Pitt B, Anker SD, Rosano GMC, Dahlstrom U, Lund LH. Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: an analysis of 11 215 patients from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2018;**20**:1326–1334.
343. Lund LH, Carrero JJ, Farahmand B, Henriksson KM, Jonsson A, Jernberg T, Dahlstrom U. Association between enrolment in a heart failure quality registry and subsequent mortality–a nationwide cohort study. *Eur J Heart Fail* 2017;**19**:1107–1116.
344. Clark AL, Goode K, Cleland JG. The prevalence and incidence of left bundle branch block in ambulant patients with chronic heart failure. *Eur J Heart Fail* 2008;**10**:696–702.
345. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet* 2000;**355**:1126–1130.
346. Berger R, Moertl D, Peter S, Ahmadi R, Huelsmann M, Yamuti S, Wagner B, Pacher R. N-terminal pro-B-type natriuretic peptide-guided, intensive patient management in addition to multidisciplinary care in chronic heart failure a 3-arm, prospective, randomized pilot study. *J Am Coll Cardiol* 2010;**55**:645–653.
347. Jourdain P, Jondeau G, Funck F, Gueffet P, Le Helloco A, Donal E, Aupetit JF, Aumont MC, Galinier M, Eicher JC, Cohen-Solal A, Juilliere Y. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. *J Am Coll Cardiol* 2007;**49**:1733–1739.
348. Lainchbury JG, Troughton RW, Strangman KM, Frampton CM, Pilbrow A, Yandle TG, Hamid AK, Nicholls MG, Richards AM. N-terminal pro-B-type natriuretic peptide-guided treatment for chronic heart failure: results from the BATTLESCARRED (NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) trial. *J Am Coll Cardiol* 2009;**55**:53–60.
349. Pfisterer M, Buser P, Rickli H, Gutmann M, Erne P, Rickenbacher P, Vuillomenet A, Jeker U, Dubach P, Beer H, Yoon SI, Suter T, Osterhues HH, Schieber MM, Hilti P, Schindler R, Brunner-La Rocca HP, TIME-CHF Investigators. BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. *JAMA* 2009;**301**:383–392.
350. Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, Januzzi JL, Jr., Mark DB, Pina IL, Passmore G, Whellan DJ, Yang H, Cooper LS, Leifer ES, Desvigne-Nickens P, O'Connor CM. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA* 2017;**318**:713–720.
351. Porapakkham P, Porapakkham P, Zimmet H, Billah B, Krum H. B-type natriuretic peptide-guided heart failure therapy: a meta-analysis. *Arch Intern Med* 2010;**170**:507–514.
352. Troughton RW, Frampton CM, Brunner-La Rocca HP, Pfisterer M, Eurlings LW, Erntell H, Persson H, O'Connor CM, Moertl D, Karlstrom P, Dahlstrom U, Gaggin HK, Januzzi JL, Berger R, Richards AM, Pinto YM, Nicholls MG. Effect of B-type natriuretic peptide-guided treatment of chronic heart failure on total mortality and hospitalization: an individual patient meta-analysis. *Eur Heart J* 2014;**35**:1559–1567.
353. Anand IS, Fisher LD, Chiang YT, Latini R, Masson S, Maggioni AP, Glazer RD, Tognoni G, Cohn JN, Val-HeFT Investigators. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). *Circulation* 2003;**107**:1278–1283.
354. Zile MR, Claggett BL, Prescott MF, McMurray JJ, Packer M, Rouleau JL, Swedberg K, Desai AS, Gong J, Shi VC, Solomon SD. Prognostic implications of changes in N-terminal pro-B-type natriuretic peptide in patients with heart failure. *J Am Coll Cardiol* 2016;**68**:2425–2436.
355. Brahmbhatt DH, Cowie MR. Remote management of heart failure: an overview of telemonitoring technologies. *Card Fail Rev* 2019;**5**:86–92.
356. Cleland JG, Clark RA, Pellicori P, Inglis SC. Caring for people with heart failure and many other medical problems through and beyond the COVID-19 pandemic: the advantages of universal access to home telemonitoring. *Eur J Heart Fail* 2020;**22**:995–998.
357. Inglis SC, Clark RA, Dierckx R, Prieto-Merino D, Cleland JG. Structured telephone support or non-invasive telemonitoring for patients with heart failure. *Heart* 2017;**103**:255–257.
358. Frederix I, Caiani EG, Dendale P, Anker S, Bax J, Bohm A, Cowie M, Crawford J, de Groot N, Dilaveris P, Hansen T, Koehler F, Krstacic G, Lambrinou E, Lancellotti P, Meier P, Neubeck L, Parati G, Piotrowicz E, Tubaro M, van der Velde E. ESC e-Cardiology Working Group Position Paper: Overcoming challenges in digital health implementation in cardiovascular medicine. *Eur J Prev Cardiol* 2019;**26**:1166–1177.
359. Lin MH, Yuan WL, Huang TC, Zhang HF, Mai JT, Wang JF. Clinical effectiveness of telemedicine for chronic heart failure: a systematic review and meta-analysis. *J Investig Med* 2017;**65**:899–911.
360. Adamson PB, Ginn G, Anker SD, Bourge RC, Abraham WT. Remote haemodynamic-guided care for patients with chronic heart failure: a meta-analysis of completed trials. *Eur J Heart Fail* 2017;**19**:426–433.
361. Chaudhry SI, Mattera JA, Curtis JP, Spertus JA, Herrin J, Lin Z, Phillips CO, Hodshon BV, Cooper LS, Krumholz HM. Telemonitoring in patients with heart failure. *N Engl J Med* 2010;**363**:2301–2309.
362. Koehler F, Winkler S, Schieber M, Sechtem U, Stangl K, Bohm M, Boll H, Baumann G, Honold M, Koehler K, Gelbrich G, Kirwan BA, Anker SD, Telemedical Interventional Monitoring in Heart Failure Investigators. Impact of remote telemedical management on mortality and hospitalizations in ambulatory patients with chronic heart failure: the telemedical interventional monitoring in heart failure study. *Circulation* 2011;**123**:1873–1880.
363. Koehler F, Koehler K, Deckwart O, Prescher S, Wegscheider K, Winkler S, Vettorazzi E, Polze A, Stangl K, Hartmann O, Marx A, Neuhaus P, Scherf M, Kirwan BA, Anker SD. Telemedical Interventional Management in Heart Failure II (TIM-HF2), a randomised, controlled trial investigating the impact of telemedicine on unplanned cardiovascular hospitalisations and mortality in heart failure patients: study design and description of the intervention. *Eur J Heart Fail* 2018;**20**:1485–1493.
364. Koehler F, Koehler K, Deckwart O, Prescher S, Wegscheider K, Kirwan BA, Winkler S, Vettorazzi E, Bruch L, Oeff M, Zugck C, Doerr G, Naegele H, Stork S, Butter C, Sechtem U, Angermann C, Gola G, Prondzinsky R, Edelmann F, Spethmann S, Schellong SM, Schulze PC, Bauersachs J, Wellge B, Schoebel C, Tajsic M, Dreger H, Anker SD, Stangl K. Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): a randomised, controlled, parallel-group, unmasked trial. *Lancet* 2018;**392**:1047–1057.
365. Kalter-Leibovici O, Freimark D, Freedman LS, Kaufman G, Ziv A, Murad H, Benderly M, Silverman BG, Friedman N, Cukierman-Yaffe T, Asher E, Grupper A, Goldman D, Amitai M, Matetzky S, Shani M, Silber H, Israel Heart Failure Disease Management Study investigators. Disease management in the treatment of patients with chronic heart failure who have universal access to health care: a randomized controlled trial. *BMC Med* 2017;**15**:90.
366. Jayaram NM, Khariton Y, Krumholz HM, Chaudhry SI, Mattera J, Tang F, Herrin J, Hodshon B, Spertus JA. Impact of telemonitoring on health status. *Circ Cardiovasc Qual Outcomes* 2017;**10**:e004148.
367. Shochat MK, Shotan A, Blondheim DS, Kazatsker M, Dahan I, Asif A, Rozenman Y, Kleiner I, Weinstein JM, Frimerman A, Vasilenko L, Meisel SR. Non-invasive lung IMPEDANCE-guided preemptive treatment in chronic heart failure patients: a randomized controlled trial (IMPEDANCE-HF Trial). *J Card Fail* 2016;**22**:713–722.
368. van Veldhuisen DJ, Braunschweig F, Conraads V, Ford I, Cowie MR, Jondeau G, Kautzner J, Aguilera RM, Lunati M, Yu CM, Gerritse B, Borggrefe M, DOT-HF Investigators. Intrathoracic impedance monitoring, audible patient alerts, and outcome in patients with heart failure. *Circulation* 2011;**124**:1719–1726.
369. Hindricks G, Taborsky M, Glikson M, Heinrich U, Schumacher B, Katz A, Brachmann J, Lewalter T, Goette A, Block M, Kautzner J, Sack S, Husser D, Piorkowski C, Sogaard P, IN-TIME Study Group. Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): a randomised controlled trial. *Lancet* 2014;**384**:583–590.
370. Morgan JM, Kitt S, Gill J, McComb JM, Ng GA, Raftery J, Roderick P, Seed A, Williams SG, Witte KK, Wright DJ, Harris S, Cowie MR. Remote management of heart failure using implantable electronic devices. *Eur Heart J* 2017;**38**:2352–2360.
371. Bohm M, Drexler H, Oswald H, Rybak K, Bosch R, Butter C, Klein G, Gerritse B, Monteiro J, Israel C, Bimmel D, Kaab S, Huegl B, Brachmann J, OptiLink HF Study Investigators. Fluid status telemedicine alerts for heart failure: a randomized controlled trial. *Eur Heart J* 2016;**37**:3154–3163.
372. Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB, CHAMPION Trial Study Group. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomised trial. *Lancet* 2016;**387**:453–461.
373. Lindenfeld J, Abraham WT, Maisel A, Zile M, Smart F, Costanzo MR, Mehra MR, Ducharme A, Sears SF, Desai AS, Paul S, Sood P, Johnson N, Ginn G, Adamson PB. Hemodynamic-GUIDEd management of Heart Failure (GUIDE-HF). *Am Heart J* 2019;**214**:18–27.

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374. Dierckx R, Inglis SC, Clark RA, Prieto-Merino D, Cleland JG. Telemedicine in heart failure: new insights from the Cochrane meta-analyses. *Eur J Heart Fail* 2017;**19**:304–306.
375. Fang JC, Ewald GA, Allen LA, Butler J, Westlake Canary CA, Colvin-Adams M, Dickinson MG, Levy P, Stough WG, Sweitzer NK, Teerlink JR, Whellan DJ, Albert NM, Krishnamani R, Rich MW, Walsh MN, Bonnell MR, Carson PE, Chan MC, Dries DL, Hernandez AF, Hershberger RE, Katz SD, Moore S, Rodgers JE, Rogers JG, Vest AR, Givertz MM, Heart Failure Society of America Guidelines Committee. Advanced (stage D) heart failure: a statement from the Heart Failure Society of America Guidelines Committee. *J Card Fail* 2015;**21**:519–534.
376. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, Gustafsson F, Tsui S, Barge-Caballero E, De Jonge N, Frigerio M, Hamdan R, Hasin T, Hulsmann M, Nalbantgil S, Potena L, Bauersachs J, Gkouziouta A, Ruhparwar A, Ristic AD, Straburzynska-Migaj E, McDonagh T, Seferovic P, Ruschitzka F. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018;**20**:1505–1535.
377. Truby LK, Rogers JG. Advanced heart failure: epidemiology, diagnosis, and therapeutic approaches. *JACC Heart Fail* 2020;**8**:523–536.
378. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, Long JW, Ascheim DD, Tierney AR, Levitan RG, Watson JT, Meier P, Ronan NS, Shapiro PA, Lazar RM, Miller LW, Gupta L, Frazier OH, Desvigne-Nickens P, Oz MC, Poirier VL, Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med* 2001;**345**:1435–1443.
379. Ammar KA, Jacobsen SJ, Mahoney DW, Kors JA, Redfield MM, Burnett JC, Jr., Rodeheffer RJ. Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. *Circulation* 2007;**115**:1563–1570.
380. Xanthakis V, Enserro DM, Larson MG, Wollert KC, Januzzi JL, Levy D, Aragam J, Benjamin EJ, Cheng S, Wang TJ, Mitchell GF, Vasan RS. Prevalence, neurohormonal correlates, and prognosis of heart failure stages in the community. *JACC Heart Fail* 2016;**4**:808–815.
381. Stevenson LW, Pagani FD, Young JB, Jessup M, Miller L, Kormos RL, Naftel DC, Ulisney K, Desvigne-Nickens P, Kirklin JK. INTERMACS profiles of advanced heart failure: the current picture. *J Heart Lung Transplant* 2009;**28**:535–541.
382. Barge-Caballero E, Segovia-Cubero J, Almenar-Bonet L, Gonzalez-Vilchez F, Villa-Arranz A, Delgado-Jimenez J, Lage-Galle E, Perez-Villa F, Lambert-Rodriguez JL, Manito-Lorite N, Arizon-Del Prado JM, Brossa-Loidi V, Pascual-Figal D, Fuente-Galan Lde L, Sanz-Julve M, Muniz-Garcia J, Crespo-Leiro M. Preoperative INTERMACS profiles determine postoperative outcomes in critically ill patients undergoing emergency heart transplantation: analysis of the Spanish National Heart Transplant Registry. *Circ Heart Fail* 2013;**6**:763–772.
383. Goldstein DJ, Meyns B, Xie R, Cowger J, Pettit S, Nakatani T, Netuka I, Shaw S, Yanase M, Kirklin JK. Third annual report from the ISHLT Mechanically Assisted Circulatory Support Registry: a comparison of centrifugal and axial continuous-flow left ventricular assist devices. *J Heart Lung Transplant* 2019;**38**:352–363.
384. Kittleson MM, Shah P, Lala A, McLean RC, Pamboukian S, Horstmanshof DA, Thibodeau J, Shah K, Teuteberg J, Gilotra NA, Taddei-Peters WC, Cascino TM, Richards B, Khalatbari S, Jeffries N, Stevenson LW, Mann D, Aaronson KD, Stewart GC, REVIVAL Investigators. INTERMACS profiles and outcomes of ambulatory advanced heart failure patients: a report from the REVIVAL Registry. *J Heart Lung Transplant* 2020;**39**:16–26.
385. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, Danziger-Isakov L, Kirklin JK, Kirk R, Kushwaha SS, Lund LH, Potena L, Ross HJ, Taylor DO, Verschuuren EAM, Zuckermann A, International Society for Heart Lung Transplantation (ISHLT) Infectious Diseases, Pediatric and Heart Failure and Transplantation Councils. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant* 2016;**35**:1–23.
386. Baumwol J. "I need help"–a mnemonic to aid timely referral in advanced heart failure. *J Heart Lung Transplant* 2017;**36**:593–594.
387. Maack C, Eschenhagen T, Hamdani N, Heinzel FR, Lyon AR, Manstein DJ, Metzger J, Papp Z, Tocchetti CG, Yilmaz MB, Anker SD, Balligand JL, Bauersachs J, Brutsaert D, Carrier L, Chlopicki S, Cleland JG, de Boer RA, Dietl A, Fischmeister R, Harjola VP, Heymans S, Hilfiker-Kleiner D, Holzmeister J, de Keulenaer G, Limongelli G, Linke WA, Lund LH, Masip J, Metra M, Mueller C, Pieske B, Ponikowski P, Ristic A, Ruschitzka F, Seferovic PM, Skouri H, Zimmermann WH, Mebazaa A. Treatments targeting inotropy. *Eur Heart J* 2019;**40**:3626–3644.
388. Ahmad T, Miller PE, McCullough M, Desai NR, Riello R, Psotka M, Bohm M, Allen LA, Teerlink JR, Rosano GMC, Lindenfeld J. Why has positive inotropy failed in chronic heart failure? Lessons from prior inotrope trials. *Eur J Heart Fail* 2019;**21**:1064–1078.
389. Comin-Colet J, Manito N, Segovia-Cubero J, Delgado J, Garcia Pinilla JM, Almenar L, Crespo-Leiro MG, Sionis A, Blasco T, Pascual-Figal D, Gonzalez-Vilchez F, Lambert-Rodriguez JL, Grau M, Bruguera J, LION-HEART Study Investigators. Efficacy and safety of intermittent intravenous outpatient administration of levosimendan in patients with advanced heart failure: the LION-HEART multicentre randomised trial. *Eur J Heart Fail* 2018;**20**:1128–1136.
390. Nizamic T, Murad MH, Allen LA, McIlvennan CK, Wordingham SE, Matlock DD, Dunlay SM. Ambulatory inotrope infusions in advanced heart failure: a systematic review and meta-analysis. *JACC Heart Fail* 2018;**6**:757–767.
391. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, Redfield MM, Deswal A, Rouleau JL, LeWinter MM, Ofili EO, Stevenson LW, Semigran MJ, Felker GM, Chen HH, Hernandez AF, Anstrom KJ, McNulty SE, Velazquez EJ, Ibarra JC, Mascette AM, Braunwald E, Heart Failure Clinical Research Network. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med* 2012;**367**:2296–2304.
392. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, Jaski BE, Fang JC, Feller ED, Haas GJ, Anderson AS, Schollmeyer MP, Sobotka PA, UNLOAD Trial Investigators. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol* 2007;**49**:675–683.
393. Gustafsson F, Rogers JG. Left ventricular assist device therapy in advanced heart failure: patient selection and outcomes. *Eur J Heart Fail* 2017;**19**:595–602.
394. Barge-Caballero E, Almenar-Bonet L, Gonzalez-Vilchez F, Lambert-Rodriguez JL, Gonzalez-Costello J, Segovia-Cubero J, Castel-Lavilla MA, Delgado-Jimenez J, Garrido-Bravo IP, Rangel-Sousa D, Martinez-Selles M, De la Fuente-Galan L, Rabago-AracilJuan- G, Sanz-Julve M, Hervas-Sotomayor D, Mirabet-Perez S, Muniz J, Crespo-Leiro MG. Clinical outcomes of temporary mechanical circulatory support as a direct bridge to heart transplantation: a nationwide Spanish registry. *Eur J Heart Fail* 2018;**20**:178–186.
395. Potapov EV, Antonides C, Crespo-Leiro MG, Combes A, Farber G, Hannan MM, Kukucka M, de Jonge N, Loforte A, Lund LH, Mohacsi P, Morshuis M, Netuka I, Ozbaran M, Pappalardo F, Scandroglio AM, Schweiger M, Tsui S, Zimpfer D, Gustafsson F. 2019 EACTS Expert Consensus on long-term mechanical circulatory support. *Eur J Cardiothorac Surg* 2019;**56**:230–270.
396. Rogers JG, Butler J, Lansman SL, Gass A, Portner PM, Pasque MK, Pierson RN, 3rd, INTrEPID Investigators. Chronic mechanical circulatory support for inotrope-dependent heart failure patients who are not transplant candidates: results of the INTrEPID Trial. *J Am Coll Cardiol* 2007;**50**:741–747.
397. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, Sun B, Tatooles AJ, Delgado RM, 3rd, Long JW, Wozniak TC, Ghumman W, Farrar DJ, Frazier OH, HeartMate II Investigators. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med* 2009;**361**:2241–2251.
398. Starling RC, Naka Y, Boyle AJ, Gonzalez-Stawinski G, John R, Jorde U, Russell SD, Conte JV, Aaronson KD, McGee EC, Jr., Cotts WG, DeNofrio D, Pham DT, Farrar DJ, Pagani FD. Results of the post-U.S. Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: a prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). *J Am Coll Cardiol* 2011;**57**:1890–1898.
399. Rogers JG, Pagani FD, Tatooles AJ, Bhat G, Slaughter MS, Birks EJ, Boyce SW, Najjar SS, Jeevanandam V, Anderson AS, Gregoric ID, Mallidi H, Leadley K, Aaronson KD, Frazier OH, Milano CA. Intrapericardial left ventricular assist device for advanced heart failure. *N Engl J Med* 2017;**376**:451–460.
400. Truby LK, Farr MA, Garan AR, Givens R, Restaino SW, Latif F, Takayama H, Naka Y, Takeda K, Topkara VK. Impact of bridge to transplantation with continuous-flow left ventricular assist devices on posttransplantation mortality. *Circulation* 2019;**140**:459–469.
401. Goldstein DJ, Naka Y, Horstmanshof D, Ravichandran AK, Schroder J, Ransom J, Itoh A, Uriel N, Cleveland JC, Jr., Raval NY, Cogswell R, Suarez EE, Lowes BD, Kim G, Bonde P, Sheikh FH, Sood P, Farrar DJ, Mehra MR. Association of clinical outcomes with left ventricular assist device use by bridge to transplant or destination therapy intent: the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3 (MOMENTUM 3) Randomized Clinical Trial. *JAMA Cardiol* 2020;**5**:411–419.
402. Mehra MR, Uriel N, Naka Y, Cleveland JC, Jr., Yuzefpolskaya M, Salerno CT, Walsh MN, Milano CA, Patel CB, Hutchins SW, Ransom J, Ewald GA, Itoh A, Raval NY, Silvestry SC, Cogswell R, John R, Bhimaraj A, Bruckner BA, Lowes BD, Um JY, Jeevanandam V, Sayer G, Mangi AA, Molina EJ, Sheikh F, Aaronson K, Pagani FD, Cotts WG, Tatooles AJ, Babu A, Chomsky D, Katz JN, Tessmann PB, Dean D, Krishnamoorthy A, Chuang J, Topuria I, Sood P, Goldstein DJ,

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MOMENTUM 3 Investigators. A fully magnetically levitated left ventricular assist device – final report. *N Engl J Med* 2019;**380**:1618–1627.
403. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL, Miller MA, Baldwin JT, Young JB. Seventh INTERMACS annual report: 15,000 patients and counting. *J Heart Lung Transplant* 2015;**34**:1495–1504.
404. Theochari CA, Michalopoulos G, Oikonomou EK, Giannopoulos S, Doulamis IP, Villela MA, Kokkinidis DG. Heart transplantation versus left ventricular assist devices as destination therapy or bridge to transplantation for 1-year mortality: a systematic review and meta-analysis. *Ann Cardiothorac Surg* 2018;**7**:3–11.
405. Mehra MR, Goldstein DJ, Uriel N, Cleveland JC, Jr., Yuzefpolskaya M, Salerno C, Walsh MN, Milano CA, Patel CB, Ewald GA, Itoh A, Dean D, Krishnamoorthy A, Cotts WG, Tatooles AJ, Jorde UP, Bruckner BA, Estep JD, Jeevanandam V, Sayer G, Horstmanshof D, Long JW, Gulati S, Skipper ER, O'Connell JB, Heatley G, Sood P, Naka Y, MOMENTUM 3 Investigators. Two-year outcomes with a magnetically levitated cardiac pump in heart failure. *N Engl J Med* 2018;**378**:1386–1395.
406. Zimpfer D, Gustafsson F, Potapov E, Pya Y, Schmitto J, Berchtold-Herz M, Morshuis M, Shaw SM, Saeed D, Lavee J, Heatley G, Gazzola C, Garbade J. Two-year outcome after implantation of a full magnetically levitated left ventricular assist device: results from the ELEVATE Registry. *Eur Heart J* 2020;**41**:3801–3809.
407. Estep JD, Starling RC, Horstmanshof DA, Milano CA, Selzman CH, Shah KB, Loebe M, Moazami N, Long JW, Stehlik J, Kasirajan V, Haas DC, O'Connell JB, Boyle AJ, Farrar DJ, Rogers JG, ROADMAP Study Investigators. Risk assessment and comparative effectiveness of left ventricular assist device and medical management in ambulatory heart failure patients: results from the ROADMAP study. *J Am Coll Cardiol* 2015;**66**:1747–1761.
408. Starling RC, Estep JD, Horstmanshof DA, Milano CA, Stehlik J, Shah KB, Bruckner BA, Lee S, Long JW, Selzman CH, Kasirajan V, Haas DC, Boyle AJ, Chuang J, Farrar DJ, Rogers JG, ROADMAP Study Investigators. Risk assessment and comparative effectiveness of left ventricular assist device and medical management in ambulatory heart failure patients: the ROADMAP study 2-year results. *JACC Heart Fail* 2017;**5**:518–527.
409. Slaughter MS, Pagani FD, McGee EC, Birks EJ, Cotts WG, Gregoric I, Howard Frazier O, Icenogle T, Najjar SS, Boyce SW, Acker MA, John R, Hathaway DR, Najarian KB, Aaronson KD, HeartWare Bridge to Transplant ADVANCE Trial Investigators. HeartWare ventricular assist system for bridge to transplant: combined results of the bridge to transplant and continued access protocol trial. *J Heart Lung Transplant* 2013;**32**:675–683.
410. Karason K, Lund LH, Dalen M, Bjorklund E, Grinnemo K, Braun O, Nilsson J, van der Wal H, Holm J, Hubbert L, Lindmark K, Szabo B, Holmberg E, Dellgren G, SweVAD Investigators. Randomized trial of a left ventricular assist device as destination therapy versus guideline-directed medical therapy in patients with advanced heart failure. Rationale and design of the SWEdish evaluation of left Ventricular Assist Device (SweVAD) trial. *Eur J Heart Fail* 2020;**22**:739–750.
411. Khush KK, Cherikh WS, Chambers DC, Harhay MO, Hayes D, Jr., Hsich E, Meiser B, Potena L, Robinson A, Rossano JW, Sadavarte A, Singh TP, Zuckermann A, Stehlik J, International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult heart transplantation report–2019; focus theme: donor and recipient size match. *J Heart Lung Transplant* 2019;**38**:1056–1066.
412. Lund LH, Edwards LB, Kucheryavaya AY, Dipchand AI, Benden C, Christie JD, Dobbels F, Kirk R, Rahmel AO, Yusen RD, Stehlik J, International Society for H, Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth official adult heart transplant report–2013; focus theme: age. *J Heart Lung Transplant* 2013;**32**:951–964.
413. Guglin M, Zucker MJ, Borlaug BA, Breen E, Cleveland J, Johnson MR, Panjrath GS, Patel JK, Starling RC, Bozkurt B, ACC Heart Failure and Transplant Member Section and Leadership Council. Evaluation for heart transplantation and LVAD implantation: JACC Council perspectives. *J Am Coll Cardiol* 2020;**75**:1471–1487.
414. Bernhardt AM, Schloglhofer T, Lauenroth V, Mueller F, Mueller M, Schoede A, Klopsch C, Driveline Expert STaglNg and carE DESTINE study group, a Ventricular Assist Device Driveline Infection Study Group. Prevention and early treatment of driveline infections in ventricular assist device patients – the DESTINE staging proposal and the first standard of care protocol. *J Crit Care* 2020;**56**:106–112.
415. DeFilippis EM, Breathett K, Donald EM, Nakagawa S, Takeda K, Takayama H, Truby LK, Sayer G, Colombo PC, Yuzefpolskaya M, Uriel N, Farr MA, Topkara VK. Psychosocial risk and its association with outcomes in continuous-flow left ventricular assist device patients. *Circ Heart Fail* 2020;**13**:e006910.
416. Jaarsma T, Hill L, Bayes-Genis A, La Rocca HB, Castiello T, Celutkiene J, Marques-Sule E, Plymen CM, Piper SE, Riegel B, Rutten FH, Ben Gal T, Bauersachs J, Coats AJS, Chioncel O, Lopatin Y, Lund LH, Lainscak M, Moura B, Mullens W, Piepoli MF, Rosano G, Seferovic P, Stromberg A. Self-care of heart failure patients: practical management recommendations from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2021;**23**:157–174.
417. Jorde UP, Kushwaha SS, Tatooles AJ, Naka Y, Bhat G, Long JW, Horstmanshof DA, Kormos RL, Teuteberg JJ, Slaughter MS, Birks EJ, Farrar DJ, Park SJ, HeartMate II Clinical Investigators. Results of the destination therapy post-food and drug administration approval study with a continuous flow left ventricular assist device: a prospective study using the INTERMACS registry (Interagency Registry for Mechanically Assisted Circulatory Support). *J Am Coll Cardiol* 2014;**63**:1751–1757.
418. Sahlollbey N, Lee CKS, Shirin A, Joseph P. The impact of palliative care on clinical and patient-centred outcomes in patients with advanced heart failure: a systematic review of randomized controlled trials. *Eur J Heart Fail* 2020;**22**:2340–2346.
419. Fendler TJ, Swetz KM, Allen LA. Team-based palliative and end-of-life care for heart failure. *Heart Fail Clin* 2015;**11**:479–498.
420. Brannstrom M, Boman K. Effects of person-centred and integrated chronic heart failure and palliative home care. PREFER: a randomized controlled study. *Eur J Heart Fail* 2014;**16**:1142–1151.
421. O'Donnell AE, Schaefer KG, Stevenson LW, DeVoe K, Walsh K, Mehra MR, Desai AS. Social worker-aided palliative care intervention in high-risk patients with Heart Failure (SWAP-HF): a pilot randomized clinical trial. *JAMA Cardiol* 2018;**3**:516–519.
422. Johnson MJ, McDonagh TA, Harkness A, McKay SE, Dargie HJ. Morphine for the relief of breathlessness in patients with chronic heart failure–a pilot study. *Eur J Heart Fail* 2002;**4**:753–756.
423. Oxberry SG, Bland JM, Clark AL, Cleland JG, Johnson MJ. Repeat dose opioids may be effective for breathlessness in chronic heart failure if given for long enough. *J Palliat Med* 2013;**16**:250–255.
424. Blinderman CD, Billings JA. Comfort care for patients dying in the hospital. *N Engl J Med* 2015;**373**:2549–2561.
425. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, Hochadel M, Komajda M, Lassus J, Lopez-Sendon JL, Ponikowski P, Tavazzi L, EuroHeart Survey Investigators, Heart Failure Association of the European Society of Cardiology. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J* 2006;**27**:2725–2736.
426. Chioncel O, Mebazaa A, Harjola VP, Coats AJ, Piepoli MF, Crespo-Leiro MG, Laroche C, Seferovic PM, Anker SD, Ferrari R, Ruschitzka F, Lopez-Fernandez S, Miani D, Filippatos G, Maggioni AP, ESC Heart Failure Long-Term Registry Investigators. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017;**19**:1242–1254.
427. Chioncel O, Mebazaa A, Maggioni AP, Harjola VP, Rosano G, Laroche C, Piepoli MF, Crespo-Leiro MG, Lainscak M, Ponikowski P, Filippatos G, Ruschitzka F, Seferovic P, Coats AJS, Lund LH, ESC-EORP-HFA Heart Failure Long-Term Registry Investigators. Acute heart failure congestion and perfusion status – impact of the clinical classification on in-hospital and long-term outcomes: insights from the ESC-EORP-HFA heart failure long-term registry. *Eur J Heart Fail* 2019;**21**:1338–1352.
428. Miro O, Garcia Sarasola A, Fuenzalida C, Calderon S, Jacob J, Aguirre A, Wu DM, Rizzi MA, Malchair P, Haro A, Herrera S, Gil V, Martin-Sanchez FJ, Llorens P, Herrero Puente P, Bueno H, Dominguez Rodriguez A, Muller CE, Mebazaa A, Chioncel O, Alquezar-Arbe A, ICA-SEMES Research Group. Departments involved during the first episode of acute heart failure and subsequent emergency department revisits and rehospitalisations: an outlook through the NOVICA cohort. *Eur J Heart Fail* 2019;**21**:1231–1244.
429. Solomon SD, Dobson J, Pocock S, Skali H, McMurray JJ, Granger CB, Yusuf S, Swedberg K, Young JB, Michelson EL, Pfeffer MA, Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) Investigators. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation* 2007;**116**:1482–1487.
430. Tomasoni D, Lombardi CM, Sbolli M, Cotter G, Metra M. Acute heart failure: more questions than answers. *Prog Cardiovasc Dis* 2020;**63**:599–606.
431. Butt JH, Fosbol EL, Gerds TA, Andersson C, McMurray JJV, Petrie MC, Gustafsson F, Madelaire C, Kristensen SL, Gislason GH, Torp-Pedersen C, Kober L, Schou M. Readmission and death in patients admitted with new-onset versus worsening of chronic heart failure: insights from a nationwide cohort. *Eur J Heart Fail* 2020;**22**:1777–1785.
432. Javaloyes P, Miro O, Gil V, Martin-Sanchez FJ, Jacob J, Herrero P, Takagi K, Alquezar-Arbe A, Lopez Diez MP, Martin E, Bibiano C, Escoda R, Gil C, Fuentes M, Llopis Garcia G, Alvarez Perez JM, Jerez A, Tost J, Llauger L, Romero R, Garrido JM, Rodriguez-Adrada E, Sanchez C, Rossello X, Parissis J, Mebazaa A, Chioncel O, Llorens P, ICA-SEMES Research Group. Clinical phenotypes of acute heart failure based on signs and symptoms of perfusion and congestion at emergency department presentation and their relationship

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with patient management and outcomes. *Eur J Heart Fail* 2019;**21**:1353–1365.
433. Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, Pinto YM, Richards M. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. *Eur Heart J* 2006;**27**:330–337.
434. Januzzi JL Jr, Chen-Tournoux AA, Christenson RH, Doros G, Hollander JE, Levy PD, Nagurney JT, Nowak RM, Pang PS, Patel D, Peacock WF, Rivers EJ, Walters EL, Gaggin HK, ICON-RELOADED Investigators. N-terminal pro-B-type natriuretic peptide in the emergency department: the ICON-RELOADED study. *J Am Coll Cardiol* 2018;**71**:1191–1200.
435. Maisel A, Mueller C, Nowak R, Peacock WF, Landsberg JW, Ponikowski P, Mockel M, Hogan C, Wu AH, Richards M, Clopton P, Filippatos GS, Di Somma S, Anand I, Ng L, Daniels LB, Neath SX, Christenson R, Potocki M, McCord J, Terracciano G, Kremastinos D, Hartmann O, von Haehling S, Bergmann A, Morgenthaler NG, Anker SD. Mid-region pro-hormone markers for diagnosis and prognosis in acute dyspnea: results from the BACH (Biomarkers in Acute Heart Failure) trial. *J Am Coll Cardiol* 2010;**55**:2062–2076.
436. Harjola VP, Parissis J, Bauersachs J, Brunner-La Rocca HP, Bueno H, Celutkiene J, Chioncel O, Coats AJS, Collins SP, de Boer RA, Filippatos G, Gayat E, Hill L, Laine M, Lassus J, Lommi J, Masip J, Mebazaa A, Metra M, Miro O, Mortara A, Mueller C, Mullens W, Peacock WF, Pentikainen M, Piepoli MF, Polyzogopoulou E, Rudiger A, Ruschitzka F, Seferovic P, Sionis A, Teerlink JR, Thum T, Varpula M, Weinstein JM, Yilmaz MB. Acute coronary syndromes and acute heart failure: a diagnostic dilemma and high-risk combination. A statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:1298–1314.
437. Harjola VP, Mullens W, Banaszewski M, Bauersachs J, Brunner-La Rocca HP, Chioncel O, Collins SP, Doehner W, Filippatos GS, Flammer AJ, Fuhrmann V, Lainscak M, Lassus J, Legrand M, Masip J, Mueller C, Papp Z, Parissis J, Platz E, Rudiger A, Ruschitzka F, Schafer A, Seferovic PM, Skouri H, Yilmaz MB, Mebazaa A. Organ dysfunction, injury and failure in acute heart failure: from pathophysiology to diagnosis and management. A review on behalf of the Acute Heart Failure Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2017;**19**:821–836.
438. Harjola VP, Parissis J, Brunner-La Rocca HP, Celutkiene J, Chioncel O, Collins SP, De Backer D, Filippatos GS, Gayat E, Hill L, Lainscak M, Lassus J, Masip J, Mebazaa A, Miro O, Mortara A, Mueller C, Mullens W, Nieminen MS, Rudiger A, Ruschitzka F, Seferovic PM, Sionis A, Vieillard-Baron A, Weinstein JM, de Boer RA, Crespo-Leiro MG, Piepoli M, Riley JP. Comprehensive in-hospital monitoring in acute heart failure: applications for clinical practice and future directions for research. A statement from the Acute Heart Failure Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2018;**20**:1081–1099.
439. Ter Maaten JM, Damman K, Hanberg JS, Givertz MM, Metra M, O'Connor CM, Teerlink JR, Ponikowski P, Cotter G, Davison B, Cleland JG, Bloomfield DM, Hillege HL, van Veldhuisen DJ, Voors AA, Testani JM. Hypochloremia, diuretic resistance, and outcome in patients with acute heart failure. *Circ Heart Fail* 2016;**9**.
440. Nunez J, Llacer P, Garcia-Blas S, Bonanad C, Ventura S, Nunez JM, Sanchez R, Facila L, de la Espriella R, Vaquer JM, Cordero A, Roque M, Chamorro C, Bodi V, Valero E, Santas E, Moreno MDC, Minana G, Carratala A, Rodriguez E, Mollar A, Palau P, Bosch MJ, Bertomeu-Gonzalez V, Lupon J, Navarro J, Chorro FJ, Gorriz JL, Sanchis J, Voors AA, Bayes-Genis A. CA125-guided diuretic treatment versus usual care in patients with acute heart failure and renal dysfunction. *Am J Med* 2020;**133**:370–380 e374.
441. Nikolaou M, Parissis J, Yilmaz MB, Seronde MF, Kivikko M, Laribi S, Paugam-Burtz C, Cai D, Pohjanjousi P, Laterre PF, Deye N, Poder P, Cohen-Solal A, Mebazaa A. Liver function abnormalities, clinical profile, and outcome in acute decompensated heart failure. *Eur Heart J* 2013;**34**:742–749.
442. Mockel M, de Boer RA, Slagman AC, von Haehling S, Schou M, Vollert JO, Wiemer JC, Ebmeyer S, Martín-Sánchez FJ, Maisel AS, Giannitsis E. Improve Management of acute heart failure with ProcAlCiTonin in EUrope: results of the randomized clinical trial IMPACT EU Biomarkers in Cardiology (BIC) 18. *Eur J Heart Fail* 2020;**22**:267–275.
443. Masip J, De Mendoza D, Planas K, Paez J, Sanchez B, Cancio B. Peripheral venous blood gases and pulse-oximetry in acute cardiogenic pulmonary oedema. *Eur Heart J Acute Cardiovasc Care* 2012;**1**:275–280.
444. Masip J, Gaya M, Paez J, Betbese A, Vecilla F, Manresa R, Ruiz P. Pulse oximetry in the diagnosis of acute heart failure. *Rev Esp Cardiol (Engl Ed)* 2012;**65**:879–884.
445. Nieminen MS, Bohm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, Hasin Y, Lopez-Sendon J, Mebazaa A, Metra M, Rhodes A, Swedberg K, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie MR, Dean V, Deckers J, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, Morais J, Oto A, Smiseth OA, Garcia MA, Dickstein K, Albuquerque A, Conthe P, Crespo-Leiro M, Ferrari R, Follath F, Gavazzi A, Janssens U, Komajda M, Morais J, Moreno R, Singer M, Singh S, Tendera M, Thygesen K, ESC Committe for Practice Guideline (CPG). Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005;**26**:384–416.
446. Nohria A, Tsang SW, Fang JC, Lewis EF, Jarcho JA, Mudge GH, Stevenson LW. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *J Am Coll Cardiol* 2003;**41**:1797–1804.
447. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, Dickstein K, Drazner MH, Fonarow GC, Jaarsma T, Jondeau G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, van Veldhuisen DJ, Zannad F, Anker SD, Rhodes A, McMurray JJ, Filippatos G, European Society of Cardiology, European Society of Intensive Care Medicine. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the Heart Failure Association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. *Eur J Heart Fail* 2010;**12**:423–433.
448. Masip J, Peacock WF, Price S, Cullen L, Martin-Sanchez FJ, Seferovic P, Maisel AS, Miro O, Filippatos G, Vrints C, Christ M, Cowie M, Platz E, McMurray J, DiSomma S, Zeymer U, Bueno H, Gale CP, Lettino M, Tavares M, Ruschitzka F, Mebazaa A, Harjola VP, Mueller C, Acute Heart Failure Study Group of the Acute Cardiovascular Care Association and the Committee on Acute Heart Failure of the Heart Failure Association of the European Society of Cardiology. Indications and practical approach to non-invasive ventilation in acute heart failure. *Eur Heart J* 2018;**39**:17–25.
449. Harjola VP, Mebazaa A, Celutkiene J, Bettex D, Bueno H, Chioncel O, Crespo-Leiro MG, Falk V, Filippatos G, Gibbs S, Leite-Moreira A, Lassus J, Masip J, Mueller C, Mullens W, Naeije R, Nordegraaf AV, Parissis J, Riley JP, Ristic A, Rosano G, Rudiger A, Ruschitzka F, Seferovic P, Sztrymf B, Vieillard-Baron A, Yilmaz MB, Konstantinides S. Contemporary management of acute right ventricular failure: a statement from the Heart Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology. *Eur J Heart Fail* 2016;**18**:226–241.
450. Chioncel O, Parissis J, Mebazaa A, Thiele H, Desch S, Bauersachs J, Harjola VP, Antohi EL, Arrigo M, Gal TB, Celutkiene J, Collins SP, DeBacker D, Iliescu VA, Jankowska E, Jaarsma T, Keramida K, Lainscak M, Lund LH, Lyon AR, Masip J, Metra M, Miro O, Mortara A, Mueller C, Mullens W, Nikolaou M, Piepoli M, Price S, Rosano G, Vieillard-Baron A, Weinstein JM, Anker SD, Filippatos G, Ruschitzka F, Coats AJS, Seferovic P. Epidemiology, pathophysiology and contemporary management of cardiogenic shock – a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:1315–1341.
451. Thiele H, Ohman EM, de Waha-Thiele S, Zeymer U, Desch S. Management of cardiogenic shock complicating myocardial infarction: an update 2019. *Eur Heart J* 2019;**40**:2671–2683.
452. Mebazaa A, Combes A, van Diepen S, Hollinger A, Katz JN, Landoni G, Hajjar LA, Lassus J, Lebreton G, Montalescot G, Park JJ, Price S, Sionis A, Yannopolos D, Harjola VP, Levy B, Thiele H. Management of cardiogenic shock complicating myocardial infarction. *Intensive Care Med* 2018;**44**:760–773.
453. Zymlinski R, Biegus J, Sokolski M, Siwolowski P, Nawrocka-Millward S, Todd J, Jankowska EA, Banasiak W, Cotter G, Cleland JG, Ponikowski P. Increased blood lactate is prevalent and identifies poor prognosis in patients with acute heart failure without overt peripheral hypoperfusion. *Eur J Heart Fail* 2018;**20**:1011–1018.
454. Menon V, Slater JN, White HD, Sleeper LA, Cocke T, Hochman JS. Acute myocardial infarction complicated by systemic hypoperfusion without hypotension: report of the SHOCK trial registry. *Am J Med* 2000;**108**:374–380.
455. Harjola P, Miro O, Martin-Sanchez FJ, Escalada X, Freund Y, Penaloza A, Christ M, Cone DC, Laribi S, Kuisma M, Tarvasmaki T, Harjola VP, EMS-AHF Study Group. Pre-hospital management protocols and perceived difficulty in diagnosing acute heart failure. *ESC Heart Fail* 2020;**7**:289–296.
456. Takahashi M, Kohsaka S, Miyata H, Yoshikawa T, Takagi A, Harada K, Miyamoto T, Sakai T, Nagao K, Sato N, Takayama M, Tokyo CCU Network Council. Association between prehospital time interval and short-term outcome in acute heart failure patients. *J Card Fail* 2011;**17**:742–747.
457. Park JH, Balmain S, Berry C, Morton JJ, McMurray JJ. Potentially detrimental cardiovascular effects of oxygen in patients with chronic left ventricular systolic dysfunction. *Heart* 2010;**96**:533–538.
458. Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J, 3CPO Trialists Noninvasive ventilation in acute cardiogenic pulmonary edema. *N Engl J Med* 2008;**359**:142–151.
459. Weng CL, Zhao YT, Liu QH, Fu CJ, Sun F, Ma YL, Chen YW, He QY. Meta-analysis: noninvasive ventilation in acute cardiogenic pulmonary edema. *Ann Intern Med* 2010;**152**:590–600.
460. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ,

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Bart BA, Mascette AM, Braunwald E, O'Connor CM, Network NHFCR. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* 2011;**364**:797–805.
461. Felker GM, Ellison DH, Mullens W, Cox ZL, Testani JM. Diuretic therapy for patients with heart failure: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;**75**:1178–1195.
462. Brisco MA, Zile MR, Hanberg JS, Wilson FP, Parikh CR, Coca SG, Tang WH, Testani JM. Relevance of changes in serum creatinine during a heart failure trial of decongestive strategies: insights from the DOSE trial. *J Card Fail* 2016;**22**:753–760.
463. Damman K, Kjekshus J, Wikstrand J, Cleland JG, Komajda M, Wedel H, Waagstein F, McMurray JJ. Loop diuretics, renal function and clinical outcome in patients with heart failure and reduced ejection fraction. *Eur J Heart Fail* 2016;**18**:328–336.
464. Ter Maaten JM, Martens P, Damman K, Dickstein K, Ponikowski P, Lang CC, Ng LL, Anker SD, Samani NJ, Filippatos G, Cleland JG, Zannad F, Hillege HL, van Veldhuisen DJ, Metra M, Voors AA, Mullens W. Higher doses of loop diuretics limit uptitration of angiotensin-converting enzyme inhibitors in patients with heart failure and reduced ejection fraction. *Clin Res Cardiol* 2020;**109**:1048–1059.
465. Cubbon RM, Woolston A, Adams B, Gale CP, Gilthorpe MS, Baxter PD, Kearney LC, Mercer B, Rajwani A, Batin PD, Kahn M, Sapsford RJ, Witte KK, Kearney MT. Prospective development and validation of a model to predict heart failure hospitalisation. *Heart* 2014;**100**:923–929.
466. Kapelios CJ, Laroche C, Crespo-Leiro MG, Anker SD, Coats AJS, Diaz-Molina B, Filippatos G, Lainscak M, Maggioni AP, McDonagh T, Mebazaa A, Metra M, Moura B, Mullens W, Piepoli MF, Rosano GMC, Ruschitzka F, Seferovic PM, Lund LH, Heart Failure Long-Term Registry Investigators Group. Association between loop diuretic dose changes and outcomes in chronic heart failure: observations from the ESC-EORP heart failure long-term registry. *Eur J Heart Fail* 2020;**22**:1424–1437.
467. Mebazaa A, Yilmaz MB, Levy P, Ponikowski P, Peacock WF, Laribi S, Ristic AD, Lambrinou E, Masip J, Riley JP, McDonagh T, Mueller C, deFilippi C, Harjola VP, Thiele H, Piepoli MF, Metra M, Maggioni A, McMurray J, Dickstein K, Damman K, Seferovic PM, Ruschitzka F, Leite-Moreira AF, Bellou A, Anker SD, Filippatos G. Recommendations on pre-hospital & early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine. *Eur J Heart Fail* 2015;**17**:544–558.
468. Damman K, Ter Maaten JM, Coster JE, Krikken JA, van Deursen VM, Krijnen HK, Hofman M, Nieuwland W, van Veldhuisen DJ, Voors AA, van der Meer P. Clinical importance of urinary sodium excretion in acute heart failure. *Eur J Heart Fail* 2020;**22**:1438–1447.
469. Mullens W, Verbrugge FH, Nijst P, Martens P, Tartaglia K, Theunissen E, Bruckers L, Droogne W, Troisfontaines P, Damman K, Lassus J, Mebazaa A, Filippatos G, Ruschitzka F, Dupont M. Rationale and design of the ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) trial. *Eur J Heart Fail* 2018;**20**:1591–1600.
470. Cox ZL, Hung R, Lenihan DJ, Testani JM. Diuretic strategies for loop diuretic resistance in acute heart failure: the 3T trial. *JACC Heart Fail* 2020;**8**:157–168.
471. Damman K, Testani JM. The kidney in heart failure: an update. *Eur Heart J* 2015;**36**:1437–1444.
472. Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, Maggioni AP, Cook T, Swedberg K, Burnett JC, Jr., Grinfeld L, Udelson JE, Zannad F, Gheorghiade M, EVEREST Trial Investigators. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J* 2013;**34**:835–843.
473. Faselis C, Arundel C, Patel S, Lam PH, Gottlieb SS, Zile MR, Deedwania P, Filippatos G, Sheriff HM, Zeng Q, Morgan CJ, Wopperer S, Nguyen T, Allman RM, Fonarow GC, Ahmed A. Loop diuretic prescription and 30-day outcomes in older patients with heart failure. *J Am Coll Cardiol* 2020;**76**:669–679.
474. Sharon A, Shpirer I, Kaluski E, Moshkovitz Y, Milovanov O, Polak R, Blatt A, Simovitz A, Shaham O, Faigenberg Z, Metzger M, Stav D, Yogev R, Golik A, Krakover R, Vered Z, Cotter G. High-dose intravenous isosorbide-dinitrate is safer and better than Bi-PAP ventilation combined with conventional treatment for severe pulmonary edema. *J Am Coll Cardiol* 2000;**36**:832–837.
475. Publication Committee for the VMAC Investigators (Vasodilatation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA* 2002;**287**:1531–1540.
476. Cotter G, Metzkor E, Kaluski E, Faigenberg Z, Miller R, Simovitz A, Shaham O, Marghitay D, Koren M, Blatt A, Moshkovitz Y, Zaidenstein R, Golik A. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. *Lancet* 1998;**351**:389–393.
477. Levy P, Compton S, Welch R, Delgado G, Jennett A, Penugonda N, Dunne R, Zalenski R. Treatment of severe decompensated heart failure with high-dose intravenous nitroglycerin: a feasibility and outcome analysis. *Ann Emerg Med* 2007;**50**:144–152.
478. Mebazaa A, Motiejunaite J, Gayat E, Crespo-Leiro MG, Lund LH, Maggioni AP, Chioncel O, Akiyama E, Harjola VP, Seferovic P, Laroche C, Julve MS, Roig E, Ruschitzka F, Filippatos G, ESC Heart Failure Long-Term Registry Investigators. Long-term safety of intravenous cardiovascular agents in acute heart failure: results from the European Society of Cardiology heart failure long-term registry. *Eur J Heart Fail* 2018;**20**:332–341.
479. Kozhuharov N, Goudev A, Flores D, Maeder MT, Walter J, Shrestha S, Gualandro DM, de Oliveira Junior MT, Sabti Z, Muller B, Noveanu M, Socrates T, Ziller R, Bayes-Genis A, Sionis A, Simon P, Michou E, Gujer S, Gori T, Wenzel P, Pfister O, Conen D, Kapos I, Kobza R, Rickli H, Breidthardt T, Munzel T, Erne P, Mueller C, Investigators G, Mueller C, Erne P, Muller B, Rickli H, Maeder M, Tavares de Oliveira M Jr, Munzel T, Bayes-Genis A, Sionis A, Goudev A, Dimov B, Hartwiger S, Arenja N, Glatz B, Herr N, Isenrich R, Mosimann T, Twerenbold R, Boeddinghaus J, Nestelberger T, Puelacher C, Freese M, Vogele J, Meissner K, Martin J, Strebel I, Wussler D, Schumacher C, Osswald S, Vogt F, Hilti J, Barata S, Schneider D, Schwarz J, Fitze B, Hartwiger S, Arenja N, Glatz B, Herr N, Isenrich R, Mosimann T, Twerenbold R, Boeddinghaus J, Nestelberger T, Puelacher C, Freese M, Vogele J, Meissner K, Martin J, Strebel I, Wussler D, Schumacher C, Osswald S, Vogt F, Hilti J, Barata S, Schneider D, Schwarz J, Fitze B, Arenja N, Rentsch K, Bossa A, Jallad S, Soeiro A, Georgiev D, Jansen T, Gebel G, Bossard M, Christ M. Effect of a strategy of comprehensive vasodilation vs usual care on mortality and heart failure rehospitalization among patients with acute heart failure: the GALACTIC randomized clinical trial. *JAMA* 2019;**322**:2292–2302.
480. Freund Y, Cachanado M, Delannoy Q, Laribi S, Yordanov Y, Gorlicki J, Chouihed T, Feral-Pierssens AL, Truchot J, Desmettre T, Occelli C, Bobbia X, Khellaf M, Ganansia O, Bokobza J, Balen F, Beaune S, Bloom B, Simon T, Mebazaa A. Effect of an emergency department care bundle on 30-day hospital discharge and survival among elderly patients with acute heart failure: the ELISABETH randomized clinical trial. *JAMA* 2020;**324**:1948–1956.
481. Khot UN, Novaro GM, Popovic ZB, Mills RM, Thomas JD, Tuzcu EM, Hammer D, Nissen SE, Francis GS. Nitroprusside in critically ill patients with left ventricular dysfunction and aortic stenosis. *N Engl J Med* 2003;**348**:1756–1763.
482. Mebazaa A, Nieminen MS, Filippatos GS, Cleland JG, Salon JE, Thakkar R, Padley RJ, Huang B, Cohen-Solal A. Levosimendan vs. dobutamine: outcomes for acute heart failure patients on beta-blockers in SURVIVE. *Eur J Heart Fail* 2009;**11**:304–311.
483. Metra M, Nodari S, D'Aloia A, Muneretto C, Robertson AD, Bristow MR, Dei Cas L. Beta-blocker therapy influences the hemodynamic response to inotropic agents in patients with heart failure: a randomized comparison of dobutamine and enoximone before and after chronic treatment with metoprolol or carvedilol. *J Am Coll Cardiol* 2002;**40**:1248–1258.
484. Packer M, Colucci W, Fisher L, Massie BM, Teerlink JR, Young J, Padley RJ, Thakkar R, Delgado-Herrera L, Salon J, Garratt C, Huang B, Sarapohja T, REVIVE Heart Failure Study Group. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. *JACC Heart Fail* 2013;**1**:103–111.
485. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, Brasseur A, Defrance P, Gottignies P, Vincent JL, SOAP II Investigators. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010;**362**:779–789.
486. Levy B, Clere-Jehl R, Legras A, Morichau-Beauchant T, Leone M, Frederique G, Quenot JP, Kimmoun A, Cariou A, Lassus J, Harjola VP, Meziani F, Louis G, Rossignol P, Duarte K, Girerd N, Mebazaa A, Vignon P, Collaborators. Epinephrine versus norepinephrine for cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol* 2018;**72**:173–182.
487. Leopold V, Gayat E, Pirracchio R, Spinar J, Parenica J, Tarvasmaki T, Lassus J, Harjola VP, Champion S, Zannad F, Valente S, Urban P, Chua HR, Bellomo R, Popovic B, Ouweneel DM, Henriques JPS, Simonis G, Levy B, Kimmoun A, Gaudard P, Basir MB, Markota A, Adler C, Reuter H, Mebazaa A, Chouihed T. Epinephrine and short-term survival in cardiogenic shock: an individual data meta-analysis of 2583 patients. *Intensive Care Med* 2018;**44**:847–856.
488. Peacock WF, Hollander JE, Diercks DB, Lopatin M, Fonarow G, Emerman CL. Morphine and outcomes in acute decompensated heart failure: an ADHERE analysis. *Emerg Med J* 2008;**25**:205–209.
489. Gil V, Dominguez-Rodriguez A, Masip J, Peacock WF, Miro O. Morphine use in the treatment of acute cardiogenic pulmonary edema and its effects on patient outcome: a systematic review. *Curr Heart Fail Rep* 2019;**16**:81–88.

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490. Miro O, Gil V, Martin-Sanchez FJ, Herrero-Puente P, Jacob J, Mebazaa A, Harjola VP, Rios J, Hollander JE, Peacock WF, Llorens P, ICA-SEMES Research Group. Morphine use in the ED and outcomes of patients with acute heart failure: a propensity score-matching analysis based on the EAHFE registry. *Chest* 2017;**152**:821–832.
491. Caspi O, Naami R, Halfin E, Aronson D. Adverse dose-dependent effects of morphine therapy in acute heart failure. *Int J Cardiol* 2019;**293**:131–136.
492. Sethi NJ, Nielsen EE, Safi S, Feinberg J, Gluud C, Jakobsen JC. Digoxin for atrial fibrillation and atrial flutter: a systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *PLoS One* 2018;**13**:e0193924.
493. Khand AU, Rankin AC, Martin W, Taylor J, Gemmell I, Cleland JG. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? *J Am Coll Cardiol* 2003;**42**:1944–1951.
494. Tebbe U, Schellong SM, Haas S, Gerlach HE, Ableitshauser C, Sieder C, Bramlage P, Riess H. Certoparin versus unfractionated heparin to prevent venous thromboembolic events in patients hospitalized because of heart failure: a subgroup analysis of the randomized, controlled CERTIFY study. *Am Heart J* 2011;**161**:322–328.
495. Dentali F, Douketis JD, Gianni M, Lim W, Crowther MA. Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. *Ann Intern Med* 2007;**146**:278–288.
496. Seferovic PM, Piepoli MF, Lopatin Y, Jankowska E, Polovina M, Anguita-Sanchez M, Stork S, Lainscak M, Milicic D, Milinkovic I, Filippatos G, Coats AJS, Heart Failure Association Board of the European Society of Cardiology. Heart Failure Association of the European Society of Cardiology quality of care centres programme: design and accreditation document. *Eur J Heart Fail* 2020;**22**:763–774.
497. Tehrani BN, Truesdell AG, Sherwood MW, Desai S, Tran HA, Epps KC, Singh R, Psotka M, Shah P, Cooper LB, Rosner C, Raja A, Barnett SD, Saulino P, deFilippi CR, Gurbel PA, Murphy CE, O'Connor CM. Standardized team-based care for cardiogenic shock. *J Am Coll Cardiol* 2019;**73**:1659–1669.
498. Basir MB, Kapur NK, Patel K, Salam MA, Schreiber T, Kaki A, Hanson I, Almany S, Timmis S, Dixon S, Kolski B, Todd J, Senter S, Marso S, Lasorda D, Wilkins C, Lalonde T, Attallah A, Larkin T, Dupont A, Marshall J, Patel N, Overly T, Green M, Tehrani B, Truesdell AG, Sharma R, Akhtar Y, McRae T, 3rd, O'Neill B, Finley J, Rahman A, Foster M, Askari R, Goldsweig A, Martin S, Bharadwaj A, Khuddus M, Caputo C, Korpas D, Cawich I, McAllister D, Blank N, Alraies MC, Fisher R, Khandelwal A, Alaswad K, Lemor A, Johnson T, Hacala M, O'Neill WW, National Cardiogenic Shock Initiative Investigators. Improved outcomes associated with the use of shock protocols: updates from the National Cardiogenic Shock Initiative. *Catheter Cardiovasc Interv* 2019;**93**:1173–1183.
499. Tehrani BN, Truesdell AG, Psotka MA, Rosner C, Singh R, Sinha SS, Damluji AA, Batchelor WB. A standardized and comprehensive approach to the management of cardiogenic shock. *JACC Heart Fail* 2020;**8**:879–891.
500. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Fuhrmann J, Bohm M, Ebelt H, Schneider S, Schuler G, Werdan K, IABP-SHOCK II Trial Investigators. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 2012;**367**:1287–1296.
501. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, de Waha A, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Lauer B, Bohm M, Ebelt H, Schneider S, Werdan K, Schuler G, Intraaortic Balloon Pump in cardiogenic shock II (IABP-SHOCK II) trial investigators. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. *Lancet* 2013;**382**:1638–1645.
502. Thiele H, Zeymer U, Thelemann N, Neumann FJ, Hausleiter J, Abdel-Wahab M, Meyer-Saraei R, Fuernau G, Eitel I, Hambrecht R, Bohm M, Werdan K, Felix SB, Hennersdorf M, Schneider S, Ouarrak T, Desch S, de Waha-Thiele S, IABP-SHOCK II Trial Investigators. Intraaortic balloon pump in cardiogenic shock complicating acute myocardial infarction: long-term 6-year outcome of the randomized IABP-SHOCK II Trial. *Circulation* 2019;**139**:395–403.
503. Seyfarth M, Sibbing D, Bauer I, Frohlich G, Bott-Flugel L, Byrne R, Dirschinger J, Kastrati A, Schomig A. A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. *J Am Coll Cardiol* 2008;**52**:1584–1588.
504. Ouweneel DM, Eriksen E, Sjauw KD, van Dongen IM, Hirsch A, Packer EJ, Vis MM, Wykrzykowska JJ, Koch KT, Baan J, de Winter RJ, Piek JJ, Lagrand WK, de Mol BA, Tijssen JG, Henriques JP. Percutaneous mechanical circulatory support versus intra-aortic balloon pump in cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol* 2017;**69**:278–287.
505. Schrage B, Ibrahim K, Loehn T, Werner N, Sinning JM, Pappalardo F, Pieri M, Skurk C, Lauten A, Landmesser U, Westenfeld R, Horn P, Pauschinger M, Eckner D, Twerenbold R, Nordbeck P, Salinger T, Abel P, Empen K, Busch MC, Felix SB, Sieweke JT, Moller JE, Pareek N, Hill J, MacCarthy P, Bergmann MW, Henriques JPS, Mobius-Winkler S, Schulze PC, Ouarrak T, Zeymer U, Schneider S, Blankenberg S, Thiele H, Schafer A, Westermann D. Impella support for acute myocardial infarction complicated by cardiogenic shock. *Circulation* 2019;**139**:1249–1258.
506. Dhruva SS, Ross JS, Mortazavi BJ, Hurley NC, Krumholz HM, Curtis JP, Berkowitz A, Masoudi FA, Messenger JC, Parzynski CS, Ngufor C, Girotra S, Amin AP, Shah ND, Desai NR. Association of use of an intravascular microaxial left ventricular assist device vs intra-aortic balloon pump with in-hospital mortality and major bleeding among patients with acute myocardial infarction complicated by cardiogenic shock. *JAMA* 2020;**323**:734–745.
507. Kar B, Gregoric ID, Basra SS, Idelchik GM, Loyalka P. The percutaneous ventricular assist device in severe refractory cardiogenic shock. *J Am Coll Cardiol* 2011;**57**:688–696.
508. Ouweneel DM, Schotborgh JV, Limpens J, Sjauw KD, Engstrom AE, Lagrand WK, Cherpanath TGV, Driessen AHG, de Mol B, Henriques JPS. Extracorporeal life support during cardiac arrest and cardiogenic shock: a systematic review and meta-analysis. *Intensive Care Med* 2016;**42**:1922–1934.
509. Combes A, Price S, Slutsky AS, Brodie D. Temporary circulatory support for cardiogenic shock. *Lancet* 2020;**396**:199–212.
510. Pappalardo F, Schulte C, Pieri M, Schrage B, Contri R, Soeffker G, Greco T, Lembo R, Mullerleile K, Colombo A, Sydow K, De Bonis M, Wagner F, Reichenspurner H, Blankenberg S, Zangrillo A, Westermann D. Concomitant implantation of Impella((R)) on top of veno-arterial extracorporeal membrane oxygenation may improve survival of patients with cardiogenic shock. *Eur J Heart Fail* 2017;**19**:404–412.
511. Anderson MB, Goldstein J, Milano C, Morris LD, Kormos RL, Bhama J, Kapur NK, Bansal A, Garcia J, Baker JN, Silvestry S, Holman WL, Douglas PS, O'Neill W. Benefits of a novel percutaneous ventricular assist device for right heart failure: the prospective RECOVER RIGHT study of the Impella RP device. *J Heart Lung Transplant* 2015;**34**:1549–1560.
512. Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozdz J, Fabien V, Filippatos G, Gohring UM, Keren A, Khintibidze I, Kragten H, Martinez FA, Metra M, Milicic D, Nicolau JC, Ohlsson M, Parkhomenko A, Pascual-Figal DA, Ruschitzka F, Sim D, Skouri H, van der Meer P, Lewis BS, Comin-Colet J, von Haehling S, Cohen-Solal A, Danchin N, Doehner W, Dargie HJ, Motro M, Butler J, Friede T, Jensen KH, Pocock S, Jankowska EA, AFFIRM-AHF Investigators. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet* 2020;**396**:1895–1904.
513. Bhagat AA, Greene SJ, Vaduganathan M, Fonarow GC, Butler J. Initiation, continuation, switching, and withdrawal of heart failure medical therapies during hospitalization. *JACC Heart Fail* 2019;**7**:1–12.
514. Prins KW, Neill JM, Tyler JO, Eckman PM, Duval S. Effects of beta-blocker withdrawal in acute decompensated heart failure: a systematic review and meta-analysis. *JACC Heart Fail* 2015;**3**:647–653.
515. Metra M, Gheorghiade M, Bonow RO, Dei Cas L. Postdischarge assessment after a heart failure hospitalization: the next step forward. *Circulation* 2010;**122**:1782–1785.
516. Greene SJ, Fonarow GC, Vaduganathan M, Khan SS, Butler J, Gheorghiade M. The vulnerable phase after hospitalization for heart failure. *Nat Rev Cardiol* 2015;**12**:220–229.
517. Lee KK, Yang J, Hernandez AF, Steimle AE, Go AS. Post-discharge Follow-up characteristics associated with 30-day readmission after heart failure hospitalization. *Med Care* 2016;**54**:365–372.
518. Edmonston DL, Wu J, Matsouaka RA, Yancy C, Heidenreich P, Pina IL, Hernandez A, Fonarow GC, DeVore AD. Association of post-discharge specialty outpatient visits with readmissions and mortality in high-risk heart failure patients. *Am Heart J* 2019;**212**:101–112.
519. Ling LH, Kistler PM, Kalman JM, Schilling RJ, Hunter RJ. Comorbidity of atrial fibrillation and heart failure. *Nat Rev Cardiol* 2016;**13**:131–147.
520. Carlisle MA, Fudim M, DeVore AD, Piccini JP. Heart failure and atrial fibrillation, like fire and fury. *JACC Heart Fail* 2019;**7**:447–456.
521. Gorenek B, Halvorsen S, Kudaiberdieva G, Bueno H, Van Gelder IC, Lettino M, Marin F, Masip J, Mueller C, Okutucu S, Poess J, Potpara TS, Price S, Lip GYH. Atrial fibrillation in acute heart failure: a position statement from the Acute Cardiovascular Care Association and European Heart Rhythm Association of the European Society of Cardiology. *Eur Heart J Acute Cardiovasc Care* 2020;**9**:348–357.
522. Slawik J, Adrian L, Hohl M, Lothschutz S, Laufs U, Bohm M. Irregular pacing of ventricular cardiomyocytes induces pro-fibrotic signalling involving paracrine effects of transforming growth factor beta and connective tissue growth factor. *Eur J Heart Fail* 2019;**21**:482–491.
523. Kotecha D, Lam CS, Van Veldhuisen DJ, Van Gelder IC, Voors AA, Rienstra M. Heart failure with preserved ejection fraction and atrial fibrillation: vicious twins. *J Am Coll Cardiol* 2016;**68**:2217–2228.

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524. Smit MD, Moes ML, Maass AH, Achekar ID, Van Geel PP, Hillege HL, van Veldhuisen DJ, Van Gelder IC. The importance of whether atrial fibrillation or heart failure develops first. *Eur J Heart Fail* 2012;**14**:1030–1040.
525. Swedberg K, Olsson LG, Charlesworth A, Cleland J, Hanrath P, Komajda M, Metra M, Torp-Pedersen C, Poole-Wilson P. Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: results from COMET. *Eur Heart J* 2005;**26**:1303–1308.
526. Mogensen UM, Jhund PS, Abraham WT, Desai AS, Dickstein K, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, Køber L, McMurray JJV, PARADIGM-HF and ATMOSPHERE Investigators and Committees. Type of atrial fibrillation and outcomes in patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol* 2017;**70**:2490–2500.
527. Hoppe UC, Casares JM, Eiskjaer H, Hagemann A, Cleland JG, Freemantle N, Erdmann E. Effect of cardiac resynchronization on the incidence of atrial fibrillation in patients with severe heart failure. *Circulation* 2006;**114**:18–25.
528. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;**383**:955–962.
529. Reddy VY, Doshi SK, Sievert H, Buchbinder M, Neuzil P, Huber K, Halperin JL, Holmes D, PROTECT AF Investigators. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-year follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) trial. *Circulation* 2013;**127**:720–729.
530. Holmes DR, Jr., Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, Huber K, Reddy VY. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol* 2014;**64**:1–12.
531. Van Gelder IC, Wyse DG, Chandler ML, Cooper HA, Olshansky B, Hagens VE, Crijns HJ, RACE and AFFIRM Investigators. Does intensity of rate-control influence outcome in atrial fibrillation? An analysis of pooled data from the RACE and AFFIRM studies. *Europace* 2006;**8**:935–942.
532. Hess PL, Sheng S, Matsouaka R, DeVore AD, Heidenreich PA, Yancy CW, Bhatt DL, Allen LA, Peterson PN, Ho PM, Lewis WR, Hernandez AF, Fonarow GC, Piccini JP. Strict versus lenient versus poor rate control among patients with atrial fibrillation and heart failure (from the Get With The Guidelines – Heart Failure Program). *Am J Cardiol* 2020;**125**:894–900.
533. Sartipy U, Savarese G, Dahlstrom U, Fu M, Lund LH. Association of heart rate with mortality in sinus rhythm and atrial fibrillation in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2019;**21**:471–479.
534. Van Gelder IC, Rienstra M, Crijns HJ, Olshansky B. Rate control in atrial fibrillation. *Lancet* 2016;**388**:818–828.
535. Kotecha D, Flather MD, Altman DG, Holmes J, Rosano G, Wikstrand J, Packer M, Coats AJS, Manzano L, Bohm M, van Veldhuisen DJ, Andersson B, Wedel H, von Lueder TG, Rigby AS, Hjalmarson A, Kjekshus J, Cleland JGF, Beta-Blockers in Heart Failure Collaborative Group. Heart rate and rhythm and the benefit of beta-blockers in patients with heart failure. *J Am Coll Cardiol* 2017;**69**:2885–2896.
536. Kotecha D, Bunting KV, Gill SK, Mehta S, Stanbury M, Jones JC, Haynes S, Calvert MJ, Deeks JJ, Steeds RP, Strauss VY, Rahimi K, Camm AJ, Griffith M, Lip GYH, Townend JN, Kirchhof P, Rate Control Therapy Evaluation in Permanent Atrial Fibrillation (RATE-AF) Team. Effect of digoxin vs bisoprolol for heart rate control in atrial fibrillation on patient-reported quality of life: the RATE-AF randomized clinical trial. *JAMA* 2020;**324**:2497–2508.
537. Hofmann R, Steinwender C, Kammler J, Kypta A, Leisch F. Effects of a high dose intravenous bolus amiodarone in patients with atrial fibrillation and a rapid ventricular rate. *Int J Cardiol* 2006;**110**:27–32.
538. Wood MA, Brown-Mahoney C, Kay GN, Ellenbogen KA. Clinical outcomes after ablation and pacing therapy for atrial fibrillation: a meta-analysis. *Circulation* 2000;**101**:1138–1144.
539. Lim KT, Davis MJ, Powell A, Arnolda L, Moulden K, Bulsara M, Weerasooriya R. Ablate and pace strategy for atrial fibrillation: long-term outcome of AIRCRAFT trial. *Europace* 2007;**9**:498–505.
540. Gasparini M, Kloppe A, Lunati M, Anselme F, Landolina M, Martinez-Ferrer JB, Proclemer A, Morani G, Biffi M, Ricci R, Rordorf R, Mangoni L, Manotta L, Grammatico A, Leyva F, Boriani G. Atrioventricular junction ablation in patients with atrial fibrillation treated with cardiac resynchronization therapy: positive impact on ventricular arrhythmias, implantable cardioverter-defibrillator therapies and hospitalizations. *Eur J Heart Fail* 2018;**20**:1472–1481.
541. Deedwania PC, Singh BN, Ellenbogen K, Fisher S, Fletcher R, Singh SN. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the Veterans Affairs Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT). The Department of Veterans Affairs CHF-STAT Investigators. *Circulation* 1998;**98**:2574–2579.
542. Antiarrhythmic Drug Evaluation Group (A.D.E.G.). A multicentre, randomized trial on the benefit/risk profile of amiodarone, flecainide and propafenone in patients with cardiac disease and complex ventricular arrhythmias. *Eur Heart J* 1992;**13**:1251–1258.
543. Connolly SJ, Camm AJ, Halperin JL, Joyner C, Alings M, Amerena J, Atar D, Avezum A, Blomstrom P, Borggrefe M, Budaj A, Chen SA, Ching CK, Commerford P, Dans A, Davy JM, Delacretaz E, Di Pasquale G, Diaz R, Dorian P, Flaker G, Golitsyn S, Gonzalez-Hermosillo A, Granger CB, Heidbuchel H, Kautzner J, Kim JS, Lanas F, Lewis BS, Merino JL, Morillo C, Murin J, Narasimhan C, Paolasso E, Parkhomenko A, Peters NS, Sim KH, Stiles MK, Tanomsup S, Toivonen L, Tomcsanyi J, Torp-Pedersen C, Tse HF, Vardas P, Vinereanu D, Xavier D, Zhu J, Zhu JR, Baret-Cormel L, Weinling E, Staiger C, Yusuf S, Chrolavicius S, Afzal R, Hohnloser SH, PALLAS Investigators. Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med* 2011;**365**:2268–2276.
544. Chatterjee S, Ghosh J, Lichstein E, Aikat S, Mukherjee D. Meta-analysis of cardiovascular outcomes with dronedarone in patients with atrial fibrillation or heart failure. *Am J Cardiol* 2012;**110**:607–613.
545. Shelton RJ, Clark AL, Goode K, Rigby AS, Houghton T, Kaye GC, Cleland JG. A randomised, controlled study of rate versus rhythm control in patients with chronic atrial fibrillation and heart failure: (CAFE-II Study). *Heart* 2009;**95**:924–930.
546. Capucci A, Villani GQ, Aschieri D, Rosi A, Piepoli MF. Oral amiodarone increases the efficacy of direct-current cardioversion in restoration of sinus rhythm in patients with chronic atrial fibrillation. *Eur Heart J* 2000;**21**:66–73.
547. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJ, Tijssen JG, Crijns HJ, Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002;**347**:1834–1840.
548. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD, Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;**347**:1825–1833.
549. Carlsson J, Miketic S, Windeler J, Cuneo A, Haun S, Micus S, Walter S, Tebbe U, STAF Investigators. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. *J Am Coll Cardiol* 2003;**41**:1690–1696.
550. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold JM, Buxton AE, Camm AJ, Connolly SJ, Dubuc M, Ducharme A, Guerra PG, Hohnloser SH, Lambert J, Le Heuzey JY, O'Hara G, Pedersen OD, Rouleau JL, Singh BN, Stevenson LW, Stevenson WG, Thibault B, Waldo AL, Atrial Fibrillation and Congestive Heart Failure Investigators Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med* 2008;**358**:2667–2677.
551. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, Fetsch T, van Gelder IC, Haase D, Haegeli LM, Hamann F, Heidbuchel H, Hindricks G, Kautzner J, Kuck KH, Mont L, Ng GA, Rekosz J, Schoen N, Schotten U, Suling A, Taggeselle J, Themistoclakis S, Vettorazzi E, Vardas P, Wegscheider K, Willems S, Crijns H, Breithardt G, EAST-AFNET 4 Trial Investigators. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020;**383**:1305–1316.
552. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bansch D, CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018;**378**:417–427.
553. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, Noseworthy PA, Rosenberg YD, Jeffries N, Mitchell LB, Flaker GC, Pokushalov E, Romanov A, Bunch TJ, Noelker G, Ardashev A, Revishvili A, Wilber DJ, Cappato R, Kuck KH, Hindricks G, Davies DW, Kowey PR, Naccarelli GV, Reiffel JA, Piccini JP, Silverstein AP, Al-Khalidi HR, Lee KL, CABANA Investigators. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA* 2019;**321**:1261–1274.
554. Packer DL, Piccini JP, Monahan KH, Al-Khalidi HR, Silverstein AP, Noseworthy PA, Poole JE, Bahnson TD, Lee KL, Mark DB, CABANA Investigators. Ablation versus drug therapy for atrial fibrillation in heart failure: results from the CABANA trial. *Circulation* 2021;**143**:1377–1390.
555. Kuck KH, Merkely B, Zahn R, Arentz T, Seidl K, Schluter M, Tilz RR, Piorkowski C, Geller L, Kleemann T, Hindricks G. Catheter ablation versus best medical therapy in patients with persistent atrial fibrillation and congestive heart failure: the randomized AMICA trial. *Circ Arrhythm Electrophysiol* 2019;**12**:e007731.
556. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, Reddy M, Jais P, Themistoclakis S, Dello Russo A, Casella M, Pelargonio G, Narducci

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ML, Schweikert R, Neuzil P, Sanchez J, Horton R, Beheiry S, Hongo R, Hao S, Rossillo A, Forleo G, Tondo C, Burkhardt JD, Haissaguerre M, Natale A. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. *Circulation* 2016;**133**:1637–1644.
557. Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN, Monahan KH, Daniels MR, Bahnson TD, Poole JE, Rosenberg Y, Lee KL, Packer DL, CABANA Investigators. Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA* 2019;**321**:1275–1285.
558. Xiong Q, Lau YC, Senoo K, Lane DA, Hong K, Lip GY. Non-vitamin K antagonist oral anticoagulants (NOACs) in patients with concomitant atrial fibrillation and heart failure: a systemic review and meta-analysis of randomized trials. *Eur J Heart Fail* 2015;**17**:1192–1200.
559. Nielsen PB, Larsen TB, Skjoth F, Overvad TF, Lip GY. Stroke and thromboembolic event rates in atrial fibrillation according to different guideline treatment thresholds: a nationwide cohort study. *Sci Rep* 2016;**6**:27410.
560. Latchamsetty R, Bogun F. Premature ventricular complex-induced cardiomyopathy. *JACC Clin Electrophysiol* 2019;**5**:537–550.
561. Mondesert B, Khairy P, Schram G, Shohoudi A, Talajic M, Andrade JG, Dubuc M, Guerra PG, Macle L, Roy D, Dyrda K, Thibault B, Barrero M, Diaz A, Kouz S, McNicoll S, Nowakowska D, Rivard L. Impact of revascularization in patients with sustained ventricular arrhythmias, prior myocardial infarction, and preserved left ventricular ejection fraction. *Heart Rhythm* 2016;**13**:1221–1227.
562. Yarlagadda RK, Iwai S, Stein KM, Markowitz SM, Shah BK, Cheung JW, Tan V, Lerman BB, Mittal S. Reversal of cardiomyopathy in patients with repetitive monomorphic ventricular ectopy originating from the right ventricular outflow tract. *Circulation* 2005;**112**:1092–1097.
563. Berruezo A, Penela D, Jauregui B, Soto-Iglesias D, Aguinaga L, Ordonez A, Fernandez-Armenta J, Martinez M, Tercedor L, Bisbal F, Acosta J, Marti-Almor J, Acena M, Anguera I, Rossi L, Linhart M, Borras R, Doltra A, Sanchez P, Ortiz-Perez JT, Perea RJ, Prat-Gonzalez S, Teres C, Bosch X. Mortality and morbidity reduction after frequent premature ventricular complexes ablation in patients with left ventricular systolic dysfunction. *Europace* 2019;**21**:1079–1087.
564. Cronin EM, Bogun FM, Maury P, Peichl P, Chen M, Namboodiri N, Aguinaga L, Leite LR, Al-Khatib SM, Anter E, Berruezo A, Callans DJ, Chung MK, Cuculich P, d'Avila A, Deal BJ, Della Bella P, Deneke T, Dickfeld TM, Hadid C, Haqqani HM, Kay GN, Latchamsetty R, Marchlinski F, Miller JM, Nogami A, Patel AR, Pathak RK, Saenz Morales LC, Santangeli P, Sapp JL, Sarkozy A, Soejima K, Stevenson WG, Tedrow UB, Tzou WS, Varma N, Zeppenfeld K, ESC Scientific Document Group. 2019 HRS/EHRA/APHRS/LAHRS expert consensus statement on catheter ablation of ventricular arrhythmias. *Europace* 2019;**21**:1143–1144.
565. Cho SW, Gwag HB, Hwang JK, Chun KJ, Park KM, On YK, Kim JS, Park SJ. Clinical features, predictors, and long-term prognosis of pacing-induced cardiomyopathy. *Eur J Heart Fail* 2019;**21**:643–651.
566. Vijayaraman P, Herweg B, Ellenbogen KA, Gajek J. His-optimized cardiac resynchronization therapy to maximize electrical resynchronization: a feasibility study. *Circ Arrhythm Electrophysiol* 2019;**12**:e006934.
567. Abdelrahman M, Subzposh FA, Beer D, Durr B, Naperkowski A, Sun H, Oren JW, Dandamudi G, Vijayaraman P. Clinical outcomes of His bundle pacing compared to right ventricular pacing. *J Am Coll Cardiol* 2018;**71**:2319–2330.
568. Ziff OJ, Samra M, Howard JP, Bromage DI, Ruschitzka F, Francis DP, Kotecha D. Beta-blocker efficacy across different cardiovascular indications: an umbrella review and meta-analytic assessment. *BMC Med* 2020;**18**:103.
569. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R, BEAUTIFUL Investigators. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial. *Eur Heart J* 2009;**30**:2337–2345.
570. Packer M, O'Connor CM, Ghali JK, Pressler ML, Carson PE, Belkin RN, Miller AB, Neuberg GW, Frid D, Wertheimer JH, Cropp AB, DeMets DL. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival Evaluation Study Group. *N Engl J Med* 1996;**335**:1107–1114.
571. Cohn JN, Ziesche S, Smith R, Anand I, Dunkman WB, Loeb H, Cintron G, Boden W, Baruch L, Rochin P, Loss L. Effect of the calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril: V-HeFT III. Vasodilator-Heart Failure Trial (V-HeFT) Study Group. *Circulation* 1997;**96**:856–863.
572. IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial. *Lancet* 2002;**359**:1269–1275.
573. Kanamasa K, Hayashi T, Kimura A, Ikeda A, Ishikawa K. Long-term, continuous treatment with both oral and transdermal nitrates increases cardiac events in healed myocardial infarction patients. *Angiology* 2002;**53**:399–408.
574. Wilson SR, Scirica BM, Braunwald E, Murphy SA, Karwatowska-Prokopczuk E, Buros JL, Chaitman BR, Morrow DA. Efficacy of ranolazine in patients with chronic angina observations from the randomized, double-blind, placebo-controlled MERLIN-TIMI (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Segment Elevation Acute Coronary Syndromes) 36 Trial. *J Am Coll Cardiol* 2009;**53**:1510–1516.
575. Gao D, Ning N, Niu X, Hao G, Meng Z. Trimetazidine: a meta-analysis of randomised controlled trials in heart failure. *Heart* 2011;**97**:278–286.
576. Vitale C, Wajngaten M, Sposato B, Gebara O, Rossini P, Fini M, Volterrani M, Rosano GM. Trimetazidine improves left ventricular function and quality of life in elderly patients with coronary artery disease. *Eur Heart J* 2004;**25**:1814–1821.
577. Zhang L, Lu Y, Jiang H, Zhang L, Sun A, Zou Y, Ge J. Additional use of trimetazidine in patients with chronic heart failure: a meta-analysis. *J Am Coll Cardiol* 2012;**59**:913–922.
578. Goldstein RE, Boccuzzi SJ, Cruess D, Nattel S. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. The Adverse Experience Committee; and the Multicenter Diltiazem Postinfarction Research Group. *Circulation* 1991;**83**:52–60.
579. Zannad F, Anker SD, Byra WM, Cleland JGF, Fu M, Gheorghiade M, Lam CSP, Mehra MR, Neaton JD, Nessel CC, Spiro TE, van Veldhuisen DJ, Greenberg B, COMMANDER HF Investigators. Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease. *N Engl J Med* 2018;**379**:1332–1342.
580. Branch KR, Probstfield JL, Eikelboom JW, Bosch J, Maggioni AP, Cheng RK, Bhatt DL, Avezum A, Fox KAA, Connolly SJ, Shestakovska O, Yusuf S. Rivaroxaban with or without aspirin in patients with heart failure and chronic coronary or peripheral artery disease. *Circulation* 2019;**140**:529–537.
581. Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, Michler RE, Bonow RO, Doenst T, Petrie MC, Oh JK, She L, Moore VL, Desvigne-Nickens P, Sopko G, Rouleau JL, STICHES Investigators. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med* 2016;**374**:1511–1520.
582. Panza JA, Holly TA, Asch FM, She L, Pellikka PA, Velazquez EJ, Lee KL, Borges-Neto S, Farsky PS, Jones RH, Berman DS, Bonow RO. Inducible myocardial ischemia and outcomes in patients with coronary artery disease and left ventricular dysfunction. *J Am Coll Cardiol* 2013;**61**:1860–1870.
583. Cleland JG, Calvert M, Freemantle N, Arrow Y, Ball SG, Bonser RS, Chattopadhyay S, Norell MS, Pennell DJ, Senior R. The Heart Failure Revascularisation Trial (HEART). *Eur J Heart Fail* 2011;**13**:227–233.
584. Perera D, Clayton T, Petrie MC, Greenwood JP, O'Kane PD, Evans R, Sculpher M, McDonagh T, Gershlick A, de Belder M, Redwood S, Carr-White G, Marber M, REVIVED Investigators. Percutaneous revascularization for ischemic ventricular dysfunction: rationale and design of the REVIVED-BCIS2 trial: percutaneous coronary intervention for ischemic cardiomyopathy. *JACC Heart Fail* 2018;**6**:517–526.
585. Bangalore S, Guo Y, Samadashvili Z, Blecker S, Hannan EL. Revascularization in patients with multivessel coronary artery disease and severe left ventricular systolic dysfunction: everolimus-eluting stents versus coronary artery bypass graft surgery. *Circulation* 2016;**133**:2132–2140.
586. Nagendran J, Bozso SJ, Norris CM, McAlister FA, Appoo JJ, Moon MC, Freed DH, Nagendran J. Coronary artery bypass surgery improves outcomes in patients with diabetes and left ventricular dysfunction. *J Am Coll Cardiol* 2018;**71**:819–827.
587. Park S, Ahn JM, Kim TO, Park H, Kang DY, Lee PH, Jeong YJ, Hyun J, Lee J, Kim JH, Yang Y, Choe K, Park SJ, Park DW, IRIS-MAIN Registry Investigators. Revascularization in patients with left main coronary artery disease and left ventricular dysfunction. *J Am Coll Cardiol* 2020;**76**:1395–1406.
588. Marui A, Kimura T, Nishiwaki N, Mitsudo K, Komiya T, Hanyu M, Shiomi H, Tanaka S, Sakata R, CREDO-Kyoto PCI/CABG Registry Cohort-2 Investigators. Comparison of five-year outcomes of coronary artery bypass grafting versus percutaneous coronary intervention in patients with left ventricular ejection fractions </= 50% versus >50% (from the CREDO-Kyoto PCI/CABG Registry Cohort-2). *Am J Cardiol* 2014;**114**:988–996.
589. Wolff G, Dimitroulis D, Andreotti F, Kolodziejczak M, Jung C, Scicchitano P, Devito F, Zito A, Occhipinti M, Castiglioni B, Calveri G, Maisano F, Ciccone MM, De Servi S, Navarese EP. Survival benefits of invasive versus conservative strategies in heart failure in patients with reduced ejection fraction and coronary artery disease: a meta-analysis. *Circ Heart Fail* 2017;**10**:e003255.
590. Gaudino M, Hameed I, Khan FM, Tam DY, Rahouma M, Yongle R, Naik A, Di Franco A, Demetres M, Petrie MC, Jolicoeur EM, Girardi LN, Fremes SE.

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Treatment strategies in ischaemic left ventricular dysfunction: a network meta-analysis. *Eur J Cardiothorac Surg* 2021;**59**:293–301.
591. Genereux P, Pibarot P, Redfors B, Mack MJ, Makkar RR, Jaber WA, Svensson LG, Kapadia S, Tuzcu EM, Thourani VH, Babaliaros V, Herrmann HC, Szeto WY, Cohen DJ, Lindman BR, McAndrew T, Alu MC, Douglas PS, Hahn RT, Kodali SK, Smith CR, Miller DC, Webb JG, Leon MB. Staging classification of aortic stenosis based on the extent of cardiac damage. *Eur Heart J* 2017;**38**:3351–3358.
592. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Johann B, Capodanno D, Conradi L, De Bonis M, De Paulis R, Delgado V, Freemantle N, Gilard M, Haugaa KH, Jeppsson A, Jüni P, Pierard L, Prendergast PD, Rafael Sádaba J, Tribouilloy C, Wojakowski W; ESC/EACTS Scientific Document Group. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2021; doi:10.1093/eurheartj/ehab395.
593. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S, PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;**363**:1597–1607.
594. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ, PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;**364**:2187–2198.
595. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J Jr, Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK, US CoreValve Clinical Investigators. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014;**370**:1790–1798.
596. Popma JJ, Adams DH, Reardon MJ, Yakubov SJ, Kleiman NS, Heimansohn D, Hermiller J, Jr., Hughes GC, Harrison JK, Coselli J, Diez J, Kafi A, Schreiber T, Gleason TG, Conte J, Buchbinder M, Deeb GM, Carabello B, Serruys PW, Chenoweth S, Oh JK, CoreValve United States Clinical Investigators. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol* 2014;**63**:1972–1981.
597. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG, PARTNER 2 Investigators. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016;**374**:1609–1620.
598. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, Chetcuti S, Gleason T, Heiser J, Lange R, Merhi W, Oh JK, Olsen PS, Piazza N, Williams M, Windecker S, Yakubov SJ, Grube E, Makkar R, Lee JS, Conte J, Vang E, Nguyen H, Chang Y, Mugglin AS, Serruys PW, Kappetein AP, SURTAVI Investigators. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2017;**376**:1321–1331.
599. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, Bajwa T, Heiser JC, Merhi W, Kleiman NS, Askew J, Sorajja P, Rovin J, Chetcuti SJ, Adams DH, Teirstein PS, Zorn GL, 3rd, Forrest JK, Tchetche D, Resar J, Walton A, Piazza N, Ramlawi B, Robinson N, Petrossian G, Gleason TG, Oh JK, Boulware MJ, Qiao H, Mugglin AS, Reardon MJ, Evolut Low Risk Trial Investigators. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med* 2019;**380**:1706–1715.
600. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, Leipsic J, Hahn RT, Blanke P, Williams MR, McCabe JM, Brown DL, Babaliaros V, Goldman S, Szeto WY, Genereux P, Pershad A, Pocock SJ, Alu MC, Webb JG, Smith CR, PARTNER 3 Investigators. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 2019;**380**:1695–1705.
601. Elder DH, Wei L, Szwejkowski BR, Libianto R, Nadir A, Pauriah M, Rekhraj S, Lim TK, George J, Doney A, Pringle SD, Choy AM, Struthers AD, Lang CC. The impact of renin-angiotensin-aldosterone system blockade on heart failure outcomes and mortality in patients identified to have aortic regurgitation: a large population cohort study. *J Am Coll Cardiol* 2011;**58**:2084–2091.
602. Chaliki HP, Mohty D, Avierinos JF, Scott CG, Schaff HV, Tajik AJ, Enriquez-Sarano M. Outcomes after aortic valve replacement in patients with severe aortic regurgitation and markedly reduced left ventricular function. *Circulation* 2002;**106**:2687–2693.
603. Tornos P, Sambola A, Permanyer-Miralda G, Evangelista A, Gomez Z, Soler-Soler J. Long-term outcome of surgically treated aortic regurgitation: influence of guideline adherence toward early surgery. *J Am Coll Cardiol* 2006;**47**:1012–1017.
604. Yoon SH, Schmidt T, Bleiziffer S, Schofer N, Fiorina C, Munoz-Garcia AJ, Yzeiraj E, Amat-Santos IJ, Tchetche D, Jung C, Fujita B, Mangieri A, Deutsch MA, Ubben T, Deuschl F, Kuwata S, De Biase C, Williams T, Dhoble A, Kim WK, Ferrari E, Barbanti M, Vollema EM, Miceli A, Giannini C, Attizzani GF, Kong WKF, Gutierrez-Ibanes E, Jimenez Diaz VA, Wijeysundera HC, Kaneko H, Chakravarty T, Makar M, Sievert H, Hengstenberg C, Prendergast BD, Vincent F, Abdel-Wahab M, Nombela-Franco L, Silaschi M, Tarantini G, Butter C, Ensminger SM, Hildick-Smith D, Petronio AS, Yin WH, De Marco F, Testa L, Van Mieghem NM, Whisenant BK, Kuck KH, Colombo A, Kar S, Moris C, Delgado V, Maisano F, Nietlispach F, Mack MJ, Schofer J, Schaefer U, Bax JJ, Frerker C, Latib A, Makkar RR. Transcatheter aortic valve replacement in pure native aortic valve regurgitation. *J Am Coll Cardiol* 2017;**70**:2752–2763.
605. Feldman T, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, Smalling RW, Siegel R, Rose GA, Engeron E, Loghin C, Trento A, Skipper ER, Fudge T, Letsou GV, Massaro JM, Mauri L, EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 2011;**364**:1395–1406.
606. Tamargo M, Obokata M, Reddy YNV, Pislaru SV, Lin G, Egbe AC, Nishimura RA, Borlaug BA. Functional mitral regurgitation and left atrial myopathy in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020;**22**:489–498.
607. Dziadzko V, Clavel MA, Dziadzko M, Medina-Inojosa JR, Michelena H, Maalouf J, Nkomo V, Thapa P, Enriquez-Sarano M. Outcome and undertreatment of mitral regurgitation: a community cohort study. *Lancet* 2018;**391**:960–969.
608. Goliasch G, Bartko PE, Pavo N, Neuhold S, Wurm R, Mascherbauer J, Lang IM, Strunk G, Hulsmann M. Refining the prognostic impact of functional mitral regurgitation in chronic heart failure. *Eur Heart J* 2018;**39**:39–46.
609. Bertrand PB, Schwammenthal E, Levine RA, Vandervoort PM. Exercise dynamics in secondary mitral regurgitation: pathophysiology and therapeutic implications. *Circulation* 2017;**135**:297–314.
610. Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, Lefevre T, Piot C, Rouleau F, Carrie D, Nejjari M, Ohlmann P, Leclercq F, Saint Etienne C, Teiger E, Leroux L, Karam N, Michel N, Gilard M, Donal E, Trochu JN, Cormier B, Armoiry X, Boutitie F, Maucort-Boulch D, Barnel C, Samson G, Guerin P, Vahanian A, Mewton N, MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018;**379**:2297–2306.
611. Iung B, Armoiry X, Vahanian A, Boutitie F, Mewton N, Trochu JN, Lefevre T, Messika-Zeitoun D, Guerin P, Cormier B, Brochet E, Thibault H, Himbert D, Thivolet S, Leurent G, Bonnet G, Donal E, Piriou N, Piot C, Habib G, Rouleau F, Carrie D, Nejjari M, Ohlmann P, Saint Etienne C, Leroux L, Gilard M, Samson G, Rioufol G, Maucort-Boulch D, Obadia JF, MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation: outcomes at 2 years. *Eur J Heart Fail* 2019;**21**:1619–1627.
612. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, Rajagopal V, Sarembock IJ, Brieke A, Marx SO, Cohen DJ, Weissman NJ, Mack MJ, COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018;**379**:2307–2318.
613. Senni M, Adamo M, Metra M, Alfieri O, Vahanian A. Treatment of functional mitral regurgitation in chronic heart failure: can we get a 'proof of concept' from the MITRA-FR and COAPT trials? *Eur J Heart Fail* 2019;**21**:852–861.
614. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. *JACC Cardiovasc Imaging* 2019;**12**:353–362.
615. Coats AJS, Anker SD, Baumbach A, Alfieri O, von Bardeleben RS, Bauersachs J, Bax JJ, Boveda S, Celutkiene J, Cleland JG, Dagres N, Deneke T, Farmakis D, Filippatos G, Hausleiter J, Hindricks G, Jankowska EA, Lainscak M, Leclercq C, Lund LH, McDonagh T, Mehra MR, Metra M, Mewton N, Mueller C, Mullens W, Muneretto C, Obadia JF, Ponikowski P, Praz F, Rudolph V, Ruschitzka F, Vahanian A, Windecker S, Zamorano JL, Edvardsen T, Heidbuchel H, Seferovic PM, Prendergast B. The management of secondary mitral regurgitation in patients with heart failure: a joint position statement from the Heart Failure Association (HFA), European Association of Cardiovascular Imaging (EACVI), European Heart Rhythm Association (EHRA), and European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC. *Eur Heart J* 2021;**42**:1254–1269.
616. Adamo M, Fiorelli F, Melica B, D'Ortona R, Lupi L, Giannini C, Silva G, Fiorina C, Branca L, Chiari E, Chizzola G, Spontoni P, Espada Guerreiro C, Curello S, Petronio AS, Metra M. COAPT-like profile predicts long-term outcomes in patients with secondary mitral regurgitation undergoing MitraClip implantation. *JACC Cardiovasc Interv* 2021;**14**:15–25.

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617. Godino C, Munafo A, Scotti A, Estevez-Loureiro R, Portoles Hernandez A, Arzamendi D, Fernandez Peregrina E, Taramasso M, Fam NP, Ho EC, Asgar A, Vitrella G, Raineri C, Adamo M, Fiorina C, Montalto C, Fraccaro C, Giannini C, Fiorelli F, Popolo Rubbio A, Ooms JF, Compagnone M, Maffeo D, Bettari L, Furholz M, Tamburino C, Petronio AS, Grasso C, Agricola E, Van Mieghem NM, Tarantini G, Curello S, Praz F, Pascual I, Potena L, Colombo A, Maisano F, Metra M, Margonato A, Crimi G, Saia F. MitraClip in secondary mitral regurgitation as a bridge to heart transplantation: 1-year outcomes from the International MitraBridge Registry. *J Heart Lung Transplant* 2020;**39**:1353–1362.
618. Witte KK, Lipiecki J, Siminiak T, Meredith IT, Malkin CJ, Goldberg SL, Stark MA, von Bardeleben RS, Cremer PC, Jaber WA, Celermajer DS, Kaye DM, Sievert H. The REDUCE FMR trial: a randomized sham-controlled study of percutaneous mitral annuloplasty in functional mitral regurgitation. *JACC Heart Fail* 2019;**7**:945–955.
619. Geyer M, Keller K, Sotiriou E, Tamm AR, Ruf TF, Kreidel F, Beiras-Fernandez A, Gori T, Schulz E, Munzel T, von Bardeleben RS. Association of transcatheter direct mitral annuloplasty with acute anatomic, haemodynamic, and clinical outcomes in severe mitral valve regurgitation. *ESC Heart Fail* 2020;**7**:3336–3344.
620. Giallauria F, Di Lorenzo A, Parlato A, Testa C, Bobbio E, Vigorito C, Coats AJS. Individual patient data meta-analysis of the effects of the CARILLON® mitral contour system. *ESC Heart Fail* 2020;**7**:3383–3391.
621. Lipiecki J, Fahrat H, Monzy S, Caillot N, Siminiak T, Johnson T, Vogt S, Stark MA, Goldberg SL. Long-term prognosis of patients treated by coronary sinus-based percutaneous annuloplasty: single centre experience. *ESC Heart Fail* 2020;**7**:3329–3335.
622. Ruf TF, Kreidel F, Tamm AR, Geyer M, Hahad O, Zirbs JC, Schwidtal BL, Beiras-Fernandez A, Witte KK, Munzel T, von Bardeleben RS. Transcatheter indirect mitral annuloplasty induces annular and left atrial remodelling in secondary mitral regurgitation. *ESC Heart Fail* 2020;**7**:1400–1408.
623. Sorajja P, Moat N, Badhwar V, Walters D, Paone G, Bethea B, Bae R, Dahle G, Mumtaz M, Grayburn P, Kapadia S, Babaliaros V, Guerrero M, Satler L, Thourani V, Bedogni F, Rizik D, Denti P, Dumonteil N, Modine T, Sinhal A, Chuang ML, Popma JJ, Blanke P, Leipsic J, Muller D. Initial feasibility study of a new transcatheter mitral prosthesis: the first 100 patients. *J Am Coll Cardiol* 2019;**73**:1250–1260.
624. Zack CJ, Fender EA, Chandrashekar P, Reddy YNV, Bennett CE, Stulak JM, Miller VM, Nishimura RA. National trends and outcomes in isolated tricuspid valve surgery. *J Am Coll Cardiol* 2017;**70**:2953–2960.
625. Taramasso M, Benfari G, van der Bijl P, Alessandrini H, Attinger-Toller A, Biasco L, Lurz P, Braun D, Brochet E, Connelly KA, de Bruijn S, Denti P, Deuschl F, Estevez-Loureiro R, Fam N, Frerker C, Gavazzoni M, Hausleiter J, Ho E, Juliard JM, Kaple R, Besler C, Kodali S, Kreidel F, Kuck KH, Latib A, Lauten A, Monivas V, Mehr M, Muntane-Carol G, Nazif T, Nickening G, Pedrazzini G, Philippon F, Pozzoli A, Praz F, Puri R, Rodes-Cabau J, Schafer U, Schofer J, Sievert H, Tang GHL, Thiele H, Topilsky Y, Rommel KP, Delgado V, Vahanian A, Von Bardeleben RS, Webb JG, Weber M, Windecker S, Winkel M, Zuber M, Leon MB, Hahn RT, Bax JJ, Enriquez-Sarano M, Maisano F. Transcatheter versus medical treatment of patients with symptomatic severe tricuspid regurgitation. *J Am Coll Cardiol* 2019;**74**:2998–3008.
626. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, White IR, Caulfield MJ, Deanfield JE, Smeeth L, Williams B, Hingorani A, Hemingway H. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet* 2014;**383**:1899–1911.
627. Cohn JN, Pfeffer MA, Rouleau J, Sharpe N, Swedberg K, Straub M, Wiltse C, Wright TJ, MOXCON Investigators. Adverse mortality effect of central sympathetic inhibition with sustained-release moxonidine in patients with heart failure (MOXCON). *Eur J Heart Fail* 2003;**5**:659–667.
628. Kato S, Onishi K, Yamanaka T, Takamura T, Dohi K, Yamada N, Wada H, Nobori T, Ito M. Exaggerated hypertensive response to exercise in patients with diastolic heart failure. *Hypertens Res* 2008;**31**:679–684.
629. Uijl A, Savarese G, Vaartjes I, Dahlstrom U, Brugts JJ, Linssen GCM, van Empel V, Brunner-La Rocca HP, Asselbergs FW, Lund LH, Hoes AW, Koudstaal S. Identification of distinct phenotypic clusters in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2021;**23**:973–982.
630. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure-lowering treatment on cardiovascular outcomes and mortality: 14 - effects of different classes of antihypertensive drugs in older and younger patients: overview and meta-analysis. *J Hypertens* 2018;**36**:1637–1647.
631. Vaduganathan M, Pareek M, Kristensen AMD, Biering-Sorensen T, Byrne C, Almarzooq Z, Olesen TB, Olsen MH, Bhatt DL. Prevention of heart failure events with intensive versus standard blood pressure lowering across the spectrum of kidney function and albuminuria: a SPRINT substudy. *Eur J Heart Fail* 2021;**23**:384–392.
632. Fagard RH, Celis H, Thijs L, Wouters S. Regression of left ventricular mass by antihypertensive treatment: a meta-analysis of randomized comparative studies. *Hypertension* 2009;**54**:1084–1091.
633. Cautela J, Tartiere JM, Cohen-Solal A, Bellemain-Appaix A, Theron A, Tibi T, Januzzi JL, Jr., Roubille F, Girerd N. Management of low blood pressure in ambulatory heart failure with reduced ejection fraction patients. *Eur J Heart Fail* 2020;**22**:1357–1365.
634. Kang SH, Kim J, Park JJ, Oh IY, Yoon CH, Kim HJ, Kim K, Choi DJ. Risk of stroke in congestive heart failure with and without atrial fibrillation. *Int J Cardiol* 2017;**248**:182–187.
635. Abdul-Rahim AH, Perez AC, Fulton RL, Jhund PS, Latini R, Tognoni G, Wikstrand J, Kjekshus J, Lip GY, Maggioni AP, Tavazzi L, Lees KR, McMurray JJ, Investigators of the Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA), GISSI-Heart Failure (GISSI-HF) Committees and Investigators. Risk of stroke in chronic heart failure patients without atrial fibrillation: analysis of the Controlled Rosuvastatin in Multinational Trial Heart Failure (CORONA) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) trials. *Circulation* 2015;**131**:1486–1494; discussion 1494.
636. Abdul-Rahim AH, Perez AC, MacIsaac RL, Jhund PS, Claggett BL, Carson PE, Komajda M, McKelvie RS, Zile MR, Swedberg K, Yusuf S, Pfeffer MA, Solomon SD, Lip GYH, Lees KR, McMurray JJV, Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity-Preserved (CHARM-Preserved) and the Irbesartan in Heart Failure with Preserved Systolic Function (I-Preserve) Steering Committees. Risk of stroke in chronic heart failure patients with preserved ejection fraction, but without atrial fibrillation: analysis of the CHARM-Preserved and I-Preserve trials. *Eur Heart J* 2017;**38**:742–750.
637. Mehra MR, Vaduganathan M, Fu M, Ferreira JP, Anker SD, Cleland JGF, Lam CSP, van Veldhuisen DJ, Byra WM, Spiro TE, Deng H, Zannad F, Greenberg B. A comprehensive analysis of the effects of rivaroxaban on stroke or transient ischaemic attack in patients with heart failure, coronary artery disease, and sinus rhythm: the COMMANDER HF trial. *Eur Heart J* 2019;**40**:3593–3602.
638. Kotecha D, Chudasama R, Lane DA, Kirchhof P, Lip GY. Atrial fibrillation and heart failure due to reduced versus preserved ejection fraction: a systematic review and meta-analysis of death and adverse outcomes. *Int J Cardiol* 2016;**203**:660–666.
639. Adelborg K, Szepligeti S, Sundboll J, Horvath-Puho E, Henderson VW, Ording A, Pedersen L, Sorensen HT. Risk of stroke in patients with heart failure: a population-based 30-year cohort study. *Stroke* 2017;**48**:1161–1168.
640. Witt BJ, Brown RD Jr, Jacobsen SJ, Weston SA, Ballman KV, Meverden RA, Roger VL. Ischemic stroke after heart failure: a community-based study. *Am Heart J* 2006;**152**:102–109.
641. Homma S, Thompson JL, Pullicino PM, Levin B, Freudenberger RS, Teerlink JR, Ammon SE, Graham S, Sacco RL, Mann DL, Mohr JP, Massie BM, Labovitz AJ, Anker SD, Lok DJ, Ponikowski P, Estol CJ, Lip GY, Di Tullio MR, Sanford AR, Mejia V, Gabriel AP, del Valle ML, Buchsbaum R, WARCEF Investigators. Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med* 2012;**366**:1859–1869.
642. Hopper I, Skiba M, Krum H. Updated meta-analysis on antithrombotic therapy in patients with heart failure and sinus rhythm. *Eur J Heart Fail* 2013;**15**:69–78.
643. Bauersachs J, Konig T, van der Meer P, Petrie MC, Hilfiker-Kleiner D, Mbakwem A, Hamdan R, Jackson AM, Forsyth P, de Boer RA, Mueller C, Lyon AR, Lund LH, Piepoli MF, Heymans S, Chioncel O, Anker SD, Ponikowski P, Seferovic PM, Johnson MR, Mebazaa A, Sliwa K. Pathophysiology, diagnosis and management of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Study Group on peripartum cardiomyopathy. *Eur J Heart Fail* 2019;**21**:827–843.
644. Singh DP, Patel H. Left ventricular non-compaction cardiomyopathy. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2021; PMID 30725710.
645. Subahi A, Hassan AAI, Abubakar H, Ibrahim W. Isolated left ventricular non-compaction (LVNC) and recurrent strokes: to anticoagulate or not to anticoagulate, that is the question. *BMJ Case Rep* 2017;**2017**:bcr2017220954.
646. Seferovic PM, Petrie MC, Filippatos GS, Anker SD, Rosano G, Bauersachs J, Paulus WJ, Komajda M, Cosentino F, de Boer RA, Farmakis D, Doehner W, Lambrinou E, Lopatin Y, Piepoli MF, Theodorakis MJ, Wiggers H, Lekakis J, Mebazaa A, Mamas MA, Tschope C, Hoes AW, Seferovic JP, Logue J, McDonagh T, Riley JP, Milinkovic I, Polovina M, van Veldhuisen DJ, Lainscak M, Maggioni AP, Ruschitzka F, McMurray JJV. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018;**20**:853–872.
647. Seferovic PM, Coats AJS, Ponikowski P, Filippatos G, Huelsmann M, Jhund PS, Polovina MM, Komajda M, Seferovic J, Sari I, Cosentino F, Ambrosio G, Metra M, Piepoli M, Chioncel O, Lund LH, Thum T, De Boer RA, Mullens W, Lopatin Y, Volterrani M, Hill L, Bauersachs J, Lyon A, Petrie MC, Anker S, Rosano

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GMC. European Society of Cardiology/Heart Failure Association position paper on the role and safety of new glucose-lowering drugs in patients with heart failure. *Eur J Heart Fail* 2020;**22**:196–213.
648. Cosentino F, Cannon CP, Cherney DZI, Masiukiewicz U, Pratley R, Dagogo-Jack S, Frederich R, Charbonnel B, Mancuso J, Shih WJ, Terra SG, Cater NB, Gantz I, McGuire DK, VERTIS CV Investigators. Efficacy of ertugliflozin on heart failure-related events in patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease: results of the VERTIS CV trial. *Circulation* 2020;**142**:2205–2215.
649. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, Pratley R, Greenberg M, Wang S, Huyck S, Gantz I, Terra SG, Masiukiewicz U, Cannon CP. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol* 2021;**6**:148–158.
650. Seferovic PM, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Cleland JGF, de Boer RA, Drexel H, Ben Gal T, Hill L, Jaarsma T, Jankowska EA, Anker MS, Lainscak M, Lewis BS, McDonagh T, Metra M, Milicic D, Mullens W, Piepoli MF, Rosano G, Ruschitzka F, Volterrani M, Voors AA, Filippatos G, Coats AJS. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:1169–1186.
651. Eurich DT, Weir DL, Majumdar SR, Tsuyuki RT, Johnson JA, Tjosvold L, Vanderloo SE, McAlister FA. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34,000 patients. *Circ Heart Fail* 2013;**6**:395–402.
652. Andersson C, Olesen JB, Hansen PR, Weeke P, Norgaard ML, Jorgensen CH, Lange T, Abildstrom SZ, Schramm TK, Vaag A, Kober L, Torp-Pedersen C, Gislason GH. Metformin treatment is associated with a low risk of mortality in diabetic patients with heart failure: a retrospective nationwide cohort study. *Diabetologia* 2010;**53**:2546–2553.
653. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I, SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;**369**:1317–1326.
654. Zannad F, Cannon CP, Cushman WC, Bakris GL, Menon V, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Lam H, White WB, EXAMINE Investigators. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet* 2015;**385**:2067–2076.
655. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F, Peterson ED, Holman RR, TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015;**373**:232–242.
656. Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, Alexander JH, Pencina M, Toto RD, Wanner C, Zinman B, Woerle HJ, Baanstra D, Pfarr E, Schnaidt S, Meinicke T, George JT, von Eynatten M, McGuire DK, CARMELINA Investigators. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. *JAMA* 2019;**321**:69–79.
657. McMurray JJV, Ponikowski P, Bolli GB, Lukashevich V, Kozlovski P, Kothny W, Lewsey JD, Krum H, VIVIDD Trial Committees and Investigators. Effects of vildagliptin on ventricular function in patients with type 2 diabetes mellitus and heart failure: a randomized placebo-controlled trial. *JACC Heart Fail* 2018;**6**:8–17.
658. Sinha B, Ghosal S. Meta-analyses of the effects of DPP-4 inhibitors, SGLT2 inhibitors and GLP1 receptor analogues on cardiovascular death, myocardial infarction, stroke and hospitalization for heart failure. *Diabetes Res Clin Pract* 2019;**150**:8–16.
659. Savarese G, D'Amore C, Federici M, De Martino F, Dellegrottaglie S, Marciano C, Ferrazzano F, Losco T, Lund LH, Trimarco B, Rosano GM, Perrone-Filardi P. Effects of dipeptidyl peptidase 4 inhibitors and sodium-glucose linked cotransporter-2 inhibitors on cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis. *Int J Cardiol* 2016;**220**:595–601.
660. Kristensen SL, Rorth R, Jhund PS, Docherty KF, Sattar N, Preiss D, Kober L, Petrie MC, McMurray JJV. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol* 2019;**7**:776–785.
661. Jorsal A, Kistorp C, Holmager P, Tougaard RS, Nielsen R, Hanselmann A, Nilsson B, Moller JE, Hjort J, Rasmussen J, Boesgaard TW, Schou M, Videbaek L, Gustafsson I, Flyvbjerg A, Wiggers H, Tarnow L. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE)-a multicentre, double-blind, randomised, placebo-controlled trial. *Eur J Heart Fail* 2017;**19**:69–77.
662. Margulies KB, Hernandez AF, Redfield MM, Givertz MM, Oliveira GH, Cole R, Mann DL, Whellan DJ, Kiernan MS, Felker GM, McNulty SE, Anstrom KJ, Shah MR, Braunwald E, Cappola TP, NHLBI Heart Failure Clinical Research Network. Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA* 2016;**316**:500–508.
663. Gerstein HC, Jung H, Ryden L, Diaz R, Gilbert RE, Yusuf S, ORIGIN Investigators. Effect of basal insulin glargine on first and recurrent episodes of heart failure hospitalization: the ORIGIN trial (Outcome Reduction With Initial Glargine Intervention). *Circulation* 2018;**137**:88–90.
664. Cosmi F, Shen L, Magnoli M, Abraham WT, Anand IS, Cleland JG, Cohn JN, Cosmi D, De Berardis G, Dickstein K, Franzosi MG, Gullestad L, Jhund PS, Kjekshus J, Kober L, Lepore V, Lucisano G, Maggioni AP, Masson S, McMurray JJV, Nicolucci A, Petrarolo V, Robusto F, Staszewsky L, Tavazzi L, Teli R, Tognoni G, Wikstrand J, Latini R. Treatment with insulin is associated with worse outcome in patients with chronic heart failure and diabetes. *Eur J Heart Fail* 2018;**20**:888–895.
665. Shen L, Rorth R, Cosmi D, Kristensen SL, Petrie MC, Cosmi F, Latini R, Kober L, Anand IS, Carson PE, Granger CB, Komajda M, McKelvie RS, Solomon SD, Staszewsky L, Swedberg K, Huynh T, Zile MR, Jhund PS, McMurray JJV. Insulin treatment and clinical outcomes in patients with diabetes and heart failure with preserved ejection fraction. *Eur J Heart Fail* 2019;**21**:974–984.
666. Tzoulaki I, Molokhia M, Curcin V, Little MP, Millett CJ, Ng A, Hughes RI, Khunti K, Wilkins MR, Majeed A, Elliott P. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. *BMJ* 2009;**339**:b4731.
667. Roumie CL, Min JY, D'Agostino McGowan L, Presley C, Grijalva CG, Hackstadt AJ, Hung AM, Greevy RA, Elasy T, Griffin MR. Comparative safety of sulfonylurea and metformin monotherapy on the risk of heart failure: a cohort study. *J Am Heart Assoc* 2017;**6**.
668. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. *Lancet* 2007;**370**:1129–1136.
669. Vargas-Uricoechea H, Bonelo-Perdomo A. Thyroid dysfunction and heart failure: mechanisms and associations. *Curr Heart Fail Rep* 2017;**14**:48–58.
670. Kannan L, Shaw PA, Morley MP, Brandimarto J, Fang JC, Sweitzer NK, Cappola TP, Cappola AR. Thyroid dysfunction in heart failure and cardiovascular outcomes. *Circ Heart Fail* 2018;**11**:e005266.
671. Sato Y, Yoshihisa A, Kimishima Y, Kiko T, Kanno Y, Yokokawa T, Abe S, Misaka T, Sato T, Oikawa M, Kobayashi A, Yamaki T, Kunii H, Nakazato K, Takeishi Y. Low T3 syndrome is associated with high mortality in hospitalized patients with heart failure. *J Card Fail* 2019;**25**:195–203.
672. Stott DJ, Rodondi N, Kearney PM, Ford I, Westendorp RGJ, Mooijaart SP, Sattar N, Aubert CE, Aujesky D, Bauer DC, Baumgartner C, Blum MR, Browne JP, Byrne S, Collet TH, Dekkers OM, den Elzen WPJ, Du Puy RS, Ellis G, Feller M, Floriani C, Hendry K, Hurley C, Jukema JW, Kean S, Kelly M, Krebs D, Langhorne P, McCarthy G, McCarthy V, McConnachie A, McDade M, Messow M, O'Flynn A, O'Riordan D, Poortvliet RKE, Quinn TJ, Russell A, Sinnott C, Smit JWA, Van Dorland HA, Walsh KA, Walsh EK, Watt T, Wilson R, Gussekloo J, TRUST Study Group. Thyroid hormone therapy for older adults with subclinical hypothyroidism. *N Engl J Med* 2017;**376**:2534–2544.
673. Feller M, Snel M, Moutzouri E, Bauer DC, de Montmollin M, Aujesky D, Ford I, Gussekloo J, Kearney PM, Mooijaart S, Quinn T, Stott D, Westendorp R, Rodondi N, Dekkers OM. Association of thyroid hormone therapy with quality of life and thyroid-related symptoms in patients with subclinical hypothyroidism: a systematic review and meta-analysis. *JAMA* 2018;**320**:1349–1359.
674. Peeters RP. Subclinical hypothyroidism. *N Engl J Med* 2017;**376**:2556–2565.
675. Packer M, Lam CSP, Lund LH, Maurer MS, Borlaug BA. Characterization of the inflammatory-metabolic phenotype of heart failure and a preserved ejection fraction: a hypothesis to explain influence of sex on the evolution and potential treatment of the disease. *Eur J Heart Fail* 2020;**22**:1551–1567.
676. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation* 2017;**136**:6–19.
677. Rao VN, Fudim M, Mentz RJ, Michos ED, Felker GM. Regional adiposity and heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020;**22**:1540–1550.
678. Carbone S, Lavie CJ, Arena R. Obesity and heart failure: focus on the obesity paradox. *Mayo Clin Proc* 2017;**92**:266–279.
679. Horwich TB, Fonarow GC, Clark AL. Obesity and the obesity paradox in heart failure. *Prog Cardiovasc Dis* 2018;**61**:151–156.
680. Adamopoulos C, Meyer P, Desai RV, Karatzidou K, Ovalle F, White M, Aban I, Love TE, Deedwania P, Anker SD, Ahmed A. Absence of obesity paradox in

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patients with chronic heart failure and diabetes mellitus: a propensity-matched study. *Eur J Heart Fail* 2011;**13**:200–206.
681. Zamora E, Lupon J, Enjuanes C, Pascual-Figal D, de Antonio M, Domingo M, Comin-Colet J, Vila J, Penafiel J, Farre N, Alonso N, Santesmases J, Troya M, Bayes-Genis A. No benefit from the obesity paradox for diabetic patients with heart failure. *Eur J Heart Fail* 2016;**18**:851–858.
682. Piepoli MF, Corra U, Veglia F, Bonomi A, Salvioni E, Cattadori G, Metra M, Lombardi C, Sinagra G, Limongelli G, Raimondo R, Re F, Magri D, Belardinelli R, Parati G, Mina C, Scardovi AB, Guazzi M, Cicoira M, Scrutinio D, Di Lenarda A, Bussotti M, Frigerio M, Correale M, Villani GQ, Paolillo S, Passino C, Agostoni P, MECKI Score Research Group. Exercise tolerance can explain the obesity paradox in patients with systolic heart failure: data from the MECKI Score Research Group. *Eur J Heart Fail* 2016;**18**:545–553.
683. Streng KW, Voors AA, Hillege HL, Anker SD, Cleland JG, Dickstein K, Filippatos G, Metra M, Ng LL, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zwinderman AH, Zannad F, Damman K, van der Meer P, Lang CC. Waist-to-hip ratio and mortality in heart failure. *Eur J Heart Fail* 2018;**20**:1269–1277.
684. Carbone S, Elagizi A, Lavie CJ. Obesity and mortality risk in heart failure: when adipose tissue distribution matters. *Eur J Heart Fail* 2018;**20**:1278–1280.
685. Packer M. Do most patients with obesity or type 2 diabetes, and atrial fibrillation, also have undiagnosed heart failure? A critical conceptual framework for understanding mechanisms and improving diagnosis and treatment. *Eur J Heart Fail* 2020;**22**:214–227.
686. Vitale C, Jankowska E, Hill L, Piepoli M, Doehner W, Anker SD, Lainscak M, Jaarsma T, Ponikowski P, Rosano GMC, Seferovic P, Coats AJ. Heart Failure Association/European Society of Cardiology position paper on frailty in patients with heart failure. *Eur J Heart Fail* 2019;**21**:1299–1305.
687. Denfeld QE, Winters-Stone K, Mudd JO, Gelow JM, Kurdi S, Lee CS. The prevalence of frailty in heart failure: a systematic review and meta-analysis. *Int J Cardiol* 2017;**236**:283–289.
688. Bielecka-Dabrowa A, Ebner N, Dos Santos MR, Ishida J, Hasenfuss G, von Haehling S. Cachexia, muscle wasting, and frailty in cardiovascular disease. *Eur J Heart Fail* 2020;**22**:2314–2326.
689. Khan H, Kalogeropoulos AP, Georgiopoulou VV, Newman AB, Harris TB, Rodondi N, Bauer DC, Kritchevsky SB, Butler J. Frailty and risk for heart failure in older adults: the health, aging, and body composition study. *Am Heart J* 2013;**166**:887–894.
690. Woods NF, LaCroix AZ, Gray SL, Aragaki A, Cochrane BB, Brunner RL, Masaki K, Murray A, Newman AB, Women's Health Initiative. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. *J Am Geriatr Soc* 2005;**53**:1321–1330.
691. Vidan MT, Blaya-Novakova V, Sanchez E, Ortiz J, Serra-Rexach JA, Bueno H. Prevalence and prognostic impact of frailty and its components in non-dependent elderly patients with heart failure. *Eur J Heart Fail* 2016;**18**:869–875.
692. Dewan P, Jackson A, Jhund PS, Shen L, Ferreira JP, Petrie MC, Abraham WT, Desai AS, Dickstein K, Kober L, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, McMurray JJV. The prevalence and importance of frailty in heart failure with reduced ejection fraction – an analysis of PARADIGM-HF and ATMOSPHERE. *Eur J Heart Fail* 2020;**22**:2123–2133.
693. Sanders NA, Supiano MA, Lewis EF, Liu J, Claggett B, Pfeffer MA, Desai AS, Sweitzer NK, Solomon SD, Fang JC. The frailty syndrome and outcomes in the TOPCAT trial. *Eur J Heart Fail* 2018;**20**:1570–1577.
694. Evans WJ, Morley JE, Argiles J, Bales C, Baracos V, Guttridge D, Jatoi A, Kalantar-Zadeh K, Lochs H, Mantovani G, Marks D, Mitch WE, Muscaritoli M, Najand A, Ponikowski P, Rossi Fanelli F, Schambelan M, Schols A, Schuster M, Thomas D, Wolfe R, Anker SD. Cachexia: a new definition. *Clin Nutr* 2008;**27**:793–799.
695. Loncar G, Springer J, Anker M, Doehner W, Lainscak M. Cardiac cachexia: hic et nunc. *J Cachexia Sarcopenia Muscle* 2016;**7**:246–260.
696. von Haehling S, Lainscak M, Springer J, Anker SD. Cardiac cachexia: a systematic overview. *Pharmacol Ther* 2009;**121**:227–252.
697. Anker MS, Holcomb R, Muscaritoli M, von Haehling S, Haverkamp W, Jatoi A, Morley JE, Strasser F, Landmesser U, Coats AJS, Anker SD. Orphan disease status of cancer cachexia in the USA and in the European Union: a systematic review. *J Cachexia Sarcopenia Muscle* 2019;**10**:22–34.
698. Bauer J, Morley JE, Schols A, Ferrucci L, Cruz-Jentoft AJ, Dent E, Baracos VE, Crawford JA, Doehner W, Heymsfield SB, Jatoi A, Kalantar-Zadeh K, Lainscak M, Landi F, Laviano A, Mancuso M, Muscaritoli M, Prado CM, Strasser F, von Haehling S, Coats AJS, Anker SD. Sarcopenia: a time for action. An SCWD position paper. *J Cachexia Sarcopenia Muscle* 2019;**10**:956–961.
699. Ameri P, Canepa M, Anker MS, Belenkov Y, Bergler-Klein J, Cohen-Solal A, Farmakis D, Lopez-Fernandez T, Lainscak M, Pudil R, Ruschitska F, Seferovic P, Filippatos G, Coats A, Suter T, Von Haehling S, Ciardiello F, de Boer RA, Lyon AR, Tocchetti CG, Heart Failure Association Cardio-Oncology Study Group of the European Society of Cardiology. Cancer diagnosis in patients with heart failure: epidemiology, clinical implications and gaps in knowledge. *Eur J Heart Fail* 2018;**20**:879–887.
700. Fonseca G, Dos Santos MR, de Souza FR, Takayama L, Rodrigues Pereira RM, Negrao CE, Alves MNN. Discriminating sarcopenia in overweight/obese male patients with heart failure: the influence of body mass index. *ESC Heart Fail* 2020;**7**:84–91.
701. Emami A, Saitoh M, Valentova M, Sandek A, Evertz R, Ebner N, Loncar G, Springer J, Doehner W, Lainscak M, Hasenfuss G, Anker SD, von Haehling S. Comparison of sarcopenia and cachexia in men with chronic heart failure: results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). *Eur J Heart Fail* 2018;**20**:1580–1587.
702. Fulster S, Tacke M, Sandek A, Ebner N, Tschope C, Doehner W, Anker SD, von Haehling S. Muscle wasting in patients with chronic heart failure: results from the studies investigating co-morbidities aggravating heart failure (SICA-HF). *Eur Heart J* 2013;**34**:512–519.
703. Springer J, Springer JI, Anker SD. Muscle wasting and sarcopenia in heart failure and beyond: update 2017. *ESC Heart Fail* 2017;**4**:492–498.
704. von Haehling S, Ebner N, Dos Santos MR, Springer J, Anker SD. Muscle wasting and cachexia in heart failure: mechanisms and therapies. *Nat Rev Cardiol* 2017;**14**:323–341.
705. Caminiti G, Volterrani M, Iellamo F, Marazzi G, Massaro R, Miceli M, Mammi C, Piepoli M, Fini M, Rosano GM. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. *J Am Coll Cardiol* 2009;**54**:919–927.
706. Anand IS, Gupta P. Anemia and iron deficiency in heart failure: current concepts and emerging therapies. *Circulation* 2018;**138**:80–98.
707. Iorio A, Senni M, Barbati G, Greene SJ, Poli S, Zambon E, Di Nora C, Cioffi G, Tarantini L, Gavazzi A, Sinagra G, Di Lenarda A. Prevalence and prognostic impact of non-cardiac co-morbidities in heart failure outpatients with preserved and reduced ejection fraction: a community-based study. *Eur J Heart Fail* 2018;**20**:1257–1266.
708. Okonko DO, Mandal AK, Missouris CG, Poole-Wilson PA. Disordered iron homeostasis in chronic heart failure: prevalence, predictors, and relation to anemia, exercise capacity, and survival. *J Am Coll Cardiol* 2011;**58**:1241–1251.
709. McDonagh T, Damy T, Doehner W, Lam CSP, Sindone A, van der Meer P, Cohen-Solal A, Kindermann I, Manito N, Pfister O, Pohjantahti-Maaroos H, Taylor J, Comin-Colet J. Screening, diagnosis and treatment of iron deficiency in chronic heart failure: putting the 2016 European Society of Cardiology heart failure guidelines into clinical practice. *Eur J Heart Fail* 2018;**20**:1664–1672.
710. Cappellini MD, Comin-Colet J, de Francisco A, Dignass A, Doehner W, Lam CS, Macdougall IC, Rogler G, Camaschella C, Kadir R, Kassebaum NJ, Spahn DR, Taher AT, Musallam KM, IRON CORE Group. Iron deficiency across chronic inflammatory conditions: international expert opinion on definition, diagnosis, and management. *Am J Hematol* 2017;**92**:1068–1078.
711. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. *Lancet* 2016;**387**:907–916.
712. Sierpinski R, Josiak K, Suchocki T, Wojtas-Polc K, Mazur G, Butrym A, Rozentryt P, van der Meer P, Comin-Colet J, von Haehling S, Kosmala W, Przewlocka-Kosmala M, Banasiak W, Nowak J, Voors AA, Anker SD, Cleland JGF, Ponikowski P, Jankowska EA. High soluble transferrin receptor in patients with heart failure: a measure of iron deficiency and a strong predictor of mortality. *Eur J Heart Fail* 2020 Oct 27. doi: 10.1002/ejhf.2036 [Epub ahead of print].
713. Rocha BML, Cunha GJL, Falcao Menezes LF. The burden of iron deficiency in heart failure: therapeutic approach. *J Am Coll Cardiol* 2018;**71**:782–793.
714. Klip IT, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W, Lok DJ, Rosentryt P, Torrens A, Polonski L, van Veldhuisen DJ, van der Meer P, Jankowska EA. Iron deficiency in chronic heart failure: an international pooled analysis. *Am Heart J* 2013;**165**:575–582.e3.
715. Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, Borodulin-Nadzieja L, Banasiak W, Polonski L, Filippatos G, McMurray JJ, Anker SD, Ponikowski P. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. *Eur Heart J* 2010;**31**:1872–1880.
716. von Haehling S, Jankowska EA, van Veldhuisen DJ, Ponikowski P, Anker SD. Iron deficiency and cardiovascular disease. *Nat Rev Cardiol* 2015;**12**:659–669.
717. Stugiewicz M, Tkaczyszyn M, Kasztura M, Banasiak W, Ponikowski P, Jankowska EA. The influence of iron deficiency on the functioning of skeletal muscles: experimental evidence and clinical implications. *Eur J Heart Fail* 2016;**18**:762–773.
718. Jankowska EA, Malyszko J, Ardehali H, Koc-Zorawska E, Banasiak W, von Haehling S, Macdougall IC, Weiss G, McMurray JJ, Anker SD, Gheorghiade M, Ponikowski P. Iron status in patients with chronic heart failure. *Eur Heart J* 2013;**34**:827–834.
719. Swedberg K, Young JB, Anand IS, Cheng S, Desai AS, Diaz R, Maggioni AP, McMurray JJ, O'Connor C, Pfeffer MA, Solomon SD, Sun Y, Tendera M, van

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Veldhuisen DJ, RED-HF Committees, RED-HF Investigators. Treatment of anemia with darbepoetin alfa in systolic heart failure. *N Engl J Med* 2013;**368**:1210–1219.
720. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Luscher TF, Bart B, Banasiak W, Niegowska J, Kirwan BA, Mori C, von Eisenhart Rothe B, Pocock SJ, Poole-Wilson PA, Ponikowski P, FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009;**361**:2436–2448.
721. Comin-Colet J, Lainscak M, Dickstein K, Filippatos GS, Johnson P, Luscher TF, Mori C, Willenheimer R, Ponikowski P, Anker SD. The effect of intravenous ferric carboxymaltose on health-related quality of life in patients with chronic heart failure and iron deficiency: a subanalysis of the FAIR-HF study. *Eur Heart J* 2013;**34**:30–38.
722. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, McDonagh T, Parkhomenko A, Tavazzi L, Levesque V, Mori C, Roubert B, Filippatos G, Ruschitzka F, Anker SD, CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J* 2015;**36**:657–668.
723. van Veldhuisen DJ, Ponikowski P, van der Meer P, Metra M, Bohm M, Doletsky A, Voors AA, Macdougall IC, Anker SD, Roubert B, Zakin L, Cohen-Solal A, EFFECT-HF Investigators. Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency. *Circulation* 2017;**136**:1374–1383.
724. Jankowska EA, Tkaczyszyn M, Suchocki T, Drozd M, von Haehling S, Doehner W, Banasiak W, Filippatos G, Anker SD, Ponikowski P. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. *Eur J Heart Fail* 2016;**18**:786–795.
725. Anker SD, Kirwan BA, van Veldhuisen DJ, Filippatos G, Comin-Colet J, Ruschitzka F, Luscher TF, Arutyunov GP, Motro M, Mori C, Roubert B, Pocock SJ, Ponikowski P. Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. *Eur J Heart Fail* 2018;**20**:125–133.
726. Filippatos G, Farmakis D, Colet JC, Dickstein K, Luscher TF, Willenheimer R, Parissis J, Gaudesius G, Mori C, von Eisenhart Rothe B, Greenlaw N, Ford I, Ponikowski P, Anker SD. Intravenous ferric carboxymaltose in iron-deficient chronic heart failure patients with and without anaemia: a subanalysis of the FAIR-HF trial. *Eur J Heart Fail* 2013;**15**:1267–1276.
727. von Haehling S, Ebner N, Evertz R, Ponikowski P, Anker SD. Iron deficiency in heart failure: an overview. *JACC Heart Fail* 2019;**7**:36–46.
728. Lewis GD, Malhotra R, Hernandez AF, McNulty SE, Smith A, Felker GM, Tang WHW, LaRue SJ, Redfield MM, Semigran MJ, Givertz MM, Van Buren P, Whellan D, Anstrom KJ, Shah MR, Desvigne-Nickens P, Butler J, Braunwald E, NHLBI Heart Failure Clinical Research Network. Effect of oral iron repletion on exercise capacity in patients with heart failure with reduced ejection fraction and iron deficiency: the IRONOUT HF randomized clinical trial. *JAMA* 2017;**317**:1958–1966.
729. Mullens W, Damman K, Testani JM, Martens P, Mueller C, Lassus J, Tang WHW, Skouri H, Verbrugge FH, Orso F, Hill L, Ural D, Lainscak M, Rossignol P, Metra M, Mebazaa A, Seferovic P, Ruschitzka F, Coats A. Evaluation of kidney function throughout the heart failure trajectory – a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:584–603.
730. Ter Maaten JM, Damman K, Verhaar MC, Paulus WJ, Duncker DJ, Cheng C, van Heerebeek L, Hillege HL, Lam CS, Navis G, Voors AA. Connecting heart failure with preserved ejection fraction and renal dysfunction: the role of endothelial dysfunction and inflammation. *Eur J Heart Fail* 2016;**18**:588–598.
731. van der Pol A, van Gilst WH, Voors AA, van der Meer P. Treating oxidative stress in heart failure: past, present and future. *Eur J Heart Fail* 2019;**21**:425–435.
732. Lofman I, Szummer K, Dahlstrom U, Jernberg T, Lund LH. Associations with and prognostic impact of chronic kidney disease in heart failure with preserved, mid-range, and reduced ejection fraction. *Eur J Heart Fail* 2017;**19**:1606–1614.
733. Lofman I, Szummer K, Evans M, Carrero JJ, Lund LH, Jernberg T. Incidence of, associations with and prognostic impact of worsening renal function in heart failure with different ejection fraction categories. *Am J Cardiol* 2019;**124**:1575–1583.
734. Schefold JC, Filippatos G, Hasenfuss G, Anker SD, von Haehling S. Heart failure and kidney dysfunction: epidemiology, mechanisms and management. *Nat Rev Nephrol* 2016;**12**:610–623.
735. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J* 2014;**35**:455–469.
736. Braunwald E. Diabetes, heart failure, and renal dysfunction: the vicious circles. *Prog Cardiovasc Dis* 2019;**62**:298–302.
737. Zannad F, Ferreira JP, Pocock SJ, Zeller C, Anker SD, Butler J, Filippatos G, Hauske SJ, Brueckmann M, Pfarr E, Schnee J, Wanner C, Packer M. Cardiac and kidney benefits of empagliflozin in heart failure across the spectrum of kidney function: insights from EMPEROR-Reduced. *Circulation* 2021;**143**:310–321.
738. Heerspink HJL, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JFE, McMurray JJV, Lindberg M, Rossing P, Sjostrom CD, Toto RD, Langkilde AM, Wheeler DC, DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;**383**:1436–1446.
739. Metra M, Davison B, Bettari L, Sun H, Edwards C, Lazzarini V, Piovanelli B, Carubelli V, Bugatti S, Lombardi C, Cotter G, Dei Cas L. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. *Circ Heart Fail* 2012;**5**:54–62.
740. Testani JM, Kimmel SE, Dries DL, Coca SG. Prognostic importance of early worsening renal function after initiation of angiotensin-converting enzyme inhibitor therapy in patients with cardiac dysfunction. *Circ Heart Fail* 2011;**4**:685–691.
741. Damman K, Tang WH, Felker GM, Lassus J, Zannad F, Krum H, McMurray JJ. Current evidence on treatment of patients with chronic systolic heart failure and renal insufficiency: practical considerations from published data. *J Am Coll Cardiol* 2014;**63**:853–871.
742. House AA. Management of heart failure in advancing CKD: core curriculum 2018. *Am J Kidney Dis* 2018;**72**:284–295.
743. Kotecha D, Gill SK, Flather MD, Holmes J, Packer M, Rosano G, Bohm M, McMurray JJV, Wikstrand J, Anker SD, van Veldhuisen DJ, Manzano L, von Lueder TG, Rigby AS, Andersson B, Kjekshus J, Wedel H, Ruschitzka F, Cleland JGF, Damman K, Redon J, Coats AJS, Beta-Blockers in Heart Failure Collaborative Group. Impact of renal impairment on beta-blocker efficacy in patients with heart failure. *J Am Coll Cardiol* 2019;**74**:2893–2904.
744. Jhund PS, Solomon SD, Docherty KF, Heerspink HJL, Anand IS, Bohm M, Chopra V, de Boer RA, Desai AS, Ge J, Kitakaze M, Merkley B, O'Meara E, Shou M, Tereshchenko S, Verma S, Vinh PN, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Bengtsson O, Langkilde AM, Sjostrand M, McMurray JJV. Efficacy of dapagliflozin on renal function and outcomes in patients with heart failure with reduced ejection fraction: results of DAPA-HF. *Circulation* 2021;**143**:298–309.
745. Boerrigter G, Costello-Boerrigter LC, Abraham WT, Sutton MG, Heublein DM, Kruger KM, Hill MR, McCullough PA, Burnett JC Jr. Cardiac resynchronization therapy improves renal function in human heart failure with reduced glomerular filtration rate. *J Card Fail* 2008;**14**:539–546.
746. Roehm B, Vest AR, Weiner DE. Left ventricular assist devices kidney disease and dialysis. *Am J Kidney Dis* 2018;**71**:257–266.
747. Goldenberg I, Moss AJ, McNitt S, Zareba W, Andrews ML, Hall WJ, Greenberg H, Case RB, Multicenter Automatic Defibrillator Implantation Trial-II Investigators. Relations among renal function, risk of sudden cardiac death, and benefit of the implanted cardiac defibrillator in patients with ischemic left ventricular dysfunction. *Am J Cardiol* 2006;**98**:485–490.
748. Goldenberg I, Younis A, Aktas MK, McNitt S, Zareba W, Kutyifa V. Competing risk analysis of ventricular arrhythmia events in heart failure patients with moderately compromised renal dysfunction. *Europace* 2020;**22**:1384–1390.
749. Coiro S, Girerd N, Sharma A, Rossignol P, Tritto I, Pitt B, Pfeffer MA, McMurray JJV, Ambrosio G, Dickstein K, Moss A, Zannad F. Association of diabetes and kidney function according to age and systolic function with the incidence of sudden cardiac death and non-sudden cardiac death in myocardial infarction survivors with heart failure. *Eur J Heart Fail* 2019;**21**:1248–1258.
750. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, Adams KF, Anand I, Arias-Mendoza A, Biering-Sorensen T, Bohm M, Bonderman D, Cleland JGF, Corbalan R, Crespo-Leiro MG, Dahlstrom U, Echeverria Correa LE, Fang JC, Filippatos G, Fonseca C, Goncalvesova E, Goudev AR, Howlett JG, Lanfear DE, Lund M, Macdonald P, Mareev V, Momomura SI, O'Meara E, Parkhomenko A, Ponikowski P, Ramires FJA, Serpytis P, Sliwa K, Spinar J, Suter TM, Tomcsanyi J, Vandekerckhove H, Vinereanu D, Voors AA, Yilmaz MB, Zannad F, Sharpsten L, Legg JC, Abbasi SA, Varin C, Malik FI, Kurtz CE, GALACTIC-HF Investigators. Omecamtiv mecarbil in chronic heart failure with reduced ejection fraction: GALACTIC-HF baseline characteristics and comparison with contemporary clinical trials. *Eur J Heart Fail* 2020;**22**:2160–2171.
751. Urso C, Brucculeri S, Caimi G. Acid-base and electrolyte abnormalities in heart failure: pathophysiology and implications. *Heart Fail Rev* 2015;**20**:493–503.
752. Butler J, Vijayakumar S, Pitt B. Need to revisit heart failure treatment guidelines for hyperkalaemia management during the use of mineralocorticoid receptor antagonists. *Eur J Heart Fail* 2018;**20**:1247–1251.
753. Vardeny O, Claggett B, Anand I, Rossignol P, Desai AS, Zannad F, Pitt B, Solomon SD, Randomized Aldactone Evaluation Study (RALES) Investigators. Incidence, predictors, and outcomes related to hypo- and hyperkalemia in

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patients with severe heart failure treated with a mineralocorticoid receptor antagonist. *Circ Heart Fail* 2014;**7**:573–579.
754. Rossignol P, Dobre D, McMurray JJ, Swedberg K, Krum H, van Veldhuisen DJ, Shi H, Messig M, Vincent J, Girerd N, Bakris G, Pitt B, Zannad F. Incidence, determinants, and prognostic significance of hyperkalemia and worsening renal function in patients with heart failure receiving the mineralocorticoid receptor antagonist eplerenone or placebo in addition to optimal medical therapy: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). *Circ Heart Fail* 2014;**7**:51–58.
755. Nunez J, Bayes-Genis A, Zannad F, Rossignol P, Nunez E, Bodi V, Minana G, Santas E, Chorro FJ, Mollar A, Carratala A, Navarro J, Gorriz JL, Lupon J, Husser O, Metra M, Sanchis J. Long-term potassium monitoring and dynamics in heart failure and risk of mortality. *Circulation* 2018;**137**:1320–1330.
756. Linde C, Qin L, Bakhai A, Furuland H, Evans M, Ayoubkhani D, Palaka E, Bennett H, McEwan P. Serum potassium and clinical outcomes in heart failure patients: results of risk calculations in 21 334 patients in the UK. *ESC Heart Fail* 2019;**6**:280–290.
757. Cooper LB, Benson L, Mentz RJ, Savarese G, DeVore AD, Carrero JJ, Dahlstrom U, Anker SD, Lainscak M, Hernandez AF, Pitt B, Lund LH. Association between potassium level and outcomes in heart failure with reduced ejection fraction: a cohort study from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2020;**22**:1390–1398.
758. Rossignol P, Lainscak M, Crespo-Leiro MG, Laroche C, Piepoli MF, Filippatos G, Rosano GMC, Savarese G, Anker SD, Seferovic PM, Ruschitzka F, Coats AJS, Mebazaa A, McDonagh T, Sahuquillo A, Penco M, Maggioni AP, Lund LH, Heart Failure Long-Term Registry Investigators Group. Unravelling the interplay between hyperkalaemia, renin-angiotensin-aldosterone inhibitor use and clinical outcomes. Data from 9222 chronic heart failure patients of the ESC-HFA-EORP Heart Failure Long-Term Registry. *Eur J Heart Fail* 2020;**22**:1378–1389.
759. Ahmed A, Zannad F, Love TE, Tallaj J, Gheorghiade M, Ekundayo OJ, Pitt B. A propensity-matched study of the association of low serum potassium levels and mortality in chronic heart failure. *Eur Heart J* 2007;**28**:1334–1343.
760. Rosano GMC, Tamargo J, Kjeldsen KP, Lainscak M, Agewall S, Anker SD, Ceconi C, Coats AJS, Drexel H, Filippatos G, Kaski JC, Lund L, Niessner A, Ponikowski P, Savarese G, Schmidt TA, Seferovic P, Wassmann S, Walther T, Lewis BS. Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology. *Eur Heart J Cardiovasc Pharmacother* 2018;**4**:180–188.
761. Ferreira JP, Mogensen UM, Jhund PS, Desai AS, Rouleau JL, Zile MR, Rossignol P, Zannad F, Packer M, Solomon SD, McMurray JJV. Serum potassium in the PARADIGM-HF trial. *Eur J Heart Fail* 2020;**22**:2056–2064.
762. Rossignol P, Duarte K, Girerd N, Karoui M, McMurray JJV, Swedberg K, van Veldhuisen DJ, Pocock S, Dickstein K, Zannad F, Pitt B. Cardiovascular risk associated with serum potassium in the context of mineralocorticoid receptor antagonist use in patients with heart failure and left ventricular dysfunction. *Eur J Heart Fail* 2020;**22**:1402–1411.
763. Desai AS, Liu J, Pfeffer MA, Claggett B, Fleg J, Lewis EF, McKinlay S, O'Meara E, Shah SJ, Sweitzer NK, Solomon S, Pitt B. Incident hyperkalemia, hypokalemia, and clinical outcomes during spironolactone treatment of heart failure with preserved ejection fraction: analysis of the TOPCAT trial. *J Card Fail* 2018;**24**:313–320.
764. Desai AS. Hyperkalemia in patients with heart failure: incidence, prevalence, and management. *Curr Heart Fail Rep* 2009;**6**:272–280.
765. Savarese G, Xu H, Trevisan M, Dahlstrom U, Rossignol P, Pitt B, Lund LH, Carrero JJ. Incidence, predictors, and outcome associations of dyskalemia in heart failure with preserved, mid-range, and reduced ejection fraction. *JACC Heart Fail* 2019;**7**:65–76.
766. Rosano GMC, Spoletini I, Agewall S. Pharmacology of new treatments for hyperkalaemia: patiromer and sodium zirconium cyclosilicate. *Eur Heart J Suppl* 2019;**21**:A28–A33.
767. Anker SD, Kosiborod M, Zannad F, Pina IL, McCullough PA, Filippatos G, van der Meer P, Ponikowski P, Rasmussen HS, Lavin PT, Singh B, Yang A, Deedwania P. Maintenance of serum potassium with sodium zirconium cyclosilicate (ZS-9) in heart failure patients: results from a phase 3 randomized, double-blind, placebo-controlled trial. *Eur J Heart Fail* 2015;**17**:1050–1056.
768. Pitt B, Bakris GL, Bushinsky DA, Garza D, Mayo MR, Stasiv Y, Christ-Schmidt H, Berman L, Weir MR. Effect of patiromer on reducing serum potassium and preventing recurrent hyperkalaemia in patients with heart failure and chronic kidney disease on RAAS inhibitors. *Eur J Heart Fail* 2015;**17**:1057–1065.
769. Trevisan M, de Deco P, Xu H, Evans M, Lindholm B, Bellocco R, Barany P, Jernberg T, Lund LH, Carrero JJ. Incidence, predictors and clinical management of hyperkalaemia in new users of mineralocorticoid receptor antagonists. *Eur J Heart Fail* 2018;**20**:1217–1226.
770. Ferreira JP, Rossello X, Pocock SJ, Rossignol P, Claggett BL, Rouleau JL, Solomon SD, Pitt B, Pfeffer MA, Zannad F. Spironolactone dose in heart failure with preserved ejection fraction: findings from TOPCAT. *Eur J Heart Fail* 2020;**22**:1615–1624.
771. Volterrani M, Perrone V, Sangiorgi D, Giacomini E, Iellamo F, Degli Esposti L, LHUs Study Group. Effects of hyperkalaemia and non-adherence to renin-angiotensin-aldosterone system inhibitor therapy in patients with heart failure in Italy: a propensity-matched study. *Eur J Heart Fail* 2020;**22**:2049–2055.
772. Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang IZ, Investigators PEARL-HF. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. *Eur Heart J* 2011;**32**:820–828.
773. Pitt B, Bakris GL, Weir MR, Freeman MW, Lainscak M, Mayo MR, Garza D, Zawadzki R, Berman L, Bushinsky DA. Long-term effects of patiromer for hyperkalaemia treatment in patients with mild heart failure and diabetic nephropathy on angiotensin-converting enzymes/angiotensin receptor blockers: results from AMETHYST-DN. *ESC Heart Fail* 2018;**5**:592–602.
774. Agarwal R, Rossignol P, Romero A, Garza D, Mayo MR, Warren S, Ma J, White WB, Williams B. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* 2019;**394**:1540–1550.
775. Rossignol P, Williams B, Mayo MR, Warren S, Arthur S, Ackourey G, White WB, Agarwal R. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): results in the pre-specified subgroup with heart failure. *Eur J Heart Fail* 2020;**22**:1462–1471.
776. Pitt B, Bushinsky DA, Kitzman DW, Ruschitzka F, Metra M, Filippatos G, Rossignol P, Du Mond C, Garza D, Berman L, Lainscak M, Patiromer Investigators. Evaluation of an individualized dose titration regimen of patiromer to prevent hyperkalaemia in patients with heart failure and chronic kidney disease. *ESC Heart Fail* 2018;**5**:257–266.
777. Ali W, Bakris G. Evolution of patiromer use: a review. *Curr Cardiol Rep* 2020;**22**:94.
778. Farmakis D, Filippatos G, Parissis J, Kremastinos DT, Gheorghiade M. Hyponatremia in heart failure. *Heart Fail Rev* 2009;**14**:59–63.
779. Rodriguez M, Hernandez M, Cheungpasitporn W, Kashani KB, Riaz I, Rangaswami J, Herzog E, Guglin M, Krittanawong C. Hyponatremia in heart failure: pathogenesis and management. *Curr Cardiol Rev* 2019;**15**:252–261.
780. Albert NM, Nutter B, Forney J, Slifcak E, Tang WH. A randomized controlled pilot study of outcomes of strict allowance of fluid therapy in hyponatremic heart failure (SALT-HF). *J Card Fail* 2013;**19**:1–9.
781. Dunlap ME, Hauptman PJ, Amin AN, Chase SL, Chiodo JA, 3rd, Chiong JR, Dasta JF. Current management of hyponatremia in acute heart failure: a report from the Hyponatremia Registry for Patients With Euvolemic and Hypervolemic Hyponatremia (HN Registry). *J Am Heart Assoc* 2017;**6**:e005261.
782. Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA* 2007;**297**:1319–1331.
783. Felker GM, Mentz RJ, Cole RT, Adams KF, Egnaczyk GF, Fiuzat M, Patel CB, Echols M, Khouri MG, Tauras JM, Gupta D, Monds P, Roberts R, O'Connor CM. Efficacy and safety of tolvaptan in patients hospitalized with acute heart failure. *J Am Coll Cardiol* 2017;**69**:1399–1406.
784. Matsue Y, Ter Maaten JM, Suzuki M, Torii S, Yamaguchi S, Fukamizu S, Ono Y, Fujii H, Kitai T, Nishioka T, Sugi K, Onishi Y, Noda M, Kagiyama N, Satoh Y, Yoshida K, van der Meer P, Damman K, Voors AA, Goldsmith SR. Early treatment with tolvaptan improves diuretic response in acute heart failure with renal dysfunction. *Clin Res Cardiol* 2017;**106**:802–812.
785. Konstam MA, Kiernan M, Chandler A, Dhingra R, Mody FV, Eisen H, Haught WH, Wagoner L, Gupta D, Patten R, Gordon P, Korr K, Fileccia R, Pressler SJ, Gregory D, Wedge P, Dowling D, Romeling M, Konstam JM, Massaro JM, Udelson JE, SECRET of CHF Investigators, Coordinators, and Committee Members. Short-term effects of tolvaptan in patients with acute heart failure and volume overload. *J Am Coll Cardiol* 2017;**69**:1409–1419.
786. Licata G, Di Pasquale P, Parrinello G, Cardinale A, Scandurra A, Follone G, Argano C, Tuttolomondo A, Paterna S. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-term effects. *Am Heart J* 2003;**145**:459–466.
787. Paterna S, Di Pasquale P, Parrinello G, Amato P, Cardinale A, Follone G, Giubilato A, Licata G. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as a bolus, in refractory congestive heart failure. *Eur J Heart Fail* 2000;**2**:305–313.

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788. Griffin M, Soufer A, Goljo E, Colna M, Rao VS, Jeon S, Raghavendra P, D'Ambrosi J, Riello R, Coca SG, Mahoney D, Jacoby D, Ahmad T, Chen M, Tang WHW, Turner J, Mullens W, Wilson FP, Testani JM. Real world use of hypertonic saline in refractory acute decompensated heart failure: a U.S. center's experience. *JACC Heart Fail* 2020;**8**:199–208.
789. Cuthbert JJ, Pellicori P, Rigby A, Pan D, Kazmi S, Shah P, Clark AL. Low serum chloride in patients with chronic heart failure: clinical associations and prognostic significance. *Eur J Heart Fail* 2018;**20**:1426–1435.
790. Testani JM, Hanberg JS, Arroyo JP, Brisco MA, Ter Maaten JM, Wilson FP, Bellumkonda L, Jacoby D, Tang WH, Parikh CR. Hypochloraemia is strongly and independently associated with mortality in patients with chronic heart failure. *Eur J Heart Fail* 2016;**18**:660–668.
791. Marchenko R, Sigal A, Wasser TE, Reyer J, Green J, Mercogliano C, Khan MS, Donato AA. Hypochloraemia and 30 day readmission rate in patients with acute decompensated heart failure. *ESC Heart Fail* 2020;**7**:903–907.
792. Grodin JL, Simon J, Hachamovitch R, Wu Y, Jackson G, Halkar M, Starling RC, Testani JM, Tang WH. Prognostic role of serum chloride levels in acute decompensated heart failure. *J Am Coll Cardiol* 2015;**66**:659–666.
793. Hanberg JS, Rao V, Ter Maaten JM, Laur O, Brisco MA, Perry Wilson F, Grodin JL, Assefa M, Samuel Broughton J, Planavsky NJ, Ahmad T, Bellumkonda L, Tang WH, Parikh CR, Testani JM. Hypochloremia and diuretic resistance in heart failure: mechanistic insights. *Circ Heart Fail* 2016;**9**.
794. Verbrugge FH, Martens P, Ameloot K, Haemels V, Penders J, Dupont M, Tang WHW, Droogne W, Mullens W. Acetazolamide to increase natriuresis in congestive heart failure at high risk for diuretic resistance. *Eur J Heart Fail* 2019;**21**:1415–1422.
795. Axson EL, Ragutheeswaran K, Sundaram V, Bloom CI, Bottle A, Cowie MR, Quint JK. Hospitalisation and mortality in patients with comorbid COPD and heart failure: a systematic review and meta-analysis. *Respir Res* 2020;**21**:54.
796. Canepa M, Straburzynska-Migaj E, Drozdz J, Fernandez-Vivancos C, Pinilla JMG, Nyolczas N, Temporelli PL, Mebazaa A, Lainscak M, Laroche C, Maggioni AP, Piepoli MF, Coats AJS, Ferrari R, Tavazzi L, ESC-HFA Heart Failure Long-Term Registry Investigators. Characteristics, treatments and 1-year prognosis of hospitalized and ambulatory heart failure patients with chronic obstructive pulmonary disease in the European Society of Cardiology Heart Failure Long-Term Registry. *Eur J Heart Fail* 2018;**20**:100–110.
797. Uijl A, Koudstaal S, Direk K, Denaxas S, Groenwold RHH, Banerjee A, Hoes AW, Hemingway H, Asselbergs FW. Risk factors for incident heart failure in age- and sex-specific strata: a population-based cohort using linked electronic health records. *Eur J Heart Fail* 2019;**21**:1197–1206.
798. Caravita S, Vachiery JL. Obstructive ventilatory disorder in heart failure–caused by the heart or the lung? *Curr Heart Fail Rep* 2016;**13**:310–318.
799. Magnussen H, Canepa M, Zambito PE, Brusasco V, Meinertz T, Rosenkranz S. What can we learn from pulmonary function testing in heart failure? *Eur J Heart Fail* 2017;**19**:1222–1229.
800. Canepa M, Franssen FME, Olschewski H, Lainscak M, Bohm M, Tavazzi L, Rosenkranz S. Diagnostic and therapeutic gaps in patients with heart failure and chronic obstructive pulmonary disease. *JACC Heart Fail* 2019;**7**:823–833.
801. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2020 report. https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf (31 May 2020).
802. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. www.ginasthma.org (28 May 2021).
803. Brook RD, Anderson JA, Calverley PM, Celli BR, Crim C, Denvir MA, Magder S, Martinez FJ, Rajagopalan S, Vestbo J, Yates J, Newby DE, SUMMIT Investigators. Cardiovascular outcomes with an inhaled beta2-agonist/corticosteroid in patients with COPD at high cardiovascular risk. *Heart* 2017;**103**:1536–1542.
804. Vestbo J, Anderson JA, Brook RD, Calverley PM, Celli BR, Crim C, Martinez F, Yates J, Newby DE, SUMMIT Investigators. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet* 2016;**387**:1817–1826.
805. Hohlfeld JM, Vogel-Claussen J, Biller H, Berliner D, Berschneider K, Tillmann HC, Hiltl S, Bauersachs J, Welte T. Effect of lung deflation with indacaterol plus glycopyrronium on ventricular filling in patients with hyperinflation and COPD (CLAIM): a double-blind, randomised, crossover, placebo-controlled, single-centre trial. *Lancet Respir Med* 2018;**6**:368–378.
806. Pearse SG, Cowie MR. Sleep-disordered breathing in heart failure. *Eur J Heart Fail* 2016;**18**:353–361.
807. Cowie MR, Gallagher AM. Sleep disordered breathing and heart failure: what does the future hold? *JACC Heart Fail* 2017;**5**:715–723.
808. Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, Levy P, Simonds AK, Somers VK, Zannad F, Teschler H. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. *N Engl J Med* 2015;**373**:1095–1105.
809. Costanzo MR, Ponikowski P, Javaheri S, Augostini R, Goldberg L, Holcomb R, Kao A, Khayat RN, Oldenburg O, Stellbrink C, Abraham WT, remedé System Pivotal Trial Study Group. Transvenous neurostimulation for central sleep apnoea: a randomised controlled trial. *Lancet* 2016;**388**:974–982.
810. Costanzo MR, Ponikowski P, Coats A, Javaheri S, Augostini R, Goldberg LR, Holcomb R, Kao A, Khayat RN, Oldenburg O, Stellbrink C, McKane S, Abraham WT, remedé System Pivotal Trial Study Group. Phrenic nerve stimulation to treat patients with central sleep apnoea and heart failure. *Eur J Heart Fail* 2018;**20**:1746–1754.
811. Kjekshus J, Apetrei E, Barrios V, Böhm M, Cleland JG, Cornel JH, Dunselman P, Fonseca C, Goudev A, Grande P, Gullestad L, Hjalmarson A, Hradec J, Jánosi A, Kamenský G, Komajda M, Korewicki J, Kuusi T, Mach F, Mareev V, McMurray JJ, Ranjith N, Schaufelberger M, Vanhaecke J, van Veldhuisen DJ, Waagstein F, Wedel H, Wikstrand J, CORONA Group. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007;**357**:2248–2261.
812. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G, GISSI-HF Investigators. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;**372**:1231–1239.
813. Al-Gobari M, Le HH, Fall M, Gueyffier F, Burnand B. No benefits of statins for sudden cardiac death prevention in patients with heart failure and reduced ejection fraction: a meta-analysis of randomized controlled trials. *PLoS One* 2017;**12**:e0171168.
814. Rogers JK, Jhund PS, Perez AC, Bohm M, Cleland JG, Gullestad L, Kjekshus J, van Veldhuisen DJ, Wikstrand J, Wedel H, McMurray JJ, Pocock SJ. Effect of rosuvastatin on repeat heart failure hospitalizations: the CORONA trial (Controlled Rosuvastatin Multinational Trial in Heart Failure). *JACC Heart Fail* 2014;**2**:289–297.
815. Feinstein MJ, Jhund P, Kang J, Ning H, Maggioni A, Wikstrand J, Kjekshus J, Tavazzi L, McMurray J, Lloyd-Jones DM. Do statins reduce the risk of myocardial infarction in patients with heart failure? A pooled individual-level reanalysis of CORONA and GISSI-HF. *Eur J Heart Fail* 2015;**17**:434–441.
816. Thanassoulis G, Brophy JM, Richard H, Pilote L. Gout, allopurinol use, and heart failure outcomes. *Arch Intern Med* 2010;**170**:1358–1364.
817. Borghi C, Palazzuoli A, Landolfo M, Cosentino E. Hyperuricemia: a novel old disorder-relationship and potential mechanisms in heart failure. *Heart Fail Rev* 2020;**25**:43–51.
818. Doehner W, Springer J, Landmesser U, Struthers AD, Anker SD. Uric acid in chronic heart failure–current pathophysiological concepts. *Eur J Heart Fail* 2008;**10**:1269–1270.
819. Huang H, Huang B, Li Y, Huang Y, Li J, Yao H, Jing X, Chen J, Wang J. Uric acid and risk of heart failure: a systematic review and meta-analysis. *Eur J Heart Fail* 2014;**16**:15–24.
820. White WB, Saag KG, Becker MA, Borer JS, Gorelick PB, Whelton A, Hunt B, Castillo M, Gunawardhana L, CARES Investigators. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med* 2018;**378**:1200–1210.
821. Hare JM, Mangal B, Brown J, Fisher C, Jr., Freudenberger R, Colucci WS, Mann DL, Liu P, Givertz MM, Schwarz RP, OPT-CHF Investigators. Impact of oxypurinol in patients with symptomatic heart failure. Results of the OPT-CHF study. *J Am Coll Cardiol* 2008;**51**:2301–2309.
822. Ogino K, Kato M, Furuse Y, Kinugasa Y, Ishida K, Osaki S, Kinugawa T, Igawa O, Hisatome I, Shigemasa C, Anker SD, Doehner W. Uric acid-lowering treatment with benzbromarone in patients with heart failure: a double-blind placebo-controlled crossover preliminary study. *Circ Heart Fail* 2010;**3**:73–81.
823. Givertz MM, Anstrom KJ, Redfield MM, Deswal A, Haddad H, Butler J, Tang WH, Dunlap ME, LeWinter MM, Mann DL, Felker GM, O'Connor CM, Goldsmith SR, Ofili EO, Saltzberg MT, Margulies KB, Cappola TP, Konstam MA, Semigran MJ, McNulty SE, Lee KL, Shah MR, Hernandez AF, NHLBI Heart Failure Clinical Research Network. Effects of xanthine oxidase inhibition in hyperuricemic heart failure patients: the Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) study. *Circulation* 2015;**131**:1763–1771.
824. Verma S, Eikelboom JW, Nidorf SM, Al-Omran M, Gupta N, Teoh H, Friedrich JO. Colchicine in cardiac disease: a systematic review and meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord* 2015;**15**:96.
825. Frommeyer G, Krawczyk J, Dechering DG, Kochhauser S, Leitz P, Fehr M, Eckardt L. Colchicine increases ventricular vulnerability in an experimental whole-heart model. *Basic Clin Pharmacol Toxicol* 2017;**120**:505–508.
826. Arfe A, Scotti L, Varas-Lorenzo C, Nicotra F, Zambon A, Kollhorst B, Schink T, Garbe E, Herings R, Straatman H, Schade R, Villa M, Lucchi S, Valkhoff V, Romio S, Thiessard F, Schuemie M, Pariente A, Sturkenboom M, Corrao G, Safety of Non-steroidal Anti-inflammatory Drugs Project Consortium. Non-

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steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study. *BMJ* 2016;**354**:i4857.
827. Khalid Y, Dasu N, Shah A, Brown K, Kaell A, Levine A, Dasu K, Raminfard A. Incidence of congestive heart failure in rheumatoid arthritis: a review of literature and meta-regression analysis. *ESC Heart Fail* 2020;**7**:3745–3753.
828. Mantel A, Holmqvist M, Andersson DC, Lund LH, Askling J. Association between rheumatoid arthritis and risk of ischemic and nonischemic heart failure. *J Am Coll Cardiol* 2017;**69**:1275–1285.
829. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT, Anti-TNF Therapy Against Congestive Heart Failure Investigators. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. *Circulation* 2003;**107**:3133–3140.
830. Mann DL, McMurray JJ, Packer M, Swedberg K, Borer JS, Colucci WS, Djian J, Drexler H, Feldman A, Kober L, Krum H, Liu P, Nieminen M, Tavazzi L, van Veldhuisen DJ, Waldenstrom A, Warren M, Westheim A, Zannad F, Fleming T. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). *Circulation* 2004;**109**:1594–1602.
831. Kotyla PJ. Bimodal function of anti-TNF treatment: shall we be concerned about anti-TNF treatment in patients with rheumatoid arthritis and heart failure? *Int J Mol Sci* 2018;**19**:1739.
832. Baumhakel M, Schlimmer N, Kratz M, Hackett G, Jackson G, Bohm M. Cardiovascular risk, drugs and erectile function–a systematic analysis. *Int J Clin Pract* 2011;**65**:289–298.
833. Jaarsma T. Sexual function of patients with heart failure: facts and numbers. *ESC Heart Fail* 2017;**4**:3–7.
834. Levine AB, Punihaole D, Levine TB. Characterization of the role of nitric oxide and its clinical applications. *Cardiology* 2012;**122**:55–68.
835. Giannetta E, Feola T, Gianfrilli D, Pofi R, Dall'Armi V, Badagliacca R, Barbagallo F, Lenzi A, Isidori AM. Is chronic inhibition of phosphodiesterase type 5 cardioprotective and safe? A meta-analysis of randomized controlled trials. *BMC Med* 2014;**12**:185.
836. Angermann CE, Ertl G. Depression, anxiety, and cognitive impairment: comorbid mental health disorders in heart failure. *Curr Heart Fail Rep* 2018;**15**:398–410.
837. Sbolli M, Fiuzat M, Cani D, O'Connor CM. Depression and heart failure: the lonely comorbidity. *Eur J Heart Fail* 2020;**22**:2007–2017.
838. Jha MK, Qamar A, Vaduganathan M, Charney DS, Murrough JW. Screening and management of depression in patients with cardiovascular disease: JACC state-of-the-art review. *J Am Coll Cardiol* 2019;**73**:1827–1845.
839. Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, Czajkowski SM, DeBusk R, Hosking J, Jaffe A, Kaufmann PG, Mitchell P, Norman J, Powell LH, Raczynski JM, Schneiderman N, Enhancing Recovery in Coronary Heart Disease Patients Investigators. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) randomized trial. *JAMA* 2003;**289**:3106–3116.
840. O'Connor CM, Jiang W, Kuchibhatla M, Silva SG, Cuffe MS, Callwood DD, Zakhary B, Stough WG, Arias RM, Rivelli SK, Krishnan R, SADHART-CHF Investigators. Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial. *J Am Coll Cardiol* 2010;**56**:692–699.
841. Angermann CE, Gelbrich G, Stork S, Gunold H, Edelmann F, Wachter R, Schunkert H, Graf T, Kindermann I, Haass M, Blankenberg S, Pankuweit S, Prettin C, Gottwik M, Bohm M, Faller H, Deckert J, Ertl G, MOOD-HF Study Investigators and Committee Members. Effect of escitalopram on all-cause mortality and hospitalization in patients with heart failure and depression: the MOOD-HF randomized clinical trial. *JAMA* 2016;**315**:2683–2693.
842. de Boer RA, Meijers WC, van der Meer P, van Veldhuisen DJ. Cancer and heart disease: associations and relations. *Eur J Heart Fail* 2019;**21**:1515–1525.
843. Farmakis D, Mantzourani M, Filippatos G. Anthracycline-induced cardiomyopathy: secrets and lies. *Eur J Heart Fail* 2018;**20**:907–909.
844. Zamorano JL, Lancellotti P, Rodriguez Munoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GY, Lyon AR, Lopez Fernandez T, Mohty D, Piepoli MF, Tamargo J, Torbicki A, Suter TM, Zamorano JL, Aboyans V, Achenbach S, Agewall S, Badimon L, Baron-Esquivias G, Baumgartner H, Bax JJ, Bueno H, Carerj S, Dean V, Erol C, Fitzsimons D, Gaemperli O, Kirchhof P, Kolh P, Lancellotti P, Lip GY, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Roffi M, Torbicki A, Vaz Carneiro A, Windecker S, Authors/Task Force Members, ESC Committee for Practice Guidelines, Document Reviewers. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2017;**19**:9–42.
845. Zamorano JL, Gottfridsson C, Asteggiano R, Atar D, Badimon L, Bax JJ, Cardinale D, Cardone A, Feijen EAM, Ferdinandy P, Lopez-Fernandez T, Gale CP, Maduro JH, Moslehi J, Omland T, Plana Gomez JC, Scott J, Suter TM, Minotti G. The cancer patient and cardiology. *Eur J Heart Fail* 2020;**22**:2290–2309.
846. Lyon AR, Dent S, Stanway S, Earl H, Brezden-Masley C, Cohen-Solal A, Tocchetti CG, Moslehi JJ, Groarke JD, Bergler-Klein J, Khoo V, Tan LL, Anker MS, von Haehling S, Maack C, Pudil R, Barac A, Thavendiranathan P, Ky B, Neilan TG, Belenkov Y, Rosen SD, Iakobishvili Z, Sverdlov AL, Hajjar LA, Macedo AVS, Manisty C, Ciardiello F, Farmakis D, de Boer RA, Skouri H, Suter TM, Cardinale D, Witteles RM, Fradley MG, Herrmann J, Cornell RF, Wechelaker A, Mauro MJ, Milojkovic D, de Lavallade H, Ruschitzka F, Coats AJS, Seferovic PM, Chioncel O, Thum T, Bauersachs J, Andres MS, Wright DJ, Lopez-Fernandez T, Plummer C, Lenihan D. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. *Eur J Heart Fail* 2020;**22**:1945–1960.
847. Ganatra S, Carver JR, Hayek SS, Ky B, Leja MJ, Lenihan DJ, Lenneman C, Mousavi N, Park JH, Perales MA, Ryan TD, Scherrer-Crosbie M, Steingart RM, Yang EH, Zaha V, Barac A, Liu JE. Chimeric antigen receptor T-cell therapy for cancer and heart: JACC council perspectives. *J Am Coll Cardiol* 2019;**74**:3153–3163.
848. Lenneman CG, Sawyer DB. Cardio-oncology: an update on cardiotoxicity of cancer-related treatment. *Circ Res* 2016;**118**:1008–1020.
849. Lyon AR, Yousaf N, Battisti NML, Moslehi J, Larkin J. Immune checkpoint inhibitors and cardiovascular toxicity. *Lancet Oncol* 2018;**19**:e447–e458.
850. Boekel NB, Duane FK, Jacobse JN, Hauptmann M, Schaapveld M, Sonke GS, Gietema JA, Hooning MJ, Seynaeve CM, Maas A, Darby SC, Aleman BMP, Taylor CW, van Leeuwen FE. Heart failure after treatment for breast cancer. *Eur J Heart Fail* 2020;**22**:366–374.
851. Farmakis D, Parissis J, Filippatos G. Insights into onco-cardiology: atrial fibrillation in cancer. *J Am Coll Cardiol* 2014;**63**:945–953.
852. Tromp J, Boerman LM, Sama IE, Maass S, Maduro JH, Hummel YM, Berger MY, de Bock GH, Gietema JA, Berendsen AJ, van der Meer P. Long-term survivors of early breast cancer treated with chemotherapy are characterized by a pro-inflammatory biomarker profile compared to matched controls. *Eur J Heart Fail* 2020;**22**:1239–1246.
853. Hasin T, Gerber Y, Weston SA, Jiang R, Killian JM, Manemann SM, Cerhan JR, Roger VL. Heart failure after myocardial infarction is associated with increased risk of cancer. *J Am Coll Cardiol* 2016;**68**:265–271.
854. Banke A, Schou M, Videbaek L, Moller JE, Torp-Pedersen C, Gustafsson F, Dahl JS, Kober L, Hildebrandt PR, Gislason GH. Incidence of cancer in patients with chronic heart failure: a long-term follow-up study. *Eur J Heart Fail* 2016;**18**:260–266.
855. Meijers WC, de Boer RA. Common risk factors for heart failure and cancer. *Cardiovasc Res* 2019;**115**:844–853.
856. de Boer RA, Hulot JS, Tocchetti CG, Aboumsallem JP, Ameri P, Anker SD, Bauersachs J, Bertero E, Coats AJS, Celutkiene J, Chioncel O, Dodion P, Eschenhagen T, Farmakis D, Bayes-Genis A, Jager D, Jankowska EA, Kitsis RN, Konety SH, Larkin J, Lehmann L, Lenihan DJ, Maack C, Moslehi JJ, Muller OJ, Nowak-Sliwinska P, Piepoli MF, Ponikowski P, Pudil R, Rainer PP, Ruschitzka F, Sawyer D, Seferovic PM, Suter T, Thum T, van der Meer P, Van Laake LW, von Haehling S, Heymans S, Lyon AR, Backs J. Common mechanistic pathways in cancer and heart failure. A scientific roadmap on behalf of the Translational Research Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2020;**22**:2272–2289.
857. Selvaraj S, Bhatt DL, Claggett B, Djousse L, Shah SJ, Chen J, Imran TF, Qazi S, Sesso HD, Gaziano JM, Schrag D. Lack of association between heart failure and incident cancer. *J Am Coll Cardiol* 2018;**71**:1501–1510.
858. Meijers WC, Maglione M, Bakker SJL, Oberhuber R, Kieneker LM, de Jong S, Haubner BJ, Nagengast WB, Lyon AR, van der Vegt B, van Veldhuisen DJ, Westenbrink BD, van der Meer P, Sillje HHW, de Boer RA. Heart failure stimulates tumor growth by circulating factors. *Circulation* 2018;**138**:678–691.
859. Lancellotti P, Suter TM, Lopez-Fernandez T, Galderisi M, Lyon AR, Van der Meer P, Cohen Solal A, Zamorano JL, Jerusalem G, Moonen M, Aboyans V, Bax JJ, Asteggiano R. Cardio-oncology services: rationale, organization, and implementation. *Eur Heart J* 2019;**40**:1756–1763.
860. Farmakis D, Keramida K, Filippatos G. How to build a cardio-oncology service? *Eur J Heart Fail* 2018;**20**:1732–1734.
861. Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, Rubino M, Veglia F, Fiorentini C, Cipolla CM. Anthracycline-induced

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cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol* 2010;**55**:213–220.
862. Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, Civelli M, Lamantia G, Colombo N, Curigliano G, Fiorentini C, Cipolla CM. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation* 2015;**131**:1981–1988.
863. Gulati G, Heck SL, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW, Gravdehaug B, von Knobelsdorff-Brenkenhoff F, Bratland A, Storas TH, Hagve TA, Rosjo H, Steine K, Geisler J, Omland T. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 x 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. *Eur Heart J* 2016;**37**:1671–1680.
864. Pituskin E, Mackey JR, Koshman S, Jassal D, Pitz M, Haykowsky MJ, Pagano JJ, Chow K, Thompson RB, Vos LJ, Ghosh S, Oudit GY, Ezekowitz JA, Paterson DI. Multidisciplinary approach to novel therapies in cardio-oncology research (MANTICORE 101-Breast): a randomized trial for the prevention of trastuzumab-associated cardiotoxicity. *J Clin Oncol* 2017;**35**:870–877.
865. Celutkiene J, Pudil R, Lopez-Fernandez T, Grapsa J, Nihoyannopoulos P, Bergler-Klein J, Cohen-Solal A, Farmakis D, Tocchetti CG, von Haehling S, Barberis V, Flachskampf FA, Ceponiene I, Haegler-Laube E, Suter T, Lapinskas T, Prasad S, de Boer RA, Wechalekar K, Anker MS, Iakobishvili Z, Bucciarelli-Ducci C, Schulz-Menger J, Cosyns B, Gaemperli O, Belenkov Y, Hulot JS, Galderisi M, Lancellotti P, Bax J, Marwick TH, Chioncel O, Jaarsma T, Mullens W, Piepoli M, Thum T, Heymans S, Mueller C, Moura B, Ruschitzka F, Zamorano JL, Rosano G, Coats AJS, Asteggiano R, Seferovic P, Edvardsen T, Lyon AR. Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: a position statement on behalf of the Heart Failure Association (HFA), the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2020;**22**:1504–1524.
866. Keramida K, Farmakis D, Bingcang J, Sulemane S, Sutherland S, Bingcang RA, Ramachandran K, Tzavara C, Charalampopoulos G, Filippiadis D, Kouris N, Nihoyannopoulos P. Longitudinal changes of right ventricular deformation mechanics during trastuzumab therapy in breast cancer patients. *Eur J Heart Fail* 2019;**21**:529–535.
867. Thavendiranathan P, Negishi T, Somerset E, Negishi K, Penicka M, Lemieux J, Aakhus S, Miyazaki S, Shirazi M, Galderisi M, Marwick TH, SUCCOUR Investigators. Strain-guided management of potentially cardiotoxic cancer therapy. *J Am Coll Cardiol* 2021;**77**:392–401.
868. Michel L, Mincu RI, Mahabadi AA, Settelmeier S, Al-Rashid F, Rassaf T, Totzeck M. Troponins and brain natriuretic peptides for the prediction of cardiotoxicity in cancer patients: a meta-analysis. *Eur J Heart Fail* 2020;**22**:350–361.
869. Pudil R, Mueller C, Celutkiene J, Henriksen PA, Lenihan D, Dent S, Barac A, Stanway S, Moslehi J, Suter TM, Ky B, Sterba M, Cardinale D, Cohen-Solal A, Tocchetti CG, Farmakis D, Bergler-Klein J, Anker MS, Von Haehling S, Belenkov Y, Iakobishvili Z, Maack C, Ciardiello F, Ruschitzka F, Coats AJS, Seferovic P, Lainscak M, Piepoli MF, Chioncel O, Bax J, Hulot JS, Skouri H, Hagler-Laube ES, Asteggiano R, Fernandez TL, de Boer RA, Lyon AR. Role of serum biomarkers in cancer patients receiving cardiotoxic cancer therapies: a position statement from the Cardio-Oncology Study Group of the Heart Failure Association and the Cardio-Oncology Council of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:1966–1983.
870. Hu JR, Florido R, Lipson EJ, Naidoo J, Ardehali R, Tocchetti CG, Lyon AR, Padera RF, Johnson DB, Moslehi J. Cardiovascular toxicities associated with immune checkpoint inhibitors. *Cardiovasc Res* 2019;**115**:854–868.
871. Banke A, Fosbol EL, Moller JE, Gislason GH, Andersen M, Bernsdorf M, Jensen MB, Schou M, Ejlertsen B. Long-term effect of epirubicin on incidence of heart failure in women with breast cancer: insight from a randomized clinical trial. *Eur J Heart Fail* 2018;**20**:1447–1453.
872. Platz E, Jhund PS, Claggett BL, Pfeffer MA, Swedberg K, Granger CB, Yusuf S, Solomon SD, McMurray JJ. Prevalence and prognostic importance of precipitating factors leading to heart failure hospitalization: recurrent hospitalizations and mortality. *Eur J Heart Fail* 2018;**20**:295–303.
873. Tomasoni D, Italia L, Adamo M, Inciardi RM, Lombardi CM, Solomon SD, Metra M. COVID 19 and heart failure: from infection to inflammation and angiotensin II stimulation. Searching for evidence from a new disease. *Eur J Heart Fail* 2020;**22**:957–966;**23**:512–526.
874. Corrales-Medina VF, Alvarez KN, Weissfeld LA, Angus DC, Chirinos JA, Chang CC, Newman A, Loehr L, Folsom AR, Elkind MS, Lyles MF, Kronmal RA, Yende S. Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. *JAMA* 2015;**313**:264–274.
875. Violi F, Cangemi R, Falcone M, Taliani G, Pieralli F, Vannucchi V, Nozzoli C, Venditti M, Chirinos JA, Corrales-Medina VF, SIXTUS Study Group. Cardiovascular complications and short-term mortality risk in community-acquired pneumonia. *Clin Infect Dis* 2017;**64**:1486–1493.
876. Rey JR, Caro-Codon J, Rosillo SO, Iniesta AM, Castrejon-Castrejon S, Marco-Clement I, Martin-Polo L, Merino-Argos C, Rodriguez-Sotelo L, Garcia-Veas JM, Martinez-Marin LA, Martinez-Cossiani M, Buno A, Gonzalez-Valle L, Herrero A, Lopez-Sendon JL, Merino JL, CARD-COVID Investigators. Heart failure in COVID-19 patients: prevalence, incidence and prognostic implications. *Eur J Heart Fail* 2020;**22**:2205–2215.
877. Cannata A, Bromage DI, Rind IA, Gregorio C, Bannister C, Albarjas M, Piper S, Shah AM, McDonagh TA. Temporal trends in decompensated heart failure and outcomes during COVID-19: a multisite report from heart failure referral centres in London. *Eur J Heart Fail* 2020;**22**:2219–2224.
878. Konig S, Hohenstein S, Meier-Hellmann A, Kuhlen R, Hindricks G, Bollmann A, Helios Hospitals G. In-hospital care in acute heart failure during the COVID-19 pandemic: insights from the German-wide Helios hospital network. *Eur J Heart Fail* 2020;**22**:2190–2201.
879. Zhang Y, Coats AJS, Zheng Z, Adamo M, Ambrosio G, Anker SD, Butler J, Xu D, Mao J, Khan MS, Bai L, Mebazaa A, Ponikowski P, Tang Q, Ruschitzka F, Seferovic P, Tschope C, Zhang S, Gao C, Zhou S, Senni M, Zhang J, Metra M. Management of heart failure patients with COVID-19: a joint position paper of the Chinese Heart Failure Association & National Heart Failure Committee and the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:941–956.
880. Modin D, Jorgensen ME, Gislason G, Jensen JS, Kober L, Claggett B, Hegde SM, Solomon SD, Torp-Pedersen C, Biering-Sorensen T. Influenza vaccine in heart failure. *Circulation* 2019;**139**:575–586.
881. Vardeny O, Claggett B, Udell JA, Packer M, Zile M, Rouleau J, Swedberg K, Desai AS, Lefkowitz M, Shi V, McMurray JJV, Solomon SD, PARADIGM-HF Investigators. Influenza vaccination in patients with chronic heart failure: the PARADIGM-HF trial. *JACC Heart Fail* 2016;**4**:152–158.
882. Gotsman I, Shuvy M, Tahiroglu I, Zwas DR, Keren A. Influenza vaccination and outcome in heart failure. *Am J Cardiol* 2020;**128**:134–139.
883. Bhatt AS, Jering KS, Vaduganathan M, Claggett BL, Cunningham JW, Rosenthal N, Signorovitch J, Thune JJ, Vardeny O, Solomon SD. Clinical outcomes in patients with heart failure hospitalized with COVID-19. *JACC Heart Fail* 2021;**9**:65–73.
884. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomström-Lundqvist C, Cífková R, De Bonis M, Iung B, Johnson MR, Kintscher U, Kranke P, Lang IM, Morais J, Pieper PG, Presbitero P, Price S, Rosano GMC, Seeland U, Simoncini T, Swan L, Warnes CA, ESC Scientific Document Group. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J* 2018;**39**:3165–3241.
885. Sliwa K, van der Meer P, Petrie MC, Frogoudaki A, Johnson MR, Hilfiker-Kleiner D, Hamdan R, Jackson AM, Ibrahim B, Mbakwem A, Tschope C, Regitz-Zagrosek V, Omerovic E, Roos-Hesselink J, Gatzoulis M, Tutarel O, Price S, Heymans S, Coats AJS, Muller C, Chioncel O, Thum T, de Boer RA, Jankowska E, Ponikowski P, Lyon AR, Rosano G, Seferovic PM, Bauersachs J. Risk stratification and management of women with cardiomyopathy/heart failure planning pregnancy or presenting during/after pregnancy: a position statement from the Heart Failure Association of the European Society of Cardiology Study Group on Peripartum Cardiomyopathy. *Eur J Heart Fail* 2021;**23**:527–540.
886. Sliwa K, Petrie MC, van der Meer P, Mebazaa A, Hilfiker-Kleiner D, Jackson AM, Maggioni AP, Laroche C, Regitz-Zagrosek V, Schaufelberger M, Tavazzi L, Roos-Hesselink JW, Seferovic P, van Spaendonck-Zwarts K, Mbakwem A, Bohm M, Mouquet F, Pieske B, Johnson MR, Hamdan R, Ponikowski P, Van Veldhuisen DJ, McMurray JJV, Bauersachs J. Clinical presentation, management, and 6-month outcomes in women with peripartum cardiomyopathy: an ESC EORP registry. *Eur Heart J* 2020;**41**:3787–3797.
887. Davis MB, Arany Z, McNamara DM, Goland S, Elkayam U. Peripartum cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;**75**:207–221.
888. Moulig V, Pfeffer TJ, Ricke-Hoch M, Schlothauer S, Koenig T, Schwab J, Berliner D, Pfister R, Michels G, Haghikia A, Falk CS, Duncker D, Veltmann C, Hilfiker-Kleiner D, Bauersachs J. Long-term follow-up in peripartum cardiomyopathy patients with contemporary treatment: low mortality, high cardiac recovery, but significant cardiovascular co-morbidities. *Eur J Heart Fail* 2019;**21**:1534–1542.
889. Stapel B, Kohlhaas M, Ricke-Hoch M, Haghikia A, Erschow S, Knuuti J, Silvola JM, Roivainen A, Saraste A, Nickel AG, Saar JA, Sieve I, Pietzsch S, Muller M, Bogeski I, Kappl R, Jauhiainen M, Thackeray JT, Scherr M, Bengel FM, Hagl C, Tudorache I, Bauersachs J, Maack C, Hilfiker-Kleiner D. Low STAT3 expression sensitizes to toxic effects of beta-adrenergic receptor stimulation in peripartum cardiomyopathy. *Eur Heart J* 2017;**38**:349–361.
890. Hilfiker-Kleiner D, Haghikia A, Berliner D, Vogel-Claussen J, Schwab J, Franke A, Schwarzkopf M, Ehlermann P, Pfister R, Michels G, Westenfeld R, Stangl V, Kindermann I, Kuhl U, Angermann CE, Schlitt A, Fischer D, Podewski E, Bohm M, Sliwa K, Bauersachs J. Bromocriptine for the treatment of peripartum cardiomyopathy: a multicentre randomized study. *Eur Heart J* 2017;**38**:2671–2679.

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891. Sliwa K, Blauwet L, Tibazarwa K, Libhaber E, Smedema JP, Becker A, McMurray J, Yamac H, Labidi S, Struman I, Hilfiker-Kleiner D. Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy: a proof-of-concept pilot study. *Circulation* 2010;**121**:1465–1473.
892. Arbustini E, Narula N, Dec GW, Reddy KS, Greenberg B, Kushwaha S, Marwick T, Pinney S, Bellazzi R, Favalli V, Kramer C, Roberts R, Zoghbi WA, Bonow R, Tavazzi L, Fuster V, Narula J. The MOGE(S) classification for a phenotype-genotype nomenclature of cardiomyopathy: endorsed by the World Heart Federation. *J Am Coll Cardiol* 2013;**62**:2046–2072.
893. Hazebroek MR, Kemna MJ, Schalla S, Sanders-van Wijk S, Gerretsen SC, Dennert R, Merken J, Kuznetsova T, Staessen JA, Brunner-La Rocca HP, van Paassen P, Cohen Tervaert JW, Heymans S. Prevalence and prognostic relevance of cardiac involvement in ANCA-associated vasculitis: eosinophilic granulomatosis with polyangiitis and granulomatosis with polyangiitis. *Int J Cardiol* 2015;**199**:170–179.
894. Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastasakis A, Bohm M, Duboc D, Gimeno J, de Groote P, Imazio M, Heymans S, Klingel K, Komajda M, Limongelli G, Linhart A, Mogensen J, Moon J, Pieper PG, Seferovic PM, Schueler S, Zamorano JL, Caforio AL, Charron P. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. *Eur Heart J* 2016;**37**:1850–1858.
895. Seferovic PM, Polovina M, Bauersachs J, Arad M, Gal TB, Lund LH, Felix SB, Arbustini E, Caforio ALP, Farmakis D, Filippatos GS, Gialafos E, Kanjuh V, Krljanac G, Limongelli G, Linhart A, Lyon AR, Maksimovic R, Milicic D, Milinkovic I, Noutsias M, Oto A, Oto O, Pavlovic SU, Piepoli MF, Ristic AD, Rosano GMC, Seggewiss H, Asanin M, Seferovic JP, Ruschitzka F, Celutkiene J, Jaarsma T, Mueller C, Moura B, Hill L, Volterrani M, Lopatin Y, Metra M, Backs J, Mullens W, Chioncel O, de Boer RA, Anker S, Rapezzi C, Coats AJS, Tschope C. Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:553–576.
896. members Authors/Task Force, Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014;**35**:2733–2779.
897. Bondue A, Arbustini E, Bianco A, Ciccarelli M, Dawson D, De Rosa M, Hamdani N, Hilfiker-Kleiner D, Meder B, Leite-Moreira AF, Thum T, Tocchetti CG, Varricchi G, Van der Velden J, Walsh R, Heymans S. Complex roads from genotype to phenotype in dilated cardiomyopathy: scientific update from the Working Group of Myocardial Function of the European Society of Cardiology. *Cardiovasc Res* 2018;**114**:1287–1303.
898. Hershberger RE, Givertz MM, Ho CY, Judge DP, Kantor PF, McBride KL, Morales A, Taylor MRG, Vatta M, Ware SM. Genetic evaluation of cardiomyopathy–a Heart Failure Society of America practice guideline. *J Card Fail* 2018;**24**:281–302.
899. Merlo M, Cannata A, Gobbo M, Stolfo D, Elliott PM, Sinagra G. Evolving concepts in dilated cardiomyopathy. *Eur J Heart Fail* 2018;**20**:228–239.
900. Linschoten M, Teske AJ, Baas AF, Vink A, Dooijes D, Baars HF, Asselbergs FW. Truncating titin (TTN) variants in chemotherapy-induced cardiomyopathy. *J Card Fail* 2017;**23**:476–479.
901. Wasielewski M, van Spaendonck-Zwarts KY, Westerink ND, Jongbloed JD, Postma A, Gietema JA, van Tintelen JP, van den Berg MP. Potential genetic predisposition for anthracycline-associated cardiomyopathy in families with dilated cardiomyopathy. *Open Heart* 2014;**1**:e000116.
902. Ware JS, Amor-Salamanca A, Tayal U, Govind R, Serrano I, Salazar-Mendiguchia J, Garcia-Pinilla JM, Pascual-Figal DA, Nunez J, Guzzo-Merello G, Gonzalez-Vioque E, Bardaji A, Manito N, Lopez-Garrido MA, Padron-Barthe L, Edwards E, Whiffin N, Walsh R, Buchan RJ, Midwinter W, Wilk A, Prasad S, Pantazis A, Baski J, O'Regan DP, Alonso-Pulpon L, Cook SA, Lara-Pezzi E, Barton PJ, Garcia-Pavia P. Genetic etiology for alcohol-induced cardiac toxicity. *J Am Coll Cardiol* 2018;**71**:2293–2302.
903. Ware JS, Li J, Mazaika E, Yasso CM, DeSouza T, Cappola TP, Tsai EJ, Hilfiker-Kleiner D, Kamiya CA, Mazzarotto F, Cook SA, Halder I, Prasad SK, Pisarcik J, Hanley-Yanez K, Alharethi R, Damp J, Hsich E, Elkayam U, Sheppard R, Kealey A, Alexis J, Ramani G, Safirstein J, Boehmer J, Pauly DF, Wittstein IS, Thohan V, Zucker MJ, Liu P, Gorcsan J, 3rd, McNamara DM, Seidman CE, Seidman JG, Arany Z, IPAC Investigators, Imac. Shared genetic predisposition in peripartum and dilated cardiomyopathies. *N Engl J Med* 2016;**374**:233–241.
904. van Spaendonck-Zwarts KY, Posafalvi A, van den Berg MP, Hilfiker-Kleiner D, Bollen IA, Sliwa K, Alders M, Almomani R, van Langen IM, van der Meer P, Sinke RJ, van der Velden J, Van Veldhuisen DJ, van Tintelen JP, Jongbloed JD. Titin gene mutations are common in families with both peripartum cardiomyopathy and dilated cardiomyopathy. *Eur Heart J* 2014;**35**:2165–2173.
905. Choi SH, Weng LC, Roselli C, Lin H, Haggerty CM, Shoemaker MB, Barnard J, Arking DE, Chasman DI, Albert CM, Chaffin M, Tucker NR, Smith JD, Gupta N, Gabriel S, Margolin L, Shea MA, Shaffer CM, Yoneda ZT, Boerwinkle E, Smith NL, Silverman EK, Redline S, Vasan RS, Burchard EG, Gogarten SM, Laurie C, Blackwell TW, Abecasis G, Carey DJ, Fornwalt BK, Smelser DT, Baras A, Dewey FE, Jaquish CE, Papanicolaou GJ, Sotoodehnia N, Van Wagoner DR, Psaty BM, Kathiresan S, Darbar D, Alonso A, Heckbert SR, Chung MK, Roden DM, Benjamin EJ, Murray MF, Lunetta KL, Lubitz SA, Ellinor PT, DiscovEHR study and the NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium. Association between titin loss-of-function variants and early-onset atrial fibrillation. *JAMA* 2018;**320**:2354–2364.
906. Hazebroek MR, Krapels I, Verdonschot J, van den Wijngaard A, Vanhoutte E, Hoos M, Snijders L, van Montfort L, Witjens M, Dennert R, Crijns H, Brunner-La Rocca HP, Brunner HG, Heymans S. Prevalence of pathogenic gene mutations and prognosis do not differ in isolated left ventricular dysfunction compared with dilated cardiomyopathy. *Circ Heart Fail* 2018;**11**:e004682.
907. Leone O, Veinot JP, Angelini A, Baandrup UT, Basso C, Berry G, Bruneval P, Burke M, Butany J, Calabrese F, d'Amati G, Edwards WD, Fallon JT, Fishbein MC, Gallagher PJ, Halushka MK, McManus B, Pucci A, Rodriguez ER, Saffitz JE, Sheppard MN, Steenbergen C, Stone JR, Tan C, Thiene G, van der Wal AC, Winters GL. 2011 consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology. *Cardiovasc Pathol* 2012;**21**:245–274.
908. Halliday BP, Owen R, Gregson J, Vassiliou VS, Chen X, Wage R, Lota AS, Khalique Z, Tayal U, Hammersley DJ, Jones RE, Baksi AJ, Cowie MR, Cleland JGF, Pennell DJ, Prasad SK. Myocardial remodelling after withdrawing therapy for heart failure in patients with recovered dilated cardiomyopathy: insights from TRED-HF. *Eur J Heart Fail* 2021;**23**:293–301.
909. Olivotto I, Oreziak A, Barriales-Villa R, Abraham TP, Masri A, Garcia-Pavia P, Saberi S, Lakdawala NK, Wheeler MT, Owens A, Kubanek M, Wojakowski W, Jensen MK, Gimeno-Blanes J, Afshar K, Myers J, Hegde SM, Solomon SD, Sehnert AJ, Zhang D, Li W, Bhattacharya M, Edelberg JM, Waldman CB, Lester SJ, Wang A, Ho CY, Jacoby D, EXPLORER-HCM Study Investigators. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2020;**396**:759–769.
910. Cadrin-Tourigny J, Bosman LP, Nozza A, Wang W, Tadros R, Bhonsale A, Bourfiss M, Fortier A, Lie OH, Saguner AM, Svensson A, Andorin A, Tichnell C, Murray B, Zeppenfeld K, van den Berg MP, Asselbergs FW, Wilde AAM, Krahn AD, Talajic M, Rivard L, Chelko S, Zimmerman SL, Kamel IR, Crosson JE, Judge DP, Yap SC, van der Heijden JF, Tandri H, Jongbloed JDH, Guertin MC, van Tintelen JP, Platonov PG, Duru F, Haugaa KH, Khairy P, Hauer RNW, Calkins H, Te Riele A, James CA. A new prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J* 2019;**40**:1850–1858.
911. Leren IS, Saberniak J, Haland TF, Edvardsen T, Haugaa KH. Combination of ECG and echocardiography for identification of arrhythmic events in early ARVC. *JACC Cardiovasc Imaging* 2017;**10**:503–513.
912. Towbin JA, McKenna WJ, Abrams DJ, Ackerman MJ, Calkins H, Darrieux FCC, Daubert JP, de Chillou C, DePasquale EC, Desai MY, Estes NAM, 3rd, Hua W, Indik JH, Ingles J, James CA, John RM, Judge DP, Keegan R, Krahn AD, Link MS, Marcus FI, McLeod CJ, Mestroni L, Priori SG, Saffitz JE, Sanatani S, Shimizu W, van Tintelen JP, Wilde AAM, Zareba W. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. *Heart Rhythm* 2019;**16**:e301–e372.
913. Kristensen SL, Levy WC, Shadman R, Nielsen JC, Haarbo J, Videbaek L, Bruun NE, Eiskjaer H, Wiggers H, Brandes A, Thogersen AM, Hassager C, Svendsen JH, Hofsten DE, Torp-Pedersen C, Pehrson S, Signorovitch J, Kober L, Thune JJ. Risk models for prediction of implantable cardioverter-defibrillator benefit: insights from the DANISH trial. *JACC Heart Fail* 2019;**7**:717–724.
914. Corrado D, Wichter T, Link MS, Hauer R, Marchlinski F, Anastasakis A, Bauce B, Basso C, Brunckhorst C, Tsatsopoulou A, Tandri H, Paul M, Schmied C, Pelliccia A, Duru F, Protonotarios N, Estes NA, 3rd, McKenna WJ, Thiene G, Marcus FI, Calkins H. Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force consensus statement. *Eur Heart J* 2015;**36**:3227–3237.
915. Elliott PM, Anastasakis A, Asimaki A, Basso C, Bauce B, Brooke MA, Calkins H, Corrado D, Duru F, Green KJ, Judge DP, Kelsell D, Lambiase PD, McKenna WJ, Pilichou K, Protonotarios A, Saffitz JE, Syrris P, Tandri H, Te Riele A, Thiene G, Tsatsopoulou A, Tintelen JP. Definition and treatment of arrhythmogenic cardiomyopathy: an updated expert panel report. *Eur J Heart Fail* 2019;**21**:955–964.
916. Mazzarotto F, Tayal U, Buchan RJ, Midwinter W, Wilk A, Whiffin N, Govind R, Mazaika E, de Marvao A, Dawes TJW, Felkin LE, Ahmad M, Theotokis PI, Edwards E, Ing AY, Thomson KL, Chan LLH, Sim D, Baksi AJ, Pantazis A, Roberts AM, Watkins H, Funke B, O'Regan DP, Olivotto I, Barton PJR, Prasad

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SK, Cook SA, Ware JS, Walsh R. Reevaluating the genetic contribution of monogenic dilated cardiomyopathy. *Circulation* 2020;**141**:387–398.
917. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Helio T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A, Schultheiss HP, Seggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P, Elliott PM, European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2013;**34**:2636-2648, 2648a-2648d.
918. Heymans S, Eriksson U, Lehtonen J, Cooper LT, Jr. The quest for new approaches in myocarditis and inflammatory cardiomyopathy. *J Am Coll Cardiol* 2016;**68**:2348–2364.
919. Tschope C, Ammirati E, Bozkurt B, Caforio ALP, Cooper LT, Felix SB, Hare JM, Heidecker B, Heymans S, Hubner N, Kelle S, Klingel K, Maatz H, Parwani AS, Spillmann F, Starling RC, Tsutsui H, Seferovic P, Van Linthout S. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol* 2021;**18**:169–193.
920. Wahbi K, Ben Yaou R, Gandjbakhch E, Anselme F, Gossios T, Lakdawala NK, Stalens C, Sacher F, Babuty D, Trochu JN, Moubarak G, Savvatis K, Porcher R, Laforet P, Fayssoil A, Marijon E, Stojkovic T, Behin A, Leonard-Louis S, Sole G, Labombarda F, Richard P, Metay C, Quijano-Roy S, Dabaj I, Klug D, Vantyghem MC, Chevalier P, Ambrosi P, Salort E, Sadoul N, Waintraub X, Chikhaoui K, Mabo P, Combes N, Maury P, Sellal JM, Tedrow UB, Kalman JM, Vohra J, Androulakis AFA, Zeppenfeld K, Thompson T, Barnerias C, Becane HM, Bieth E, Boccara F, Bonnet D, Bouhour F, Boule S, Brehin AC, Chapon F, Cintas P, Cuisset JM, Davy JM, De Sandre-Giovannoli A, Demurger F, Desguerre I, Dieterich K, Durigneux J, Echaniz-Laguna A, Eschalier R, Ferreiro A, Ferrer X, Francannet C, Fradin M, Gaborit B, Gay A, Hagege A, Isapof A, Jeru I, Juntas Morales R, Lagrue E, Lamblin N, Lascols O, Laugel V, Lazarus A, Leturcq F, Levy N, Magot A, Manel V, Martins R, Mayer M, Mercier S, Meune C, Michaud M, Minot-Myhie MC, Muchir A, Nadaj-Pakleza A, Pereon Y, Petiot P, Petit F, Praline J, Rollin A, Sabouraud P, Sarret C, Schaeffer S, Taithe F, Tard C, Tiffreau V, Toutain A, Vatier C, Walther-Louvier U, Eymard B, Charron P, Vigouroux C, Bonne G, Kumar S, Elliott P, Duboc D. Development and validation of a new risk prediction score for life-threatening ventricular tachyarrhythmias in laminopathies. *Circulation* 2019;**140**:293–302.
921. Echeverria LE, Marcus R, Novick G, Sosa-Estani S, Ralston K, Zaidel EJ, Forsyth C, ALP RI, Mendoza I, Falconi ML, Mitelman J, Morillo CA, Pereiro AC, Pinazo MJ, Salvatella R, Martinez F, Perel P, Liprandi AS, Pineiro DJ, Molina GR. WHF IASC roadmap on Chagas disease. *Glob Heart* 2020;**15**:26.
922. Martinez F, Perna E, Perrone SV, Liprandi AS. Chagas disease and heart failure: an expanding issue worldwide. *Eur Cardiol* 2019;**14**:82–88.
923. Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, Evanovich LL, Hung J, Joglar JA, Kantor P, Kimmelstiel C, Kittleson M, Link MS, Maron MS, Martinez MW, Miyake CY, Schaff HV, Semsarian C, Sorajja P. 2020 AHA/ACC Guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2020;**142**:e533–e557.
924. Walsh R, Mazzarotto F, Whiffin N, Buchan R, Midwinter W, Wilk A, Li N, Felkin L, Ingold N, Govind R, Ahmad M, Mazaika E, Allouba M, Zhang X, de Marvao A, Day SM, Ashley E, Colan SD, Michels M, Pereira AC, Jacoby D, Ho CY, Thomson KL, Watkins H, Barton PJR, Olivotto I, Cook SA, Ware JS. Quantitative approaches to variant classification increase the yield and precision of genetic testing in Mendelian diseases: the case of hypertrophic cardiomyopathy. *Genome Med* 2019;**11**:5.
925. Ingles J, Goldstein J, Thaxton C, Caleshu C, Corty EW, Crowley SB, Dougherty K, Harrison SM, McGlaughon J, Milko LV, Morales A, Seifert BA, Strande N, Thomson K, Peter van Tintelen J, Wallace K, Walsh R, Wells Q, Whiffin N, Witkowski L, Semsarian C, Ware JS, Hershberger RE, Funke B. Evaluating the clinical validity of hypertrophic cardiomyopathy genes. *Circ Genom Precis Med* 2019;**12**:e002460.
926. Thomson KL, Ormondroyd E, Harper AR, Dent T, McGuire K, Baksi J, Blair E, Brennan P, Buchan R, Bueser T, Campbell C, Carr-White G, Cook S, Daniels M, Deevi SVV, Goodship J, Hayesmoore JBG, Henderson A, Lamb T, Prasad S, Rayner-Matthews P, Robert L, Sneddon L, Stark H, Walsh R, Ware JS, Farrall M, Watkins HC, NIHR BioResource - Rare Diseases Consortium. Analysis of 51 proposed hypertrophic cardiomyopathy genes from genome sequencing data in sarcomere negative cases has negligible diagnostic yield. *Genet Med* 2019;**21**:1576–1584.
927. Tuohy CV, Kaul S, Song HK, Nazer B, Heitner SB. Hypertrophic cardiomyopathy: the future of treatment. *Eur J Heart Fail* 2020;**22**:228–240.
928. O'Mahony C, Akhtar MM, Anastasiou Z, Guttmann OP, Vriesendorp PA, Michels M, Magri D, Autore C, Fernandez A, Ochoa JP, Leong KMW, Varnava AM, Monserrat L, Anastasakis A, Garcia-Pavia P, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, Omar RZ, Elliott PM. Effectiveness of the 2014 European Society of Cardiology guideline on sudden cardiac death in hypertrophic cardiomyopathy: a systematic review and meta-analysis. *Heart* 2019;**105**:623–631.
929. O'Mahony C, Jichi F, Ommen SR, Christiaans I, Arbustini E, Garcia-Pavia P, Cecchi F, Olivotto I, Kitaoka H, Gotsman I, Carr-White G, Mogensen J, Antoniades L, Mohiddin SA, Maurer MS, Tang HC, Geske JB, Siontis KC, Mahmoud KD, Vermeer A, Wilde A, Favalli V, Guttmann OP, Gallego-Delgado M, Dominguez F, Tanini I, Kubo T, Keren A, Bueser T, Waters S, Issa IF, Malcolmson J, Burns T, Sekhri N, Hoeger CW, Omar RZ, Elliott PM. International external validation study of the 2014 European Society of Cardiology Guidelines on Sudden Cardiac Death Prevention in Hypertrophic Cardiomyopathy (EVIDENCE-HCM). *Circulation* 2018;**137**:1015–1023.
930. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PM, Hypertrophic Cardiomyopathy Outcomes Investigators. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J* 2014;**35**:2010–2020.
931. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, Fedorowski A, Furlan R, Kenny RA, Martin A, Probst V, Reed MJ, Rice CP, Sutton R, Ungar A, van Dijk JG, ESC Scientific Document Group. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J* 2018;**39**:1883–1948.
932. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, Calkins H, Corrado D, Cox MG, Daubert JP, Fontaine G, Gear K, Hauer R, Nava A, Picard MH, Protonotarios N, Saffitz JE, Sanborn DM, Steinberg JS, Tandri H, Thiene G, Towbin JA, Tsatsopoulou A, Wichter T, Zareba W. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation* 2010;**121**:1533–1541.
933. Corrado D, van Tintelen PJ, McKenna WJ, Hauer RNW, Anastastakis A, Asimaki A, Basso C, Bauce B, Brunckhorst C, Bucciarelli-Ducci C, Duru F, Elliott P, Hamilton RM, Haugaa KH, James CA, Judge D, Link MS, Marchlinski FE, Mazzanti A, Mestroni L, Pantazis A, Pelliccia A, Marra MP, Pilichou K, Platonov PGA, Protonotarios A, Rampazzo A, Saffitz JE, Saguner AM, Schmied C, Sharma S, Tandri H, Te Riele A, Thiene G, Tsatsopoulou A, Zareba W, Zorzi A, Wichter T, Marcus FI, Calkins H, International Experts. Arrhythmogenic right ventricular cardiomyopathy: evaluation of the current diagnostic criteria and differential diagnosis. *Eur Heart J* 2020;**41**:1414–1429.
934. Reichl K, Kreykes SE, Martin CM, Shenoy C. Desmoplakin variant-associated arrhythmogenic cardiomyopathy presenting as acute myocarditis. *Circ Genom Precis Med* 2018;**11**:e002373.
935. Lopez-Ayala JM, Pastor-Quirante F, Gonzalez-Carrillo J, Lopez-Cuenca D, Sanchez-Munoz JJ, Oliva-Sandoval MJ, Gimeno JR. Genetics of myocarditis in arrhythmogenic right ventricular dysplasia. *Heart Rhythm* 2015;**12**:766–773.
936. Pelliccia A, Solberg EE, Papadakis M, Adami PE, Biffi A, Caselli S, La Gerche A, Niebauer J, Pressler A, Schmied CM, Serratosa L, Halle M, Van Buuren F, Borjesson M, Carre F, Panhuyzen-Goedkoop NM, Heidbuchel H, Olivotto I, Corrado D, Sinagra G, Sharma S. Recommendations for participation in competitive and leisure time sport in athletes with cardiomyopathies, myocarditis, and pericarditis: position statement of the Sport Cardiology Section of the European Association of Preventive Cardiology (EAPC). *Eur Heart J* 2019;**40**:19–33.
937. Sedaghat-Hamedani F, Haas J, Zhu F, Geier C, Kayvanpour E, Liss M, Lai A, Frese K, Pribe-Wolferts R, Amr A, Li DT, Samani OS, Carstensen A, Bordalo DM, Muller M, Fischer C, Shao J, Wang J, Nie M, Yuan L, Hassfeld S, Schwartz C, Zhou M, Zhou Z, Shu Y, Wang M, Huang K, Zeng Q, Cheng L, Fehlmann T, Ehlermann P, Keller A, Dieterich C, Streckfuss-Bomeke K, Liao Y, Gotthardt M, Katus HA, Meder B. Clinical genetics and outcome of left ventricular noncompaction cardiomyopathy. *Eur Heart J* 2017;**38**:3449–3460.
938. Towbin JA, Lorts A, Jefferies JL. Left ventricular non-compaction cardiomyopathy. *Lancet* 2015;**386**:813–825.
939. Towbin JA, Jefferies JL. Cardiomyopathies due to left ventricular noncompaction, mitochondrial and storage diseases, and inborn errors of metabolism. *Circ Res* 2017;**121**:838–854.
940. Shen MJ, Arora R, Jalife J. Atrial myopathy. *JACC Basic Transl Sci* 2019;**4**:640–654.
941. Reddy YNV, Borlaug BA. Left atrial myopathy in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020;**22**:486–488.
942. Reddy YNV, Obokata M, Gersh BJ, Borlaug BA. High prevalence of occult heart failure with preserved ejection fraction among patients with atrial fibrillation and dyspnea. *Circulation* 2018;**137**:534–535.
943. Packer M, Lam CSP, Lund LH, Redfield MM. Interdependence of atrial fibrillation and heart failure with a preserved ejection fraction reflects a common underlying atrial and ventricular myopathy. *Circulation* 2020;**141**:4–6.
944. To AC, Flamm SD, Marwick TH, Klein AL. Clinical utility of multimodality LA imaging: assessment of size, function, and structure. *JACC Cardiovasc Imaging* 2011;**4**:788–798.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab368/6358045 by guest on 08 September 2021

945. Farmakis D, Mueller C, Apple FS. High-sensitivity cardiac troponin assays for cardiovascular risk stratification in the general population. *Eur Heart J* 2020;**41**:4050–4056.
946. Westermann D, Neumann JT, Sorensen NA, Blankenberg S. High-sensitivity assays for troponin in patients with cardiac disease. *Nat Rev Cardiol* 2017;**14**:472–483.
947. Santema BT, Kloosterman M, Van Gelder IC, Mordi I, Lang CC, Lam CSP, Anker SD, Cleland JG, Dickstein K, Filippatos G, Van der Harst P, Hillege HL, Ter Maaten JM, Metra M, Ng LL, Ponikowski P, Samani NJ, Van Veldhuisen DJ, Zwinderman AH, Zannad F, Damman K, Van der Meer P, Rienstra M, Voors AA. Comparing biomarker profiles of patients with heart failure: atrial fibrillation vs. sinus rhythm and reduced vs. preserved ejection fraction. *Eur Heart J* 2018;**39**:3867–3875.
948. Richards M, Di Somma S, Mueller C, Nowak R, Peacock WF, Ponikowski P, Mockel M, Hogan C, Wu AH, Clopton P, Filippatos GS, Anand I, Ng L, Daniels LB, Neath SX, Shah K, Christenson R, Hartmann O, Anker SD, Maisel A. Atrial fibrillation impairs the diagnostic performance of cardiac natriuretic peptides in dyspneic patients: results from the BACH Study (Biomarkers in ACute Heart *Failure). JACC Heart Fail* 2013;**1**:192–199.
949. Kamel H, Longstreth WT, Jr., Tirschwell DL, Kronmal RA, Broderick JP, Palesch YY, Meinzer C, Dillon C, Ewing I, Spilker JA, Di Tullio MR, Hod EA, Soliman EZ, Chaturvedi S, Moy CS, Janis S, Elkind MS. The AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke randomized trial: rationale and methods. *Int J Stroke* 2019;**14**:207–214.
950. Zelniker TA, Bonaca MP, Furtado RHM, Mosenzon O, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Budaj A, Kiss RG, Padilla F, Gause-Nilsson I, Langkilde AM, Raz I, Sabatine MS, Wiviott SD. Effect of dapagliflozin on atrial fibrillation in patients with type 2 diabetes mellitus: insights from the DECLARE-TIMI 58 trial. *Circulation* 2020;**141**:1227–1234.
951. Global Burden of Disease Study Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;**386**:743–800.
952. Cooper LT Jr, Keren A, Sliwa K, Matsumori A, Mensah GA. The global burden of myocarditis: part 1: a systematic literature review for the Global Burden of Diseases, Injuries, and Risk Factors 2010 study. *Glob Heart* 2014;**9**:121–129.
953. Merken J, Hazebroek M, Van Paassen P, Verdonschot J, Van Empel V, Knackstedt C, Abdul Hamid M, Seiler M, Kolb J, Hoermann P, Ensinger C, Brunner-La Rocca HP, Poelzl G, Heymans S. Immunosuppressive therapy improves both short- and long-term prognosis in patients with virus-negative nonfulminant inflammatory cardiomyopathy. *Circ Heart Fail* 2018;**11**:e004228.
954. Ammirati E, Frigerio M, Adler ED, Basso C, Birnie DH, Brambatti M, Friedrich MG, Klingel K, Lehtonen J, Moslehi JJ, Pedrotti P, Rimoldi OE, Schultheiss HP, Tschope C, Cooper LT, Jr., Camici PG. Management of acute myocarditis and chronic inflammatory cardiomyopathy: an expert consensus document. *Circ Heart Fail* 2020;**13**:e007405.
955. Grigoratos C, Di Bella G, Aquaro GD. Diagnostic and prognostic role of cardiac magnetic resonance in acute myocarditis. *Heart Fail Rev* 2019;**24**:81–90.
956. Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, Kindermann I, Gutberlet M, Cooper LT, Liu P, Friedrich MG. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. *J Am Coll Cardiol* 2018;**72**:3158–3176.
957. Birnie DH, Nery PB, Ha AC, Beanlands RS. Cardiac sarcoidosis. *J Am Coll Cardiol* 2016;**68**:411–421.
958. Bang V, Ganatra S, Shah SP, Dani SS, Neilan TG, Thavendiranathan P, Resnic FS, Piemonte TC, Barac A, Patel R, Sharma A, Parikh R, Chaudhry GM, Vesely M, Hayek SS, Leja M, Venesy D, Patten R, Lenihan D, Nohria A, Cooper LT. Management of patients with giant cell myocarditis: JACC review topic of the week. *J Am Coll Cardiol* 2021;**77**:1122–1134.
959. Sinagra G, Porcari A, Gentile P, Artico J, Fabris E, Bussani R, Merlo M. Viral presence-guided immunomodulation in lymphocytic myocarditis: an update. *Eur J Heart Fail* 2021;**23**:211–216.
960. Gannon MP, Schaub E, Grines CL, Saba SG. State of the art: evaluation and prognostication of myocarditis using cardiac MRI. *J Magn Reson Imaging* 2019;**49**:e122–e131.
961. Maisch B, Hufnagel G, Kolsch S, Funck R, Richter A, Rupp H, Herzum M, Pankuweit S. Treatment of inflammatory dilated cardiomyopathy and (peri)myocarditis with immunosuppression and i.v. immunoglobulins. *Herz* 2004;**29**:624–636.
962. Kociol RD, Cooper LT, Fang JC, Moslehi JJ, Pang PS, Sabe MA, Shah RV, Sims DB, Thiene G, Vardeny O, American Heart Association Heart Failure Transplantation Committee of the Council on Clinical Cardiology. Recognition and initial management of fulminant myocarditis: a scientific statement from the American Heart Association. *Circulation* 2020;**141**:e69–e92.
963. Felix SB, Staudt A, Dorffel WV, Stangl V, Merkel K, Pohl M, Docke WD, Morgera S, Neumayer HH, Wernecke KD, Wallukat G, Stangl K, Baumann G. Hemodynamic effects of immunoadsorption and subsequent immunoglobulin substitution in dilated cardiomyopathy: three-month results from a randomized study. *J Am Coll Cardiol* 2000;**35**:1590–1598.
964. Bajaj NS, Gupta K, Gharpure N, Pate M, Chopra L, Kalra R, Prabhu SD. Effect of immunomodulation on cardiac remodelling and outcomes in heart failure: a quantitative synthesis of the literature. *ESC Heart Fail* 2020;**7**:1319–1330.
965. Martinez-Naharro A, Hawkins PN, Fontana M. Cardiac amyloidosis. *Clin Med (Lond)* 2018;**18**:s30–s35.
966. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol* 2019;**73**:2872–2891.
967. Gonzalez-Lopez E, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, Robles C, Bornstein B, Salas C, Lara-Pezzi E, Alonso-Pulpon L, Garcia-Pavia P. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J* 2015;**36**:2585–2594.
968. Helder MR, Schaff HV, Nishimura RA, Gersh BJ, Dearani JA, Ommen SR, Mereuta OM, Theis JD, Dogan A, Edwards WD. Impact of incidental amyloidosis on the prognosis of patients with hypertrophic cardiomyopathy undergoing septal myectomy for left ventricular outflow tract obstruction. *Am J Cardiol* 2014;**114**:1396–1399.
969. Treibel TA, Fontana M, Gilbertson JA, Castelletti S, White SK, Scully PR, Roberts N, Hutt DF, Rowczenio DM, Whelan CJ, Ashworth MA, Gillmore JD, Hawkins PN, Moon JC. Occult transthyretin cardiac amyloid in severe calcific aortic stenosis: prevalence and prognosis in patients undergoing surgical aortic valve replacement. *Circ Cardiovasc Imaging* 2016;**9**.
970. Cavalcante JL, Rijal S, Abdelkarim I, Althouse AD, Sharbaugh MS, Fridman Y, Soman P, Forman DE, Schindler JT, Gleason TG, Lee JS, Schelbert EB. Cardiac amyloidosis is prevalent in older patients with aortic stenosis and carries worse prognosis. *J Cardiovasc Magn Reson* 2017;**19**:98.
971. Castano A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, Rubin J, Chiuzan C, Nazif T, Vahl T, George I, Kodali S, Leon MB, Hahn R, Bokhari S, Maurer MS. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J* 2017;**38**:2879–2887.
972. Nitsche C, Aschauer S, Kammerlander AA, Schneider M, Poschner T, Duca F, Binder C, Koschutnik M, Stiftinger J, Goliasch G, Siller-Matula J, Winter MP, Anvari-Pirsch A, Andreas M, Geppert A, Beitzke D, Loewe C, Hacker M, Agis H, Kain R, Lang I, Bonderman D, Hengstenberg C, Mascherbauer J. Light-chain and transthyretin cardiac amyloidosis in severe aortic stenosis: prevalence, screening possibilities, and outcome. *Eur J Heart Fail* 2020;**22**:1852–1862.
973. Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, Burazor I, Caforio ALP, Damy T, Eriksson U, Fontana M, Gillmore JD, Gonzalez-Lopez E, Grogan M, Heymans S, Imazio M, Kindermann I, Kristen AV, Maurer MS, Merlini G, Pantazis A, Pankuweit S, Rigopoulos AG, Linhart A. Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur J Heart Fail* 2021;**23**:512–526.
974. Boldrini M, Cappelli F, Chacko L, Restrepo-Cordoba MA, Lopez-Sainz A, Giannoni A, Aimo A, Baggiano A, Martinez-Naharro A, Whelan C, Quarta C, Passino C, Castiglione V, Chubuchnyi V, Spini V, Taddei C, Vergaro G, Petrie A, Ruiz-Guerrero L, Monivas V, Mingo-Santos S, Mirelis JG, Dominguez F, Gonzalez-Lopez E, Perlini S, Pontone G, Gillmore J, Hawkins PN, Garcia-Pavia P, Emdin M, Fontana M. Multiparametric echocardiography scores for the diagnosis of cardiac amyloidosis. *JACC Cardiovasc Imaging* 2020;**13**:909–920.
975. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, Wechalekar AD, Berk JL, Quarta CC, Grogan M, Lachmann HJ, Bokhari S, Castano A, Dorbala S, Johnson GB, Glaudemans AW, Rezk T, Fontana M, Palladini G, Milani P, Guidalotti PL, Flatman K, Lane T, Vonberg FW, Whelan CJ, Moon JC, Ruberg FL, Miller EJ, Hutt DF, Hazenberg BP, Rapezzi C, Hawkins PN. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation* 2016;**133**:2404–2412.
976. Zhao L, Tian Z, Fang Q. Diagnostic accuracy of cardiovascular magnetic resonance for patients with suspected cardiac amyloidosis: a systematic review and meta-analysis. *BMC Cardiovasc Disord* 2016;**16**:129.
977. Bhuiyan T, Helmke S, Patel AR, Ruberg FL, Packman J, Cheung K, Grogan D, Maurer MS. Pressure-volume relationships in patients with transthyretin (ATTR) cardiac amyloidosis secondary to V122I mutations and wild-type transthyretin: Transthyretin Cardiac Amyloid Study (TRACS). *Circ Heart Fail* 2011;**4**:121–128.
978. Cheung CC, Roston TM, Andrade JG, Bennett MT, Davis MK. Arrhythmias in cardiac amyloidosis: challenges in risk stratification and treatment. *Can J Cardiol* 2020;**36**:416–423.
979. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C, ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018;**379**:1007–1016.

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980. Damy T, Garcia-Pavia P, Hanna M, Judge DP, Merlini G, Gundapaneni B, Patterson TA, Riley S, Schwartz JH, Sultan MB, Witteles R. Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study. *Eur J Heart Fail* 2021;**23**:277–285.
981. Solomon SD, Adams D, Kristen A, Grogan M, Gonzalez-Duarte A, Maurer MS, Merlini G, Damy T, Slama MS, Brannagan TH, 3rd, Dispenzieri A, Berk JL, Shah AM, Garg P, Vaishnaw A, Karsten V, Chen J, Gollob J, Vest J, Suhr O. Effects of patisiran, an RNA interference therapeutic, on cardiac parameters in patients with hereditary transthyretin-mediated amyloidosis. *Circulation* 2019;**139**:431–443.
982. Suhr OB, Coelho T, Buades J, Pouget J, Conceicao I, Berk J, Schmidt H, Waddington-Cruz M, Campistol JM, Bettencourt BR, Vaishnaw A, Gollob J, Adams D. Efficacy and safety of patisiran for familial amyloidotic polyneuropathy: a phase II multi-dose study. *Orphanet J Rare Dis* 2015;**10**:109.
983. Rosenblum H, Castano A, Alvarez J, Goldsmith J, Helmke S, Maurer MS. TTR (transthyretin) stabilizers are associated with improved survival in patients with TTR cardiac amyloidosis. *Circ Heart Fail* 2018;**11**:e004769.
984. Kremastinos DT, Farmakis D. Iron overload cardiomyopathy in clinical practice. *Circulation* 2011;**124**:2253–2263.
985. Farmakis D, Triposkiadis F, Lekakis J, Parissis J. Heart failure in haemoglobinopathies: pathophysiology, clinical phenotypes, and management. *Eur J Heart Fail* 2017;**19**:479–489.
986. Aessopos A, Farmakis D, Deftereos S, Tsironi M, Tassiopoulos S, Moyssakis I, Karagiorga M. Thalassemia heart disease: a comparative evaluation of thalassemia major and thalassemia intermedia. *Chest* 2005;**127**:1523–1530.
987. Farmakis D, Aessopos A. Pulmonary hypertension associated with hemoglobinopathies: prevalent but overlooked. *Circulation* 2011;**123**:1227–1232.
988. Baumgartner H, De Backer J, Babu-Narayan SV, Budts W, Chessa M, Diller GP, Lung B, Kluin J, Lang IM, Meijboom F, Moons P, Mulder BJM, Oechslin E, Roos-Hesselink JW, Schwerzmann M, Sondergaard L, Zeppenfeld K, ESC Scientific Document Group. 2020 ESC Guidelines for the management of adult congenital heart disease. *Eur Heart J* 2021;**42**:563–645.
989. Diller GP, Kempny A, Alonso-Gonzalez R, Swan L, Uebing A, Li W, Babu-Narayan S, Wort SJ, Dimopoulos K, Gatzoulis MA. Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a large tertiary centre. *Circulation* 2015;**132**:2118–2125.
990. Budts W, Roos-Hesselink J, Radle-Hurst T, Eicken A, McDonagh TA, Lambrinou E, Crespo-Leiro MG, Walker F, Frogoudaki AA. Treatment of heart failure in adult congenital heart disease: a position paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology. *Eur Heart J* 2016;**37**:1419–1427.
991. Lluri G, Lin J, Reardon L, Miner P, Whalen K, Aboulhosn J. Early experience with sacubitril/valsartan in adult patients with congenital heart disease. *World J Pediatr Congenit Heart Surg* 2019;**10**:292–295.
992. Appadurai V, Thoreau J, Malpas T, Nicolae M. Sacubitril/valsartan in adult congenital heart disease patients with chronic heart failure – a single centre case series and call for an international registry. *Heart Lung Circ* 2020;**29**:137–141.
993. Maurer SJ, Pujol Salvador C, Schiele S, Hager A, Ewert P, Tutarel O. Sacubitril/valsartan for heart failure in adults with complex congenital heart disease. *Int J Cardiol* 2020;**300**:137–140.
994. Van De Bruaene A, Meier L, Droogne W, De Meester P, Troost E, Gewillig M, Budts W. Management of acute heart failure in adult patients with congenital heart disease. *Heart Fail Rev* 2018;**23**:1–14.
995. Minchin M, Roland M, Richardson J, Rowark S, Guthrie B. Quality of care in the United Kingdom after removal of financial incentives. *N Engl J Med* 2018;**379**:948–957.
996. Song Z, Ji Y, Safran DG, Chernew ME. Health care spending, utilization, and quality 8 years into global payment. *N Engl J Med* 2019;**381**:252–263.
997. Aktaa S, Batra G, Wallentin L, Baigent C, Erlinge D, James S, Ludman P, Maggioni AP, Price S, Weston C, Casadei B, Gale CP. European Society of Cardiology methodology for the development of quality indicators for the quantification of cardiovascular care and outcomes. *Eur Heart J Qual Care Clin Outcomes* 2020. doi: 10.1093/ehjqcco/qcaa069.
998. Arbelo E, Aktaa S, Bollmann A, D'Avila A, Drossart I, Dwight J, Hills MT, Hindricks G, Kusumoto FM, Lane DA, Lau DH, Lettino M, Lip GYH, Lobban T, Pak HN, Potpara T, Saenz LC, Van Gelder IC, Varosy P, Gale CP, Dagres N, Reviewers, Boveda S, Deneke T, Defaye P, Conte G, Lenarczyk R, Providencia R, Guerra JM, Takahashi Y, Pisani C, Nava S, Sarkozy A, Glotzer TV, Martins Oliveira M. Quality indicators for the care and outcomes of adults with atrial fibrillation. *Europace* 2021;**23**:494–495.
999. Schiele F, Aktaa S, Rossello X, Ahrens I, Claeys MJ, Collet JP, Fox KAA, Gale CP, Huber K, Iakobishvili Z, Keys A, Lambrinou E, Leonardi S, Lettino M, Masoudi FA, Price S, Quinn T, Swahn E, Thiele H, Timmis A, Tubaro M, Vrints CJM, Walker D, Bueno H, Scientific Document Group ESC, Halvorsen S, Jernberg T, Jortveit J, Blondal M, Ibanez B, Hassager C. 2020 Update of the quality indicators for acute myocardial infarction: a position paper of the Association for Acute Cardiovascular Care: the study group for quality indicators from the ACVC and the NSTE-ACS guideline group. *Eur Heart J Acute Cardiovasc Care* 2021;**10**:224–233.
1000. Collet JP, Thiele H, Barbato E, Barthelemy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Juni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM, ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;**42**:1289–1367.
1001. Wallentin L, Gale CP, Maggioni A, Bardinet I, Casadei B. EuroHeart: European Unified Registries On Heart Care Evaluation and Randomized Trials. *Eur Heart J* 2019;**40**:2745–2749.

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