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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

HF definition related to the ejection fraction

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

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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.

^aSigns may not be present in the early stages of HF (especially in HFpEF) and in optimally treated patients.

^bFor 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.

^cFor the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF.

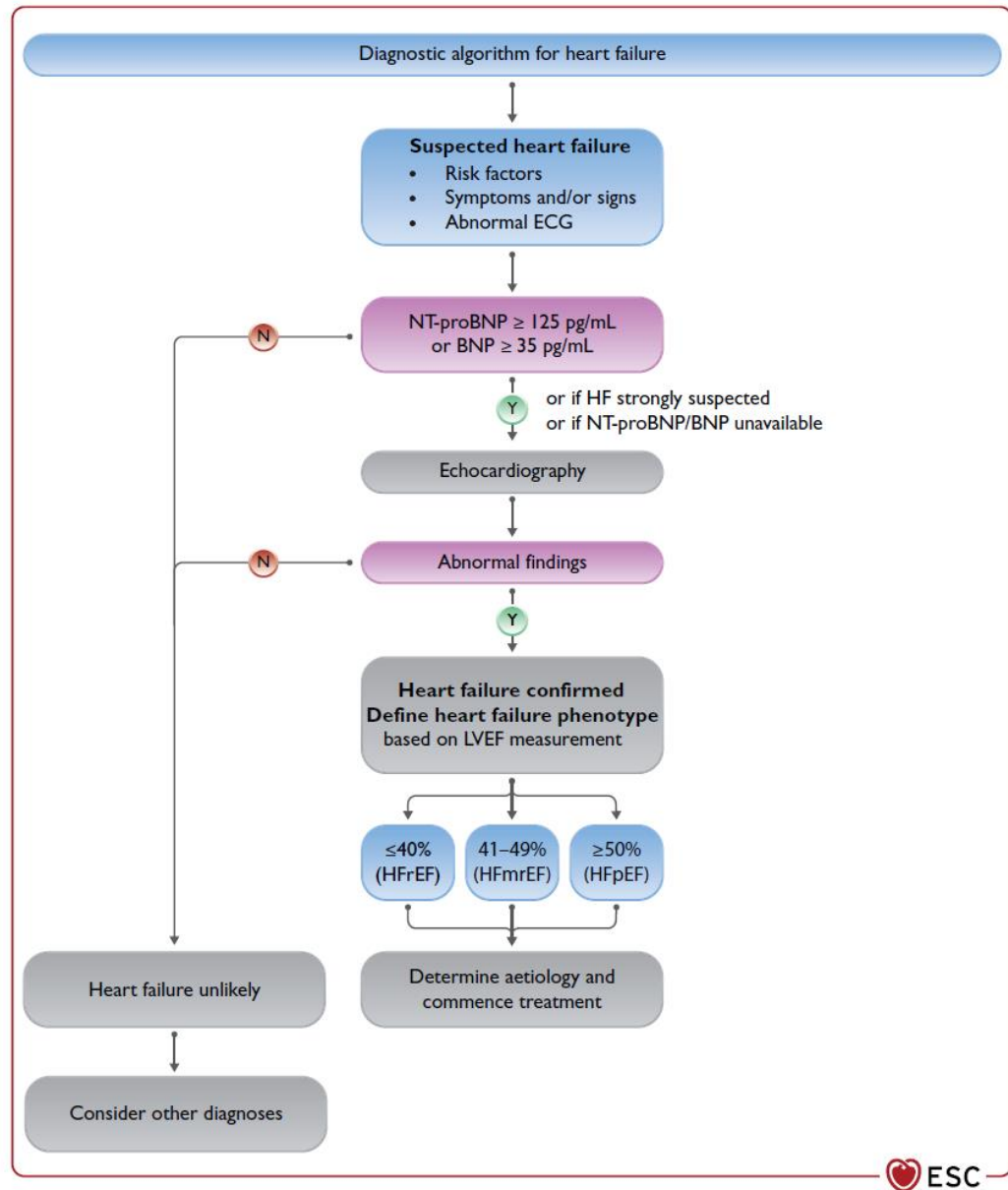


Figure 1 The diagnostic algorithm for heart failure. BNP = B-type natriuretic peptide; ECG = electrocardiogram; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular 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).

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

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

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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.

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.

^aClass of recommendation.

^bLevel of evidence.

^cReferences are listed in section 4.2 for this item.

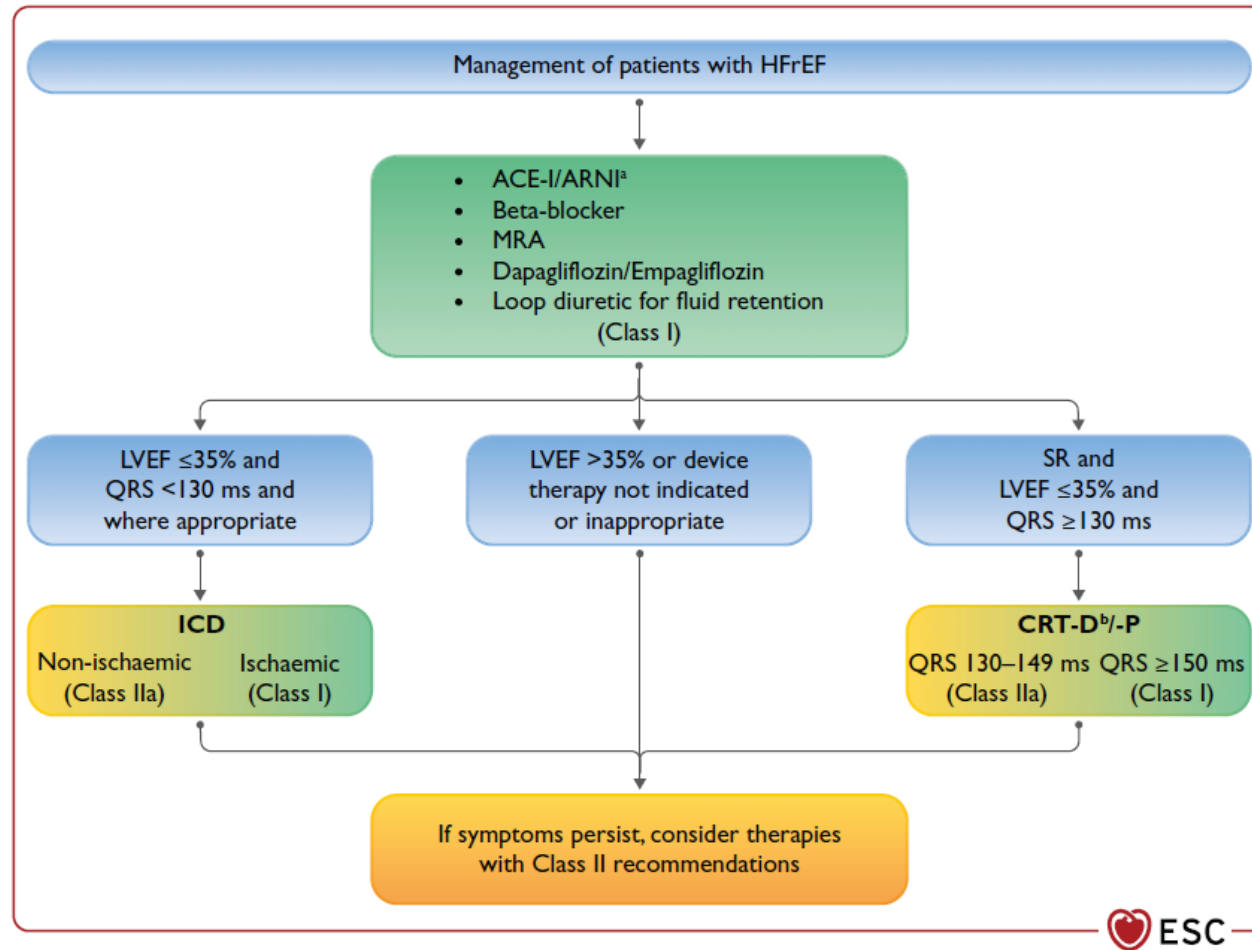


Figure 2 Therapeutic algorithm of Class I Therapy Indications for a patient with heart failure with reduced ejection fraction. ACE-I = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; ICD = implantable cardioverter-defibrillator; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; QRS = Q, R, and S waves of an ECG; SR = sinus rhythm. ^aAs a replacement for ACE-I. ^bWhere 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 \leq 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.

^aClass of recommendation.

^bLevel of evidence.

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

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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.

^aIndicates an ACE-I where the dosing target is derived from post-myocardial infarction trials.

^bIndicates 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.

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

^dIndicates 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).

^eA maximum dose of 50 mg twice daily can be administered to patients weighing over 85 kg.

^fSpiroglactone has an optional starting dose of 12.5 mg in patients where renal status or hyperkalaemia warrant caution.

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 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

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.

^aClass of recommendation.

^bLevel of evidence.

^cThe ARBs with evidence in HFrEF are candesartan, losartan, and valsartan.

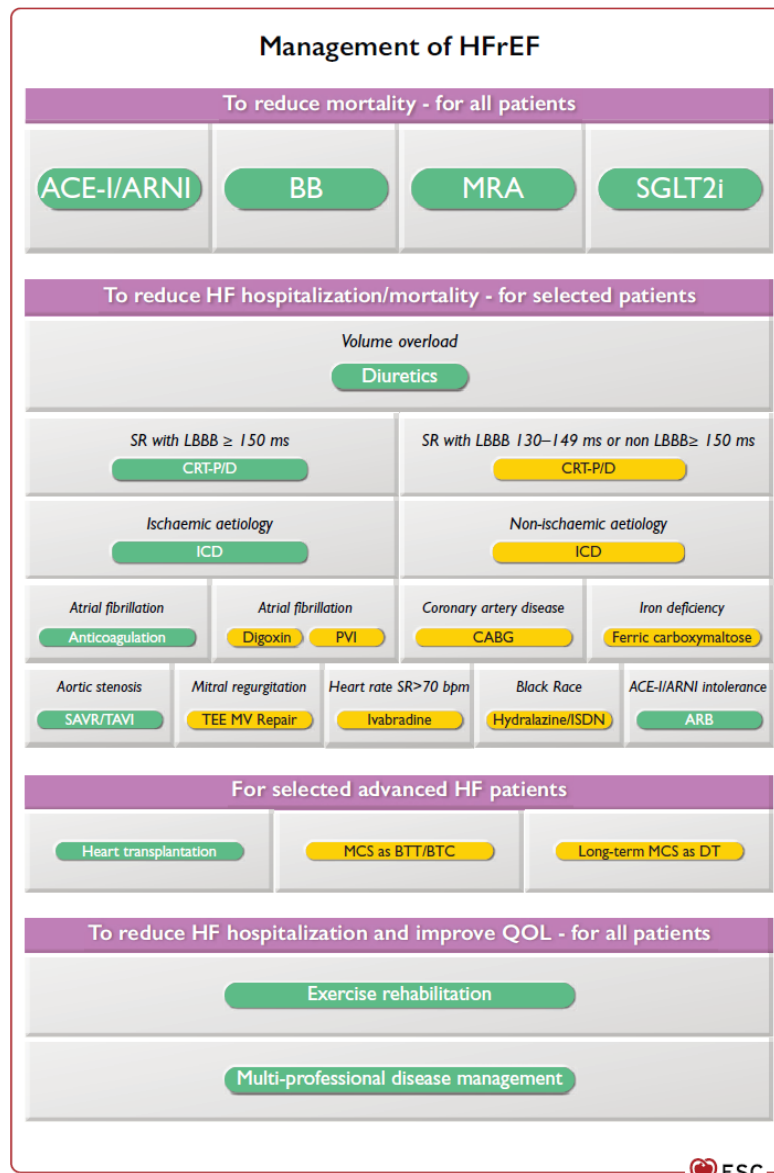


Figure 3 Central illustration. Strategic phenotypic overview of the management of heart failure with reduced ejection fraction. ACE-I= angiotensin-converting enzyme inhibitor; ARB= angiotensin receptor blocker; ARNI= angiotensin receptor-neprilysin inhibitor; BB= beta-blocker; b.p.m.= beats per minute; 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 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.

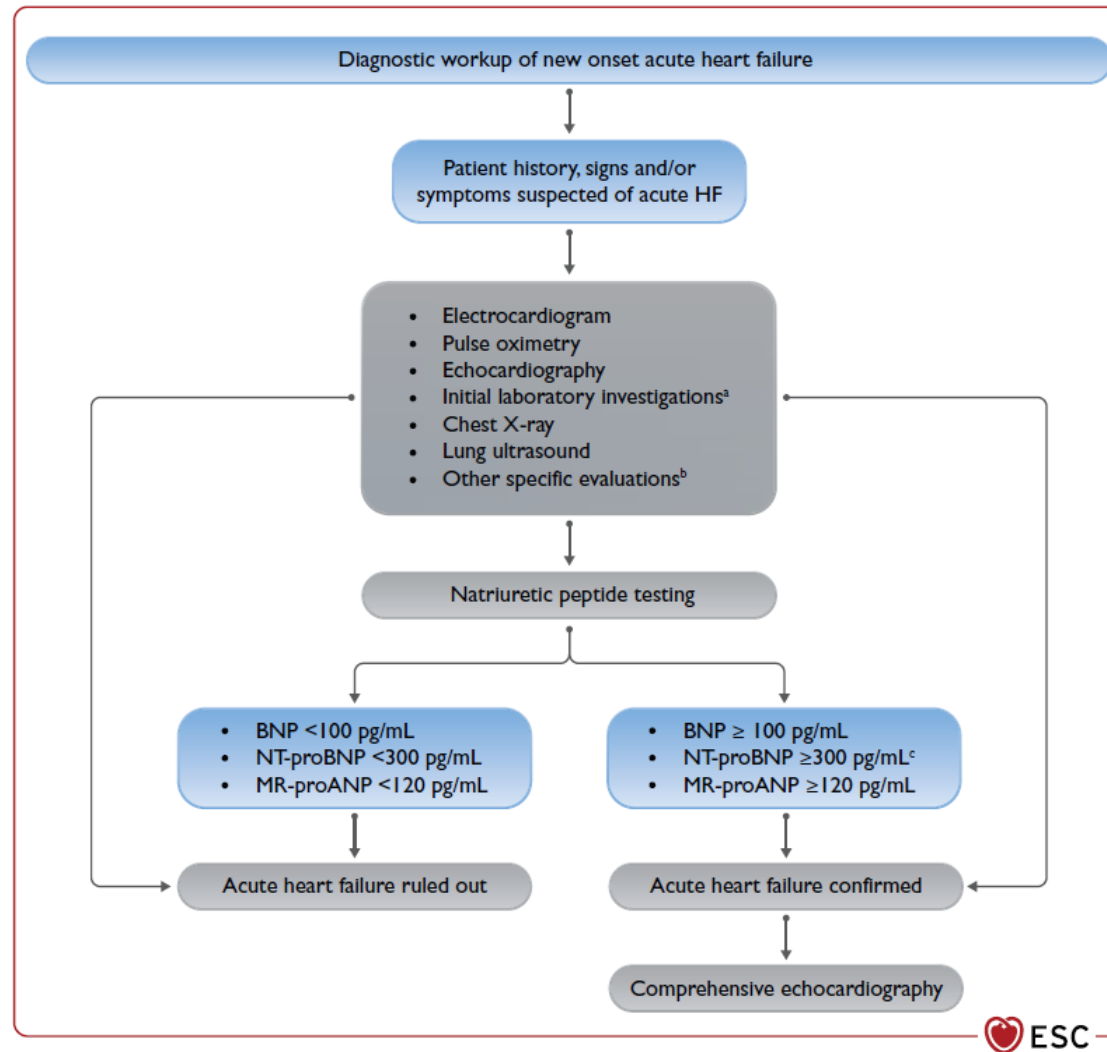


Figure 6 Diagnostic workup of new onset acute heart failure. ACS = acute coronary syndrome; BNP = B-type natriuretic peptide; CT = computed tomography; HF = heart failure; MR-proANP = mid-regional pro-atrial natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TSH = thyroid-stimulating hormone. ^aInitial 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. ^bSpecific evaluation includes coronary angiography, in case of suspected ACS, and CT in case of suspected pulmonary embolism. ^cRule-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}

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	Recommended
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.

^aBased on clinical conditions.

^bContinuous ECG monitoring can be considered based on clinical conditions.

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

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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.

^aClass of recommendation.

^bLevel of evidence.

^cNYHA class II–IV.

^dAll of the following criteria must be fulfilled: LVEF 20–50%, LVESD <70 mm,

REMEMBER:

Heart team and the role of geriatric medicine in heart team.