

HEART FAILURE

Relevant Guidelines

ESC 2026 guidelines on heart failure

2026 ESC Guidelines for the management of heart failure

ACCF/AHA 2022 guideline on heart failure

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *Circulation* 2022

AHA/ACC 2023 guideline on Chronic Coronary Disease

2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation*. 2023

ACC/AHA/ACCP/HRS 2023 guideline on AF

2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2023

ESC 2026 GL on chronic kidney disease

2026 ESC Guidelines for the management of cardiovascular disease and chronic kidney disease, in collaboration with the European Renal Association (ERA). *Eur Heart J*. 2026.

ESC 2023 Guidelines in diabetes

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J*. 2023.

AHA/ACC 2025 guideline on hypertension.

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AHA/ACC 2026 Guideline on Cardiovascular-Kidney-Metabolic Syndrome

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ESC 2022 Guidelines on ventricular arrhythmias and prevention of sudden cardiac death

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ESC 2022 Guidelines on noncardiac surgery

2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. *Eur Heart J*. 2022

AHA/ACC 2024 Guideline on noncardiac surgery

2024 AHA/ACC/ACS/ASNC/HRS/SCA/SCCT/SCMR/SVM Guideline for Perioperative Cardiovascular Management for Noncardiac Surgery. *JACC* 2024

ESC 2020 Guidelines on sports

Pelliccia A, Sharma S, Gati S, et al. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J*. 2020.

ESC 2022 Guidelines on cardio-oncology

2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022.

ESC 2025 guidelines on pregnancy.

ESC Guidelines on the management of cardiovascular diseases and pregnancy. *Eur Heart J*. 2025.

Relevant Scientific Statements and Important Position Papers

AHA 2019 Scientific Statement on Device Therapy and Arrhythmia Management in patients with LVAD

Device Therapy and Arrhythmia Management in Left Ventricular Assist Device Recipients: A Scientific Statement From the American Heart Association. *Circulation*. 2019;139:e967-e989.

AHA 2016 Statement on Right-Sided heart failure.

Evaluation and Management of Right-Sided Heart Failure: A Scientific Statement From the American Heart Association. *Circulation*. 2018

AHA 2021 Statement on Cardiogenic Shock

Invasive Management of Acute Myocardial Infarction Complicated by Cardiogenic Shock: A Scientific Statement From the American Heart Association. *Circulation*. 2021;143:e815-e829.

AHA 2022 Statement on Cardio-oncology

Cardio-Oncology Drug Interactions: A Scientific Statement From the American Heart Association. *Circulation*

AHA 2022 Statement on Mechanical Circulatory Support

Escalating and De-escalating Temporary Mechanical Circulatory Support in Cardiogenic Shock: A Scientific Statement From the American Heart Association. *Circulation*. 2022;146:e50-e68.

ACC 2023 Decision Pathway on HFpEF

2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction. *JACC* 2023

HRS/APHRS/LAHRS 2023 guideline on physiologic pacing

2023 HRS/APHRS/LAHRS guideline on cardiac physiologic pacing for the avoidance and mitigation of heart failure. *Heart Rhythm*. 2023;20:e17-e91.

AHA 2025 Statement on Heart Failure Prevention

Risk-Based Primary Prevention of Heart Failure: A Scientific Statement From the American Heart Association. *Circulation*. 2025 May 20;151(20):e1006-e1026.

EHRA 2025 Statement on ventricular arrhythmias in acute heart failure

Ventricular arrhythmias in acute heart failure: a clinical consensus statement of the Association for Acute CardioVascular Care, the European Heart Rhythm Association, and the Heart Failure Association of the European Society of Cardiology, *EP Europace*. 2025

AHA 2026 Statement on Older Adults with HF.

Strategies for Optimizing Heart Failure Care in the Older Adult: A Scientific Statement From the American Heart Association. *Circulation*. 2026.

CLASSIFICATION, EPIDEMIOLOGY, AND PATHOPHYSIOLOGY OF HEART FAILURE

Definitions and Classification

Heart failure (HF) is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. There is a consequent failure to deliver oxygen according to metabolic requirements, despite normal filling pressures (or only at the expense of increased filling pressures). Patients have the following features:

typical symptoms (breathlessness at rest or on exercise, fatigue, tiredness, ankle oedema), and

typical signs (tachycardia, tachypnoea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral oedema, hepatomegaly), and

objective evidence of a structural or functional abnormality of the heart at rest (cardiomegaly, third heart sound, cardiac murmurs, abnormality on the echocardiogram such as reduced LVEF or valve disease or other structural disorder, raised natriuretic peptide concentration).

The AHA/ACC definition and classifications of HF as well as the Second Universal Definition of Heart Failure (2026) are presented in Table 1.¹⁻³ Table 2 presents the NYHA functional classification, and Table 3 and Figures 1 and 2 the Stages of HF.

Heart failure with **preserved ejection fraction** (>40% according to ACC/AHA, or >50%) according to ESC), (HFpEF), or diastolic HF is seen in approximately 40-50% of patients with HF.⁴ The condition should be distinguished from heart failure with recovered ejection fraction that bares a better prognosis.⁵ The diagnosis of HFpEF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF.^{6,7} **Left heart failure** refers to predominant congestion of the pulmonary veins with fluid retention and pulmonary oedema. **Right heart failure** refers to predominant congestion of the systemic veins with fluid retention and peripheral oedema.⁸ These conditions may coexist and the most common cause of right ventricular failure is raised pulmonary artery pressure due to left ventricular failure. **High output heart failure** refers to the syndrome caused by circulatory high output conditions such as obesity, liver failure, arteriovenous shunts, lung disease, anaemia, thyrotoxicosis, haematologic disorders, Paget's disease, and beri-beri.⁹ **Preload** refers to left and/or right atrial pressures (volume overload), and **afterload** to the work of the myocardium (pressure overload or high impedance).

Epidemiology

The prevalence of heart failure is approximately 2% of the adult population worldwide, ranging from less than 2% of people younger than 60 years to more than 10% of those older than 75 years.¹⁰ Heart failure is a global problem with an estimated prevalence of 38 million patients worldwide, a number that is increasing with the ageing of the population. It is the most common diagnosis in patients aged 65 years or older admitted to hospital and in high-income nations.¹¹ The lifetime risk of developing heart failure is estimated 20% for all persons older than 40 years.¹² In the US approximately 6 million have heart failure in 2019 that led to 86177 deaths.¹³ The incidence of HF in Europe is about 3/1000 person-years (all age-groups) or about 5/1000 person-years in adults.¹⁴ With ageing population, there is a shift towards heart failure with preserved LVEF that predominates in patients over 70 years old. Although there is a trend for reduction of hospitalization for HF both in Europe and the US,^{15,16} the incidence of heart failure has not declined in the past 20 years, and despite recent advances in its management, mortality rates in hospitalized patients is 30% at one year.⁴ Socioeconomically deprived individuals have more comorbidities, despite their younger age.¹⁶ Prediction models such may predict incident HF or risk of hospitalization in patients with or without heart disease.¹⁷⁻¹⁹

In patients with or without prevalence of **heart failure with preserved LVEF** is estimated 50% among heart failure populations.^{5,6} It is dominant in the elderly who have multiple noncardiac comorbidities that mainly affect their prognosis,²⁰ but may also seen in younger patients (≤ 65 years of age).²¹ The mortality rate for patients with diastolic heart failure is slightly better than those with systolic heart failure (approaching 30% in one year, compared with 1% for age-matched controls).^{22,23} However, progression from normal to abnormal diastolic function is an independent predictor of mortality in patients with normal LVEF.²⁴

Aetiology

Hypertension and **coronary artery disease** are the commonest causes of heart failure in industrialized countries, whereas in underdeveloped countries other causes, such as infectious diseases, are more important (Table 4 and Figures 3 and 4).^{10,25,26} Extensive myocardial necrosis can result in pump failure. Small infarctions may also cause regional contractile dysfunction and adverse remodelling with myocyte hypertrophy, apoptosis, and deposition of extracellular matrix. Long-standing untreated hypertension is associated with both systolic and diastolic heart failure, and the majority of patients presenting with heart failure have hypertension. Even modest decreases in systolic blood pressure reduce mortality and risk for heart failure.²⁷ Dual (both ischemic and nonischemic) cardiomyopathy may be

seen in up to 16% of patients with coronary artery disease referred for clinical cardiovascular magnetic resonance imaging.²⁸ **Valvular heart disease**, **cardiomyopathies** and **congenital heart disease** are also important causes. **Overweight** and **obesity** and **abdominal adiposity** are associated with increased risk of heart failure.^{29,30} **Renal** and **liver failure** may result in heart failure. acute decompensated HF is frequently due to cardiorenal dysfunction or accompanied by azotemia.³¹ The term **cardiorenal syndromes** now encompasses a spectrum of disorders involving both the heart and kidneys in which acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other (Table 5).³²⁻³⁴ The term **cardiohepatic syndrome** refers to the combination of hepatic congestion and reduced hepatic perfusion,³⁵ whereas **cirrhotic cardiomyopathy** denotes advanced cirrhosis with systolic and diastolic dysfunction.³⁶ **Sickle cell disease** is associated with pulmonary hypertension, LV dysfunction and microvascular disorders.³⁷ Patients with **sarcoidosis** are at an increased risk for HF.³⁸ **Arteriovenous fistulas** and dialysis initiation result in RV remodeling and dysfunction, especially in the elderly.³⁹ Patients with **diabetes mellitus**, and especially type 1, have a 2 to 4-times higher risk for heart failure and higher mortality compared to non-diabetics.⁴⁰ Patients with **metabolic syndrome** (abdominal adiposity, hypertriglyceridemia, low HDL, hypertension and fasting hyperglycemia) are also at higher risk of cardiovascular disease and heart failure. An association of **thiazolidinediones** with heart failure is well established.⁴¹ **Glucagon-like peptide-1 receptor agonists (GLP-1RA)** use was associated with a lower risk of heart failure compared with **dipeptidyl peptidase-4 inhibitors (DPP-4i)** and similar risks compared with **sodium-glucose cotransporter-2 inhibitors (SGLT-2i)** in routine clinical care.⁴² **Long-chain monounsaturated fatty acids** (LCMUFAs) such as erucic acid that is a component of rapeseed oil (also found in low quantities in canola oil) are cardiotoxic and have been associated with heart failure.⁴³ LCMUFAs are present in mustard oils and related products, some fish species, and processed meat and poultry products. Both **hyperthyroidism** and **hypothyroidism** can be reversible causes of heart failure.^{44,45} **Alcohol** is a direct myocardial toxin and a reversible cause of heart failure,^{46,47} and **titin** truncating variants predispose to alcoholic cardiomyopathy.⁴⁸ **Cigarette smoking** is a risk factor for heart failure independent of traditional risk factors.⁴⁹ Long-term use of **cocaine** results in activation of the sympathetic nervous system, causing left ventricular dysfunction both directly and through promotion of coronary thrombosis, coronary spasm, and atherosclerosis.⁴⁶ **Insomnia** symptoms are associated with incident heart failure.⁵⁰ Oral molecular targeted antineoplastic agents are associated with (LV dysfunction, hypertension, and arrhythmia/QT prolongation. Several **anticancer therapies** (including chemotherapeutic agents and radiotherapy) may cause HF directly, through their cardiotoxic effects or, indirectly, through other mechanisms, such as myocarditis, ischaemia, systemic or pulmonary hypertension, arrhythmias or valve disease.^{14,51-53} A genetic background may also be

involved.⁵⁴ All **NSAIDS**, and especially selective COX-2 inhibitors increase the risk of heart failure,⁵⁵ especially in patients with type 2 diabetes and exposure for more than 14 days.⁵⁶ Long-term **anabolic-androgenic steroids** use is associated with both systolic and diastolic myocardial dysfunction, as well as coronary atherosclerosis.⁵⁷ **Hydroxychloroquine** increases the risk of cardiovascular complications in older patients with baseline HF or at high risk for developing HF.⁵⁸ **Increased resting heart rate** is associated with cardiovascular morbidity and mortality in the general population and in patients with cardiovascular disease.⁵⁹ Changes over time also have predictive value, especially in patients in sinus rhythm.⁶⁰ **Persistent tachycardias**, both supraventricular and ventricular are established causes of heart failure (tachycardiopathies-see Chapter 42), and atrial fibrillation is independently associated with an adverse outcome in patients hospitalized for heart failure.⁶¹ **RV only pacing** imposes an increased risk of HF diagnosis particularly during the first 30 and 180 days post-implantation.⁶² **Pulmonary arterial hypertension** may lead to RV failure. **Male sex, less education, physical inactivity, and overweight**, have also been identified as independent risk factors for CHF.⁶³ **Physical activity** may reduce the risk of heart failure.^{64 65,66} **Obstructive sleep apnoea** is associated with hypertension and a higher incidence of heart failure, but can also be seen in the absence of heart disease.⁶⁷ **Central sleep apnoea** is almost uniquely associated with heart failure and represents an independent risk factor for reduced survival.⁶⁸ **Rheumatoid arthritis** and **SLE** are associated with an increased risk of heart failure.^{69,70} Patients with **inflammatory bowel disease** had a moderately higher risk of developing HF for ≥ 20 years after IBD diagnosis than the general population.⁷¹ **Mitochondrial diseases** caused by genetic variants in the mitochondrial or nuclear DNA (prevalence 1 in 5,000 individuals), may result in heart failure and arrhythmic events.^{72,73} **HIV infection** is also an important cause of left or biventricular dysfunction. HIV-induced heart failure is mainly a systolic dysfunction, but diastolic dysfunction may also appear.⁷⁴ Multisystem inflammatory syndrome in children is a rare but severe postinflammatory complication of **SARS-CoV-2** infection that can cause acute myocardial dysfunction, arrhythmias or conduction abnormalities, and coronary artery dilation.⁷⁵ A strong association between **preterm birth** before 32 weeks of gestation and HF in childhood and young adulthood has been demonstrated although the absolute risk is low.⁷⁶

Pathophysiology

Ventricular pressure-volume analysis is the reference method for study of cardiac mechanics (Figure 5).^{77,78} The previously normal heart is subject to either an acute (eg myocardial infarction) or a chronic insult (eg hypertension) that results in altered loading conditions. These activate compensatory mechanisms such as increased ventricular preload, or the Frank-

Starling mechanism, by ventricular dilatation and volume expansion, peripheral vasoconstriction, renal sodium and water retention to enhance ventricular preload, and initiation of the adrenergic nervous system, which raises heart rate and contractile function.¹⁰

Heart failure with reduced LVEF

Increases in sympathetic outflow directed at the heart, kidneys, and skeletal muscle are the characteristics of heart failure with reduced LVEF.⁷⁹ Mechanisms responsible for sympathetic activation are not fully elucidated. The afferent autonomic disturbance considered principally responsible for eliciting increased efferent sympathetic discharge is the loss of its inhibition by cardiopulmonary reflexes arising from stretch-sensitive mechanoreceptors sited in ventricles, atria, and the pulmonary veins. In addition, a paradoxical muscle sympathetic reflex activation in response to increased atrial pressure is a recently described neurogenic disturbance common to heart failure with both reduced and preserved LVEF.⁸⁰ These processes are controlled mainly by activation of various neurohormonal vasoconstrictor systems, including RAAS, the adrenergic nervous system, and non-osmotic release of arginine-vasopressin. Initially these mechanisms are beneficial and adaptive, sustaining heart rate, blood pressure, and cardiac output, and thus maintaining organ perfusion. In the long-term, they result in disruptions of β -adrenergic signaling and impaired mobilization of intracellular calcium with consequent myocyte hypertrophy to preserve wall stress as the heart dilates, apoptosis, fibroblast proliferation, and interstitial collagen accumulation. Loss of myocyte cells and increased myocardial strain cause eccentric hypertrophy of the remaining myocytes, both directly and through neurohormonal activation, leading to fibrosis, progressive left ventricular dilatation, a change in the shape of the left ventricle from elliptical to spherical, and, often, functional mitral regurgitation. These changes in size, shape and pump function of the heart, named left ventricular remodelling, result in increased myocardial oxygen consumption and reduced efficiency of myocardial contraction, and determine the clinical course of heart failure.⁸¹ The consequences of these structural changes are a reduction in stroke volume, an increase in systemic vascular resistance, and development of signs and symptoms of congestion and tissue hypoperfusion. Eventually in untreated cases cardiac cachexia develops due to activation of proinflammatory cytokines such as tumor necrosis factor α and interleukin 2, with consequent cardiac cell death.⁸² Misfolded proteins that are central in the pathophysiology of neurodegenerative disorders such as Parkinson's and Alzheimer disease, have also been found to play a role in pathologic cardiac hypertrophy and dilated and ischemic cardiomyopathies, thus leading to the suggestion that proteotoxicity is a key contributor to the progression of heart failure.⁸² Subtle biochemical evidence of myocyte injury precedes imaging evidence of increasing LV mass and dilation, replacement fibrosis, and clinical cardiovascular events.⁸³

Apart from causing further myocardial injury, activation of neurohormonal vasoconstrictor systems has detrimental effects on other organs such as the kidneys, liver, muscles, intestines, and lungs, and create a 'vicious cycle', that accounts for many of the clinical features of heart failure, including cardiac electrical instability. Heart failure may cause renal failure (cardiorenal syndrome), and the opposite may occur (renocardiac syndrome).^{32,33,84} Hepatic congestion and reduced hepatic perfusion may also occur.³⁵ Abnormal liver function tests such as (increased γ GT, bilirubin, and alkaline phosphatase are frequently seen in patients with chronic and, especially, acute heart failure, and are associated with adverse prognosis. Transaminases are moderately increased or even remain normal.^{24,36} In cirrhotic cardiomyopathy there is advanced cirrhosis with systolic and diastolic dysfunction, and electrophysiological abnormalities such as chronotropic incompetence and prolonged QT interval.³⁶

Iron deficiency carries an adverse prognostic significance and is due to a combination of reduced iron uptake (malnutrition, fluid overload), impaired iron storage (inflammation, chronic kidney disease), and iron loss (antiplatelets).⁸⁵

Up to 40% of patients with HF develop **AF**.⁸⁶ Patients with **HFrEF and CAD** are at risk for stroke or TIA in the period following an episode of worsening heart failure in the absence of atrial fibrillation. Most strokes are of ischaemic origin and nearly half are either disabling or fatal.⁸⁷

RV hypertrophy predicts an increased risk of heart failure which is usually attributable to LV dysfunction.⁸⁸ Pulmonary hypertension is a common hemodynamic complication of heart failure.⁸⁹ Right ventricular function should be assessed, especially in patients with ischaemic cardiomyopathy. MR severity, RBBB, LVEF, and the presence of RV scar are independent predictors of RV ejection fraction (RVEF).⁹⁰ Afterload is a primary determinant of normal right ventricular (RV) function, and RVEF is inversely proportional to pulmonary artery pressure. RV systolic function is, therefore, highly sensitive to changes in afterload, with minor increases in afterload causing large decreases in stroke volume. Acute right heart failure can occur because of abruptly increased RV afterload or decreased RV. Chronic **right heart failure** most commonly results from gradual increases in RV afterload caused by pulmonary hypertension most frequently from left heart failure, although chronic volume overload from right-sided lesions such as tricuspid regurgitation can also lead to its development.³⁵ One-year mortality of patients with severe RV dysfunction is high, approximately 40%, but survival depends on the aetiology. Left-sided heart disease is the most common cause of severe RV dysfunction but prognosis is worst in patients with chronic lung disease.⁹¹

Heart failure with preserved LVEF

Heart failure with preserved LVEF may be seen in various conditions such as diastolic dysfunction, pressure overload hypertrophy from valvular disease (especially AS), pericardial disease and RV dysfunction (Table 4). Its pathophysiology is incompletely understood.

Diastolic dysfunction is caused by a decrease in ventricular relaxation and/or an increase in ventricular stiffness and myocyte lengthening load, probably due to fibrosis and myocardial hypertrophy.⁹² Common causes are long-standing arterial hypertension, ischemic heart disease, diabetes, severe sepsis, and increased age. Systemic senile amyloidosis (wild-type transthyretin amyloidosis or isolate atrial amyloidosis), is an established predisposing factor for HFpEF.^{93,94} The relative risk of HFpEF increases with cardiac radiation exposure during contemporary conformal breast cancer radiotherapy.⁹⁵ Other causes of restrictive physiology may also lead to HFpEF.⁹⁶ The role of abnormal mitochondrial function in HFpEF and the impact of mitochondrial therapies on morbidity and mortality in this patient population are also under research.⁹⁷ **Diastolic heart failure** occurs when the ventricular chamber is unable to accept an adequate volume of blood during diastole, at normal diastolic pressures and at volumes sufficient to maintain an appropriate stroke volume.^{98,99} A role of kidney dysfunction is also possible.⁸⁴ Systolic dysfunction may coexist: LVEF is an imperfect measure of systolic function and stroke volume, and cardiac output may be reduced despite a normal LVEF. RV dysfunction is common in HFpEF patients, and associated with clinical and echocardiographic evidence of more advanced HF and predictive of poorer outcomes.^{100,101} Additional mechanisms such as myocardial ischemia, rhythm disturbance, and stress-induced valve insufficiency may contribute to symptoms in HFpEF.¹⁰²

Both systolic and diastolic heart failure may occur, and a decrease in LVEF to <55%, as well as any worsening of diastolic LV function are independently associated with increased mortality.⁸⁸ In addition to being a marker of increased risk due to its association with hypertension, diabetes mellitus, ischemia, and reduced systolic function, diastolic dysfunction may also be a direct contributor to adverse outcomes by limiting cardiac output reserve, accelerating neuroendocrine activation, and promoting physical inactivity. Lower pulse pressure (especially <53 mmHg) is an independent predictor of mortality in patients with reduced LVEF (<30%).¹⁰³ However, an analysis of a large dataset has found that the relationship between survival and LVEF assessed by echocardiography in routine clinical practice is u-shaped. Patients with an LVEF of 60–65% have the lowest risk of mortality regardless of age, sex, or other relevant confounders. Patients with LVEF ≥65% had a higher all-cause mortality.¹⁰⁴

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