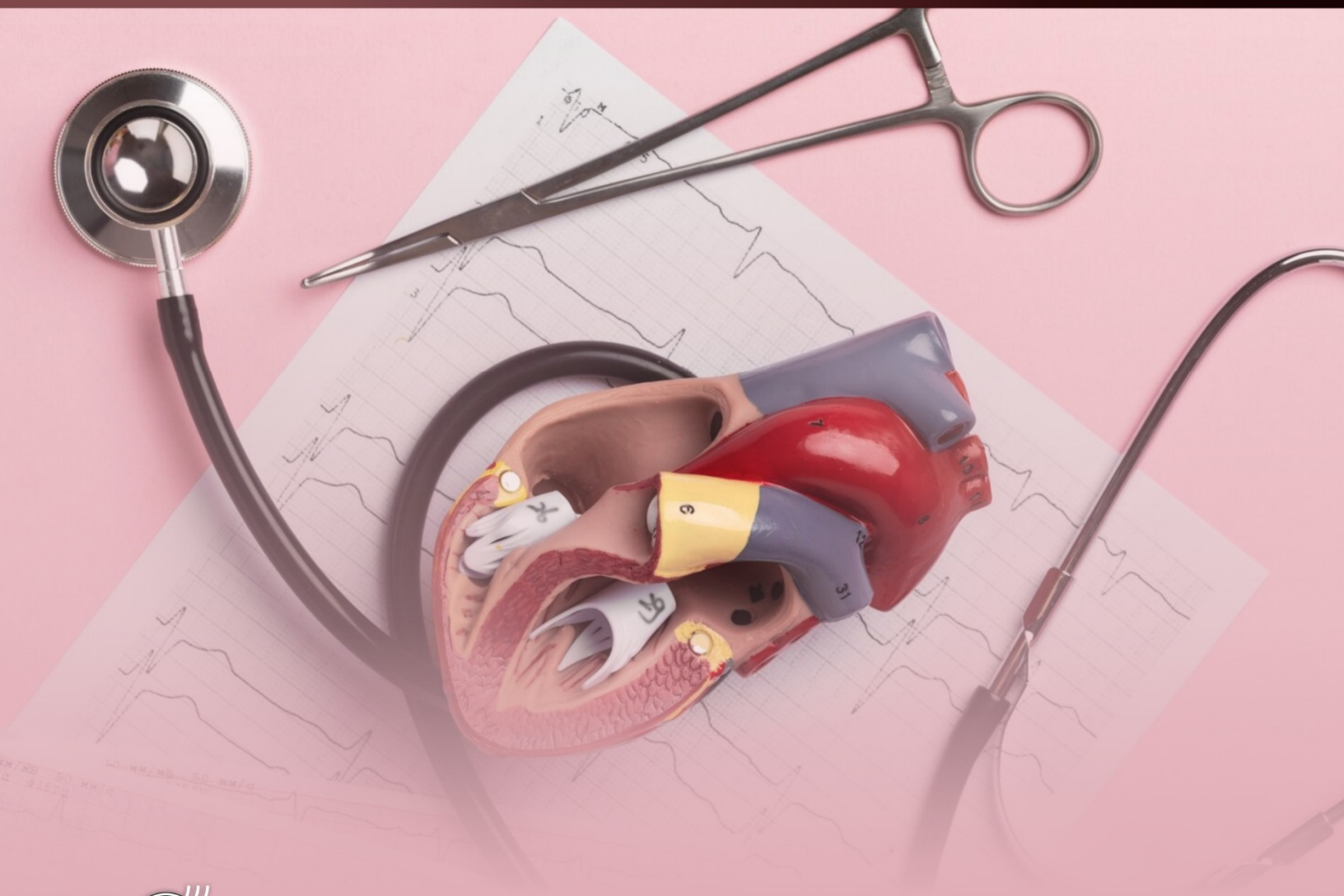
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HEART FAILURE



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Abbreviations and symbols

Abbreviation or symbol	Meaning
1RM	One-repetition maximum
ACEi / ACE inhibitor	Angiotensin-converting enzyme inhibitor
ACP	Advance care planning
ACR	Acute cellular rejection
ACS	Acute coronary syndrome
ADHF	Acute decompensated heart failure
AF	Atrial fibrillation
AHF	Acute heart failure
AKI	Acute kidney injury
AL	Immunoglobulin light-chain amyloidosis
AMI	Acute myocardial infarction
AMR	Antibody-mediated rejection
AR	Aortic regurgitation
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor–neprilysin inhibitor
ARVC	Arrhythmogenic right ventricular cardiomyopathy
AS	Aortic stenosis
ASV	Adaptive servo-ventilation
ATP	Adenosine triphosphate; antitachycardia pacing (according to context)
ATTR	Transthyretin amyloidosis
AV	Atrioventricular
BAT	Baroreflex activation therapy
BMI	Body mass index
BNP	B-type natriuretic peptide
BP	Blood pressure
BTC	Bridge to candidacy
BTR	Bridge to recovery
BTT	Bridge to transplantation
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CAV	Cardiac allograft vasculopathy
CCM	Cardiac contractility modulation

Abbreviation or symbol	Meaning
CCTA	Coronary computed tomography angiography
CHF	Chronic heart failure
CI	Cardiac index; confidence interval (according to context)
CK	Creatine kinase
CKD	Chronic kidney disease
CMR	Cardiovascular magnetic resonance
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPET	Cardiopulmonary exercise testing
CPO	Cardiac power output
CR	Cardiac rehabilitation
CRT	Cardiac resynchronisation therapy
CRT-D	Cardiac resynchronisation therapy with defibrillation
CRT-P	Cardiac resynchronisation therapy with pacing
CSA	Central sleep apnoea
CSP	Conduction-system pacing
CT	Computed tomography
CV	Cardiovascular
DBD	Donation after brain death
DCD	Donation after circulatory death
DHF	Decompensated heart failure
DOAC	Direct oral anticoagulant
DSA	Donor-specific antibody
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
ECV	Extracellular volume fraction
EDV	End-diastolic volume
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency

Abbreviation or symbol	Meaning
EMB	Endomyocardial biopsy
EROA	Effective regurgitant orifice area
ESC	European Society of Cardiology
ESV	End-systolic volume
FAC	Fractional area change
FDG	Fluorodeoxyglucose
FDG-PET	Fluorodeoxyglucose positron-emission tomography
FMT	Foundational medical therapy
GDIT	Guideline-directed interventional therapy
GDMT	Guideline-directed medical therapy
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
GLP-1RA	Glucagon-like peptide-1 receptor agonist
GLS	Global longitudinal strain
H□FPEF	Clinical and echocardiographic score estimating HFpEF probability
HCTZ	Hydrochlorothiazide
HF	Heart failure
HFA	Heart Failure Association
HFA-PEFF	Heart Failure Association diagnostic framework for HFpEF
HFH	Heart failure hospitalisation
HFimpEF	Heart failure with improved ejection fraction
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Heart rate; hazard ratio (according to context)
HT	Heart transplantation
IABP	Intra-aortic balloon pump
ICD	Implantable cardioverter-defibrillator
INR	International normalised ratio
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
ISHLT	International Society for Heart and Lung Transplantation
IV	Intravenous
K	Potassium

Abbreviation or symbol	Meaning
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire clinical summary score
LA	Left atrium
LAA	Left atrial appendage
LAVI	Left atrial volume index
LBBB	Left bundle branch block
LBBP	Left bundle branch pacing
LGE	Late gadolinium enhancement
LUS	Lung ultrasound
LV	Left ventricle
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end-systolic diameter
MAP	Mean arterial pressure
MCS	Mechanical circulatory support
MR	Mitral regurgitation
MRA	Mineralocorticoid receptor antagonist
MR-proANP	Mid-regional pro-atrial natriuretic peptide
NIV	Non-invasive ventilation
NP	Natriuretic peptide
NSAID	Non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
OAC	Oral anticoagulation
OSA	Obstructive sleep apnoea
PA	Pulmonary artery
PAC	Pulmonary artery catheter
PaO□	Arterial oxygen partial pressure
PAPi	Pulmonary artery pulsatility index
PASP	Pulmonary artery systolic pressure
PAWP	Pulmonary artery wedge pressure
PCI	Percutaneous coronary intervention
PCr	Phosphocreatine

Abbreviation or symbol	Meaning
PCWP	Pulmonary capillary wedge pressure
PDE5	Phosphodiesterase type 5
PE	Pulmonary embolism
PH	Pulmonary hypertension
PKG	Protein kinase G
PVC	Premature ventricular complex
pVO□	Peak oxygen uptake
PVR	Pulmonary vascular resistance
QoL	Quality of life
RAAS	Renin–angiotensin–aldosterone system
RAP	Right atrial pressure
RER	Respiratory exchange ratio
RHC	Right-heart catheterisation
RPE	Rating of perceived exertion
RR	Risk ratio or rate ratio (as specified)
RRT	Renal replacement therapy
RV	Right ventricle
RVAD	Right ventricular assist device
SAVR	Surgical aortic valve replacement
SBP	Systolic blood pressure
SCAI	Society for Cardiovascular Angiography and Interventions
sGC	Soluble guanylate cyclase
SGLT2	Sodium–glucose cotransporter 2
SGLT2i	Sodium–glucose cotransporter 2 inhibitor
SmPC	Summary of Product Characteristics
SMR	Secondary mitral regurgitation
SPECT	Single-photon emission computed tomography
SpO□	Peripheral oxygen saturation
SPPB	Short Physical Performance Battery
STEMI	ST-elevation myocardial infarction
SZC	Sodium zirconium cyclosilicate
T2*	Effective transverse relaxation time used for myocardial iron assessment
TAPSE	Tricuspid annular plane systolic excursion

Abbreviation or symbol	Meaning
TAVI	Transcatheter aortic valve implantation
TEER	Transcatheter edge-to-edge repair
tMCS	Temporary mechanical circulatory support
TOE	Transoesophageal echocardiography
TR	Tricuspid regurgitation
TRV	Tricuspid regurgitation velocity
TSAT	Transferrin saturation
TSH	Thyroid-stimulating hormone
uACR / UACR	Urine albumin-to-creatinine ratio
uNa	Urinary sodium concentration
VA-ECMO	Veno-arterial extracorporeal membrane oxygenation
VF	Ventricular fibrillation
VKA	Vitamin K antagonist
V̇O□ / VO□	Oxygen consumption
VT	Ventricular tachycardia
VTE	Venous thromboembolism
WCD	Wearable cardioverter-defibrillator

1. Definition, Classification, Epidemiology, Natural History and Prevention

1.1. Definition and clinical boundaries

Heart failure is a clinical syndrome rather than a single pathological entity, characterized by a constellation of typical symptoms—such as dyspnea, peripheral edema, and fatigue—often accompanied by objective signs including elevated jugular venous pressure, pulmonary rales, and ankle swelling. It arises from structural and/or functional cardiac abnormalities that lead to increased intracardiac filling pressures and/or an inability of the heart to deliver adequate cardiac output at rest and/or during physical exertion. [1, 2]

Determining the underlying cause of cardiac dysfunction is a fundamental component of heart failure diagnosis, as the specific etiology directly influences therapeutic decision-making. In most cases, heart failure results from myocardial impairment, which may involve systolic dysfunction, diastolic dysfunction, or a combination of both. Nevertheless, disorders of the cardiac valves, pericardium, and endocardium, as well as abnormalities of cardiac rhythm and conduction, may also independently cause or significantly contribute to the development and progression of heart failure. [1, 3]

Patients with non-cardiovascular conditions—such as anemia, pulmonary, renal, thyroid, or hepatic disorders—may present with symptoms and clinical signs that closely resemble those of heart failure. In the absence of demonstrable cardiac dysfunction, however, these patients do not meet the diagnostic criteria for heart failure. Nevertheless, such comorbid conditions frequently coexist with heart failure and may contribute to the onset, worsening, or clinical complexity of the heart failure syndrome. [1, 4]

The syndrome is recognized through integration of historical symptoms, physical findings, cardiac imaging, circulating biomarkers and clinical context. Breathlessness, reduced exercise capacity and fatigue are common but not specific; oedema, elevated jugular venous pressure and pulmonary congestion add diagnostic support. Conversely, a patient may have marked structural disease, elevated natriuretic peptides or abnormal imaging in the absence of symptoms, representing a preclinical state rather than necessarily symptomatic HF. [1, 2]

A precise distinction should also be maintained between aetiology and phenotype. Ischaemic disease, a genetic cardiomyopathy, cardiac amyloidosis or valve disease refers to a causal substrate. Reduced or preserved LVEF, predominant systemic congestion, exercise-induced filling pressure elevation or right-ventricular failure describes how a substrate is expressed. These classifications are complementary and should not compete with one another. [1, 3]

The clinical diagnosis is dynamic. Symptoms may disappear after effective treatment, but this does not imply that structural disease or vulnerability has resolved. Similarly, a patient's LVEF may improve from a clearly reduced value to one within the conventionally preserved range. The history of ventricular dysfunction retains prognostic and therapeutic relevance even if the latest imaging examination appears reassuring. [2, 5]

The immediate practical consequence is that HF is never diagnosed from LVEF alone. LVEF is a dimensionless ratio and does not directly measure cardiac output, filling pressure, contractile reserve, myocardial tissue composition or exercise haemodynamics. A low LVEF may coexist with few symptoms; an apparently normal LVEF may coexist with profoundly elevated ventricular filling pressures and debilitating exertional limitation. [6, 7]

Conditions such as anaemia, pulmonary disease, thyroid dysfunction, renal salt retention and hepatic disease can mimic individual features of HF or contribute to its manifestations. These are not mutually exclusive alternatives. The patient may have both clinically relevant HF and another condition responsible for a proportion of the reported dyspnoea or fatigue, making causal attribution an ongoing task rather than a one-time diagnostic decision. [1, 4]

1.1.1. Cardinal manifestations and diagnostic interpretation

Table 1.1. Cardinal manifestations and diagnostic interpretation [1, 4, 8]

Symptoms / findings	Clinical interpretation	Important limitation
Exertional dyspnoea / orthopnoea	Suggests elevated cardiac filling pressures, pulmonary congestion or reduced reserve	May also occur in obesity, lung disease, anaemia or deconditioning
Fatigue and reduced functional capacity	May reflect low forward output, reduced exercise reserve or skeletal-muscle dysfunction	Affected by age, sleep, mood and coexisting disease
Elevated jugular venous pressure	Supports systemic venous congestion	May predominate with right-sided disease or constriction
Peripheral oedema / ascites	May reflect sodium retention and systemic congestion	Also occurs with venous, hepatic and renal disease
BNP / NT-proBNP elevation	Supports myocardial wall stress and HF probability	Age, atrial fibrillation, renal disease, obesity alter interpretation
Echocardiographic abnormalities	Establishes anatomic / functional substrate and informs phenotype	A normal resting LVEF does not exclude HFpEF

Clinical reasoning must combine the probability of HF before testing with the pattern of positive and negative findings. A test that is highly useful for exclusion may not have the same value for confirmation. This is particularly important for natriuretic peptides, which are sensitive to volume status and several extracardiac variables. The strongest diagnosis emerges from concordance between symptoms, examination, evidence of cardiac disease and tests that support elevated filling pressure or impaired function. [4, 8]

1.2. Classification according to the 2026 ESC framework

The former three-part LVEF classification was convenient for organizing trial populations, yet it created interpretative ambiguity at intermediate LVEF values. In the 2026 ESC framework, patients with symptomatic HF are categorized as HFrEF when LVEF is below 50%, and as HFpEF when LVEF is at least 50% and the required corroborating abnormalities are present. The former HFmrEF category is retained here only as a historical research descriptor for legacy trials and observational studies, not as a current separate disease phenotype [1].

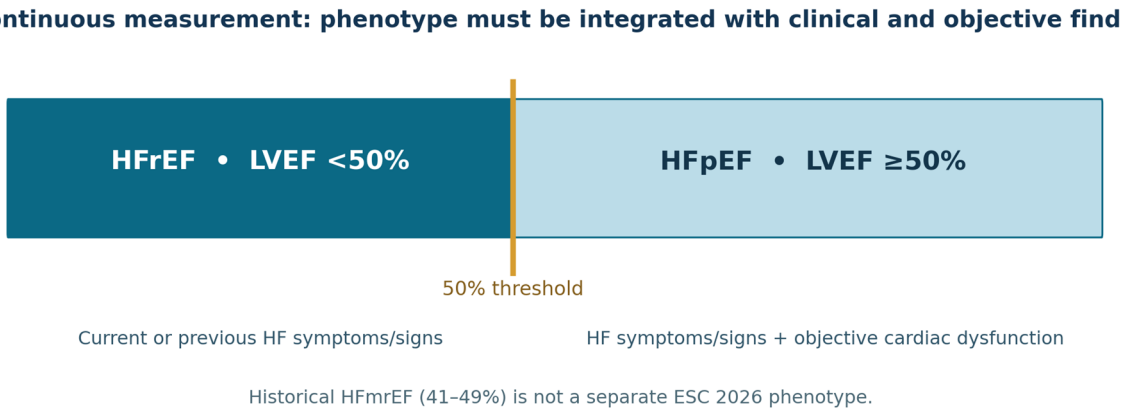


Figure 1.1. Left ventricular ejection fraction phenotype framework (concepts aligned with ESC 2026 [1]).

Table 1.2. LVEF phenotype criteria [1, 2]

ESC 2026 phenotype	Core clinical criteria	Clinical interpretation
HFrEF	Current or previous symptoms and/or signs of HF, with LVEF <50%.	The 41–49% subgroup has not vanished biologically; it is reclassified.
HFpEF	Current or previous manifestations of HF; LVEF ≥50%; objective cardiac structural / functional abnormalities supporting HF.	Preserved EF is not synonymous with normal myocardial function.
HF with improved EF	Longitudinal descriptor for a patient with previously reduced LVEF and subsequently higher LVEF.	Do not automatically relabel recovered HFrEF as de novo HFpEF.

1.2.1. Historical perspective: why 41–49% mattered

In historical clinical-trial nomenclature, heart failure (HF) has been classified into distinct phenotypes according to left ventricular ejection fraction (LVEF). Historically, according to the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, three major categories were defined: heart failure with reduced ejection fraction (HFrEF), characterized by an LVEF ≤40%; heart failure with mildly reduced ejection fraction (HFmrEF), defined by an LVEF of 41%–49%; and heart failure with preserved ejection fraction (HFpEF), defined by an LVEF ≥50%. [9]

The rationale underlying this classification was largely derived from the inclusion criteria used in randomized clinical trials demonstrating prognostic benefit from various therapeutic interventions in patients with HF and an LVEF ≤40%. The HFmrEF category was subsequently introduced to provide a more precise characterization of patients who had been underrepresented or excluded from trials primarily designed for HFrEF. [9]

In this context, the original term “mid-range ejection fraction” was replaced by “mildly reduced ejection fraction” to better reflect the substantial similarities between patients with HFmrEF and those with HFrEF in terms of clinical characteristics, prognosis, and response to pharmacological therapy. [1]

Similarly, the therapeutic response profile observed in patients with HFmrEF substantially overlaps with that seen in HFrEF and is less comparable to that of HFpEF. [1] These observations support the concept of a biological and therapeutic continuum between HF with reduced and mildly reduced ejection fraction.

Particular attention should also be paid to longitudinal changes in LVEF. Ejection fraction should not be regarded as a static parameter, but rather as a dynamic variable influenced by disease progression, underlying aetiology, and response to treatment. Accordingly, a relevant proportion of patients with an LVEF between 41% and 49% may subsequently experience deterioration in systolic function and transition towards lower LVEF values. [1]

This historical continuity matters when interpreting landmark drug trials: an efficacy estimate observed among patients with LVEF ≤40% cannot be declared identical throughout the entire newly defined HFrEF range without consideration of study eligibility, subgroup estimates and direct randomized evidence. The revised clinical classification streamlines practice, but evidence remains heterogeneous within the category. Clinical decisions must therefore follow the actual 2026 recommendation and its level of evidence, not merely a change in terminology.

1.2.2. Why LVEF is necessary but insufficient

The use of a single LVEF threshold to differentiate HFrEF from HFpEF should, however, be interpreted with caution. Any numerical cut-off is, to some extent, arbitrary, and LVEF should always be considered within the individual clinical context. Reproducibility of LVEF assessment is influenced both by the imaging modality employed and by intra- and inter-observer variability. Furthermore, in certain clinical settings, LVEF may overestimate true left ventricular systolic performance; significant mitral regurgitation represents an important example. [6, 10]

Natriuretic peptides provide important supportive evidence for the diagnosis of HF, particularly in situations in which clinical manifestations and imaging findings are not sufficiently conclusive. Their concentrations should nevertheless be interpreted in the context of the patient's overall clinical profile and concomitant comorbidities. [8, 11]

Another major consideration is the dynamic nature of LVEF under treatment. Pharmacological therapies and device-based interventions may promote left ventricular reverse remodelling, resulting in improvement of systolic function and an increase in LVEF in patients with HFrEF. Patients who achieve improvement in LVEF generally have a more favourable prognosis than those in whom systolic dysfunction persists. [1, 2]

Nevertheless, normalization or improvement of LVEF should not automatically be interpreted as resolution of the underlying cardiomyopathic process. Consequently, in most such patients, optimal medical therapy should be continued even after recovery of ventricular function, except in carefully selected circumstances. [1, 5]

This revised classification reflects a shift away from a predominantly threshold-based approach to LVEF towards a framework that more coherently integrates pathophysiological mechanisms, clinical phenotype, longitudinal ventricular function, and therapeutic response in patients with heart failure. [1]

LVEF is derived from the difference between end-diastolic and end-systolic ventricular volumes divided by end-diastolic volume. Because the denominator matters, a small stiff ventricle may eject a comparatively high proportion of its contained volume while delivering inadequate stroke volume at increased filling pressures. Likewise, valvular regurgitation may lead to an apparently reassuring LVEF even when effective forward output is compromised. [6, 10]

For serial assessment, differences between imaging techniques, loading conditions, image quality, beat selection, arrhythmias and observer variability should be taken seriously. A modest change in an isolated EF measurement is not necessarily evidence of biological progression or reverse remodelling. Greater confidence

comes from concordant changes in chamber volumes, ventricular dimensions, global longitudinal strain, biomarkers, symptoms and functional status. [6, 12]

Etiological investigation is indispensable in either phenotype. Cardiac amyloidosis, hypertrophic or infiltrative cardiomyopathy, myocarditis, haemochromatosis, arrhythmogenic cardiomyopathy, valve disease and congenital abnormalities may not be adequately captured by the binary EF label. Phenotype identifies a treatment framework; aetiology may identify the treatment that alters the natural history most directly. [3, 13, 14]

1.2.3. Multidimensional clinical phenotyping beyond LVEF

A patient with HF can be classified along several independent but interacting axes. LVEF describes one aspect of left ventricular pump performance; clinical stage describes the position in the disease continuum; functional class describes symptoms; haemodynamic profile describes congestion and perfusion; aetiology identifies the underlying mechanism; and comorbidity burden determines treatment tolerance and competing risk. None of these domains should be used as a substitute for the others. [1, 2]

A practical phenotype summary should therefore state the underlying cause when known, the current LVEF and its prior trajectory, the ESC stage, current functional limitation, presence or absence of congestion, the rhythm and important valvular or right ventricular abnormalities. Renal function, blood pressure, potassium, obesity, diabetes, frailty and relevant treatment history should be included when they change management. This information is more clinically useful than a one-word label such as HFrEF or HFpEF. [1, 3]

Table 1.3. Multidimensional clinical phenotyping [1–3]

Phenotyping axis	Clinical example	Decision enabled
Clinical stage	Pre-HF or previous symptomatic disease	Prevention vs full symptomatic-HF care
Ejection-fraction history	Current LVEF 55% following prior documented reduction	Avoid inappropriate reclassification / therapy withdrawal
Aetiological substrate	Ischaemic scar, severe valve lesion, amyloidosis	Causal intervention or disease-specific therapy
Haemodynamic status	Congestion with maintained or impaired perfusion	Decongestion and level of care
Rhythm / electrical profile	AF, conduction disease, wide QRS	Rate/rhythm strategies and device assessment
Multisystem profile	CKD, diabetes, obesity, frailty	Treatment selection, dosing and follow-up

This multidimensional description is especially important in patients with apparently preserved systolic function. An older person with marked concentric hypertrophy and arterial stiffness, an individual with obesity-related exercise intolerance, and a patient with ATTR cardiomyopathy may all have an LVEF exceeding 50%, yet their disease mechanisms, diagnostic priorities and disease-specific treatment options differ substantially. A binary LVEF classification is an entry point into a diagnostic and therapeutic pathway, not the endpoint of clinical reasoning. [15, 16]

Longitudinal phenotyping also helps prevent misleading comparisons. A patient with LVEF 45% recovering from more severe dysfunction may have a different risk profile from a patient whose LVEF has gradually declined from 60% to 45%. Both are categorized within the revised HFrEF spectrum, but the first may represent successful reverse remodelling and the second progressive myocardial disease. The trajectory, not only the latest measurement, should influence surveillance and the search for a reversible cause. [2, 5]

In an academic setting, this approach supports structured case presentations and improves the interpretation of heterogeneous research populations. It also clarifies why recommendations derived from carefully selected trials must be interpreted alongside real-world multimorbidity. As later chapters discuss specific investigations and treatments, each clinical algorithm should be linked to the phenotype dimensions that determine its eligibility and usefulness.

1.3. Staging: from risk to advanced disease

The 2026 ESC recommendations incorporate a stage-based continuum that is complementary to clinical phenotype. Stage A identifies risk without established cardiac abnormality or HF manifestations. Stage B identifies pre-HF with demonstrable cardiac changes but no current or prior HF symptoms. Stage C describes symptomatic HF, including patients with a documented history of symptoms whose clinical condition has improved. Stage D corresponds to advanced HF requiring specialized assessment and often advanced therapeutic or supportive options [1].

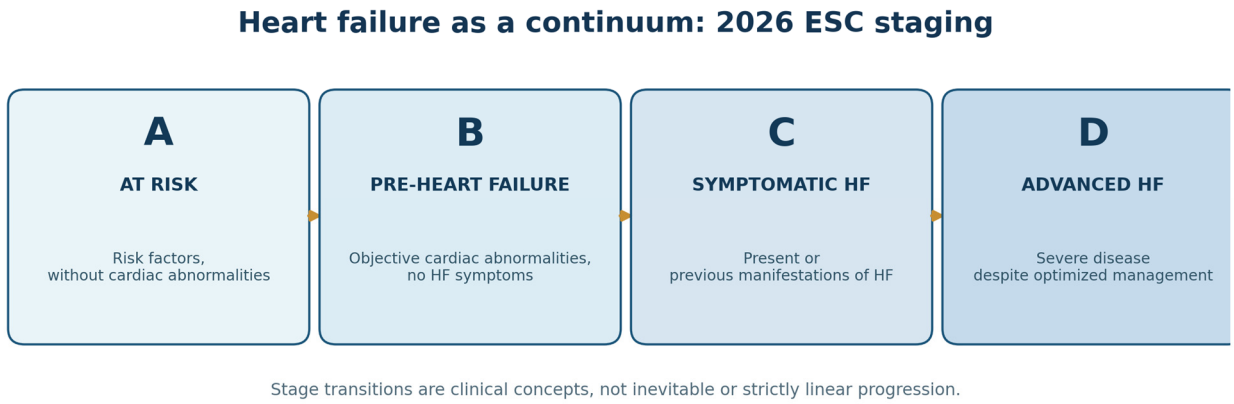


Figure 1.2. Visual representation of ESC 2026 stages A–D. The framework is intended for prevention and treatment planning, not as a claim that all patients progress sequentially. [1]

Table 1.4. Stages of heart failure [1, 2]

Stage	Defining perspective	Practical priority
A — At risk	Risk factors, but no symptoms or demonstrable cardiac abnormalities	Risk estimation, behavioural and risk-factor interventions
B — Pre-HF	Objective cardiac abnormalities without HF signs/symptoms	Identify substrate and deploy appropriate prevention therapy
C — Symptomatic HF	Current or past symptoms/signs attributable to cardiac dysfunction	Phenotype, aetiology and guideline-directed HF management
D — Advanced HF	Severe disease with major burden despite optimized management	Expert advanced-HF referral, symptom support, candidacy assessment

1.3.1. Stage A: prevention before measurable cardiac injury

A prevention-oriented assessment should characterize lifetime risk exposures and their cumulative interaction. Elevated blood pressure, diabetes, adiposity, chronic kidney disease, coronary disease, cardiotoxic treatment exposure and certain inherited conditions are major drivers of future HF. The same patient may have several coexisting risk factors that amplify one another rather than acting as independent, additive determinants. [17]

The operational aim in Stage A is not to label an asymptomatic person as having manifest HF, but to prevent myocardial damage and unfavourable remodelling. Regular clinical review, appropriate blood-pressure and metabolic treatment, smoking cessation, physical activity and correction of modifiable exposures are crucial. Certain stage-specific pharmacological strategies have explicit 2026 ESC recommendations and must be distinguished from general preventive counselling [1].

1.3.2. Stage B: detecting preclinical cardiac injury

Stage B represents the moment at which disease biology becomes objectively demonstrable before ordinary activities are limited by characteristic HF symptoms. Patients may have reduced ventricular systolic function, pathological remodelling, evidence of relevant structural disease or other objectively recognized abnormalities. A systematic search for a potentially treatable substrate is appropriate rather than waiting for overt congestion or hospitalization. [1, 2]

A diagnosis of Stage B is therapeutically important. It should trigger a reassessment of causal exposures, ischaemic disease, pressure overload, valvular pathology, rhythm disorders and inherited cardiomyopathy. Treatment is chosen according to the actual abnormality and evidence threshold. For example, the 2026 ESC guidance includes ACE inhibitor or ARB treatment for selected asymptomatic patients with LVEF ≤40%, and a beta-blocker recommendation in Stage B with LVEF <50%; these indications cannot be generalized indiscriminately to all individuals labelled Stage B [1, 18].

1.3.3. Stage C and the consequences of prior symptoms

Stage C is not restricted to a patient who is breathless on the day of examination. A person with documented HF symptoms whose volume status and functional capacity have normalized after treatment remains within the symptomatic-history stage. The distinction is clinically consequential because therapies that modify outcomes should not usually be discontinued merely because oedema has resolved or LVEF has improved. [1, 2, 5]

Stage C requires a parallel description of clinical severity, predominant haemodynamics, functional limitation and underlying cause. New York Heart Association functional class is valuable for standardized symptom communication, but it cannot be treated as a surrogate for stage, mortality risk or degree of myocardial pathology. A patient with mild current symptoms may have extensive fibrosis, recurrent arrhythmias or high-risk genetics. [19]

1.3.4. Stage D: recognition rather than late rescue

Advanced disease is identified through persistent severe manifestations, recurrent instability, major functional impairment and failure to achieve an acceptable course despite comprehensive management. Markedly reduced LVEF is common but not obligatory: a patient with profound right-sided failure, restrictive physiology or advanced HFpEF may require equally urgent expert evaluation. Recurrent hospitalization, intravenous inotrope dependence, progressive organ dysfunction and inability to tolerate standard therapy are particularly important warning signs. [20, 21]

Stage D should prompt referral while transplantation, durable mechanical support, specialized intervention or supportive care remain viable possibilities. The decision involves haemodynamics, right ventricular reserve, pulmonary vascular disease, frailty, kidney and liver function, cognitive and psychosocial assessment, and patient goals. The advanced heart failure chapter will examine INTERMACS classification, transplantation, ventricular assist devices and palliative care in detail. [22, 23]

1.4. Clinical terminology and dynamic presentations

The 2026 ESC nomenclature adopts “decompensated heart failure” as the preferred term for clinically significant worsening that leads to urgent evaluation or treatment escalation, replacing the previous overarching emphasis on “acute heart failure.” In clinical communication, current terminology should be distinguished from historical labels used in earlier studies [1]. Sudden pulmonary oedema, progressive fluid accumulation and cardiogenic shock remain different clinical presentations, and all require their own haemodynamic and treatment pathways.

From a clinical perspective, HF may present as a chronic or acute syndrome. Chronic heart failure (CHF) includes patients with an established diagnosis as well as those in whom symptoms and signs develop progressively over time. When a previously stable patient with CHF experiences clinical deterioration, either suddenly or gradually, the condition is considered decompensated heart failure. Such episodes may require hospitalization, although selected patients can be managed in the outpatient setting with intensified therapy, including intravenous diuretics. Heart failure may also present for the first time as an acute clinical syndrome, and both acute de novo HF and acute decompensation of pre-existing HF are addressed within the framework of acute heart failure. [1, 9]

In certain patients, heart failure may be a reversible condition. Complete recovery can occur in specific etiologies, such as alcohol-induced cardiomyopathy, viral myocarditis, Takotsubo syndrome, peripartum cardiomyopathy, or tachycardiomyopathy. Moreover, some individuals with left ventricular systolic dysfunction may experience partial or even complete restoration of systolic function following appropriate pharmacological and device-based therapies. [3, 5, 13]

The most widely used and straightforward system for describing the clinical severity of heart failure is the New York Heart Association (NYHA) functional classification. This classification is based exclusively on symptom burden and functional limitation; however, it does not fully capture the prognostic complexity of heart failure, as numerous other parameters provide more accurate risk stratification. Importantly, patients with relatively mild symptoms may still carry a substantial risk of hospitalization and mortality. [19]

Table 1.5. Clinical terminology in heart failure [1, 2, 19]

Term	Meaning	How to use in the monograph
Chronic HF	Established HF syndrome with an evolving long-term clinical trajectory	Describes temporal course, not necessarily clinical stability
Decompensated HF	Clinical worsening requiring urgent assessment or intensification of treatment	Preferred ESC 2026 overarching term for episodes of worsening
HF with improved LVEF	Patient with prior reduced LVEF subsequently demonstrating ventricular improvement	Retain historical dysfunction and treatment context
NYHA functional class	Symptoms and limitation according to ordinary activity	Do not equate directly with ESC stages A–D
Right-sided HF	Clinical consequences of RV dysfunction or systemic venous congestion	Search for pulmonary, left-sided, valvular and primary RV disease

The boundary between stability and worsening is especially important in outpatient care. Gradual deterioration may be clinically meaningful even without emergency admission. Escalating diuretic requirements, recurrent unscheduled visits, progressive reduction in activity and worsening kidney function all indicate a need to reassess the therapeutic plan and, in selected patients, the level of specialist care. [22, 24]

1.5. Epidemiology and health-system burden

Heart failure (HF) represents a major and progressively expanding global public health burden. Its prevalence in the general adult population is estimated at approximately 1%–3%, although substantial heterogeneity exists according to geographical region, age, sex, population characteristics, healthcare setting, and the diagnostic criteria applied. [25, 26] Contemporary European estimates indicate a prevalence ranging from approximately 12 to 58 cases per 1,000 individuals. [27] Importantly, these figures are likely to underestimate the true population burden, as most epidemiological studies capture predominantly clinically recognized and formally diagnosed cases, whereas asymptomatic or undiagnosed disease remains incompletely ascertained.

The prevalence of HF increases steeply with advancing age, from approximately 1% among individuals younger than 55 years to more than 10% in those aged ≥70 years. [25–28] Age is likewise one of the strongest determinants of HF incidence. In Europe, crude incidence estimates currently range from approximately 2 to 13 cases per 1,000 person-years, varying from fewer than 1 case per 1,000 person-years among individuals aged 45–54 years to more than 12 cases per 1,000 person-years in those aged >74 years. [28, 29] Across broader adult populations, an incidence of approximately 3–5 cases per 1,000 person-years has been reported, although estimates vary considerably according to age structure, study methodology, and case ascertainment.

The epidemiology of HF reflects a complex interplay between demographic, cardiovascular, metabolic, environmental, and socioeconomic determinants. In addition to conventional cardiovascular risk factors, educational attainment, socioeconomic status, neighbourhood deprivation, climatic conditions, and exposure to air pollution have all been associated with HF risk and contribute to marked geographical variation in disease burden. [25] Population ageing, increasing rates of obesity and metabolic disease, and improved survival following cardiovascular events are further reshaping the epidemiological profile of HF worldwide.

A particularly important epidemiological paradox has emerged over recent decades. Although the crude incidence of HF is increasing in many Western populations, largely as a consequence of population ageing, age-standardized incidence rates have declined over the past three decades. [1, 29] This favourable trend is likely attributable to more effective prevention and treatment of hypertension, coronary artery disease (CAD), myocardial infarction, and other major cardiovascular disorders. Nevertheless, the absolute number of individuals developing HF continues to increase because the population at risk is becoming both larger and older.

The epidemiological trajectory among younger adults is less reassuring. In this population, HF incidence appears to have plateaued or, in some studies, increased. [28, 30] Several mechanisms may account for this observation, including the growing prevalence of obesity, diabetes, hypertension, and other cardiometabolic risk factors; the increasing number of patients with congenital heart disease surviving into adulthood; and changes in diagnostic awareness and surveillance patterns. At the same time, improvements in cardiovascular treatment and HF management have reduced mortality, thereby increasing the number of individuals living with established HF and further contributing to the rising prevalence of the syndrome. [25]

Sex-related differences are also evident. Women account for approximately half, and in some population-based cohorts slightly more than half, of all patients with HF. [31, 32] However, sex distribution varies substantially according to HF phenotype, with women disproportionately represented among patients with preserved left ventricular ejection fraction and men predominating among those with reduced ejection fraction.

Prevalence estimates are highly sensitive to the denominator and to ascertainment. Community screening studies may detect previously unrecognized HF, while hospital discharge databases identify a more clinically severe subgroup. Registries enriched for patients referred to specialist clinics often overrepresent ischaemic and low-EF disease and may underrepresent older, frail individuals with HFpEF who are treated outside specialist programmes. [26]

The population burden should therefore be described with simultaneous attention to crude rates, age-standardized rates, incident cases, prevalent cases and hospitalization events. An increasing absolute number of HF diagnoses does not necessarily imply worsening age-specific cardiovascular prevention. Conversely, a reduction in age-adjusted incidence may coexist with increasing bed occupancy, chronic medication use and long-term care needs because more individuals live to older ages. [25, 29]

Sex and gender also influence pathways to recognition and treatment. Differences in ventricular size, comorbidity distribution, symptom attribution and diagnostic testing may affect who receives an HF diagnosis and when. Epidemiology should not be interpreted exclusively through one LVEF cut-off, especially when the cut-off itself changed in 2026. Historical estimates comparing HFrEF and HFpEF require contextualization by the classification used at the time. [32]

1.5.1. Epidemiology by HF phenotype

The relative distribution of HF phenotypes varies according to the population studied, clinical setting, age structure, and definition of left ventricular ejection fraction (LVEF). In population-based cohorts, approximately half of all patients with HF have preserved ejection fraction, and the relative contribution of this phenotype appears to be increasing. [31] This epidemiological shift likely reflects both improved prevention and treatment of CAD and myocardial infarction, which have reduced the burden of severe systolic dysfunction, and the rising prevalence of conditions strongly associated with HF with preserved ejection fraction (HFpEF), including advanced age, hypertension, obesity, diabetes, chronic kidney disease (CKD), and atrial fibrillation.

Patients with HFpEF are characteristically older and more frequently female than those with HF with reduced ejection fraction (HFrEF). Data from the Swedish Heart Failure Registry, for example, indicate a mean age of approximately 77 years at presentation with HFpEF, with women accounting for approximately 55% of cases. [32] By comparison, patients with HFrEF were younger, with a mean age of approximately 72 years, and approximately 71% were male. [32] These differences underscore the distinct demographic and pathophysiological profiles underlying the major HF phenotypes.

HFpEF itself is increasingly recognized not as a single homogeneous disease entity but as a complex clinical syndrome encompassing several overlapping phenotypes. [1, 15] A predominantly cardiometabolic or obesity-related phenotype, characterized by younger age, higher body mass index (BMI), insulin resistance, and a greater burden of metabolic comorbidity, may account for up to half of HFpEF cases in some populations. Conversely, other regions and cohorts demonstrate a predominantly ageing and vascular phenotype, characterized by advanced age, increased arterial stiffness, hypertension, CKD, and extensive multimorbidity. [1, 15] Recognition of these phenotypic differences has important implications for risk stratification, therapeutic selection, and the development of individualized management strategies.

HFrEF, in turn, is frequently categorized according to underlying aetiology into ischaemic and non-ischaemic forms. Ischaemic heart disease accounts for approximately half of HFrEF cases in many contemporary

cohorts, although its relative contribution varies substantially across geographical regions and according to age, sex, and cardiovascular risk profile. [1, 25]

Because the 2026 definition now includes the historical 41–49% interval within HFrEF, numerators and denominators change even if the underlying patient population remains identical. Older studies that report the distribution of HFrEF, HFmrEF and HFpEF should therefore be preserved as historical results with the original thresholds explicitly stated. Recalculating percentages without access to patient-level LVEF data is inappropriate. [1]

In HFpEF, heterogeneity is particularly pronounced. Obesity-associated, older hypertensive, atrial-fibrillation–dominant, pulmonary-hypertension–associated and infiltrative phenotypes may overlap. Their relative frequencies vary between geographic regions and referral settings. These phenotypes are not merely epidemiological labels; they direct attention to differing haemodynamic mechanisms, competing risks and underlying therapies. [15, 16]

1.5.2. Social determinants, multimorbidity and access to care

Socioeconomic circumstances influence both the likelihood of developing HF and the trajectory after diagnosis. Educational attainment, exposure to smoking or air pollution, access to primary care, medication affordability, availability of cardiac imaging and the ease of specialist follow-up can affect apparent incidence and prognosis. In addition, patients who live alone, have reduced health literacy or face transportation barriers may receive delayed treatment and experience preventable episodes of clinical deterioration. [1, 4, 29]

Multimorbidity complicates both diagnosis and service delivery. Kidney disease alters natriuretic peptide interpretation and treatment tolerance; anaemia and pulmonary disease contribute to dyspnoea; frailty affects exercise prescription and advanced-treatment candidacy; depression and cognitive impairment may compromise self-care. Population-based HF research is increasingly required to account for these interacting dimensions rather than describe risk entirely through one ventricular measurement. [1, 33, 34]

1.6. Natural history and prognosis

Despite major advances in cardiovascular prevention, pharmacological therapy, device treatment, and multidisciplinary HF care, HF remains associated with substantial morbidity and mortality. Although survival following the diagnosis of HF has improved considerably during the past three decades, overall 5-year survival remains below 60% in many contemporary cohorts. [35, 36] Prognosis is strongly influenced by age, HF phenotype, comorbidity burden, clinical setting at diagnosis, and the frequency of subsequent decompensations.

Age is a particularly powerful determinant of outcome. Contemporary Danish data indicate that improvements in HF management have translated into substantially better survival among younger patients, with an estimated 5-year mortality of approximately 15% in individuals younger than 65 years and approximately 39% among those aged 65–79 years. [35] Mortality has also declined among patients aged ≥80 years, although the magnitude of improvement has been more modest than in younger populations. [35] This difference is attributable in part to the higher prevalence of frailty and multimorbidity and to the increasing contribution of non-cardiovascular causes of death with advancing age.

Differences in prognosis between HF phenotypes are more nuanced than might be inferred from LVEF alone. Mortality may be somewhat lower in HFpEF than in HFrEF when directly compared; however, the absolute difference is relatively modest because patients with HFpEF are generally older and have a greater burden of

non-cardiovascular comorbidities. [1, 37] Moreover, the risk of HF-related hospitalization remains substantial across the LVEF spectrum, emphasizing that preserved systolic function does not imply a benign clinical course.

The clinical context in which HF is first recognized also carries important prognostic information. Patients diagnosed in the outpatient setting generally have a more favourable prognosis than those whose initial diagnosis occurs during hospitalization for HF. [38] Conversely, recurrent HF hospitalizations identify a particularly high-risk population and are associated with progressive clinical deterioration, increased mortality, impaired quality of life, and escalating healthcare utilization. Each episode of decompensation may therefore be regarded not merely as an isolated event but as a marker of disease progression and increased subsequent vulnerability. [39]

Looking ahead, the absolute burden of HF and HF-related hospitalization is expected to increase substantially over the coming decades. This trajectory will be driven by the convergence of several demographic and epidemiological forces: continued population ageing, improved survival from cardiovascular disease and established HF, and an increasing prevalence of obesity and cardiometabolic risk factors, particularly among younger individuals. Thus, even in high-income countries where age-adjusted HF incidence is declining, the overall number of patients living with HF is projected to rise. These trends reinforce the need for a comprehensive strategy encompassing primordial and primary prevention, early identification of individuals at risk or with preclinical disease, timely initiation of evidence-based treatment, prevention of recurrent decompensation, and phenotype-specific management across the entire HF continuum. [25, 27]

The disease trajectory is rarely smooth. A patient may spend months or years in relative clinical stability, experience an episode of worsening with hospitalization, recover partially and then remain vulnerable to additional deterioration. Recurrent episodes should be regarded as prognostic signals and as opportunities to reassess the underlying cause, degree of decongestion, implementation of foundational therapy, device indications and quality of follow-up. [39, 40]

An apparent improvement in LVEF, symptom score or laboratory biomarker is clinically meaningful, yet cannot replace a multidimensional prognosis assessment. A preserved or recovered LVEF is compatible with residual fibrosis, scar-mediated arrhythmia risk, ventricular stiffness, right-sided disease or significant functional limitation. Conversely, some patients with longstanding low EF remain stable for extended periods under appropriate therapy. [2, 5, 41]

1.6.1. Sources of heterogeneity in outcome estimates

Table 1.6. Determinants of prognosis [1, 35, 38, 39]

Determinant	How it modifies prognosis	Measurement / interpretation
Age / frailty	Increased competing non-cardiovascular mortality; reduced physiological reserve	Avoid assuming that chronological age alone determines treatment suitability
Clinical setting	Hospitalized and recently worsening patients have greater near-term risk	Report outpatient versus post-discharge cohorts separately
HF phenotype	Different prevalence of cardiac vs non-cardiac causes of death	Use the EF thresholds applicable to study period
Renal and hepatic function	May reflect congestion, impaired perfusion or intrinsic disease	Interpret trends alongside haemodynamics
Arrhythmias / devices	Modify sudden-death risk and treatment eligibility	Include rhythm, QRS, prior therapies and clinical substrate
Treatment intensity	Outcome estimates change with uptake of contemporary therapy	Historical RCT control groups may not reflect 2026 care
Repeated worsening HF	Marks high-risk trajectory irrespective of modest symptom improvement	Capture emergency visits and ambulatory intravenous treatment

Observed prognosis also depends strongly on the chosen outcome. All-cause mortality, cardiovascular mortality, sudden death, first HF hospitalization, recurrent hospitalizations and patient-reported quality of life are not interchangeable. In addition, a trial may show benefit for a composite outcome without significant individual effects on every component. This distinction is particularly important in the 2026 ESC recommendation methodology, which differentiates combined endpoints and individual endpoints explicitly. [1, 42]

1.6.2. Prognostic assessment in ordinary practice

At the bedside, prognosis should be a repeated synthesis of symptom burden, exercise capacity, hospitalization history, blood pressure, cardiac rhythm, LVEF and chamber dimensions, RV function, valve disease, congestion, natriuretic peptides, renal function and treatment tolerance. A progressively declining trajectory, irrespective of an isolated reassuring measurement, warrants intensified follow-up or referral. [1, 43]

The patient perspective is indispensable. Prognostic discussions should not be confined to percentages and survival curves. Expected limitations in daily life, frequency of hospital visits, treatment burden, frailty, independence and personal values matter when identifying therapeutic goals. Shared decision-making and multidisciplinary support should be introduced before a crisis rather than deferred to the terminal stage. [1, 44]

1.7. Aetiology: from broad diagnostic group to actionable cause

The principal causes of heart failure, along with key diagnostic investigations, are summarized in Table 1.7. The underlying etiology of heart failure varies considerably across different geographic regions. In Western and other developed countries, coronary artery disease and hypertension represent the leading contributing factors. [1, 25]

Heart failure may also arise as a consequence of right ventricular (RV) dysfunction. RV structure and performance are adversely affected in conditions associated with pressure and/or volume overload. Although chronic RV failure most commonly develops secondary to pulmonary hypertension resulting from left

ventricular dysfunction, a variety of other conditions may directly impair RV function, including myocardial infarction, arrhythmogenic right ventricular cardiomyopathy (ARVC), and valvular heart disease. [45, 46]

The diagnosis of RV dysfunction relies on quantitative evaluation of global RV systolic performance, most frequently assessed by echocardiography. This evaluation should incorporate at least one validated parameter, such as fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), or the systolic velocity (S′) of the tricuspid annulus measured by Doppler tissue imaging. A comprehensive overview of the diagnosis and management of RV dysfunction is provided in a position statement issued by the Heart Failure Association (HFA). [46, 47]

Aetiological classification must remain independent of the LVEF label. Ischaemic heart disease, pressure overload, primary or inherited cardiomyopathy, inflammatory myocardial disease, infiltrative and storage disorders, valve disease, arrhythmia-mediated dysfunction, congenital structural disease, pericardial pathology, systemic metabolic disease and cardiotoxic therapies are all potential mechanisms. Several causes frequently coexist in the same patient. [1, 3]

The diagnostic aim is not to obtain the largest possible number of tests but to identify abnormalities that are likely to alter treatment. Detailed family history can uncover familial cardiomyopathy. The ECG may identify infarction patterns, conduction disease or arrhythmic triggers. Echocardiography can reveal valve lesions and ventricular remodelling. Cardiac magnetic resonance can characterize scar, inflammation, infiltration or iron deposition, while coronary imaging and targeted laboratory testing may determine disease-specific pathways. [3, 13, 48]

Table 1.7. Aetiological assessment and targeted investigations [1, 3, 13, 14, 48]

Aetiological family	Illustrative clinical clues	Potential focused investigations
Ischaemic	Angina, previous MI, regional wall-motion abnormalities	Coronary CTA, functional ischaemia testing, invasive angiography as indicated
Hypertensive / pressure load	Longstanding hypertension, LV hypertrophy, atrial enlargement	Ambulatory BP, echocardiography, secondary hypertension testing selectively
Valvular / structural	Murmur, regurgitation, stenosis, ventricular overload	Comprehensive echo, transoesophageal echo, CT / CMR as indicated
Genetic / primary cardiomyopathy	Family history, unusual ECG, ventricular dysfunction, sudden death	CMR, pedigree, genetic evaluation when indicated
Inflammatory / infiltrative	Myocarditis presentation, increased wall thickness, systemic red flags	CMR; amyloid laboratory screen/scintigraphy or targeted biopsy
Toxic / treatment-related	Alcohol, cardiotoxic cancer treatment, medication or other exposures	Exposure history, biomarkers, surveillance imaging
Arrhythmia-mediated	Persistent tachyarrhythmia, high ectopic burden, rapid EF decline	ECG, ambulatory monitoring, EP assessment where relevant
Right-heart / pulmonary	RV dilation, pulmonary hypertension, systemic venous congestion	RV echo parameters, lung/pulmonary vascular testing, catheterization selectively

Disease-specific diagnosis can be decisive even when general HF therapy is appropriate. For example, ATTR amyloid cardiomyopathy and AL amyloidosis require different treatment pathways; myocarditis may demand activity restriction and immunological or biopsy assessment in selected phenotypes; severe valve disease may require corrective intervention; tachycardia-mediated cardiomyopathy can improve after durable arrhythmia control. The task of a modern HF monograph is to connect general management algorithms to these causal pathways. [3, 13, 14]

1.7.1. Right ventricular and biventricular failure

Right ventricular dysfunction warrants explicit assessment because it may dominate symptoms, congestion and prognosis even when left ventricular EF is preserved. RV failure can result from left-sided disease and secondary pulmonary hypertension, primary pulmonary vascular disorders, congenital abnormalities, myocardial infarction, arrhythmogenic cardiomyopathy, severe tricuspid regurgitation or other RV myocardial disease. [45, 46]

Clinical assessment should characterize jugular venous distension, hepatomegaly, ascites, peripheral oedema and low-output manifestations. Echocardiographic evaluation should include RV size and function, tricuspid annular plane systolic excursion, fractional area change, tissue Doppler S′, estimates of pulmonary pressure, septal configuration and valve regurgitation. No single metric adequately represents the entire RV mechanical response. [47]

RV dysfunction can also alter the safety of ordinary HF interventions. Aggressive fluid administration may aggravate septal shift and venous congestion, while excessive diuresis can compromise cardiac output in selected preload-dependent patients. Interpretation requires consideration of pulmonary vascular resistance, RV–pulmonary arterial coupling, left-sided filling pressures and the underlying precipitating condition. [46, 49]

1.8. Prevention across the continuum

Prevention should begin before clinical HF develops and continue after a diagnosis has been established. Primordial prevention reduces acquisition of risk factors; primary prevention limits the transition from risk to objective myocardial disease; stage B management aims to forestall symptomatic HF; and secondary prevention after diagnosis seeks to prevent worsening, disability, hospitalization and premature death. This conceptual distinction is useful for organizing the book, although the corresponding therapeutic interventions may overlap. [1, 2]

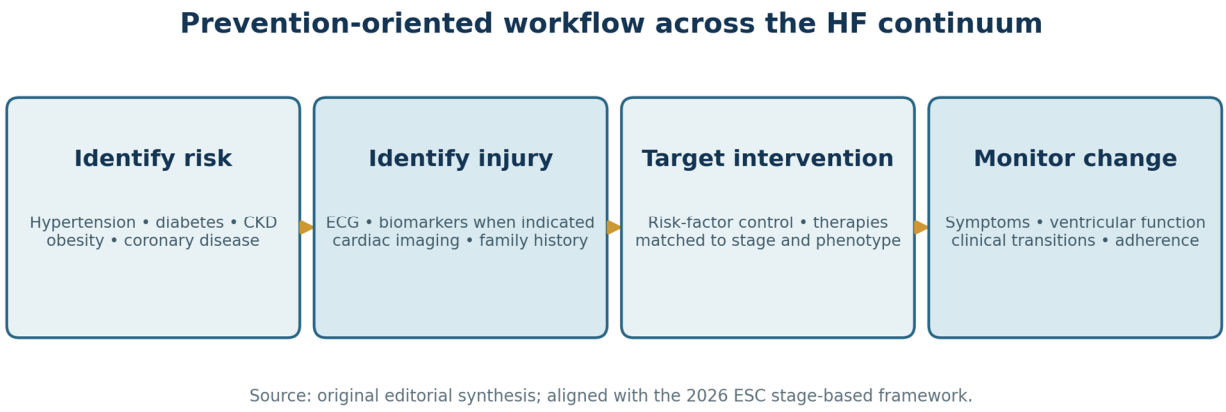


Figure 1.3. Prevention pathway based on ESC 2026 [1].

Lifestyle counselling should be individualized and reinforced periodically. It should include appropriate physical activity, a balanced dietary pattern, avoidance of smoking and heavy alcohol exposure, maintaining a healthy body weight and discouraging cocaine, amphetamines and anabolic steroids. Counselling is not a

substitute for evidence-based management of hypertension, diabetes, kidney disease or coronary disease; these approaches should be implemented in parallel [1, 50].

The 2026 ESC guideline recommends strict blood-pressure control, with systolic blood pressure below 130 mmHg for patients with hypertension or Stage B HF when clinically appropriate, to reduce incident HF risk. It also recommends SGLT2 inhibitor therapy in selected patients with type 2 diabetes and atherosclerotic risk or chronic kidney disease, and finerenone in patients with type 2 diabetes and chronic kidney disease for HF prevention. Exact eligibility and contraindications should be checked against the applicable European prescribing information [1].

Table 1.8. Prevention domains across heart failure stages [1, 48, 50]

Prevention domain	Proposed clinical action	Relation to HF stages
High blood pressure	Achieve guideline-supported BP target with individualized tolerance assessment	A/B; continues in C
Type 2 diabetes / CKD	Choose therapies with demonstrated HF-prevention effect when criteria are met	A/B; co-morbidity management in C
Obesity and inactivity	Nutrition, physical activity, sustainable weight-management strategy	All stages, adjusted to functional status
Tobacco / substance exposure	Smoking cessation; avoid excessive alcohol and cardiotoxic substances	All stages
Coronary and valvular disease	Treat the substrate and evaluate corrective interventions when indicated	B/C and selected D
Potential inherited cardiomyopathy	Family history and targeted specialist assessment	A/B with familial risk
Cardiotoxic cancer treatment	Risk stratification and appropriate longitudinal surveillance	Risk and injury prevention across stages
Symptomatic clinical worsening	Early response plan, treatment optimization and follow-up	C/D

1.8.1. Hypertension and cardiometabolic disease

Hypertension promotes left ventricular hypertrophy, impaired myocardial relaxation, atrial enlargement and progression of atherosclerotic and kidney disease. Blood-pressure control therefore has benefits extending beyond reduction of stroke or coronary events. In established symptomatic HF, however, initiation and escalation of antihypertensive agents must be matched to ejection-fraction phenotype, congestion, renal function, associated valve disease and the need to preserve well-tolerated disease-modifying therapy. [51]

Obesity contributes to HF through haemodynamic loading, sleep-disordered breathing, metabolic inflammation, endothelial dysfunction and interactions with diabetes and kidney disease. Its influence is particularly evident in some HFpEF populations. Clinical assessment should incorporate body composition and functional capacity, because BMI alone cannot distinguish visceral adiposity from sarcopenia or fluid retention. [16, 52]

In type 2 diabetes, prevention of HF is not equivalent to glycaemic control alone. Contemporary therapy selection should incorporate established cardiovascular and renal benefits, baseline kidney function and the patient’s competing clinical priorities. A medicine with favourable glucose-lowering efficacy does not necessarily have the same evidence for preventing HF hospitalization or HF-related mortality. [1, 33]

1.8.2. Prevention in patients exposed to cardiotoxic therapies

Cancer survivors and patients receiving potentially cardiotoxic treatment require a specific preventive model. Baseline clinical risk, previous coronary or myocardial disease, blood pressure, exposure to cardiotoxic drugs or radiotherapy and relevant imaging or biomarker abnormalities should inform surveillance. Detection of cancer therapy-related cardiac dysfunction before symptomatic HF may preserve both cardiac outcomes and the opportunity to continue effective anticancer treatment. [48]

Because cardiotoxicity varies by drug class and treatment regimen, the cardiac monitoring schedule should not be extrapolated from generic HF screening. The dedicated cardio-oncology guidance, current oncology regimen and multidisciplinary decision-making should determine the appropriate surveillance intensity and preventive strategy. [48]

1.8.3. Transition from prevention to structured longitudinal management

No prevention programme can eliminate every case of HF. Once signs or symptoms emerge, the priority changes toward rapid diagnostic confirmation, phenotypic characterization, identification of the cause and initiation of therapy shown to improve outcomes. Follow-up should remain proactive, especially after a recent episode of clinical worsening, medication change or objective decline in functional capacity. [1, 40]

Patients and caregivers benefit from understanding which symptoms should trigger contact with the clinical team: increasing breathlessness, new orthopnoea, progressive ankle oedema, rapid weight gain, reduced urine output, syncope or unexpectedly reduced physical capacity. These manifestations are not diagnostic alone, yet they provide actionable warning signs when interpreted against an individualized baseline and an agreed treatment plan. [53]

1.9. Comorbid risk pathways and their contributions to incident HF

Heart failure prevention can be organized around mechanisms that converge on the myocardium and the circulation. Pressure overload changes chamber geometry and ventricular–arterial interaction; coronary atherosclerosis and myocardial infarction produce scar and loss of viable myocardium; obesity and diabetes reshape metabolic and inflammatory signalling; kidney disease influences volume, vascular stiffness and endothelial function; rhythm disorders disrupt filling and may directly induce cardiomyopathy. Recognizing these mechanisms helps avoid fragmented, risk-factor-by-risk-factor management when several processes coexist in the same patient. [1, 3, 54]

The practical aim is to connect a risk exposure to an identifiable target. A patient with hypertension and diabetes may benefit from blood-pressure reduction, metabolic treatment with demonstrated cardiovascular and renal benefits, weight management and evaluation of occult coronary disease when appropriate. A patient with family history of dilated cardiomyopathy or unexplained conduction disease requires a different emphasis: pedigree, imaging and, selectively, genetic assessment. A patient receiving cardiotoxic cancer therapy may require coordinated surveillance before symptomatic HF occurs. [1, 3, 48]

1.9.1. Hypertension: chronic pressure overload and ventricular remodeling

Arterial hypertension can precede both a reduction in ejection fraction and the development of a predominantly stiff, hypertrophied ventricle. Persistent increases in arterial pressure raise ventricular wall stress, activate hypertrophic signalling and gradually alter ventricular compliance. Left atrial enlargement may follow chronic increases in filling pressure, and atrial fibrillation can subsequently aggravate symptoms

and haemodynamics. Effective blood-pressure reduction therefore acts on several elements of the cardiovascular continuum, not only on the number measured at a clinic visit. [55]

The contribution of hypertension to HF should be assessed longitudinally. The duration of elevated blood pressure, nocturnal control, exercise response, associated obesity, kidney disease and obstructive sleep apnoea may affect the severity of myocardial involvement. Office values alone may miss masked or nocturnal hypertension. Where clinically appropriate, home or ambulatory blood-pressure monitoring improves characterization of exposure and response to therapy. [55]

Regression of ventricular hypertrophy and improvement in arterial–ventricular coupling may occur after sustained management, but the degree of reversibility depends on coexisting fibrosis, age and other myocardial disease. In patients with established HF, a hypertensive phenotype should not obscure the possibility of additional ischaemic, infiltrative or valvular pathology. Similarly, hypotension arising late in the course of previously hypertensive disease may indicate declining stroke volume or restrictive physiology rather than successful control alone. [3, 55]

The 2026 ESC target for HF prevention is a systolic blood pressure below 130 mmHg in relevant patients with hypertension or pre-HF, provided the clinical situation permits [1]. This preventive target must be interpreted alongside orthostatic symptoms, frailty, severe valve lesions and renal function. In symptomatic HF, preservation of treatments with proven prognostic benefit should usually be prioritized over adding medications that lower blood pressure without modifying the HF course.

1.9.2. Type 2 diabetes and cardiometabolic injury

Type 2 diabetes affects HF risk through several pathways. Accelerated coronary atherosclerosis increases the probability of infarction and ischaemic scar. Microvascular endothelial dysfunction, altered substrate utilization, oxidative stress, mitochondrial disturbances, renal disease and metabolic inflammation may contribute to myocardial stiffness and adverse remodelling even in the absence of an infarction. The association between diabetes and HF is therefore not reducible to coronary disease alone. [1, 54]

The choice of glucose-lowering therapy has become a preventive cardiovascular decision. Different drug classes have markedly different effects on heart-failure events despite comparable effects on glycaemia. SGLT2 inhibitors are central to contemporary HF-prevention strategies in eligible patients with diabetes and cardiovascular or kidney disease. The 2026 guidance also recognizes selected roles for finerenone in diabetic CKD and for GLP-1 receptor agonists in patients with type 2 diabetes and additional cardiovascular risk factors [1].

The effects observed in diabetes outcome trials should nevertheless be interpreted according to the enrolled population and endpoint. Prevention of first HF hospitalization among individuals without established HF differs from reduction of recurrent worsening events in symptomatic HF. Likewise, reduction of a combined endpoint does not establish an identical effect on every component. These distinctions will be retained explicitly in the treatment chapters. [42]

Because diabetes commonly coexists with obesity, hypertension and kidney disease, the most useful clinical assessment is integrated. Blood pressure, urinary albumin, eGFR, lipid profile, weight pattern, physical capacity, prior atherosclerotic events and medication tolerance determine a cardiovascular management strategy. This approach is more informative than focusing exclusively on glycated haemoglobin as a surrogate for HF protection. [33, 54]

1.9.3. Obesity, physical inactivity and body composition

Obesity-related heart failure reflects a complex combination of haemodynamic and metabolic disturbances. Increased circulating volume and cardiac output demand contribute to chamber loading, while adipose tissue inflammation, insulin resistance, sleep apnoea and altered myocardial substrate metabolism may influence relaxation, vascular function and exercise tolerance. In patients with obesity-associated HFpEF, apparently preserved LVEF can coexist with elevated filling pressures and marked limitation during exertion. [52]

Body mass index is convenient for population studies but has important clinical limitations. It cannot differentiate visceral fat from peripheral adiposity, nor distinguish skeletal muscle depletion from normal lean mass. Excess fluid can further distort measured weight in patients with established HF. Waist circumference, longitudinal weight changes, functional performance and nutritional assessment add complementary information and may better identify the individual at risk. [16, 34]

Sedentary behaviour reduces cardiorespiratory fitness and promotes metabolic dysfunction independently of weight. In the prevention setting, sustained and achievable activity is preferable to recommendations that are impressive on paper but poorly tolerated or maintained. In symptomatic HF, exercise prescription must instead reflect stability, symptoms, arrhythmia risk, musculoskeletal limitations, frailty and access to supervised cardiac rehabilitation. [50, 56]

Weight-management strategies should be realistic, sensitive to sarcopenia risk and integrated with treatment of diabetes, hypertension and sleep-disordered breathing. Rapid or indiscriminate weight loss in an older frail patient may worsen muscle function despite reducing BMI. Conversely, deliberate improvement in fitness, nutrition quality and body composition can produce functional advantages not represented by change in LVEF alone. [34, 56]

1.9.4. Chronic kidney disease and cardiorenal feedback

The heart and kidney participate in a bidirectional physiological relationship. Kidney disease increases sodium retention, arterial stiffness, vascular calcification, anaemia and systemic inflammation. HF may in turn impair kidney function through reduced effective perfusion, neurohormonal activation and increased systemic venous pressure. This reciprocal relationship explains why renal function is central to prevention, prognosis and therapeutic safety. [54, 57, 58]

Urinary albumin-to-creatinine ratio and eGFR characterize different dimensions of kidney injury and should be assessed together when relevant. Albuminuria may identify microvascular disease and heightened cardiovascular risk even when eGFR is relatively preserved. The 2026 ESC diagnostic laboratory framework explicitly includes UACR when screening for associated disease in patients with suspected HF [1].

A decline in eGFR during initiation of haemodynamically active therapy does not always represent structural renal injury. In stable patients, modest early changes can accompany treatments that improve long-term cardiovascular or kidney outcomes. However, the direction and magnitude of change must be assessed in the context of blood pressure, potassium, volume status, congestion, drug exposure and associated acute illness. An unexplained progressive fall in kidney function should never be dismissed as a benign drug effect. [33, 58]

Cardiorenal care also requires avoidance of preventable injury. Non-steroidal anti-inflammatory medications, dehydration, excessive fluid loading, inappropriate diuretic dosing and unrecognized obstruction can each

destabilize kidney function and HF status. Risk communication should therefore include medication reconciliation and an explicit plan for reassessment when the clinical condition changes. [53, 58]

1.9.5. Atherosclerotic disease, myocardial infarction and residual risk

Coronary artery disease remains a major pathway to ventricular systolic dysfunction. A first myocardial infarction can produce irreversible scar, altered regional contraction, mitral regurgitation, ventricular remodelling and arrhythmic substrate. Recurrent ischaemia and extensive multivessel disease may further impair ventricular performance. Prevention of atherosclerotic events therefore has the additional benefit of preventing a substantial proportion of ischaemic heart failure. [59, 60]

Not every patient with coronary artery disease and HF has the same mechanism. Some have extensive infarct scar and severe regional dysfunction; others have diffuse microvascular disease, chronic ischaemia, hibernating myocardium or a combination of coronary disease with hypertensive or valvular pathology. Detailed anatomy and ventricular assessment are needed before deciding whether the primary objective is secondary prevention, symptom relief, revascularization or a combination. [59, 61, 62]

Secondary prevention should follow current coronary guidelines, including lipid-lowering, smoking cessation, blood-pressure management, antithrombotic treatment when indicated, physical activity and individualized revascularization decisions. These measures should be distinguished from drug treatment aimed primarily at HF hospitalization or mortality. An intervention may be highly beneficial for preventing recurrent myocardial infarction without having the same demonstrated effect on established ventricular failure. [59, 60]

1.9.6. Frailty, ageing and competing risks

Ageing increases HF risk through cumulative exposure to hypertension, coronary disease, diabetes and kidney dysfunction as well as intrinsic changes in vascular and myocardial structure. However, age is not a uniform biological process. Individuals of identical chronological age may differ profoundly in muscular reserve, cognition, mobility, nutritional status, social support and ability to tolerate treatment. Frailty provides additional prognostic information by capturing vulnerability to physiological stress. [34]

Frailty should be distinguished from cachexia and sarcopenia. Cachexia involves involuntary wasting associated with systemic disease, while sarcopenia emphasizes impaired muscle mass, strength or physical performance. They may coexist, but they are not interchangeable diagnoses and may require different nutritional or rehabilitative approaches. Importantly, a person with obesity may also be sarcopenic; apparent body size should not be interpreted as preservation of functional reserve. [34]

Prevention and treatment must balance competing outcomes. Intensive pharmacological treatment may reduce cardiovascular events yet become impractical if it causes recurrent falls, symptomatic hypotension or major treatment burden in a vulnerable patient. Conversely, frailty should not be used automatically to deny therapies likely to improve symptoms or preserve independence. The best strategy is individualized assessment with an explicit account of patient goals and the resources available for monitoring. [1, 34]

1.9.7. Anaemia, iron deficiency and functional reserve

Anaemia and iron deficiency have clinical consequences beyond their effects on laboratory values. Reduced oxygen transport and altered iron-dependent mitochondrial function contribute to exercise intolerance, fatigue and reduced skeletal-muscle efficiency. Their prevalence is substantial in established HF, and both may coexist with kidney disease, nutritional deficits, chronic inflammation or occult blood loss. [1, 63]

The clinical evaluation should distinguish aetiology from consequence. A low haemoglobin concentration may reflect renal disease, chronic inflammation, blood loss, nutritional deficiency or haematological pathology. Iron indices should be interpreted in relation to inflammatory status and kidney function. Identifying a reversible cause is necessary before extrapolating results from HF-specific iron replacement trials to other populations. [1, 33]

Recognition of anaemia and iron deficiency also matters in prevention-oriented care. They may amplify symptoms, impair activity and increase the likelihood that mild cardiac dysfunction becomes clinically apparent. Their treatment should be based on the specific diagnosis and contemporary evidence, rather than assuming that all patients with reduced exercise tolerance require empirical supplementation. Disease-specific intravenous iron recommendations will be detailed in the comorbidity chapter. [63, 64]

1.9.8. Pulmonary disease, sleep apnoea and the right heart

Chronic pulmonary disorders can precipitate or intensify HF symptoms through hypoxaemia, pulmonary vascular remodeling, elevated right ventricular afterload, physical deconditioning and respiratory limitation. Distinguishing pulmonary dyspnoea from HF is especially challenging when both conditions coexist. Clinical history, examination, pulmonary function testing, echocardiography and selected imaging should therefore be interpreted as complementary, not competing, diagnostic tools. [1, 45]

Obstructive sleep apnoea contributes to cardiovascular stress through intermittent hypoxaemia, sympathetic activation, adverse intrathoracic pressure swings and hypertension. Central sleep apnoea is frequently encountered in established HF and may reflect circulatory instability and delayed respiratory feedback. The two syndromes require distinct treatment considerations. Treatment chosen for obstructive events cannot automatically be assumed safe or effective for central events in patients with ventricular systolic dysfunction. [1, 65, 66]

The right ventricle deserves particular emphasis when pulmonary and cardiac disease coexist. Symptoms and prognosis may reflect the interaction between pulmonary vascular resistance, RV contractile function, tricuspid regurgitation, venous congestion and LV filling. Preventive action includes treating pulmonary disease appropriately, avoiding harmful exposures, diagnosing sleep-disordered breathing and identifying patients with progressive pulmonary vascular or right ventricular involvement. [46, 47]

1.10. Clinical and organisational implementation of prevention

The principal weakness of prevention programmes is often not the absence of an evidence-based intervention but failure to identify eligible patients, initiate treatment, maintain adherence and reassess the response. Preventive advice given once at a consultation is unlikely to address the accumulation of risks over years. A longitudinal model is needed in which clinical decisions are reviewed when age, comorbidity burden, renal function, cardiac structure or the patient's preferences change. [1, 53]

Effective care requires collaboration between primary care, cardiology, nephrology, endocrinology, rehabilitation and other relevant disciplines. The precise structure depends on local resources, but responsibility for action should be explicit. Screening results that are not reviewed, referrals without follow-up and medications prescribed without tolerance assessment can all interrupt an otherwise evidence-based pathway. [1, 67]

1.10.1. Transitions between settings and care teams

Multidisciplinary heart failure management programmes are designed to reduce hospitalization and mortality by ensuring that patients receive appropriate diagnostic investigations, an accurate diagnosis, evidence-based pharmacological and device therapy, structured education, and adequate long-term follow-up. [1]

A network meta-analysis of 53 randomized trials published in 2017 demonstrated that both specialized disease-management clinics and nurse-led home visits reduced all-cause mortality compared with usual care. Home visits ranked highest, although differences between effective service models were not statistically significant. [68]

Heart failure management programmes may be delivered through specialized outpatient clinics within primary, secondary, or tertiary care. [67, 68]

No single model of care has consistently demonstrated superiority across all healthcare settings. [67] Both home visits and specialized heart failure clinics have been associated with reductions in all-cause hospital admission and mortality, whereas educational interventions used in isolation have not consistently produced similar improvements. [68, 69]

Dedicated HF programmes may include outpatient specialist clinics, structured primary-care pathways, nurse-led follow-up, home visits, remote consultation and educational interventions. No single structure is optimal for all patients. Availability of trained staff, complexity of disease, access to emergency care, ability to use digital systems and family support determine the most appropriate organizational model. [67]

For patients with high-risk disease, transition from hospital to ambulatory care is especially important. Communication should identify the responsible clinician, the intended diuretic and disease-modifying drug regimen, the timetable for laboratory reassessment, objective criteria for urgent contact and the next scheduled clinical review. The discharge document is a treatment instrument, not simply a record of the inpatient episode. [40]

1.10.2. Patient education, shared decisions and self-management

Self-management education should be continuous, tailored and verified. Patients need to understand what HF means, why symptoms may recur despite apparent stability and why prognostically important treatment often continues even after clinical improvement. A written plan is preferable to relying entirely on recollection of a complex verbal consultation. [53]

Educational encounters should include practical instructions on medication use, weight and congestion monitoring, recognition of red flags and decisions requiring immediate contact with the care team. Adherence problems may be caused by treatment complexity, adverse effects, cost, limited health literacy, depression, cognitive impairment or inadequate social support. Identifying the reason is more useful than labelling the patient as simply non-adherent. [53]

A caregiver may be essential for medication organization, transportation, remote monitoring, nutritional support or communication with healthcare professionals. Their role should reflect the patient’s values and consent, with preservation of autonomy and confidentiality. Education should also be adapted for patients with visual or hearing limitations, cognitive decline, language barriers and reduced capacity to access written digital resources. [53]

Communication techniques such as teach-back can reveal misunderstandings early. The clinician explains an intervention in accessible terms and asks the patient to describe how it will be implemented. This is especially useful when discussing changes to diuretic regimens, sick-day precautions, or symptoms that should trigger urgent evaluation. Successful care depends on mutual understanding rather than only prescription accuracy. [53]

1.10.3. Measurement, audit and prevention quality indicators

A prevention programme should define what success means before outcomes are measured. Useful implementation measures include the proportion of eligible patients with documented blood pressure, renal function and albuminuria; the proportion receiving indicated preventive treatment; the frequency of timely reassessment; medication persistence; and the interval between recognition of deterioration and clinical response. [70]

Patient-reported measures should complement biological outcomes. Reduced symptom burden, preserved independence, confidence in self-care, quality of sleep, exercise tolerance and the ability to continue valued daily activities matter to patients even when they do not change a laboratory value. These outcomes should not be substituted for hospitalization or survival endpoints, but they help characterize the experience and effectiveness of care. [53, 70]

Table 1.9. Quality indicators for prevention and longitudinal care [70]

Implementation domain	Example process indicator	Why it matters
Risk recognition	Documented BP, eGFR/UACR, diabetes and relevant family history	Ensures major causal pathways are not overlooked
Treatment access	Eligible patients offered stage-appropriate therapy	Links detection with intervention
Follow-up	Timely clinical/laboratory review after important therapy changes	Identifies intolerance and missed opportunities
Transition of care	Communicated treatment plan after hospitalization	Reduces fragmentation and early clinical worsening
Patient understanding	Recorded education and action plan	Supports self-care and shared decisions
Equity	Review by socioeconomic / access barriers	Detects preventable gaps in care

The scientific and organizational themes of this chapter converge on the same message: the diagnosis and prevention of HF are longitudinal processes. The clinical phenotype may change, the available treatment evidence may evolve and the balance of competing diseases may shift. Clinical practice requires a stable conceptual framework together with explicit interpretation of current recommendations and the limits of the underlying evidence.

1.11. Interpreting guideline evidence in a heterogeneous disease

Clinical interpretation of therapeutic recommendations requires an understanding of the supporting evidence, the patients studied, the outcomes measured, and the boundary between trial data and extrapolation. This approach is particularly important after a classification change. Clinical categories are useful for communication, but randomized trials have inclusion criteria that cannot be retroactively changed by a new nomenclature. [1, 42]

The 2026 ESC guideline updates the approach to grading certainty and the wording of recommendations [1]. It distinguishes evidence derived from appropriately designed treatment studies from evidence underpinning diagnostic tests and prediction models. The type, number, precision and risk of bias of available studies

influence confidence. Consequently, the meaning of an evidence level should never be inferred solely from the number of cited papers or the prominence of the intervention in clinical practice.

1.11.1. Classes of recommendation and clinical applicability

A recommendation class expresses the balance of evidence and expert agreement concerning the desirability of an intervention for a specified patient group. It is not itself an estimate of individual absolute benefit. When a medicine is recommended to reduce a clinical event, the recommendation applies to the patients, doses and clinical circumstances defined by the guideline. Contraindications, treatment tolerance, renal function, blood pressure, interactions and the patient's therapeutic objectives remain relevant. [1]

Recommendation class and evidence level must be interpreted alongside the intervention, eligible population, relevant LVEF or disease stage, and intended benefit. Eligibility criteria remain essential even when a recommendation is summarized by its class and level. Applying the grade without this context can be misleading in patients at the borders of trial inclusion criteria or with severe multimorbidity. [1]

Recommendation updates may arise for several reasons: a positive new randomized trial, an adequately powered negative trial, the recognition of an adverse safety signal, new data from previously underrepresented populations or a methodological change in grading. Clinical interpretation of updated guidance should preserve the reasons for important changes, especially when earlier recommendations differed. Explicit discussion of superseded evidence prevents the reader from mistaking two temporally different recommendations for a contradiction. [1, 64]

1.11.2. Composite endpoints and separate outcome components

Clinical trials in HF frequently use composite outcomes that combine cardiovascular death with first or recurrent worsening HF events. A composite increases statistical efficiency and captures more of the patient's clinical burden, but it does not imply that each constituent outcome is reduced by the same magnitude. A treatment may produce a clinically important reduction in hospitalizations without demonstrating a statistically significant mortality reduction in the same trial. [42]

When presenting an intervention, a rigorous interpretation distinguishes the composite result, its constituent components, secondary endpoints and patient-centred outcomes. The number of events, duration of follow-up and degree of statistical precision determine how much weight should be placed on a particular component. Subgroup analyses and secondary outcomes may suggest heterogeneity but usually deserve more cautious language than a prespecified, adequately powered primary result. [42]

The 2026 ESC guideline explicitly clarifies wording that refers to outcomes supported individually and outcomes supported through a composite [1]. Accordingly, the statement "reduces mortality and hospitalization" must not be used reflexively when the principal evidence is a reduction in a combined outcome driven largely by hospitalization. Accurate endpoint description affects treatment expectations and informed decision-making.

1.11.3. Absolute versus relative benefit

A relative risk reduction is most informative when accompanied by the underlying event rate. A sizeable relative benefit may correspond to a modest absolute benefit in a low-risk population, whereas a smaller relative effect may translate into a substantial number of events prevented among patients with a high baseline risk. For this reason, trial tables should include, whenever ascertainable, absolute event rates and follow-up duration as well as hazard ratios and confidence intervals. [71]

Absolute effects are especially relevant for comparing preventive treatment in Stage A or B with disease-modifying treatment in Stage C or D. An asymptomatic individual may have many years of cumulative risk exposure, while a recently hospitalized patient may face an unusually high short-term event rate. The time horizon and competing causes of adverse outcome differ profoundly between these settings. [1, 71]

The number needed to treat, when presented, should be explicitly connected to a particular endpoint and time frame. An NNT calculated from one trial is not a timeless property of the drug, nor necessarily transportable to patients with different background therapy. Contemporary uptake of multiple effective treatments can alter absolute event rates and the incremental benefit of a new intervention. [71]

1.11.4. Interpreting trial evidence after the 2026 LVEF reclassification

The change from three named EF categories to two has a practical benefit: it reduces the burden of intermediate terminology and encourages clinicians to consider an expanded HFrEF spectrum. However, the underlying evidence remains granular. Trials originally enrolling patients with LVEF ≤35%, ≤40%, >40% or ≥50% studied partially overlapping but non-identical populations. Their findings should be presented according to the original protocol, rather than silently relabelled under the new classification. [1, 72, 73]

The 41–49% interval is particularly important. Although these patients are now included in the ESC HFrEF category, the magnitude and certainty of effect for individual therapies may differ across the LVEF spectrum. Some treatments have direct prospective evidence across a broad range, whereas others derive part of their support from pooled or subgroup analyses. Clinical practice should follow the explicit 2026 recommendation, while academic discussion should retain this evidence nuance. [1, 74, 75]

Similarly, data from HFpEF trials should not be reduced to the claim that all therapies have equal benefit in every patient with EF ≥50%. Obesity-related HFpEF, marked hypertensive heart disease, restrictive amyloid physiology and atrial-fibrillation–dominant disease can produce different limiting mechanisms. The challenge is to identify the clinical groups for which population-level benefits can be applied confidently and those for which disease-specific evaluation is paramount. [14, 16]

1.11.5. Limitations of subgroup analyses and observational evidence

HF research frequently examines treatment effects by age, sex, baseline EF, kidney function, rhythm, diabetes status or aetiology. These analyses are clinically useful when predefined and biologically coherent. Nevertheless, an apparent difference between two subgroups may reflect chance, inadequate sample size, multiple comparisons or imbalance in baseline risk. The relevant statistical question is generally whether a credible interaction exists, not whether a treatment is statistically significant in one subgroup and not another. [76]

Registry studies provide valuable information concerning long-term safety, treatment uptake, rare adverse events and outcomes in populations underrepresented in trials. Their main limitation is that patient selection and treatment decisions are not randomized. Confounding by disease severity may make more intensive therapy appear harmful if sicker patients receive it more often. Conversely, treatment recipients may have better healthcare access and prognosis for reasons unrelated to the intervention itself.

Randomized trial evidence should be prioritized when evaluating treatment efficacy, while registry findings should be used primarily to assess external validity, clinical implementation and hypotheses requiring further study. Both forms of evidence are valuable, but they answer different questions. An observational association should not be interpreted with the same causal certainty as the result of an appropriately randomized trial.

1.11.6. Diagnostic thresholds and probability rather than binary certainty

The limitations of numerical cut-offs extend beyond LVEF. Natriuretic peptide thresholds, measures of diastolic function and haemodynamic criteria are affected by age, rhythm, obesity, kidney function, loading conditions and methodological variability. The value of a threshold depends on the setting in which the test is used: outpatient exclusion of HF, emergency assessment of breathlessness, confirmation of HFpEF or prognostic reassessment during follow-up. [7, 8, 12]

A diagnostic test that performs well as a rule-out strategy may be less reliable for confirmation. For example, low natriuretic peptide values reduce the probability of HF in many patients, but can be misleading in obesity or particular clinical scenarios. Elevated values support the need for further assessment without establishing the diagnosis in isolation, particularly when atrial fibrillation, kidney dysfunction or acute pulmonary disease may explain the elevation. [8, 52, 77]

Echocardiography should similarly be interpreted as a constellation of findings. Ventricular dimensions, chamber volumes, wall thickness, Doppler filling variables, left atrial size, RV performance, valve function and estimated pulmonary pressure together provide stronger information than an isolated abnormal measurement. When uncertainty persists despite the standard work-up, advanced imaging, stress assessment or invasive haemodynamics may be appropriate in selected patients. [6, 12, 47]

1.12. Classification and interpretation of therapeutic evidence

The 2026 ESC guideline changes nomenclature, staging and the classification of therapies. Treatment recommendations must be interpreted against the populations studied and the revised approach to evidence grading. A change in phenotype terminology does not remove the eligibility criteria of the trials supporting an intervention. [1]

Three levels of information should be distinguished: (i) a current clinical recommendation explicitly supported by 2026 ESC guidance; (ii) a historical study observation, reported with the population and LVEF thresholds used by the trial; and (iii) an interpretative synthesis connecting mechanisms and evidence that is not itself a formal ESC recommendation. Recommendation class and evidence level should be interpreted in their original guideline context. [1]

1.13. Take-home synthesis

Heart failure is a clinical syndrome that requires objective cardiac evidence and careful differential diagnosis. [1, 2]

ESC 2026 applies two primary symptomatic LVEF phenotypes: HFrEF <50% and HFpEF ≥50% with corroborating abnormalities. [1]

Historical HFmrEF remains relevant when interpreting trial evidence but is not a current separate ESC 2026 phenotype. [1, 9]

Stages A–D connect prevention, preclinical dysfunction, symptomatic HF and advanced disease. [1, 2]

LVEF is continuous, context-dependent and insufficient to describe myocardial biology or clinical risk in isolation. [6, 7]

Epidemiological estimates must specify population, classification, time period and case ascertainment. [25, 26]

Prognosis is best described using longitudinal, multidimensional clinical information, including recurrent worsening. [39, 43]

The underlying cause should be investigated because etiological treatment may alter outcomes beyond general HF therapy. [1, 3]

Preventive treatment and guideline-directed therapies should be applied to specific eligible groups, not generalized by label alone. [1]

2. Aetiology and Pathophysiological Framework

This chapter links the causes of heart failure with the physiological mechanisms that shape its clinical expression. It distinguishes persistent myocardial or structural disease from precipitating events, contributory conditions and the resulting pressure–flow abnormalities. Genetic susceptibility, coronary and valvular loading, inflammatory and toxic injury, cellular calcium handling, neurohormonal activation and extracellular remodelling are considered alongside right-heart function, congestion, cardiorenal interaction and systemic reserve. Human mechanistic studies and clinical trials are used to separate biological plausibility from demonstrated patient benefit. Three constructed cases illustrate the approach.

2.1. From the heart-failure phenotype to a causal formulation

Heart failure is the clinical expression of an interaction between myocardial disease, abnormal loading conditions, electrical disturbances and the responses of other organs. A diagnostic label describes the syndrome; an aetiological formulation explains how it has developed in the individual patient. These are complementary tasks. The presence of a reduced or preserved left ventricular ejection fraction does not, by itself, establish whether the principal problem is coronary disease, a genetic cardiomyopathy, valvular loading, infiltrative disease, tachyarrhythmia or another process. This distinction is the basis of a cause-directed clinical approach. [1, 3]

The 2026 ESC framework groups symptomatic heart failure according to an LVEF below 50% or at least 50%, while also recognizing stages of disease. This chapter uses those contemporary phenotype labels. However, the original entry criteria of clinical trials remain unchanged: historical HFrEF, HFmrEF and HFpEF populations must be identified by their actual LVEF ranges. A revised name cannot extend a trial result automatically to every patient placed within the new category. Aetiological investigation remains relevant across both groups. [1]

A useful clinical formulation distinguishes four elements: the substrate, the precipitant, the amplifiers and the current physiological consequences. The substrate is the persistent disease or anatomical lesion. The precipitant is the event that disrupts an existing equilibrium. Amplifiers are coexisting abnormalities that sustain or worsen the syndrome. The consequences are the measurable manifestations, such as elevated filling pressures, reduced forward flow, arrhythmia or impaired exercise reserve. These categories describe roles within a causal model rather than four mutually exclusive lists of diagnoses.

For example, a patient may have an old infarct as the principal substrate, an infection as the immediate precipitant, chronic kidney disease and secondary mitral regurgitation as amplifiers, and a congested low-output state as the current presentation. Identifying the infection does not explain the underlying cardiomyopathy. Conversely, identifying the old infarct does not establish why deterioration occurred this week. The distinction helps prevent the common error of treating a trigger while leaving the persistent disease incompletely characterized.

Causation should also be considered longitudinally. Hypertension can precede ventricular dysfunction; later, low blood pressure may reflect advanced disease or treatment rather than the absence of a hypertensive contribution. Atrial fibrillation may initiate dysfunction, arise because of atrial pressure overload, or participate in a self-reinforcing loop. The clinician should therefore construct a timeline from previous

imaging, symptoms, rhythm recordings, exposures, family history and treatment response. The explanatory power of a diagnosis is stronger when its timing and physiological effects agree with the observed trajectory.

Table 2.1. A structured causal formulation for an individual patient

Domain	Question to answer	Example and interpretative safeguard
Underlying substrate	Which persistent disease or lesion is present?	Infarct scar, cardiomyopathy or valve lesion; distinguish documented disease from a presumed label.
Immediate precipitant	What changed before deterioration?	Infection, ischaemia, arrhythmia or treatment interruption; the trigger need not be the original cause.
Amplifying conditions	What limits compensation or maintains the disorder?	Renal dysfunction, obesity, anaemia, pulmonary disease or functional regurgitation; more than one may contribute.
Current physiology	What is failing now?	Congestion, inadequate forward flow, impaired reserve or combinations; blood pressure alone is insufficient.
Potential reversibility	Which components can plausibly improve?	Distinguish relief of loading abnormalities from recovery of injured myocardium and from removal of the cause.

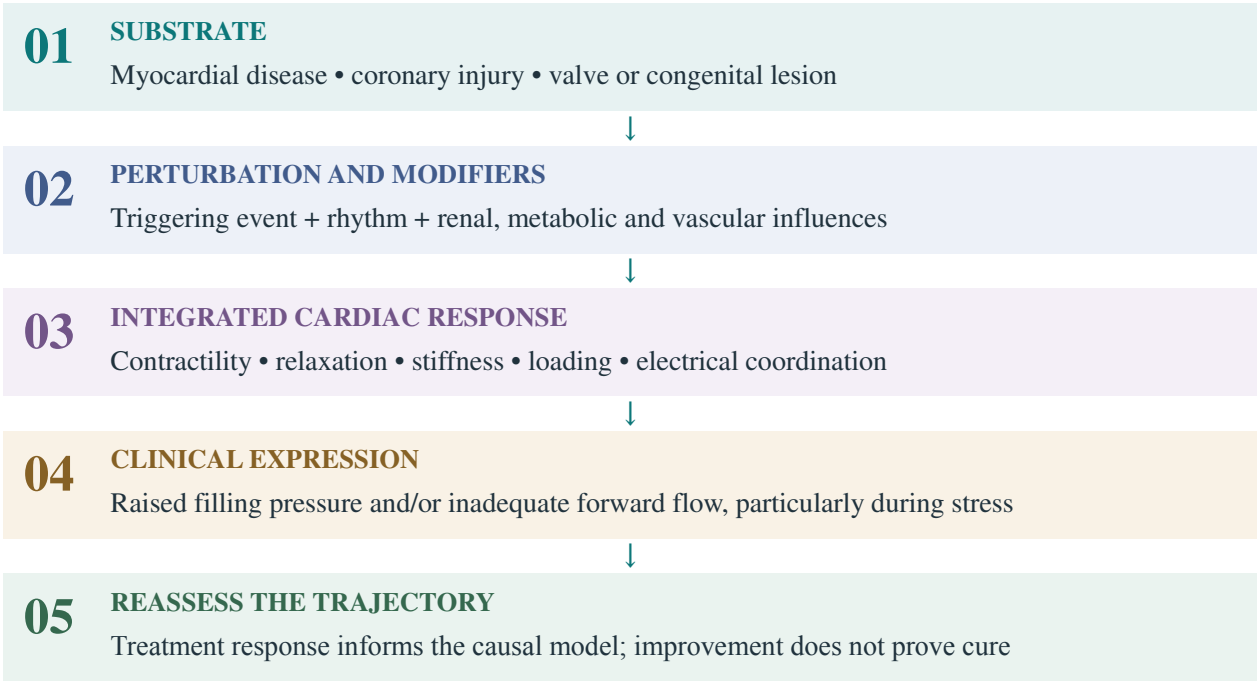


Figure 2.1. A causal map of heart failure: more than a single ejection fraction

2.2. Haemodynamic foundations: pressure, volume, flow and reserve

2.2.1. Why ejection fraction is not synonymous with cardiac performance

LVEF is a ratio, whereas systemic perfusion depends on forward flow and its distribution. A ventricle can eject a large proportion of a small end-diastolic volume and still deliver an inadequate stroke volume. Conversely, a markedly dilated ventricle may sustain a resting stroke volume despite a low ejection fraction. These possibilities follow from the definitions and explain why the same LVEF can coexist with very different chamber geometry, filling pressure, symptoms and physiological reserve.

LVEF = (EDV − ESV) / EDV × 100%; stroke volume = EDV − ESV; cardiac output = forward stroke volume × heart rate.

An illustrative calculation clarifies the distinction. An end-diastolic volume of 100 mL and an end-systolic volume of 40 mL yield an LVEF of 60% and a volumetric stroke volume of 60 mL. Volumes of 60 mL and 24 mL produce the same LVEF but a stroke volume of only 36 mL. At 70 beats per minute, the respective outputs would be 4.2 and 2.52 L/min, assuming no important regurgitant or shunt flow. These are constructed numerical examples, not diagnostic thresholds or patient observations.

In significant mitral regurgitation, total left ventricular ejection includes both forward aortic flow and backward regurgitant flow. LVEF may therefore appear relatively preserved despite compromised effective systemic output. This is a direct consequence of where the ejected blood goes. Interpretation should combine chamber volumes, regurgitant severity and forward stroke volume rather than treating an isolated LVEF as a complete measurement of myocardial health. The distinction is developed further in the valve-disease chapter.

2.2.2. Relaxation, stiffness and the meaning of filling pressure

Diastolic performance has active and passive components. Relaxation is the time-dependent decline in myocardial tension after contraction; chamber stiffness describes the increase in pressure associated with an increment in volume. They are related but not interchangeable. Delayed relaxation may impair early filling, whereas increased stiffness can cause a disproportionate pressure rise even when filling volume is modest. In human myocardial biopsy studies, increased cardiomyocyte passive tension demonstrated that diastolic dysfunction cannot be attributed solely to extracellular fibrosis; properties within the myocyte also matter. [78]

Intracavitary pressure is not identical to the pressure that distends the myocardium. A conceptual approximation is transmural pressure equals intracavitary pressure minus surrounding pressure. Raised pericardial or right-sided pressure may increase a measured left-sided filling pressure without an equivalent increase in left ventricular distending pressure. Thus, an elevated wedge pressure should be interpreted with respiratory conditions, right-heart findings and the clinical setting. This reasoning is especially relevant to right-heart failure, restrictive physiology and the Fontan circulation.

Afterload likewise cannot be reduced to a single brachial blood-pressure reading. Ejection depends on valvular obstruction, arterial resistance and pulsatile load as well as ventricular geometry. A low systolic pressure can coexist with substantial opposition to flow when stroke volume is severely reduced. Preload, in turn, describes myocardial loading before contraction; it should not be used as a synonym for total body fluid.

A patient can have extensive oedema and still have limited tolerance of an abrupt reduction in effective ventricular filling.

2.2.3. Reserve is often more informative than resting equilibrium

Exercise requires coordinated increases in heart rate, forward stroke volume, coronary supply, peripheral blood flow and oxygen extraction. Failure of several small compensatory responses can produce substantial exercise limitation despite relatively unremarkable resting measurements. In a physiological study of HFpEF, impairment was not confined to diastole: chronotropic, contractile, vascular and other reserve abnormalities coexisted. [79]

Resting stability therefore means that demand is currently being met, not that cardiovascular reserve is normal. A patient who is comfortable while seated may develop a steep increase in filling pressure or an inadequate rise in cardiac output during activity. This provides a physiological rationale for exercise-based investigation when resting tests do not explain symptoms. The choice and interpretation of such tests are addressed in the diagnostic chapter; here the central point is the distinction between a system at equilibrium and a system able to respond to stress.

Table 2.2. Physiological distinctions that prevent misleading interpretation

Do not equate	Why they differ	Clinical implication
LVEF and forward output	A ratio does not specify chamber volume or the destination of ejected blood.	Assess volumes, stroke volume, heart rate and regurgitation together.
Filling pressure and total fluid excess	Pressure depends on compliance, distribution and external constraint as well as volume.	Do not infer a large removable fluid volume from pressure alone.
Relaxation and stiffness	One is an active temporal process; the other is a pressure–volume property.	A single diastolic index cannot describe every mechanism.
Normal pressure and adequate perfusion	Vasoconstriction can preserve arterial pressure despite low output.	Examine organ perfusion and the overall haemodynamic profile.
Resting compensation and normal reserve	Demand is lower at rest, and several reserve defects may coexist.	Investigate exertional limitation when resting findings are insufficient.

[78, 79].

2.3. Aetiological investigation as hypothesis testing

The aetiological differential spans coronary, hypertensive, valvular, rhythm-related, myocardial, congenital, infectious, toxic, infiltrative, storage, pericardial, metabolic and neuromuscular causes. The matrices below preserve that breadth while separating common presentations from the tests that answer a specific causal question. They are not instructions to request every investigation in every patient. [1, 3]

An efficient investigation begins with phenotype and probability. A regional wall-motion abnormality after an infarct raises a different question from concentric thickening with neuropathy, a dilated ventricle after

cancer treatment, or progressive atrioventricular block in a family with sudden death. A test should be selected because a positive or negative result would change the causal formulation, treatment, counselling or surveillance. Testing without a prior question can generate incidental abnormalities that obscure rather than clarify the diagnosis.

The 2023 ESC cardiomyopathy framework distinguishes the morphological phenotype from its underlying cause and emphasizes integration of clinical assessment, imaging and genetics. A dilated phenotype is therefore the start of an evaluation rather than a sufficient explanation. The extent to which coronary disease, hypertension or valve disease accounts for the observed abnormality must also be judged rather than assumed. [3]

The 2026 ESC aetiological assessment similarly combines history and examination with ECG, laboratory testing and echocardiography, followed by selected additional tests according to the unresolved question. CMR, coronary imaging, nuclear imaging, genetic assessment, biopsy and haemodynamic investigation provide complementary rather than interchangeable information. The purpose is to identify an actionable cause and refine prognosis, not simply to accumulate abnormal results. This supports the question-oriented approach used in Tables 2.3–2.5. [1, Section 5.3 and Figure 7]

When several plausible causes coexist, the objective is not necessarily to nominate one exclusive diagnosis. It may be more accurate to document a dominant substrate and contributory mechanisms. For example, coronary atherosclerosis without matching infarct scar may coexist with a familial cardiomyopathy. Conversely, a genetic predisposition does not negate an acquired ischaemic insult. The decision to extend testing should depend on the unresolved discrepancy, the consequences of missing a treatable cause and the reliability of the available observations.

Chronology deserves the same scrutiny as imaging. Exposure to a potentially cardiotoxic drug should be reconstructed with the oncology record, not a vague recollection of chemotherapy. Arrhythmia burden requires more than one normal electrocardiogram. A family history should include premature sudden death, unexplained transplantation, conduction disease and apparently unrelated neuromuscular manifestations. Negative information is most useful when the relevant question has actually been asked or measured.

Table 2.3. Common cardiac causes: mechanism, clues and targeted investigation

Causal setting	Pattern that raises suspicion	Question-oriented investigation
Coronary disease	Infarct history, regional dysfunction or territorial scar.	Define anatomy and ischaemic/scar concordance; consider whether revascularization could address the clinical problem.
Hypertensive loading	Longstanding pressure burden, hypertrophy, atrial enlargement or hypertensive oedema.	Confirm blood-pressure history and pattern; investigate secondary hypertension only when supported by clinical features.
Primary valve disease	A structural valve lesion plausibly sufficient to explain loading and symptoms.	Integrated echocardiographic severity, chamber response and flow; resolve discordant measurements with specialist imaging.

Causal setting	Pattern that raises suspicion	Question-oriented investigation
Secondary regurgitation	Ventricular or atrial remodelling with functional mitral or tricuspid regurgitation.	Establish the primary substrate and assess regurgitation under documented loading conditions.
Atrial or ventricular arrhythmia	Persistent tachycardia, high ectopic burden or dysfunction disproportionate to other findings.	Ambulatory rhythm assessment, imaging and a timeline of rhythm and ventricular function.
Pacing or conduction-related dyssynchrony	Substantial ventricular pacing, broad QRS or worsening after a change in activation.	Device interrogation and assessment of activation, capture, ventricular function and competing causes.
Congenital or postoperative circulation	Shunt, obstruction, systemic right ventricle, Fontan physiology or repaired complex disease.	Anatomy-specific assessment in an adult congenital programme; CMR, exercise testing and catheterization as needed.

Tables 2.3–2.5 summarise the aetiological assessment. The three tables should be read together. They describe targeted assessment rather than an indiscriminate test panel; no recommendation classes are assigned.

Table 2.4. Myocardial, inflammatory and infiltrative causes

Causal setting	Clues beyond LVEF	Targeted clarification and safeguard
Genetic cardiomyopathy	Familial disease, premature sudden death, conduction abnormalities, ventricular arrhythmia or muscle disease.	Phenotype-directed genetic counselling and testing; a variant of uncertain significance is not a definitive causal diagnosis.
Myocarditis / immune-mediated injury	Compatible illness, chest pain, troponin release, new arrhythmia or unexplained dysfunction.	CMR and selected tissue-based evaluation; do not equate a preceding viral illness with established viral myocarditis.
Sarcoid or other inflammatory infiltration	Conduction disease, ventricular arrhythmia, patchy myocardial abnormalities or extracardiac disease.	CMR and selected FDG-PET / tissue assessment with specialist interpretation.
Amyloidosis	Thickening disproportionate to voltage, restrictive physiology, neuropathy or characteristic extracardiac features.	Monoclonal-protein assessment plus appropriate imaging; a positive bone-tracer scan alone does not identify the amyloid type.
Iron overload	Transfusion exposure or inherited iron-loading disorder, sometimes with preserved LVEF.	Systemic iron indices and dedicated myocardial T2* CMR; serum ferritin does not quantify cardiac iron reliably.
Fabry and other storage disease	Hypertrophic phenotype with renal, neurological, cutaneous or familial features.	Disease-specific biochemical and genetic assessment; interpret imaging in the multisystem context.
Neuromuscular disease	Muscle weakness, characteristic examination, elevated CK or relevant family history.	Neuromuscular evaluation and appropriately directed genetic assessment, not cardiac imaging alone.

[3, 13, 80, 81]. CK denotes creatine kinase.

Table 2.5. Toxic, metabolic, endomyocardial and pericardial contributors

Setting	Mechanism to consider	Clinical discrimination
Cancer treatment	Direct myocardial injury, immune myocarditis, vascular injury or altered loading.	Identify the actual regimen and timeline; cardiac dysfunction is not a single uniform chemotherapy effect.
Alcohol or stimulant exposure	Toxic injury, arrhythmia, hypertension or ischaemia.	Establish exposure and competing causes without assuming that exposure alone proves causation.
Thyroid or other endocrine disease	Rate, contractile, vascular and metabolic effects.	Use symptoms, examination and targeted laboratory testing rather than an indiscriminate endocrine panel.
Nutritional deficiency	Impaired metabolic function, sometimes with abnormal systemic haemodynamics.	Look for malnutrition, malabsorption or a relevant exposure history; investigate the suspected deficiency specifically.
Endomyocardial disease	Fibrosis, eosinophilic injury, restrictive filling or valvular involvement.	Integrate blood count, systemic findings and imaging; biopsy is a selected diagnostic procedure.
Pericardial disease	External constraint or ventricular interaction rather than primary myocyte failure.	Evaluate constrictive or tamponade physiology and distinguish it from restrictive myocardial disease.
High-output stress	Demand or shunting that exceeds the capacity of the circulation.	Identify the driver, such as marked anaemia or a substantial arteriovenous shunt; high output is not proof of a healthy heart.

[48]. ANCA, when indicated by suspected vasculitis, means antineutrophil cytoplasmic antibody; it is not a universal heart-failure screening test.

2.4. Genetic architecture and acquired modifiers

A genetic predisposition and an acquired exposure need not be competing explanations. A pathogenic variant may alter the myocardium’s vulnerability, while pregnancy, an arrhythmia, alcohol exposure, infection or pressure loading influences when and how the phenotype becomes apparent. The clinically important question is not simply whether the disorder is inherited, but how inherited susceptibility interacts with the patient’s observed disease trajectory. [3, 82, 83]

The identification of truncating variants in titin in dilated cardiomyopathy established an important link between sarcomeric architecture and a common ventricular phenotype. However, not every sequence variant, or even every truncating variant in every location, carries the same interpretation. Genetic findings require assessment of variant classification, phenotype concordance and family information. A gene name printed on a laboratory report cannot substitute for this process. [82]

Peripartum cardiomyopathy provides a particularly informative example of overlapping mechanisms. The shared genetic predisposition reported between peripartum and dilated cardiomyopathy supports the

possibility that pregnancy unmasks susceptibility in some patients. It does not mean that all peripartum disease is inherited or that pregnancy-related vascular, hormonal and haemodynamic influences are irrelevant. The timing of presentation, recovery and future counselling must be evaluated in the individual rather than inferred from the category alone. [83]

The practical value of identifying a genetic cause extends beyond naming the disease. It can clarify risk assessment, inform surveillance of relatives and influence interpretation of otherwise subtle findings. Conversely, overinterpretation creates harms: unnecessary anxiety, inappropriate labelling of relatives and false reassurance when a panel is negative. A negative test is not equivalent to proof that a disease has no heritable component; the question addressed by a test is limited by the genes, variant types and knowledge available.

Family information also needs longitudinal interpretation. A relative considered unaffected at one age may not remain so throughout life, whereas a non-specific symptom in a relative does not establish segregation of disease. Reassessment is most useful when it asks whether the phenotype or the interpretation of a previously reported variant has changed. Genetic counselling should explain uncertainty explicitly. The cardiomyopathy guideline provides the clinical framework, while specialist genetic interpretation remains essential. [3]

For the broader causal formulation, the distinction between predisposition and active disease is fundamental. A pathogenic variant may be relevant before measurable dysfunction occurs; it does not establish the severity of current heart failure. Similarly, a patient may have a substantial arrhythmic substrate despite only modest reduction in LVEF. The cardiac phenotype must therefore remain multidimensional: chamber geometry, scar, rhythm, conduction, haemodynamics, symptoms and family context should be considered together.

2.5. Ischaemia, pressure overload and volume overload

2.5.1. Coronary injury and the limits of viability-based reasoning

The ischaemic framework distinguishes irreversible injury from potentially recoverable dysfunction. Infarction removes viable contractile tissue and changes ventricular geometry; the remaining myocardium is exposed to altered loading. Transient ischaemia and chronically impaired perfusion may also impair performance without identical degrees of permanent scar. These components often coexist, so a label of ischaemic cardiomyopathy does not describe the proportion attributable to each mechanism.

A mechanistic expectation of recovery is not, by itself, proof that an intervention improves clinical outcomes. In REVIVED-BCIS2, patients with severe ischaemic left ventricular dysfunction and demonstrable viability did not experience a reduction in the primary composite of death or heart-failure hospitalization with PCI added to optimal medical treatment. This was a stable-disease trial, not a test of emergency reperfusion for acute infarction. [61]

The extended follow-up of STICH demonstrated a long-term survival benefit with CABG in its selected population with ischaemic cardiomyopathy. This finding concerns a different intervention and trial context. Together, the two studies argue against reducing revascularization decisions to the binary presence or absence of viable myocardium. They do not constitute a randomized head-to-head comparison of PCI and CABG. [62]

For causal assessment, coronary anatomy should therefore be read alongside myocardial phenotype and the clinical problem. Extensive atherosclerosis may explain territorial scar but not every element of global dysfunction. Improvement in angina, recovery of regional function, prevention of infarction and improved survival are distinct objectives. A scientifically precise discussion states which objective is supported and avoids replacing an outcome trial with an appealing mechanistic narrative.

2.5.2. The ventricle under sustained pressure or volume stress

Chronic pressure overload and chronic volume overload impose different initial demands but can converge on advanced ventricular dysfunction. In pressure loading, increased myocardial mass can initially help accommodate the imposed stress. In volume loading, chamber enlargement can initially sustain the required total stroke volume. The adaptive response is not synonymous with durable protection; prolonged stress may be accompanied by impaired relaxation, fibrosis, altered geometry and reduced reserve. These relationships form the physiological basis of hypertensive and valvular heart failure.

The distinction also explains why the same apparent symptom severity can arise through different pathways. A relatively small, stiff ventricle may develop marked pulmonary congestion after a modest increase in blood pressure or heart rate. A dilated ventricle with chronic regurgitation may accommodate large volumes before symptoms become obvious, yet have substantial structural disease. Apparent tolerance at rest should not be mistaken for benign loading.

Secondary regurgitation introduces feedback. Ventricular remodelling can impair leaflet coaptation; regurgitation then increases the volume burden and may promote further remodelling. Atrial enlargement can also contribute to annular dysfunction without the same primary ventricular mechanism. The distinction between a primary lesion and a secondary consequence is therefore central to treatment sequencing and reassessment. An intervention directed at the valve and a therapy directed at myocardial remodelling address related but non-identical components of the syndrome.

A simple geometrical approximation helps organize these concepts: myocardial wall stress rises with cavity pressure and radius and falls with increasing wall thickness. The thin-wall relation is not an exact quantitative model for a thick, irregular, actively contracting human ventricle. It is useful only as an explanatory approximation. Its value lies in showing why pressure, chamber enlargement and wall thickness interact, not in predicting an individual treatment threshold.

2.6. Inflammatory, toxic and disease-specific myocardial injury

Inflammatory myocardial injury can produce a spectrum ranging from subtle tissue abnormalities to ventricular dysfunction, conduction disease and haemodynamic collapse. The clinical expression depends not only on the presence of inflammation but also on its distribution, intensity, duration and interaction with electrical and contractile structures. A prior viral illness is a historical clue rather than proof of a specific myocardial infection. Diagnostic terminology should reflect the evidence actually obtained.

The 2025 ESC myocarditis and pericarditis guideline provides the contemporary disease-specific context. CMR, clinical findings and selected tissue assessment contribute different forms of information. Tissue characterization is not interchangeable with microbiological identification, and a biomarker of myocardial

injury is not a complete aetiological diagnosis. The purpose of specialized testing is to identify forms for which the diagnosis changes management, rather than to perform invasive investigation indiscriminately. [13]

Cancer therapy illustrates why a single toxic-cardiomyopathy label can be inadequate. Treatment may cause myocardial dysfunction through direct cellular injury, an immune-mediated process, vascular disease or altered blood pressure and loading. The 2022 ESC cardio-oncology guideline organizes evaluation around treatment type, baseline risk and the subsequent clinical course. The actual drug exposure and chronology are therefore indispensable to causal assessment. [48]

Similarly, alcohol and stimulant exposure should be placed within a complete formulation. Exposure, temporal association and biological plausibility strengthen a hypothesis, but they do not exclude a genetic substrate, coronary disease or an arrhythmic contribution. Improvement after withdrawal can support a causal role while still leaving uncertainty about the proportion of dysfunction attributable to that exposure. Potentially reversible causes should be identified without converting reversibility into an assurance of complete recovery.

Infiltrative and storage disorders differ fundamentally from these acquired injuries. In amyloidosis, protein deposition affects the myocardium and other cardiac structures, with haemodynamic and electrical consequences. In iron-loading disease, myocardial iron contributes to cellular injury and dysfunction. Identifying these disorders matters because management of the underlying disease is not replaced by treatment of congestion. A nonspecific label of HFpEF or dilated cardiomyopathy can conceal a disease-specific therapeutic opportunity.

Amyloid typing demonstrates the importance of combining tests. The nonbiopsy ATTR diagnostic approach established by Gillmore and colleagues depends on an appropriate scintigraphic pattern together with exclusion of a monoclonal protein, not on tracer uptake alone. A monoclonal abnormality changes the diagnostic interpretation and may require tissue typing. This is a diagnostic principle, not a reason to postpone urgent evaluation of suspected AL disease. [80]

For iron overload, the relevant CMR technique is myocardial T2* assessment. The asterisk is part of the measurement name, not optional typography. The early T2* work by Anderson and colleagues linked this measurement to myocardial iron assessment. Systemic ferritin and transferrin saturation address different questions and cannot be used as interchangeable measures of myocardial deposition. [81]

2.7. The cardiomyocyte: contractile structure, calcium and energy

At the cellular level, contraction requires coordinated electrical activation, calcium-dependent activation of the myofilaments, force generation and sufficient energy to sustain repeated work. Relaxation is also energy dependent; it is not simply the passive cessation of contraction. Disorders affecting any element can therefore influence both systolic and diastolic behaviour. The clinical phenotype reflects the combined consequences rather than an isolated molecular defect.

Sarcomeric disease illustrates the distinction between a molecular lesion and a uniform functional result. Variants affecting contractile or structural proteins can be expressed through different degrees of hypertrophy, dilatation, arrhythmia and impaired relaxation. The titin findings discussed above connect sarcomeric

integrity to ventricular disease but do not support diagnosing a specific molecular abnormality from LVEF or chamber size alone. A macroscopic phenotype is the downstream result of several interacting processes. [82]

2.7.1. Excitation–contraction coupling and the calcium transient

The sequence from electrical excitation to mechanical work depends on the timing as well as the magnitude of the intracellular calcium signal. A reduced systolic transient can limit force generation, whereas delayed calcium removal can impede relaxation. In isolated ventricular myocytes from patients with terminal heart failure, Beuckelmann and colleagues observed higher resting intracellular calcium, smaller peak transients and slower diastolic decline than in control cells. These human experimental observations connect impaired calcium cycling with abnormalities of both contraction and relaxation; they do not establish that every failing heart has an identical cellular phenotype. [84]

The physiological implication is that a ventricle may be limited in two directions at once: it may generate insufficient force during systole and fail to release tension rapidly enough during diastole. A shortened filling interval can expose the latter limitation even when a resting measurement seems acceptable. Conversely, improving one component of the transient does not guarantee improvement in integrated cardiac output if loading, rhythm or energetic limitations remain. These are system-level deductions from the coupling model rather than measured treatment effects.

2.7.2. Passive tension and intracellular signalling

The structural proteins responsible for passive tension are not mechanically inert. Human myocardial work by van Heerebeek and colleagues associated reduced protein kinase G activity in HFpEF with increased passive cardiomyocyte force and greater nitrosative/oxidative stress. Applying the kinase in vitro reduced the elevated passive force. This supports a connection between signalling state and myocyte stiffness, while leaving open how effectively a systemic intervention can reproduce that tissue-level effect in patients. [85]

The distinction between cellular and chamber behaviour is important here. Intrinsic myocyte tension is only one contributor to ventricular filling pressure; extracellular matrix, geometry, pericardial constraint and interaction with the right ventricle also contribute. A convincing cellular mechanism can therefore explain part of an observed haemodynamic phenotype without explaining all of it. The appropriate translational question is whether an intervention improves integrated function and patient outcomes, not merely whether it changes an isolated tissue property.

2.7.3. Therapeutic translation and myocardial energetics

Calcium cycling provides a further example of a plausible therapeutic target that requires clinical validation. Intracellular calcium must rise and then fall in an appropriately coordinated fashion for contraction and relaxation. The CUPID 2 trial tested a gene-transfer strategy targeting sarcoplasmic-reticulum calcium handling but did not demonstrate clinical efficacy. Failure of that particular intervention does not prove that calcium handling is unimportant; equally, the importance of calcium physiology cannot be used to claim an outcome benefit that the trial did not show. [86]

Myocardial energetics should be interpreted with the same discipline. ATP supports mechanical work, ion transport and cellular maintenance. In a human phosphorus magnetic-resonance spectroscopy study of dilated

cardiomyopathy, the phosphocreatine-to-ATP ratio carried prognostic information. This supports the clinical relevance of energetic reserve, but an observational association does not establish that raising a measured energetic marker will itself improve survival. [87]

Several distinctions are important when reading mechanistic research. A change in substrate utilization is not automatically an improvement in energy efficiency. A reduction in oxygen consumption is not necessarily beneficial if useful work falls even more. Improvement in one cellular measure may be offset by effects on rhythm, loading or other organs. Mechanistic claims should therefore specify the preparation studied, the endpoint measured and whether the intervention has been tested in humans with clinical outcomes.

This is particularly relevant to modern multidomain therapies. A drug may affect renal handling, haemodynamics, metabolism and inflammation simultaneously. Demonstrating benefit in an outcome trial validates the tested clinical strategy in that population; it does not identify one of several proposed molecular explanations as the sole mediator. A detailed pathway illustration should not be interpreted as stronger evidence than the experiment actually provides.

Table 2.6. From biological observation to a therapeutic claim

Level of evidence	What it can support	What it cannot establish alone
Cellular / tissue experiment	A process exists and can be modified under specified experimental conditions.	Net clinical benefit, safety or the dominant mechanism in an intact patient.
Human physiological study	A measurable abnormality or response occurs in a studied phenotype.	Reduction in mortality or hospitalization with long-term treatment.
Prognostic observational study	A marker is associated with subsequent outcomes.	That changing the marker will change the outcome.
Randomized clinical trial	The tested intervention changes specified outcomes in the studied population.	A single exclusive biological mechanism or unrestricted transfer to other populations.
Guideline recommendation	An evidence-based clinical position within a defined scope.	Permission to alter the entry criteria or endpoint of the trials on which it is based.

[78], [87], CUPID 2 [86]

2.8. Neurohormonal activation: compensation and chronic injury

2.8.1. A response that changes its meaning over time

Activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system is central to progression of chronic heart failure. Their immediate effects can help maintain circulation when effective output falls, through changes in rate, contractility, vascular tone and sodium conservation. However, a response that is useful during a short-lived perturbation can become damaging when persistently activated in a structurally abnormal heart. [1, 88–90]

The distinction is temporal and contextual. Raising vascular tone may support perfusion pressure while increasing the load against which the ventricle ejects. Retaining sodium may defend effective circulation

while aggravating congestion. Increasing heart rate may initially support output while shortening filling time and increasing demand. These are not contradictory actions: they are different consequences of the same compensatory response. Their net effect depends on the available ventricular, vascular and renal reserve.

The treatment evidence should be stated precisely. CONSENSUS established that enalapril improved survival in severe heart failure in its trial setting. RALES demonstrated the benefit of spironolactone in selected patients with severe systolic heart failure. These trials support intervention on neurohormonal pathways, while their populations, background therapy and safety requirements remain important when interpreting the results. [88, 89]

Human myocardial studies also show why circulating stimulation and tissue responsiveness must be distinguished. Bristow and colleagues found reduced beta-adrenergic receptor density, reduced agonist-stimulated signalling and reduced contractile responsiveness in failing human ventricles. Increased neurohormonal drive can therefore coexist with reduced myocardial responsiveness. The observation adds a receptor-level mechanism to the clinical distinction between temporary circulatory support and sustained maladaptive activation. It does not determine the dose or timing of treatment in an individual patient. [91]

Similarly, the survival benefit of carvedilol in severe chronic heart failure provides clinical evidence against the simplistic assumption that chronic adrenergic stimulation must remain beneficial because it can support short-term performance. Long-term receptor modulation and short-term haemodynamic effects are different questions. Initiation of treatment in a stable chronic setting should not be confused with manipulation of adrenergic support during shock; practical prescribing belongs in the treatment chapters. [90]

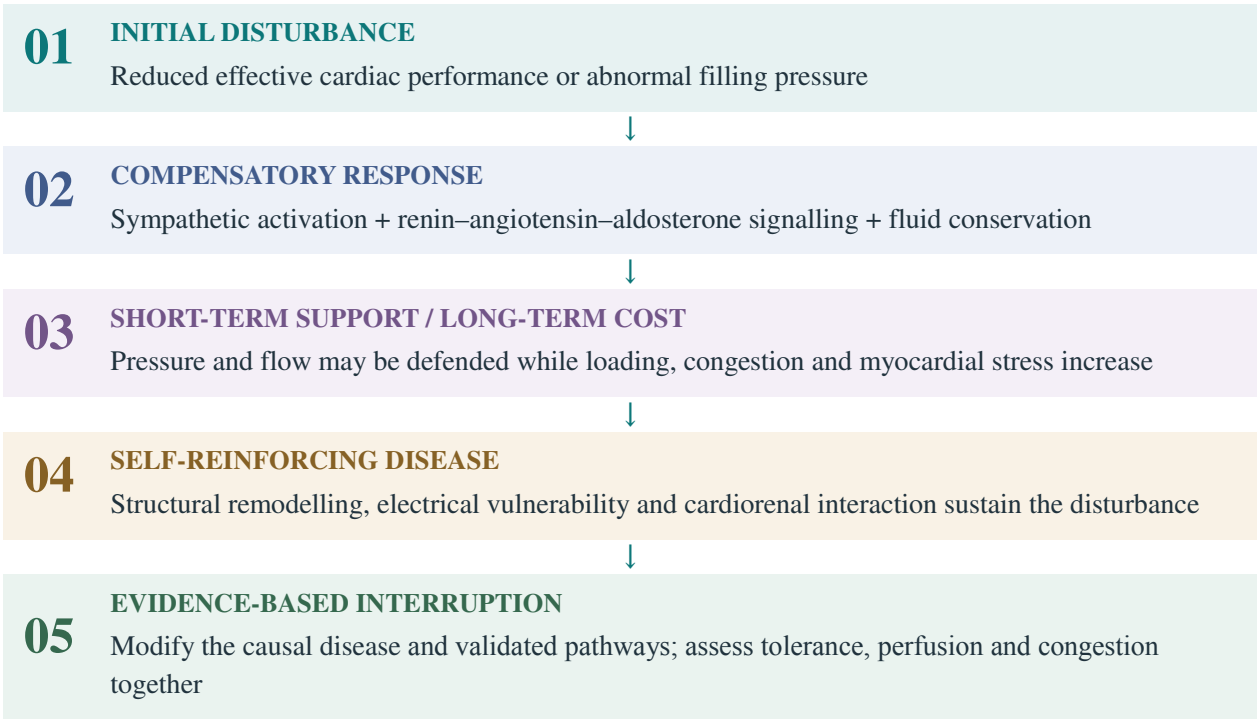
2.8.2. Counter-regulation and the limits of biomarker interpretation

The natriuretic-peptide system forms part of the counter-regulatory response to cardiac stress. Circulating concentrations are useful diagnostically and prognostically, but a high concentration does not mean that the physiological response is sufficient to reverse the syndrome. The measured biomarker reflects production, processing, clearance and the patient's clinical context. Rhythm, renal function, age, body size and treatment can all influence interpretation, as developed in the biomarker chapter.

The PARADIGM-HF comparison of sacubitril/valsartan with enalapril established an outcome benefit for the combined angiotensin-receptor/neprilysin-inhibition strategy in the studied population. It did not test an isolated increase in a circulating peptide as the treatment objective. Importantly, its historical LVEF entry criterion was initially 40% or less and subsequently 35% or less; the contemporary classification must not be substituted into that trial description. [92]

The overall neurohormonal model is therefore best understood as a network rather than a linear chain. The heart, vasculature and kidneys respond to one another. Altering one pathway can change loading and the activation of others. This explains why the biological rationale for combination treatment is broader than replacing one abnormal laboratory value with a normal value. The clinical evidence for each component, rather than pathway diagrams alone, determines its role.

Figure 2.2. Compensation, maladaptation and the targets of chronic treatment



[88–90, 92]

2.9. Extracellular matrix, remodelling and electrical vulnerability

Remodelling describes change in cardiac structure and organization, not merely a change in chamber diameter. It can involve myocyte size, extracellular matrix, ventricular shape, atrial size, valve competence and the coordination of contraction. These changes may initially distribute an abnormal load but subsequently alter the load itself. The distinction between adaptation and maladaptation is therefore defined by consequences and trajectory, rather than by the presence of enlargement alone.

Fibrosis is similarly heterogeneous. Replacement scar after cell loss is not the same biological process as diffuse interstitial expansion. A single global measure may conceal marked regional differences. Scar distribution can affect contractile function, electrical conduction and mechanical coordination, but imaging does not identify every microscopic component of the matrix. A late-gadolinium-enhancement pattern should therefore be read as tissue-characterization information within a clinical formulation, not as an automatically complete histological diagnosis.

In non-ischaemic dilated cardiomyopathy, Gulati and colleagues demonstrated an association between myocardial fibrosis detected by CMR and adverse outcomes, including sudden cardiac death. This is important prognostic evidence, but it does not by itself show that a fibrosis-guided device strategy improves survival. A marker can refine the description of risk without serving as a standalone treatment indication. [41]

Electrical and structural abnormalities can reinforce one another. Delayed regional activation produces inefficient contraction; inefficient contraction can worsen loading and functional regurgitation. Scar and altered geometry can contribute to an arrhythmic substrate, while a persistent arrhythmia can aggravate

ventricular dysfunction. Assessment of CRT and rhythm-related disease requires integrated interpretation of symptoms, LVEF, QRS characteristics, pacing burden and the ability to achieve effective resynchronization.

Reverse remodelling should consequently be assessed with more than one measurement. A smaller end-systolic volume, improved forward flow, reduced functional regurgitation, better symptoms and an increase in LVEF are related but non-identical observations. Their time courses can differ. Failure of one metric to normalize does not prove absence of benefit; normalization of one metric does not establish removal of every arrhythmic or biological vulnerability.

Inflammatory signalling is one possible contributor to remodelling, but its therapeutic interpretation requires caution. The RENEWAL programme did not demonstrate clinical benefit from the tested etanercept strategy in chronic heart failure. This argues against assuming that a raised inflammatory mediator identifies a universally treatable target. It does not negate disease-specific treatment of a defined inflammatory cardiomyopathy. Broad cytokine inhibition in a syndrome and targeted treatment of a proven aetiology are different clinical questions. [93]

Table 2.7. What a remodelling measurement does—and does not—tell us

Observation	Reasonable interpretation	Unjustified shortcut
LVEF increases	The relation between ejected and end-diastolic volume has improved.	The cardiomyopathy is cured or treatment can be stopped.
Ventricular volumes fall	Chamber geometry and loading have changed favourably in context.	All residual scar or arrhythmic risk has disappeared.
Functional regurgitation decreases	Valve competence and ventricular / atrial geometry or loading have improved.	The initial valve lesion was necessarily primary.
LGE is present	There is a relevant tissue pattern that may carry prognostic information.	The image alone establishes active inflammation or a complete device indication.
Symptoms improve	The patient's functional experience has improved.	The same magnitude of mortality reduction has been demonstrated.

[5, 41]

2.10. HFpEF as impaired cardiovascular and systemic reserve

2.10.1. Beyond an isolated diastolic abnormality

HFpEF is not adequately explained by the phrase normal systolic function with abnormal relaxation. Preserved ejection fraction describes a ratio at the time of measurement. The syndrome may involve ventricular filling, longitudinal contraction, chronotropic response, arterial loading, atrial function, right-heart performance and peripheral oxygen utilization. The combination varies between patients. This multidomain view is consistent with the clinical heterogeneity of the syndrome.

The reserve abnormalities demonstrated by Borlaug and colleagues support this broader physiological formulation. Limited exercise performance can arise when several components fail to increase appropriately, even though no single resting abnormality appears sufficient to explain the limitation. Such evidence supports investigating the mechanism of exertional symptoms, rather than using a preserved LVEF to exclude an important cardiovascular contribution. [79]

An atrium exposed to chronic elevation in ventricular filling pressure may enlarge and lose functional efficiency. Atrial fibrillation then removes organized atrial contraction and introduces irregularity, potentially increasing the haemodynamic burden. The impact is greater when ventricular filling already depends on a narrow range of rate and loading conditions. This is a physiological explanation for the poor tolerance of arrhythmia in some patients, not proof that every patient should receive the same rhythm intervention.

2.10.2. Obesity, microvascular dysfunction and overlapping phenotypes

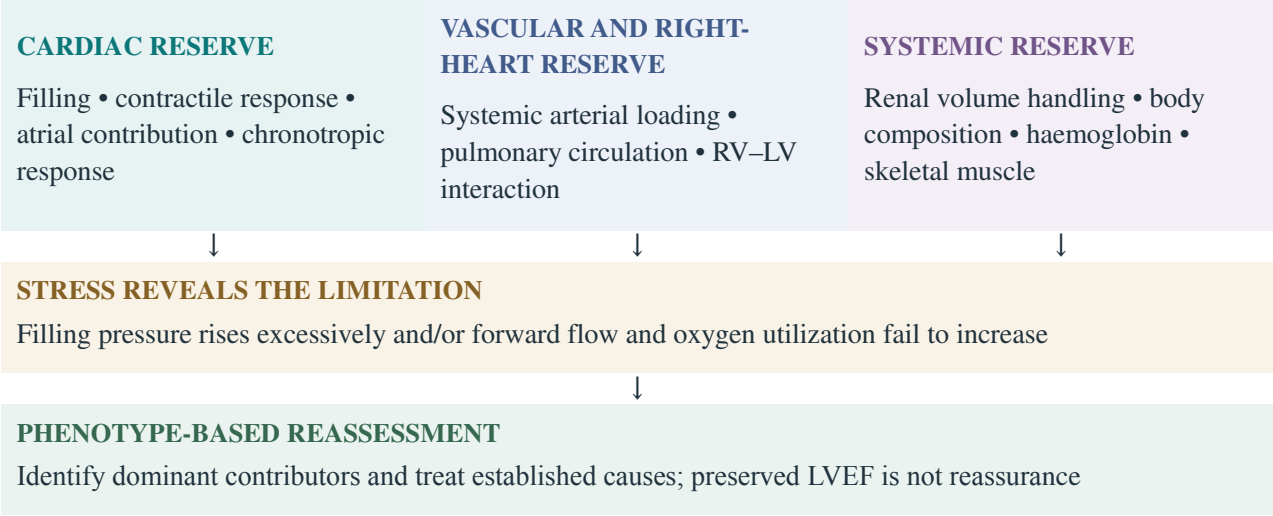
Obesity-associated HFpEF provides an example of a phenotype that cannot be represented adequately by body mass index alone. In the physiological study by Obokata and colleagues, the obese phenotype was associated with distinctive volume, right-heart and ventricular-interaction features. Lower natriuretic-peptide concentrations could coexist with substantial haemodynamic abnormalities. These observations help explain diagnostic discordance but should not be used to diagnose HFpEF in every patient with obesity and breathlessness. [52]

Coronary microvascular dysfunction is another relevant mechanism. PROMIS-HFpEF demonstrated its frequent coexistence with HFpEF and described clinical correlates. This does not establish that microvascular dysfunction is present in every phenotype, is the sole cause of the syndrome or can be treated effectively by any intervention that improves an isolated microvascular measure. The clinical meaning depends on the population and the measurement used. [94]

The useful clinical formulation is therefore additive rather than exclusive. One patient may have obesity, hypertension, atrial fibrillation and kidney disease; another may have infiltrative myocardial disease with a similar LVEF. An apparently shared endpoint of raised filling pressure can arise from different processes. Disease-specific red flags should remain visible within the phenotype, especially when ventricular thickening, conduction disease or extracardiac manifestations are disproportionate to common risk factors.

A phenotype label is also time dependent. Reduction in congestion, changes in weight, treatment of an arrhythmia or progression of renal disease can alter the apparent dominant mechanism. Reassessment should ask which components now limit function, not simply repeat the original label. This approach supports individualized management while avoiding the implication that phenotypes are fixed biological categories.

Figure 2.3. A multidomain view of exertional limitation in HFpEF



[52, 79, 94, 95].

2.11. Right ventricular failure and ventricular interdependence

The right ventricle must provide pulmonary blood flow at filling pressures compatible with systemic venous drainage. Failure can arise because contractile performance is impaired, pulmonary or valvular load is excessive, filling is inappropriate, or several of these abnormalities coexist. Relevant causes include pulmonary hypertension secondary to left-heart disease, right ventricular infarction, arrhythmogenic cardiomyopathy and valvular abnormalities. [46, 47]

A useful distinction is between intrinsic right ventricular dysfunction and failure to match an imposed load. These are not mutually exclusive. The same measured right ventricular shortening may have different implications at different pulmonary pressures. Conversely, an apparently lower pulmonary artery pressure can accompany worsening right ventricular output rather than improvement in pulmonary vascular disease. No isolated pressure or systolic index should be interpreted without flow and the clinical context.

In the HFpEF cohort studied by Melenovsky and colleagues, right-heart dysfunction reflected both intrinsic impairment and adverse loading and carried important prognostic information. The finding reinforces the need to assess the right heart even when left ventricular ejection fraction is preserved. It does not make every case of right ventricular dysfunction a primary right ventricular cardiomyopathy. [95]

Ventricular interdependence is a central mechanism. The ventricles share the septum and are constrained by the pericardium. Right ventricular enlargement or pressure loading can alter septal position and left ventricular filling. Systemic output may therefore fall even when intrinsic left ventricular contractility is not the primary abnormality. This helps explain why relieving excessive right-sided congestion can improve left-sided filling in one patient, while excessive volume removal can reduce output in another.

Tricuspid regurgitation can both reflect and aggravate the disorder. Annular enlargement, leaflet tethering and atrial remodelling may impair competence, increasing systemic venous congestion and altering the effective forward stroke volume. The regurgitant lesion should be evaluated alongside right ventricular function and

the pulmonary circulation. Treating the visible jet as the entire disease risks missing the mechanism that produced it.

Echocardiographic assessment should integrate several domains: size, longitudinal and global systolic performance, septal geometry, regurgitation, venous findings and loading. TAPSE, fractional area change and tissue-Doppler S′ describe different aspects of motion or performance and are load dependent. Their value is greatest when concordant with the broader examination, not when one favourable value is used to overrule all other evidence. Detailed measurement standards belong in the imaging chapter; the present chapter establishes the interpretative logic.

The same logic applies to advanced and congenital circulations. A systemic right ventricle is exposed to a different load from a normal subpulmonary right ventricle. A Fontan circulation has no subpulmonary pumping chamber. In both settings, conventional left-ventricular shorthand is inadequate. The relevant question is which component of that particular circulation limits forward flow while maintaining tolerable venous pressure.

2.12. Congestion and cardiorenal interaction

2.12.1. Accumulation and redistribution are different processes

Congestion is not a single compartmental abnormality. It can involve pulmonary vessels and interstitium, systemic veins, serosal spaces and peripheral tissues. In some presentations, cumulative sodium and water retention is prominent; in others, redistribution of blood and an abrupt rise in filling pressure dominate. The contrast between gradually evolving decompensation and hypertensive pulmonary oedema provides an important clinical illustration.

This distinction explains why body weight, oedema and breathlessness do not always move together. An abrupt change in vascular tone or ventricular loading can increase pulmonary pressure without a large recent increase in total body fluid. Conversely, substantial peripheral or splanchnic congestion may develop with comparatively modest resting pulmonary symptoms. A single marker of volume status should therefore not be treated as the full phenotype.

Decongestion is best understood as correction of harmful pressure and fluid distribution while preserving perfusion, rather than the pursuit of maximal fluid removal. The physiological target is compatible forward flow at tolerable filling pressures. An apparent reduction in oedema does not necessarily establish that this target has been achieved, and a transient laboratory change does not by itself prove that it has been missed.

2.12.2. The kidney is affected from both sides of the circulation

Reduced arterial delivery is only one mechanism of renal dysfunction in heart failure. Elevated venous pressure can oppose effective organ drainage and contribute to renal dysfunction. In the study by Mullens and colleagues, venous congestion was closely related to worsening renal function in advanced decompensated heart failure. This observation argues against explaining every creatinine rise solely by a fall in cardiac output. [57]

A deliberately simplified pressure-gradient model illustrates the interaction. If renal perfusion pressure is approximated by mean arterial pressure minus renal venous pressure, a mean arterial pressure of 80 mmHg and venous pressure of 10 mmHg produce a gradient of 70 mmHg. Raising the venous pressure to 25 mmHg reduces that gradient to 55 mmHg without a change in arterial pressure. These constructed values are not a validated renal-flow model: autoregulation, intra-abdominal pressure, vascular resistance and intrarenal processes also matter.

Renal dysfunction must therefore be interpreted dynamically. A creatinine increase during effective decongestion is not equivalent to the same change accompanied by persistent congestion, oliguria and worsening perfusion. Equally, the possibility of a functional change must not be used to dismiss progressive injury. The clinical inference requires the trajectory of symptoms, blood pressure, urine output, fluid balance, electrolytes and other evidence of organ function, as developed further in the cardiorenal discussion.

Apparent diuretic resistance also requires a causal assessment. Insufficient delivery, reduced absorption, inadequate dose, altered renal handling, continued sodium intake and poor adherence are different problems. Escalation without identifying the limiting step can add toxicity while leaving the actual cause unresolved. Sequential nephron blockade has a physiological rationale because different agents alter handling at different tubular sites, but that rationale does not define a universal dose or sequence.

ADVOR provided randomized evidence that adding acetazolamide to the tested loop-diuretic regimen improved decongestion in the studied acute heart-failure population. It should not be described as proof of a survival benefit or as justification for the same combination in every congested patient. The detailed protocol, renal and electrolyte assessment, and applicability belong in the decompensated-heart-failure chapter. [96]

Table 2.8. Interpreting congestion and renal-function change together

Observed pattern	Physiological possibilities	What should be clarified
Rising creatinine with improving congestion	Functional haemodynamic change, altered filtration or true injury may coexist.	Perfusion, urine output, trajectory and treatment context; do not judge from creatinine alone.
Rising creatinine with persistent congestion	Venous pressure, poor effective flow, inadequate decongestion or another renal insult.	Residual congestion, blood pressure, nephrotoxic exposure and the mechanism of poor response.
Severe breathlessness without major weight gain	Fluid redistribution, abrupt afterload change or a non-cardiac contributor.	Timing, respiratory findings, pressure profile and reversible precipitating factors.
Extensive oedema with low blood pressure	High venous pressure and limited forward-flow reserve may coexist.	The balance between reducing congestion and preserving effective filling and perfusion.
Little response to a diuretic regimen	Delivery, adherence, renal handling or an inadequate regimen.	Why the response is poor before assuming irreversibility or escalating indiscriminately.

[57, 96]

2.13. Peripheral organs, oxygen transport and functional limitation

Heart failure is expressed through the whole circulation. Symptoms and exercise limitation are influenced by pulmonary gas exchange, haemoglobin concentration, skeletal-muscle mass and function, vascular responses, renal handling and the ability to mobilize an appropriate cardiac output. Anaemia, iron deficiency, pulmonary disease, obesity, frailty and sarcopenia are important determinants rather than incidental diagnoses. Their physiological integration explains why a cardiac measurement alone often predicts functional performance imperfectly.

Oxygen consumption = cardiac output × (arterial oxygen content − venous oxygen content).

The Fick relationship separates convective delivery from tissue extraction. It follows that reduced peak oxygen consumption can arise from limited output, limited oxygen-carrying capacity, impaired extraction or combinations of these factors. A constructed example makes the scale explicit: an output of 10 L/min multiplied by an arterial–venous oxygen-content difference of 0.10 L O□/L yields oxygen consumption of 1.0 L/min. If extraction falls to 0.07 L O□/L at the same output, consumption falls to 0.70 L/min. These values illustrate the equation; they are not normal reference ranges or patient data.

Iron deficiency illustrates why haemoglobin does not capture every relevant abnormality. Iron contributes to processes beyond erythropoiesis, and iron deficiency can accompany impaired function even without anaemia. FAIR-HF demonstrated symptomatic and functional benefits of intravenous ferric carboxymaltose in its selected heart-failure population. Those results should not be converted into a mortality claim, a statement that all iron preparations are interchangeable, or a reason to omit investigation of the underlying cause of deficiency. [63]

Body composition introduces a further measurement problem. Expressing oxygen consumption per kilogram of total body mass incorporates both metabolically active tissue and adipose tissue in the denominator. Weight change can therefore alter the indexed value even when absolute oxygen consumption changes differently. This does not invalidate indexed peak oxygen consumption, but it means that interpretation in obesity or wasting should include absolute values, body composition and the clinical question rather than relying on a single ratio.

A randomized trial by Kitzman and colleagues showed that caloric restriction and aerobic exercise improved peak oxygen consumption in older patients with obesity and HFpEF, with additive effects. Neither intervention significantly improved the trial's co-primary Minnesota Living with Heart Failure Questionnaire outcome. This distinction matters: improvement in measured exercise capacity is not automatically equivalent to improvement in every quality-of-life instrument or to a reduction in major clinical events. [97]

Sarcopenia and frailty can in turn limit participation in rehabilitation, self-care and recovery after hospitalization. They should not be interpreted as evidence that the cardiac disorder is unimportant, nor should all weakness be assigned to low cardiac output. The clinical assessment should distinguish muscle loss, deconditioning, neurological or musculoskeletal limitation, malnutrition and persistent haemodynamic impairment. Several components may be modifiable even when the myocardial disease is not reversible.

Hepatic and intestinal involvement should also be interpreted within the haemodynamic context. Venous congestion and severe hypoperfusion can contribute differently to abnormal liver tests; impaired absorption and nutritional compromise are further relevant consequences of advanced disease. An abnormal organ marker may therefore identify the severity of the circulatory syndrome, a separate organ disease, or both. Attribution should remain explicit, especially when the finding affects eligibility for advanced treatment.

2.14. Recovery, remission and residual disease

Aetiology informs the probability of improvement, but it does not determine an individual outcome with certainty. Removal of a precipitant, correction of an arrhythmia, relief of abnormal loading and disease-modifying treatment may improve ventricular performance through different mechanisms. The apparent result can be similar—fewer symptoms and a higher LVEF—while the amount of residual substrate differs substantially.

The distinction between recovery and remission is therefore clinically useful. Recovery may describe improvement in a measured function; remission acknowledges that the underlying susceptibility may persist despite that improvement. These are not universally standardized biological states. They should be used to clarify uncertainty, not as labels that justify treatment withdrawal. Normalization of LVEF does not establish resolution of cardiomyopathy.

TRED-HF tested withdrawal of pharmacological treatment in a selected group with recovered dilated cardiomyopathy. Relapse occurred in a substantial proportion following withdrawal, whereas the initial continuation group did not show the same pattern during the randomized period. The trial supports caution about equating apparently recovered function with cure. It does not quantify relapse risk for every heart-failure aetiology or establish that withdrawal is appropriate when a single favourable marker is present. [5]

Arrhythmia-mediated dysfunction provides a different but complementary example. CAMERA-MRI showed that catheter ablation improved ventricular function more than medical rate control in a selected population with atrial fibrillation and otherwise unexplained systolic dysfunction. This supports an important causal contribution of atrial fibrillation in some patients, including when simple resting rate assessment appears acceptable. It is not evidence that every patient with both conditions has a purely arrhythmic cardiomyopathy. [98]

Reassessment after improvement should reconstruct what has changed. Has the trigger disappeared? Has forward flow improved? Have volumes and regurgitation changed? Is scar still present? Has arrhythmia burden fallen? Is renal function stable? Does the patient remain limited during exercise? These questions distinguish a favourable snapshot from a durable change in trajectory. The most informative follow-up comparison uses consistent methods and documented loading conditions.

Recovery also changes the interpretation of phenotype categories. A patient who previously had reduced systolic function and later reaches a preserved LVEF is not automatically equivalent to a patient whose LVEF has always been preserved. The historical trajectory is part of the phenotype. Definitions and source-specific thresholds for improved EF should be reported explicitly, together with the preceding LVEF and the treatment-associated trajectory.

Table 2.9. Improvement after treatment: a multidimensional reassessment

Dimension	Favourable change to document	Residual uncertainty
Cause and trigger	A relevant exposure ends or an arrhythmia / loading lesion is corrected.	Whether other causal substrates remain active.
Geometry and function	LVEF, chamber volumes and forward flow improve using comparable methods.	Whether improvement persists under stress or after changes in treatment.
Tissue and rhythm	Scar pattern, conduction and arrhythmic burden are reassessed when relevant.	Whether residual electrical risk persists despite improved global function.
Systemic consequences	Congestion, organ function and nutritional or functional status improve.	Whether non-cardiac limitations or irreversible organ injury remain.
Clinical trajectory	Stability is sustained over time, not merely during one visit.	Risk of relapse and the continuing need for surveillance and therapy.

[5, 98]

2.15. Connecting mechanism to treatment without overstating the evidence

A mechanistic chapter should explain why a therapy may be useful without replacing the evidence-based prescribing chapter. The biological target, observed physiological response and demonstrated clinical outcome are separate levels of argument. It is possible for a treatment to improve symptoms without a proven survival benefit, to improve an intermediate marker without clinical benefit, or to improve clinical outcomes through several incompletely resolved mechanisms.

SGLT2 inhibition is an instructive example. DAPA-HF demonstrated a reduction in its primary clinical composite with dapagliflozin in HFrEF, including patients without diabetes. This establishes that its clinical value in that setting is not dependent on treating hyperglycaemia. It does not establish a single exclusive renal, metabolic or myocardial mechanism. A scientific explanation should distinguish the outcome result from hypotheses about its mediation. [72]

FINEARTS-HF similarly provided evidence for finerenone in a population with LVEF of at least 40%. Its outcome results should be described using the trial's own population and endpoints rather than by assigning all participants retrospectively to one contemporary category. Improvement in a composite clinical outcome is not direct evidence of reversal of myocardial fibrosis, even when mineralocorticoid signalling provides a plausible biological rationale. [73]

These examples also demonstrate why a categorical change in LVEF terminology should not erase historical differences in trial design. Eligibility criteria, event definitions, background treatment, follow-up duration and statistical analysis are part of the evidence. A mechanism-to-treatment table can orient the reader, but it cannot replace those details or the current formal recommendations.

Table 2.10. Mechanistic rationale and the actual question answered by selected trials

Mechanistic domain	Evidence example	Boundary of the inference
Neurohormonal signalling	CONSENSUS, RALES and carvedilol trials support outcome-modifying strategies.	Their historical populations and safety constraints remain relevant. [88–90]
Angiotensin / neprilysin pathways	PARADIGM-HF tested sacubitril/valsartan against enalapril.	It did not test a peptide level as the treatment target. [92]
Calcium handling	CUPID 2 tested a specific gene-transfer intervention.	A plausible cellular target did not ensure clinical efficacy. [86]
Renal / metabolic interaction	DAPA-HF demonstrated benefit with and without diabetes.	The trial does not identify one exclusive mechanism of benefit. [72]
Mineralocorticoid signalling	FINEARTS-HF tested finerenone with LVEF ≥40%.	An outcome result is not a direct measurement of fibrosis reversal. [73]
Tubular sodium handling	ADVOR tested a specific combination decongestive strategy.	Improved decongestion should not be relabelled as a survival benefit. [96]
Arrhythmia-associated dysfunction	CAMERA-MRI compared ablation with medical rate control.	The selected population is not all patients with AF and heart failure. [98]
Recovery / residual substrate	TRED-HF investigated treatment withdrawal after apparent recovery.	Normalization of LVEF does not establish absence of relapse risk. [5]

2.16. Constructed clinical formulations: applying the framework

Case A. Reduced LVEF after an episode of atrial fibrillation

Consider a patient with previously undocumented ventricular function who presents with persistent atrial fibrillation, progressive exertional symptoms and a dilated left ventricle. The initial temptation is to choose between “tachycardia-induced” and “dilated” cardiomyopathy as if only one could be true. A more useful formulation is that ventricular disease is present and the contribution of the rhythm disturbance remains to be established.

The substrate assessment asks about coronary disease, family history, prior alcohol or cancer-treatment exposure and a myocardial scar pattern. The trigger assessment asks when atrial fibrillation began relative to symptoms. The amplifier assessment includes blood pressure, renal function, congestion and secondary regurgitation. Rhythm characterization should address burden and rate over time, not just the ventricular rate during one consultation.

If ventricular function improves after rhythm-directed treatment and other therapy, an arrhythmic contribution becomes more plausible. However, simultaneous changes in loading and neurohormonal treatment mean that response cannot identify one exclusive mechanism. Persistent scar or a relevant family history may remain important even when LVEF improves. The appropriate conclusion is a refined causal formulation, not an

automatic declaration of cure. CAMERA-MRI and TRED-HF address different parts of this reasoning: reversibility associated with arrhythmia treatment and uncertainty after apparent recovery. [5, 98]

Case B. Preserved LVEF, obesity and exertional breathlessness

Consider a patient with obesity, hypertension and exertional breathlessness whose resting LVEF is preserved. Neither obesity alone nor an LVEF above the categorical threshold establishes the cause of the symptoms. The clinical formulation should retain both cardiovascular and non-cardiovascular possibilities until objective findings support their contribution.

The cardiac questions concern filling pressure, ventricular and atrial structure, valve disease, right-heart performance and reserve. The systemic questions concern pulmonary disease, anaemia, muscle function, deconditioning and the effect of body composition on indexed exercise measurements. A low or only modest natriuretic-peptide concentration should be interpreted in context rather than used as an isolated verdict.

Suppose that resting evaluation is inconclusive but exertion produces a cardiovascular abnormality concordant with symptoms. The formulation then shifts from unexplained breathlessness to an objectively supported cardiovascular contribution, with obesity and other conditions acting as modifiers. It still remains necessary to distinguish a common cardiometabolic phenotype from an infiltrative or other disease-specific process when red flags are present.

Treatment response should be assessed with the endpoint that actually changes. Weight loss, absolute exercise capacity, weight-indexed oxygen consumption and questionnaire scores are not interchangeable outcomes. A scientifically accurate account can report improvement in one while acknowledging uncertainty in another. The physiological obesity and reserve studies, and the diet–exercise trial, provide the relevant distinctions without making this synthetic patient identical to a trial participant. [52, 79, 97]

Case C. Oedema, rising creatinine and a seemingly acceptable blood pressure

Consider a patient with established heart failure, increasing oedema, elevated jugular venous pressure and a rise in creatinine, while systolic blood pressure appears acceptable. Explaining the renal change simply as “poor forward flow” would omit the observed venous findings. Conversely, assuming that preserved blood pressure proves adequate perfusion would overlook the possibility of low output maintained by vasoconstriction.

The formulation should therefore include both venous congestion and effective arterial delivery, together with alternative renal insults and treatment exposure. Right ventricular function, tricuspid regurgitation, urine output, the clinical trajectory and the response to decongestive treatment help discriminate these possibilities. The goal is to establish what prevents an appropriate pressure–flow balance, not to choose a treatment from the creatinine value alone.

If congestion improves and the overall clinical trajectory is favourable despite a modest laboratory fluctuation, that pattern should be interpreted differently from progressive oliguria, worsening perfusion and unresolved congestion. Neither pattern can be reduced to a universal rule about stopping or intensifying treatment. An observed mechanism informs interpretation, while the individual decision requires multiple concordant clinical observations. [57]

2.17. Integrative conclusions and links to the clinical chapters

The aetiological diagnosis should explain both the persistent disease and its present expression. The substrate, precipitant, amplifiers and haemodynamic consequences should be documented separately when they differ. This permits a more precise response to the central clinical question: what is causing the patient's current limitation, which components are modifiable, and which vulnerabilities may persist despite improvement?

A mechanistically coherent formulation does not remove uncertainty. Instead, it makes uncertainty actionable by identifying what remains unexplained and what a further observation could resolve. An apparent inconsistency between symptoms, LVEF, biomarkers and haemodynamics is often a reason to reconsider the model rather than to discard the discordant measurement automatically. The most valuable next test is the one that addresses that inconsistency with sufficient reliability to influence care.

The subsequent diagnostic chapter develops how to measure the phenotype and determine the cause. The pharmacological, rhythm and interventional chapters address the evidence for changing outcomes. The decompensated and advanced-heart-failure chapters examine failure of physiological reserve and the timing of escalation. The comorbidity and disease-specific chapters address the conditions that frequently determine why a conventional left-ventricular treatment model is insufficient. Keeping these tasks distinct avoids duplication while preserving the causal connections that make the book clinically useful.

Table 2.11. Essential distinctions to carry forward through the book

Question	Principle
What is the disease?	The clinical syndrome, LVEF group and underlying aetiology describe different levels of diagnosis.
Why has the patient worsened now?	Separate a new precipitant from progression of the persistent substrate.
What does a normal-looking value exclude?	Only what that measurement can reliably test in the relevant clinical context.
Is the mechanism proven?	Distinguish experimental plausibility, human physiology, prognosis and randomized treatment effects.
Has the patient recovered?	Describe function, geometry, symptoms, tissue and trajectory; do not equate a higher LVEF with cure.
What should be treated?	Treat established causes and use therapies supported for the patient's actual clinical setting.

3. Diagnosis, Biomarkers and Multimodality Imaging

3.1. Clinical suspicion and the diagnostic formulation

The diagnostic task in heart failure is simultaneously syndromic and causal. Symptoms identify a problem requiring explanation; objective assessment establishes whether a cardiac abnormality is present and whether that abnormality plausibly accounts for the presentation. Clinical assessment, natriuretic peptides and echocardiography begin this process, which separates four questions: is the patient unstable, is heart failure present, what disease or loading abnormality is responsible, and which additional investigation will change management? [4, 99]

In the 2026 ESC classification, symptomatic heart failure with an LVEF below 50% is classified as HFrEF; HFpEF requires an LVEF of at least 50%, no previously documented LVEF below 50%, and objective evidence supporting the syndrome. These categories do not retrospectively alter trial inclusion criteria. An older study recruiting an LVEF of 40% or less remains evidence from that population, even when current terminology has changed. [1]

A diagnostic formulation should therefore be more informative than an ejection-fraction label. It should specify the cardiac substrate, the dominant haemodynamic disturbance, the temporal presentation and the major extracardiac contributors. “Exertional dyspnoea with obesity and a preserved ejection fraction” describes an unresolved problem; “exercise-induced elevation of left-sided filling pressure in a patient with hypertensive remodelling and obesity” describes a mechanism supported by investigation. Conversely, reduced systolic function detected incidentally in a person without previous symptoms should not be made equivalent to symptomatic heart failure without reviewing the clinical history. [9]

Diagnostic confidence increases when findings from independent domains agree. A symptom history, a biochemical signal and a cardiac imaging abnormality provide stronger corroboration than several measurements of the same underlying phenomenon. Discordance is not a reason to select the most convenient result. It is a reason to examine timing, image quality, treatment effects, competing diagnoses and the possibility that abnormalities become apparent only during exertion. The approach in Figure 3.1 summarises these principles.

Figure 3.1. A question-driven pathway from presentation to diagnosis

01	Establish urgency Respiratory failure, hypoperfusion, acute ischaemia, tamponade or a major mechanical lesion require immediate assessment and stabilization.
02	Define the clinical probability Reconstruct symptoms and trajectory; examine congestion and perfusion; identify cardiac history, risk factors and competing explanations.
03	Obtain complementary baseline evidence Combine ECG, laboratory assessment, natriuretic peptides and a comprehensive transthoracic echocardiogram.
04	Resolve the remaining question Use tissue characterization, coronary testing, exercise assessment, nuclear imaging or invasive haemodynamics only when they address an unresolved decision.
05	Document a causal diagnosis and a plan Record phenotype, aetiology, objective support, uncertainty and the trigger for reassessment.

An unstable patient does not wait for completion of the elective diagnostic sequence.

3.2. Clinical assessment, triage and differential diagnosis

The history should reconstruct a trajectory rather than assemble a checklist. Ask what activity the patient could previously perform, which activity now provokes symptoms, how rapidly this changed, and whether symptoms occur during exertion, recumbency or rest. Orthopnoea, paroxysmal nocturnal dyspnoea, declining exercise tolerance, oedema and abdominal fullness should be interpreted together. A patient who has progressively restricted activity may report few symptoms because the physiological challenge has disappeared. A history of prior symptoms remains relevant after successful treatment. [1, 4]

Examination should describe congestion and perfusion separately. Jugular venous distension and a sustained hepatojugular response support raised right-sided filling pressure; pulmonary crackles and effusions support pulmonary involvement but may be absent in chronic disease. Cool extremities, altered mentation, oliguria and a narrow pulse pressure suggest compromised perfusion. Clinical assessment remains valuable, but the ESCAPE experience also demonstrates that bedside estimates cannot be assumed to reproduce invasive haemodynamics accurately in every patient. A normal examination after diuretic treatment is not proof that the original diagnosis was wrong. [99]

Diagnostic and stabilizing actions proceed in parallel when the patient is acutely unwell. Oxygenation, respiratory effort, rhythm, blood pressure, perfusion and urgent echocardiography take priority over an exhaustive elective work-up. Acute coronary syndromes, severe valve dysfunction, dangerous arrhythmias, pulmonary embolism and tamponade require disease-specific pathways. Tamponade and pulmonary embolism are particularly important alternatives or contributors to circulatory failure; their recognition should not be obscured by a generic label of “cardiac decompensation”. [9]

Table 3.1. Clinical findings: what they support and what they do not prove

Finding or presentation	Diagnostic contribution	Important limitation
Exertional breathlessness and fatigue	Identify impaired functional reserve and justify a cardiopulmonary assessment.	Also occur with lung disease, anaemia, obesity, deconditioning and neuromuscular disease.
Orthopnoea or nocturnal dyspnoea	Increase suspicion of a haemodynamic cause when consistent with the wider history.	Symptoms require interpretation alongside sleep-disordered breathing and pulmonary disease.
Raised jugular venous pressure	Supports elevated right-sided filling pressure.	Does not identify its cause or establish fluid responsiveness.
Peripheral oedema or ascites	Suggest systemic venous congestion when corroborated.	May reflect venous insufficiency, hepatic disease, nephrotic disease or medication effects.
Crackles or bilateral B-lines	Support pulmonary interstitial involvement.	Neither finding alone separates cardiogenic oedema from all pulmonary alternatives.
Hypoperfusion or major respiratory distress	Indicate urgency and a need for immediate physiological assessment.	A relatively preserved blood pressure does not exclude severe low-output physiology.

[99, 100]

Differential diagnosis should be positive rather than residual. A clinician should be able to state which alternative mechanism is suspected and which test would discriminate it from heart failure. Spirometry after stabilization, evaluation of anaemia, chest imaging, rhythm monitoring or exercise testing may be more informative than repeating a resting echocardiogram. Cardiac and non-cardiac mechanisms frequently coexist; finding chronic obstructive pulmonary disease does not exclude heart failure, and demonstrating ventricular dysfunction does not establish that it explains every symptom. [99]

3.3. Baseline tests and laboratory phenotyping

A baseline diagnostic panel has three purposes: to corroborate the syndrome, identify causes or mimics, and define constraints relevant to subsequent treatment. The ECG should be reviewed for rhythm, atrioventricular and intraventricular conduction, Q waves, hypertrophy and acute or chronic repolarization abnormalities. A normal tracing lowers the probability of substantial cardiac disease but should not terminate evaluation of a convincing exertional syndrome. Chest radiography provides a different information domain, including pulmonary disease, pleural fluid and the distribution of congestion. [1, 4, 9]

In addition to established blood tests, the 2026 ESC diagnostic framework includes UACR in baseline assessment. This is clinically distinct from measuring creatinine: glomerular filtration and albumin leakage describe different aspects of kidney disease. The guideline’s baseline investigation recommendations are Class I, level C. [1]

Table 3.2. A purpose-led baseline investigation set

Investigation	Question addressed	Interpretive safeguard
12-lead ECG	What rhythm, conduction abnormality or ischaemic clue accompanies the syndrome?	Retrieve earlier tracings; distinguish new changes from longstanding abnormalities.
Full blood count	Is anaemia, infection or another haematological disorder contributing?	A normal haemoglobin concentration does not exclude iron deficiency.
Creatinine, eGFR, electrolytes and UACR	What are the renal, electrolyte and albuminuria phenotypes?	An isolated value during decompensation does not establish chronic kidney disease.
Liver and thyroid tests	Is there congestion, hypoperfusion, endocrine disease or a competing cause?	Interpret patterns and trends rather than attributing all abnormalities to heart failure.
Glucose or HbA1c; lipid profile	What cardiometabolic conditions require characterization?	Risk-factor identification is not itself confirmation of heart failure.
Ferritin and transferrin saturation	Is iron availability impaired?	Inflammation can raise ferritin; consider TSAT and the broader clinical context.
Natriuretic peptides	How strongly does a myocardial stress signal support the suspected syndrome?	Apply the appropriate setting, assay and patient-context interpretation.
TTE and chest radiography	What structural, functional and thoracic findings explain the presentation?	Imaging quality and competing pulmonary disease remain important.

[1, 33]

KDIGO classifies albuminuria as A1 below 30 mg/g, A2 from 30 to 300 mg/g and A3 above 300 mg/g. Abnormal kidney findings require evaluation of chronicity and cause; chronic kidney disease generally requires persistence for at least three months. Infection, exercise, acute illness and changing haemodynamics can complicate interpretation of a single urine result. Where creatinine is likely to misrepresent filtration, for example in severe muscle wasting, an alternative or combined filtration estimate may be appropriate. [33]

The practical output is a baseline phenotype, not a list of laboratory deviations. For example, reduced filtration with little albuminuria, substantial albuminuria with preserved filtration, and an acute creatinine rise during decongestion are different diagnostic situations. Each should prompt a different question about chronic disease, congestion, perfusion, medication exposure or an independent renal disorder. Similar reasoning applies to liver abnormalities: their temporal relation to congestion or low output should be recorded before assigning a primary hepatic diagnosis.

3.4. Natriuretic peptides: setting, thresholds and uncertainty

Natriuretic peptides are most useful when they change the probability of heart failure after clinical assessment. They are neither an anatomical diagnosis nor a direct measurement of filling pressure. Their exclusionary role requires a distinction between population reference intervals and clinical decision thresholds. A threshold selected for sensitivity in suspected disease should be described by its intended purpose and population. [8]

The diagnostic contribution of BNP was established in the Breathing Not Properly study, in which rapid measurement added information to clinical evaluation of acute dyspnoea. This does not mean that one concentration separates every cardiac from every non-cardiac cause. A value should modify the assessment already formed from symptoms, examination, ECG and imaging, not replace that assessment. [101]

Table 3.3. Natriuretic peptide decision limits: separate the clinical settings

Clinical setting	Decision limit	Meaning and limitations
Non-acute suspected HF: conventional exclusion thresholds	BNP <35 pg/mL; NT-proBNP <125 pg/mL.	HF becomes less likely, but persistent high clinical suspicion, particularly obesity-related HFpEF, warrants further assessment.
Non-acute NT-proBNP: age-related "HF likely" thresholds	Age <50 years: ≥125 pg/mL. Age 50–75 years: ≥250 pg/mL. Age >75 years: ≥500 pg/mL.	Support referral for cardiac imaging. Values above 125 but below the age-related threshold remain a grey zone, not an automatic exclusion.
Acute dyspnoea: exclusion thresholds	BNP <100 pg/mL; NT-proBNP <300 pg/mL; MR-proANP <120 pmol/L.	Make acute HF less likely. Do not delay stabilization or override a convincing emergency presentation.
Acute dyspnoea: NT-proBNP rule-in thresholds	Age <50 years: ≥450 pg/mL. Age 50–75 years: ≥900 pg/mL. Age >75 years: ≥1800 pg/mL.	Support acute HF in the appropriate setting; values between rule-out and rule-in limits require clinical integration.
Non-acute MR-proANP: less extensive evidence	An exclusionary value of <40 pmol/L has been studied.	Not interchangeable with BNP or NT-proBNP; evidence and local availability are more limited.

[1, 9, 102–104].

The HFA age-related approach reduces reliance on one outpatient NT-proBNP boundary across markedly different age distributions. However, the intermediate interval remains diagnostically active. A symptomatic older patient with a concentration above the sensitive exclusion threshold but below the age-related "likely" threshold has not been shown to have no disease. The choice between earlier imaging, reassessment and functional investigation depends on the pre-test probability and the consequences of a missed diagnosis. [102, 105]

MR-proANP requires particular care with units. BACH evaluated a threshold of 120 pmol/L in acute dyspnoea, whereas the non-acute study by Gohar and colleagues examined 40 pmol/L as a sensitive exclusionary threshold. These are molar concentrations, not values in pg/mL. The less extensive chronic evidence should also discourage a claim that all peptide assays have identical diagnostic performance in every outpatient population. [103, 104]

An apparent biomarker–clinical mismatch should initiate a quality check: confirm the analyte and unit, establish when the sample was obtained relative to treatment, compare with earlier values, and consider the patient's rhythm, renal function and adiposity. The analytical report should remain available rather than being replaced by a transcribed number without its assay identity. Serial assessment is most interpretable when the same analyte and laboratory method are used. [11]

3.5. Other biomarkers and serial interpretation

Biomarkers should be classified by the question they answer. Natriuretic peptides reflect myocardial stress; troponin identifies myocardial injury; renal indices and electrolytes describe extracardiac involvement and treatment safety; iron studies identify a potentially relevant systemic substrate. Their integration is clinically more useful than assuming that any one marker represents the entire heart-failure process. The direction of change should be interpreted with the circumstances in which it occurred.

Table 3.4. Context that changes the interpretation of a natriuretic peptide result

Context	Likely interpretive problem	Response to the uncertainty
Atrial fibrillation	Concentrations may be higher without an equivalent change in ventricular congestion.	Interpret alongside rhythm, ventricular rate, structural findings and the appropriate HFpEF framework.
Older age or renal dysfunction	Specificity may be reduced when an unmodified low threshold is used.	Use age, renal phenotype, prior values and imaging; do not attribute every elevation to reduced clearance.
Obesity	Concentrations may be lower despite clinically important haemodynamic disease.	Persist with objective evaluation when symptoms and phenotype remain convincing.
Early ARNI treatment	BNP may rise because neprilysin inhibition alters its handling.	NT-proBNP is less directly affected by this mechanism; neither analyte should be interpreted without context.
Acute infection, pulmonary embolism or other major stress	A raised value may reflect cardiac strain without establishing primary left-heart failure.	Evaluate the precipitating disorder and both ventricles.
Prior successful decongestion or treatment	A low or falling result may describe the treated state.	Retain the historical evidence supporting the original diagnosis.

[102], obesity physiology [52] and the PARADIGM-HF biomarker analysis [106].

High-sensitivity troponin elevation establishes myocardial injury when it exceeds the assay’s relevant reference limit; acute injury requires a rise or fall. Myocardial infarction additionally requires evidence of acute myocardial ischaemia. Thus, a patient with decompensated heart failure and elevated troponin should be evaluated for an acute coronary syndrome, but troponin alone does not establish a type 1 infarction or mandate an assumption of acute coronary occlusion. The clinical presentation, ECG, serial kinetics and imaging determine the next step. [107]

During initiation of sacubitril/valsartan, BNP may increase even when treatment is clinically appropriate. The PARADIGM-HF biomarker analysis found that NT-proBNP was less prone to this early interpretive confusion, while both biomarkers retained prognostic information. The practical implication is not that BNP becomes useless, but that the drug exposure and sampling time must accompany its interpretation. A marked rise with worsening symptoms should never be dismissed automatically as a pharmacological artefact. [106]

A prognostic association does not establish a treatment target. GUIDE-IT did not demonstrate improved clinical outcomes from an NT-proBNP-guided strategy compared with high-quality usual care in the population studied. Serial peptides can still help characterize trajectory or investigate suspected deterioration, but a target number should not substitute for assessment of congestion, perfusion, kidney function, blood pressure and treatment tolerance. Newer markers require the same distinction between association, incremental diagnostic information and demonstrated clinical utility. [108]

3.6. Transthoracic echocardiography beyond ejection fraction

A useful echocardiographic examination begins with a clinical question and a record of the conditions under which the images were acquired. Rhythm, ventricular rate, blood pressure, body size and recent treatment may change measurements or their meaning. The report should state when acoustic windows are limited and which measurements are uncertain. A visually estimated ejection fraction without a description of image quality is less useful for a borderline diagnostic decision than a reproducible quantitative examination. [6]

Biplane volumetric assessment from non-foreshortened apical views is preferable to assigning ventricular function from a single dimension or one visually selected image. Three-dimensional assessment and contrast enhancement may improve quantification in appropriate circumstances; CMR is valuable when reliable echocardiographic quantification cannot be obtained. Serial comparisons should use comparable acquisition and analysis methods. An apparent small change close to a category boundary may reflect methodological variability rather than true biological transition. [6]

Table 3.5. Minimum interpretive dataset for a heart-failure echocardiogram

Domain	Report content	Clinical question
Acquisition context	Rhythm, rate, blood pressure when available, image quality and quantification method.	How reliable and comparable are the measurements?
Left ventricle	Volumes, ejection fraction, wall thickness, mass or geometry, and regional motion.	Is there systolic dysfunction, adverse loading or a regional pattern?
Longitudinal function	GLS when technically valid, with method and quality limitations.	Is myocardial performance impaired despite a relatively preserved EF?
Diastolic assessment	Transmitral flow, annular velocities and integrated pressure assessment in the applicable algorithm.	Is relaxation abnormal, and is there evidence of elevated filling pressure?
Left atrium	Indexed volume and, where useful and technically valid, atrial function.	Is there evidence of chronic loading or atrial disease?
Right heart	RV size and function, right atrial size, TR and an estimate of pulmonary pressure when feasible.	Is right-heart involvement primary, secondary or disproportionate?
Valves and pericardium	Mechanism and severity of lesions; effusion or features suggesting constriction.	Could a correctable loading or pericardial disorder explain the syndrome?

Chamber, diastolic and right-heart standards [6, 12, 47].

LVEF is a ratio: stroke volume divided by end-diastolic volume. It is therefore influenced by chamber geometry and loading as well as myocardial contraction. A small ventricle can have a preserved fraction but a limited absolute stroke volume; substantial mitral regurgitation can maintain the calculated ejection fraction while effective forward output is impaired. These examples explain why the number should be accompanied by volumes, regional function and an assessment of valve disease. They are physiological interpretations, not alternative diagnostic thresholds.

Physiological worked example. With end-diastolic and end-systolic volumes of 80 and 32 mL, stroke volume is 48 mL and EF is 60%. With volumes of 150 and 60 mL, stroke volume is 90 mL and EF is also 60%. These constructed calculations assume no important regurgitation or shunt. They illustrate why an identical EF does not imply an identical absolute forward volume, filling requirement or exercise reserve. Stroke volume, body size and heart rate remain relevant to interpretation; neither numerical example by itself establishes heart failure.

GLS is complementary rather than a replacement for ejection fraction. It may reveal longitudinal dysfunction, but vendor, software, tracking quality, rhythm and loading affect the result. A reduced absolute strain magnitude should trigger integration with the phenotype, not a diagnosis by itself. In suspected cancer therapy-related dysfunction, serial strain interpretation belongs within the dedicated cardio-oncology framework rather than a generic heart-failure cut-off. [48]

Most importantly, the final echocardiographic conclusion should answer a clinical question. “Preserved systolic function” does not answer whether exertional breathlessness is cardiac, and “diastolic dysfunction” does not by itself establish symptomatic HFpEF. The examination should state which disease processes are supported, which cannot be assessed, and whether further characterization is likely to alter management. This distinction protects both against overdiagnosis from incidental abnormalities and against false reassurance from a single normal parameter.

3.7. Diastolic function and filling-pressure assessment

Relaxation, chamber stiffness and filling pressure are related but different physiological concepts. Annular e′ velocity contributes information about relaxation, whereas transmitral flow, E/e′ and downstream chamber or pulmonary findings contribute to pressure assessment. An abnormal relaxation pattern can be present without elevated resting filling pressure; conversely, an apparently normal transmitral pattern can occur when raised atrial pressure masks impaired relaxation. The diagnostic interpretation is therefore multiparametric. [12]

Several commonly available measurements can provide objective support in a compatible HFpEF syndrome. Table 3.6 presents commonly used measurements alongside their thresholds and limitations. They should not be counted as independent proofs of disease when several reflect the same loading abnormality. The absence of hypertrophy, for example, does not exclude HFpEF; a mildly enlarged atrium may have more than one explanation.

Table 3.6. Common echocardiographic findings supporting an HFpEF assessment

Measurement	Supportive finding	Interpretation
LV mass or concentric geometry	LV mass index ≥95 g/m² in women or ≥115 g/m² in men; or relative wall thickness >0.42.	Supportive remodelling, not a mandatory feature of every HFpEF phenotype.
Left atrial volume index	>34 mL/m² in sinus rhythm; >40 mL/m² with AF.	Interpret rhythm, valve disease, duration of loading and indexing method.
Resting E/e′	>9 supports increased likelihood of elevated filling pressure; ≥15 is more specific but less sensitive.	A context-dependent surrogate, not a direct catheter measurement or a stand-alone diagnosis.
Estimated pulmonary pressure or TR velocity	PASP >35 mmHg or resting TRV >2.8 m/s.	Requires a usable Doppler signal and consideration of pulmonary or vascular alternatives.

Interpret these supportive variables alongside the simplified 2026 ESC criteria [1]. This is not the ASE 2025 grading algorithm or a complete HFA-PEFF score.

Indexing and measurement quality deserve attention before a threshold is applied. Body-surface-area indexing can change the apparent degree of chamber enlargement, especially at extremes of body size. An indexed result should therefore remain linked to its unindexed measurement and to the patient's phenotype. Likewise, E/e′ requires technically appropriate mitral inflow and annular measurements acquired in a compatible rhythm. Significant mitral disease, fused signals or an unreliable annular trace should be described as a limitation rather than converted into a precise pressure claim. [6, 12]

The 2025 ASE update provides an integrated approach that also incorporates left atrial strain in selected circumstances. Its main algorithms and special-population pathways should be applied to the populations for which they were designed. Atrial fibrillation, significant mitral disease, mitral annular calcification, constrictive physiology and other special settings should not be forced into an unmodified general sinus-rhythm pathway. The choice of pathway should be documented before the measurements are classified. [12]

Table 3.7. Different diagnostic frameworks answer different questions

Framework or measure	Principal purpose	How to avoid misuse
LVEF-based clinical phenotype	Describe ventricular systolic phenotype within the current HF classification.	Do not infer diastolic pressure or aetiology from EF alone.
ASE 2025 diastolic assessment	Integrate echocardiographic evidence of relaxation abnormalities and filling pressure.	Use the appropriate algorithm and special-population exclusions; do not import isolated thresholds from other scores.
ESC supportive HFpEF assessment	Recognize objective structural or functional evidence supporting the syndrome.	A supportive finding is not individually definitive, and absence of one finding does not exclude disease.
HFA-PEFF	Organize clinical suspicion and three diagnostic domains, with functional testing for uncertainty.	Do not exceed the permitted score within a domain or treat a partial dataset as a complete score.
H□FPEF	Estimate HFpEF probability using clinical and echocardiographic predictors.	The score estimates probability; it does not identify every alternative aetiology.
Exercise haemodynamics	Test whether filling pressures become abnormal under physiological stress.	Interpret the pressure with posture, workload, flow and measurement quality.

[1, 7, 12, 109–111].

A particularly important limitation is the separation between resting echocardiographic classification and exercise-induced HFpEF. In a 2026 investigation of 756 patients with invasively established HFpEF, Harada and colleagues reported normal diastolic classification in 32.8% and grade 1 dysfunction in 34.8% using the updated criteria. These findings derive from a selected, referred population and are not population-screening estimates. They nevertheless caution against using a normal or low-grade resting classification as an absolute exclusion test in persistent unexplained exertional symptoms. [112]

The practical response is not to discard echocardiography. It is to state what has and has not been demonstrated: for example, “no convincing elevation of resting filling pressure; exercise-related disease remains possible.” This wording preserves the value of a technically adequate resting study while avoiding a claim that it measured physiology during a task that was never performed. When the diagnosis would change treatment, exercise assessment or invasive testing can address that remaining question.

3.8. HFpEF probability scores and diagnostic uncertainty

HFpEF should be considered when the clinical syndrome persists despite preserved ejection fraction, but preserved EF is only an entry condition. The diagnostic problem is especially difficult in older patients with obesity, atrial fibrillation, renal disease or pulmonary limitation. A patient can have several risk factors without haemodynamic heart failure, and another can have exercise-induced disease with relatively unimpressive resting studies. The scores discussed below organize this uncertainty; they do not replace investigation of valve disease, amyloidosis, pericardial disease or alternative causes of dyspnoea.

The H□FPEF score was derived against invasive assessment in patients with unexplained dyspnoea. It weights obesity and atrial fibrillation more heavily than its other variables, reflecting their diagnostic contribution in the derivation setting. Low, intermediate and high totals guide the need for further assessment, but a score calculated from inaccurate pulmonary pressure or annular velocity measurements will inherit those inaccuracies. [109]

Table 3.8. H□FPEF score: components and correct use

Component	Definition	Points
Heavy	Body mass index >30 kg/m²	2
Hypertensive treatment	Two or more antihypertensive medications	1
Atrial fibrillation	Paroxysmal or persistent AF	3
Pulmonary hypertension	Estimated pulmonary artery systolic pressure >35 mmHg	1
Elder	Age >60 years	1
Filling pressure	E/e′ >9	1
Interpretive bands	Total 0–1: low; 2–5: intermediate; 6–9: high probability.	0–9

[109]

HFA-PEFF uses a stepwise process with functional, morphological and biomarker domains. A major criterion contributes two points and a minor criterion one, with a maximum of two points from any one domain. Totals of five or six support HFpEF, zero or one make it less likely, and two to four require further evaluation. The complete published criteria, including rhythm-specific interpretation and the corrigendum, should be used rather than reconstructing a score from an abbreviated table. [7]

The two scores can disagree because they weight different information. Comparative investigation against invasive diagnosis confirms that the choice of tool can alter classification. A discordant result should prompt examination of the constituent variables, not an arbitrary preference for the higher total. It is particularly important to check whether the patient resembles the validation population and whether all required measurements are available. Missing measurements should be reported as missing, not treated as normal. [113, 114]

Figure 3.2. Resolving uncertainty in a preserved-ejection-fraction presentation

01	Confirm that the problem remains unexplained Review symptom trajectory, previous EF, medication effects, rhythm, valve disease, pulmonary disease and anaemia.
02	Build a complete resting assessment Use technically valid imaging and contextualized biomarkers; calculate a chosen probability score only from a complete applicable dataset.
03	Identify concordance or discordance Strong objective concordance may establish the diagnosis. Intermediate probability or a clinical–test mismatch requires an explicit next question.
04	Reproduce the physiological challenge Consider CPET and exercise echocardiography; use exercise haemodynamics when non-invasive assessment remains inconclusive and the answer will change care.
05	Return to the causal diagnosis A confirmed pressure abnormality establishes physiology, not necessarily aetiology. Reassess the underlying disease and competing limitations.

Normal resting measurements do not prove that filling pressures remain normal during exercise.

3.9. Right-heart function and the pulmonary circulation

The right ventricle should be assessed as a functional chamber, not as an appendage to the left-ventricular report. RV size, shape, systolic performance, tricuspid regurgitation, right atrial size and estimated pulmonary pressure together characterize a right-heart phenotype. Longitudinal indices such as TAPSE and tissue Doppler S′ are useful but describe only part of RV mechanics; fractional area change, strain or three-dimensional assessment may provide complementary information when technically appropriate. [47]

A poor-quality or absent tricuspid regurgitation signal is a limitation of pressure estimation, not evidence of a normal pulmonary pressure. Likewise, severe tricuspid regurgitation and uncertainty in right atrial pressure can affect the estimate. The report should distinguish an estimated pressure from a directly measured haemodynamic quantity. It should also identify whether the right-heart changes appear proportionate to the degree of left-heart disease or raise suspicion of an additional pulmonary vascular, thromboembolic or respiratory process. [47]

Table 3.9. Right-heart findings and the next diagnostic question

Pattern	Potential interpretation	Useful next step
RV dysfunction with established left-heart disease	Secondary pulmonary vascular loading, ventricular interaction or biventricular disease.	Reassess left-sided loading, valve disease and the degree of disproportion.
Marked RV enlargement with relatively modest left-heart findings	Pulmonary vascular disease, thromboembolism, shunt or primary RV disease may contribute.	Target testing to the clinical probability; consider specialist pulmonary vascular assessment.
Severe TR and systemic venous congestion	A valve-related and chamber-related feedback process may dominate.	Define mechanism, RV reserve and extracardiac organ involvement.
Raised estimated pulmonary pressure	Suggests, but does not invasively classify, pulmonary hypertension.	Use right-heart catheterization when classification will change the decision.
Low or uncertain TR velocity despite clinical suspicion	Incomplete Doppler information or altered valve haemodynamics.	Do not equate an unmeasurable signal with exclusion of pulmonary hypertension.

Invasive classification distinguishes elevated pulmonary pressure caused predominantly by left-heart filling pressure from a significant pulmonary vascular component. Under the 2022 ESC/ERS definition, pulmonary hypertension requires mean pulmonary artery pressure above 20 mmHg; post-capillary disease includes PAWP above 15 mmHg. Pulmonary vascular resistance then helps distinguish isolated from combined post- and pre-capillary disease, using a boundary of 2 Wood units. These haemodynamic definitions should not be substituted for echocardiographic diagnostic thresholds. [45]

The clinical implication is a decision about mechanism, not simply severity. A patient with raised pulmonary pressure may need assessment of left-heart disease, pulmonary vascular disease, chronic thromboembolic disease, lung disease or more than one process. The sequence should be selected by the phenotype. Repeatedly increasing confidence in an echocardiographic pressure estimate cannot answer a question that requires direct measurement of wedge pressure, cardiac output and pulmonary vascular resistance.

3.10. Lung ultrasound and integrated congestion assessment

Lung ultrasound adds a bedside view of pulmonary interstitial involvement and pleural fluid to the cardiac examination. A diffuse bilateral B-line pattern can support pulmonary congestion, while serial examinations using the same protocol can describe its evolution. However, B-lines are an ultrasound sign, not a histological or aetiological diagnosis; pulmonary fibrosis, inflammation and other lung processes can produce interstitial patterns. Pleural abnormalities, focal consolidation and the distribution of findings should therefore be reviewed alongside the cardiac phenotype. [100]

The examination should be reproducible. Record the protocol, patient position, areas scanned and technical limitations. Counts obtained with different numbers of scanning zones or different equipment settings should not be assumed to be interchangeable. A change in B-line burden is most meaningful when technique and clinical context are comparable. Focused point-of-care ultrasound can accelerate a decision, but it should not be described as a complete echocardiographic examination when important structures and quantitative measurements were not assessed. [100]

Congestion is not one compartment. Pulmonary interstitial involvement, right-sided venous pressure, peripheral oedema and intravascular filling are related but can diverge. A patient may have substantial systemic venous congestion with few pulmonary findings, or striking pulmonary oedema from pressure redistribution without a large increase in total body water. Both congestion and perfusion require assessment; imaging should refine the clinical evaluation rather than reduce it to a single ultrasound target.

The inferior vena cava is particularly vulnerable to overinterpretation. Its dimensions and respiratory behaviour can support an estimate of right atrial pressure in a suitable setting, but depend on ventilation, breathing effort and other physiological conditions. A large vena cava is not a stand-alone measure of total body fluid, and a small one does not establish that a fluid bolus will improve cardiac output. The clinician should state which pressure or volume-related question is being addressed before acting on the image. [47]

A practical integrated congestion record combines symptoms, jugular venous pressure, peripheral findings, body-weight trajectory, renal and electrolyte trends, cardiac ultrasound and lung findings. If these domains disagree, the record should preserve the disagreement and suggest an explanation. For instance, falling weight with persistent breathlessness may represent residual pulmonary congestion, a non-cardiac limitation or excessive volume removal with impaired perfusion. The next test should be selected to distinguish those mechanisms rather than to validate an already chosen treatment.

3.11. Cardiac magnetic resonance and tissue characterization

CMR is most valuable when it answers a question that remains unresolved after clinical assessment and echocardiography: the accuracy of ventricular volumes, the nature of myocardial injury, the distribution of scar, a suspected infiltrative process or an alternative cardiomyopathy. Its strength lies in combining anatomy, function and tissue characterization rather than in replacing every other imaging modality. The examination should be tailored to the suspected disease and to the decision that may follow. [3, 115]

Late gadolinium enhancement identifies a distribution of abnormal extracellular contrast retention. Subendocardial or transmural enhancement in a coronary territory supports ischaemic injury, whereas a mid-

wall or subepicardial pattern raises a different aetiological question. These patterns should not be interpreted as universally specific diagnoses: overlapping diseases and mixed mechanisms occur. Distinguishing ischaemic from non-ischaemic scar requires clinical and coronary information when relevant.

Table 3.10. CMR tissue information: interpretation without overclaiming specificity

Technique or pattern	Information provided	Major interpretive caution
Cine imaging and ventricular volumes	Reproducible assessment of chamber volumes, function and regional motion.	Rhythm, acquisition quality and analysis method still matter.
Late gadolinium enhancement	Location and pattern of focal injury or fibrosis; potential arrhythmic substrate.	Absence of LGE does not exclude all myocardial disease or diffuse fibrosis.
Native T1 and extracellular volume	Tissue composition and extracellular expansion in a compatible phenotype.	Use local sequence- and scanner-specific reference ranges; ECV requires suitable haematocrit information.
T2-based assessment	Evidence supporting myocardial oedema or active injury.	An abnormal signal does not identify the pathogen or prove a specific immune mechanism.
T2* assessment	Quantification of myocardial iron-related signal decay.	T2* is not interchangeable with conventional T2 imaging.
Stress perfusion	Evidence of impaired perfusion under stress.	Epicardial obstruction and microvascular dysfunction require different causal interpretations.

[116], [117], [81]

Mapping values are not portable universal cut-offs. Native T1 and T2 depend on field strength, sequence, acquisition and processing; extracellular volume estimation also depends on the blood measurement and the conditions of contrast acquisition. A report should therefore identify the method and its reference range. The result should be integrated with morphology and enhancement pattern rather than interpreted as a molecular diagnosis. In particular, extracellular expansion can support an amyloid phenotype but does not distinguish AL from ATTR reliably. [14, 116, 118]

For suspected myocardial inflammation, the updated Lake Louise framework combines evidence from T2-based markers of oedema and T1-based markers of myocardial injury. A coherent combination provides stronger support than one isolated abnormal sequence. CMR cannot establish every histological subtype, and its sensitivity depends on the presentation and timing. In a high-risk syndrome, a reassuring or equivocal study should not automatically displace the indication for specialist investigation or biopsy. [13, 117]

Scar can also carry prognostic information. The association between myocardial fibrosis and adverse outcomes in dilated cardiomyopathy, including the study by Gulati and colleagues, demonstrates why tissue characterization adds information beyond LVEF. However, association does not establish that one scar measurement should independently determine device treatment in all phenotypes. The clinical conclusion should integrate arrhythmic history, genotype where relevant, ventricular function and the applicable disease-specific recommendations. [41, 119]

For myocardial iron assessment, T2* quantification should be distinguished from T2 measurements. Anderson and colleagues linked this measurement with myocardial iron and ventricular dysfunction, providing a basis for detecting disease before advanced failure and for monitoring chelation. A ferritin concentration or a preserved ejection fraction does not substitute for tissue assessment when cardiac siderosis is suspected. [81]

Choice of modality also requires an explicit safety and feasibility assessment. Before CMR, establish device and implant status, whether an appropriate device protocol is available, the patient's ability to tolerate the examination and whether the clinical question requires contrast. For contrast-based CT or CMR, assess renal context, prior reactions and the relevant agent-specific policy rather than treating all contrast materials as equivalent. A technically excellent test that cannot answer the question, or cannot be performed safely and reliably, is not the optimal investigation. [3, 59]

3.12. Coronary CT, stress imaging and myocardial viability

Coronary disease may be the cause of myocardial dysfunction, a contributor to symptoms or an important coexisting disorder. These possibilities should not be collapsed into one label. Coronary CT angiography is principally an anatomical test, whereas stress echocardiography, perfusion CMR, SPECT and PET evaluate aspects of inducible ischaemia or perfusion. The appropriate test depends on the likelihood of obstructive disease, image quality, rhythm, calcification, renal context and whether the result will lead to a feasible intervention. [59]

A non-invasive test should be chosen for the unresolved question rather than simply because heart failure is present. If the question is whether obstructive coronary disease is plausible, anatomical assessment may be useful; if the question concerns inducible ischaemia or perfusion, functional imaging may be more informative. Acute coronary syndromes and high-risk presentations require their own pathways. Elective testing should not delay evaluation of a convincing acute ischaemic syndrome.

Table 3.11. Selecting coronary and myocardial investigations

Unresolved clinical question	Potential investigation	What the result does not establish alone
Is there obstructive epicardial coronary disease?	CCTA or invasive angiography, according to probability and clinical context.	Whether every symptom or the entire cardiomyopathy is caused by the coronary lesions.
Is inducible ischaemia present and where?	Stress echocardiography, perfusion CMR, SPECT or PET.	That revascularization will necessarily improve survival or ventricular function.
Is the injury pattern compatible with prior infarction?	CMR with LGE in the context of coronary anatomy.	The current physiological significance of every coronary stenosis.
Is dysfunctional myocardium viable?	Selected viability assessment using an appropriate validated modality.	A stand-alone indication for PCI or a guaranteed recovery of function.
Is a valve lesion responsible for a low-flow presentation?	Integrated valve imaging, sometimes including stress echocardiography or CT.	That the coronary work-up alone will resolve the haemodynamic problem.

The distinction between tissue viability and benefit from a revascularization strategy is essential. REVIVED-BCIS2 enrolled patients with severe ischaemic LV dysfunction and demonstrable viability but did not show a reduction in death or heart-failure hospitalization with PCI added to optimal medical therapy. This result should prevent an automatic inference from “viable myocardium” to “prognostically effective PCI”. It does not establish that PCI is never appropriate, nor does it make all revascularization strategies, symptom indications or acute coronary presentations equivalent. [61]

The final decision belongs to an integrated clinical and, when appropriate, Heart Team assessment. Coronary anatomy, symptom burden, ventricular disease, surgical and procedural risk, expected completeness of treatment, comorbidities and patient priorities all contribute. Imaging should supply a defined piece of evidence to that decision. A report that ends with “viability present” without stating its extent, method and clinical implications leaves the central decision unresolved.

3.13. Nuclear imaging in amyloidosis and inflammatory disease

Nuclear imaging is not one investigation with one biological meaning. Perfusion studies, bone-avid tracer scintigraphy and FDG PET interrogate different processes. A technically positive examination should be interpreted only within the pathway for the tracer and disease being investigated. This is especially important in cardiac amyloidosis, where failure to distinguish light-chain disease from transthyretin disease can redirect the patient toward an inappropriate treatment pathway. [14]

Clinical suspicion of cardiac amyloidosis can arise from otherwise unexplained ventricular thickening, restrictive physiology, conduction disease, atrial arrhythmias or characteristic extracardiac features. Apical sparing and an apparent discrepancy between wall thickness and ECG voltage are supportive clues, not obligatory findings. The central laboratory assessment comprises serum free light chains plus serum and urine immunofixation. Routine protein electrophoresis alone is not an equivalent exclusion test for a monoclonal process. [14]

Gillmore and colleagues established the non-biopsy ATTR diagnostic approach in which compatible cardiac findings, grade 2 or 3 uptake with a bone-avid tracer, and absence of a monoclonal protein support ATTR cardiomyopathy without cardiac biopsy. Tomographic confirmation is important to distinguish true myocardial retention from blood-pool activity. The strength of the pathway lies in the combination of imaging and biochemical exclusion, not in the scan viewed alone. [80]

Figure 3.3. Suspected cardiac amyloidosis: the conditional meaning of a positive scan

01	Recognize a compatible cardiac phenotype Use the clinical pattern, echocardiography and, where appropriate, CMR. No single red flag is mandatory.
02	Perform a complete monoclonal protein screen Serum free light chains plus serum and urine immunofixation. Interpret renal effects on free light chains appropriately.
03	If the monoclonal screen is abnormal Do not assign ATTR from a positive bone scan alone. Arrange specialist assessment, tissue confirmation and accurate amyloid typing as indicated.
04	If no monoclonal process is detected Grade 2 or 3 myocardial bone-tracer uptake, confirmed tomographically in a compatible phenotype, can support a non-biopsy ATTR diagnosis.
05	Resolve equivocal or discordant findings Grade 0 or 1 uptake, persistent suspicion or conflicting biochemical and imaging evidence requires further assessment; genotype confirmed ATTR.

FDG PET has a different role in suspected cardiac sarcoidosis: identifying metabolically active inflammation in conjunction with perfusion, cardiac structure and the extracardiac phenotype. Preparation to suppress physiological myocardial glucose uptake is critical. Inadequate suppression can create an uninterpretable study, and uptake is not specific for sarcoidosis. The consensus framework therefore emphasizes technical preparation, integrated interpretation and consistency when scans are used for longitudinal assessment. [120]

The diagnostic report should state what the tracer result permits and what remains unresolved. For amyloidosis, that includes the monoclonal screen and whether uptake is truly myocardial. For inflammatory imaging, it includes preparation quality, the pattern of uptake, perfusion findings and extracardiac targets that might permit safer tissue diagnosis. A generic conclusion of “positive nuclear scan” is insufficient for a treatment decision.

3.14. Exercise testing and stress echocardiography

Exercise evaluation is especially useful when resting data do not explain exertional symptoms. CPET quantifies an integrated response involving ventilation, gas exchange, circulation and peripheral oxygen use. Peak oxygen uptake, ventilatory efficiency, oxygen pulse, chronotropic response, blood pressure, symptoms and ECG findings should be interpreted together, with attention to effort and test quality. A reduced peak oxygen uptake establishes limitation, but not its cause by itself. [121, 122]

The conditions of the examination are part of the result. The report should identify the exercise modality, protocol, achieved workload, symptom limitation, relevant medication exposure and the physiological evidence that the effort was interpretable. Indexing oxygen uptake to total body mass can complicate comparisons in severe obesity; musculoskeletal limitation and frailty can prevent an adequate cardiovascular challenge. A submaximal test should not be assigned the same diagnostic meaning as a technically adequate symptom-limited test. [52, 121]

Table 3.12. Functional investigations: complementary rather than interchangeable

Investigation	Principal contribution	Important limitation
Six-minute walk test	Practical measure of functional performance and longitudinal change.	Limited mechanistic specificity; influenced by motivation, mobility and comorbidity.
CPET	Characterizes integrated exercise limitation and may help distinguish competing patterns.	A low peak oxygen uptake does not alone prove elevated LV filling pressure.
Exercise echocardiography	Assesses dynamic filling indices, pulmonary pressure, valve behaviour or ischaemia.	Image quality, timing and Doppler feasibility may limit interpretation.
Invasive exercise assessment	Measures pressure–flow behaviour when non-invasive testing leaves an important question unresolved.	Requires specialist expertise; technical and protocol differences affect the result.

Exercise echocardiography can detect dynamic abnormalities that are absent at rest, including elevation of filling-pressure surrogates, worsening regurgitation and pulmonary pressure responses. However, exertional tachycardia, signal fusion and incomplete Doppler acquisition may make the relevant measurement unavailable precisely when symptoms occur. An absent measurement is not a negative test. The simultaneous invasive–echocardiographic work by Obokata and colleagues illustrates the value of validating a stress surrogate against directly measured physiology. [123]

The result should determine the next action. A convincing non-cardiac limitation may redirect investigation; concordant stress findings can strengthen the diagnosis; persistent discordance may justify invasive exercise testing. In selected cases, combined invasive CPET can separate elevated filling pressure, abnormal pulmonary vascular response, inadequate output reserve and peripheral limitations. The choice depends on the question and local expertise rather than on a requirement that every symptomatic patient undergo every modality.

3.15. Invasive haemodynamics: measurement and interpretation

Right-heart catheterization should be used when direct haemodynamic information is expected to change the diagnosis, risk assessment or management. Examples include unexplained dyspnoea after an inconclusive non-invasive evaluation, pulmonary hypertension requiring classification, advanced heart-failure assessment and selected unstable or complex haemodynamic states. It is not a routine substitute for an adequate clinical and echocardiographic assessment in every stable patient. [45]

The measured values are only as reliable as the acquisition. The report should specify transducer reference, patient position, respiratory conditions, oxygen exposure, rhythm and the method of cardiac output measurement. Wedge pressure requires a technically convincing occlusion tracing; severe respiratory swings, large V waves and valvular disease can complicate its relation to other measures of left-sided pressure. A directly recorded number is not automatically a physiologically valid number. Specialist interpretation is particularly important when a borderline value will determine the diagnosis.

Table 3.13. Invasive measurements used in diagnostic reasoning

Measurement	Common interpretive reference	Boundary or method caution
Resting PCWP / PAWP	A value ≥15 mmHg supports raised left-sided filling pressure in commonly used HFpEF diagnostic frameworks.	Loading conditions, respiration and technical quality influence a borderline measurement.
Exercise PCWP	A value ≥25 mmHg is commonly used with supine exercise in HFpEF investigations.	Posture and exercise protocol matter; thresholds must match the protocol used.
Resting LV end-diastolic pressure	A value ≥16 mmHg is a commonly cited supportive invasive criterion.	LVEDP and mean wedge pressure are related but not identical, particularly with valve or atrial disease.
PCWP / cardiac-output slope	A slope >2 mmHg per L/min has been associated with abnormal exercise pressure–flow behaviour.	Requires reliable paired pressure and flow measurements; it is not equivalent to one peak pressure.
Pulmonary vascular resistance	Calculated as (mean PA pressure – PAWP) / cardiac output, in Wood units.	Errors in wedge pressure or output can change the pulmonary hypertension classification.

Borlaug and colleagues demonstrated that exercise haemodynamics can reveal HFpEF in patients with exertional symptoms whose resting evaluation is not diagnostic. The central concept is impaired reserve: the circulation may maintain acceptable pressure at rest but require a disproportionate increase during activity. This is why absence of resting congestion cannot, by itself, resolve an exertional diagnostic question. The reference standard must reproduce the physiological state associated with the symptoms. [110]

Pressure should also be interpreted relative to flow. The investigation by Eisman and colleagues linked an abnormal exercise PCWP–cardiac-output slope with impaired exercise capacity and subsequent heart-failure events. This does not make a derived slope immune to technical error: output methodology, respiratory averaging, workload and the number of observations can alter its reliability. A pressure–flow relationship is useful because it adds physiological context, not because it eliminates the need for careful measurement. [111]

Boundary values require explicit caution. The ≥15 mmHg threshold used in some HFpEF diagnostic frameworks and the >15 mmHg definition used for post-capillary pulmonary hypertension answer related but not identical questions. A value precisely at a boundary should not determine a major clinical conclusion without review of quality and context. When the haemodynamics remain equivocal, the report should explain whether repeat assessment under different physiological conditions is justified.

Invasive assessment must end with an interpretation, not merely a pressure table. State whether the study supports elevated left-sided pressure, a pulmonary vascular component, low output, abnormal reserve, constriction or another mechanism, and whether those findings explain the symptoms. If the study does not resolve the clinical question, that uncertainty should remain visible. Incomplete certainty is preferable to a falsely definitive diagnosis based on an imprecise measurement.

3.16. Biopsy, genetics and selected diagnostic pathways

Endomyocardial biopsy is a targeted investigation for circumstances in which histology, immunohistochemistry or molecular characterization can change treatment. It should not be regarded as the inevitable final step of every unexplained cardiomyopathy. High-risk inflammatory presentations, suspected specific myocarditis subtypes, selected infiltrative disease and unresolved tissue-typing questions can justify biopsy. The anticipated diagnostic yield and the consequences of a positive or negative result should be discussed before the procedure. [124]

Biopsy interpretation is constrained by sampling. Patchy disease can be missed, and tissue must be acquired, handled and analysed for the specific clinical question. A negative biopsy does not exclude every myocardial process. Conversely, a histological abnormality must be interpreted within the clinical syndrome and technical context. The HFA/HFSA/JHFS position statement emphasizes the role of biopsy as part of an integrated specialist pathway rather than an isolated laboratory endpoint. [124]

The threshold for specialist assessment should be low when new severe dysfunction is accompanied by major arrhythmia, conduction block, persistent myocardial injury or systemic features suggesting a treatable inflammatory process. CMR may support myocarditis, but it does not identify every subtype that requires a different therapy. The 2025 ESC myocarditis framework provides the relevant disease-specific context; the decision to pursue tissue should reflect presentation, risk and expected therapeutic consequences. [13]

Genetic testing similarly begins with phenotyping, a pedigree and counselling. A pathogenic or likely pathogenic variant can clarify disease, influence surveillance and inform family assessment. A variant of uncertain significance should not be treated as an established causal diagnosis or used indiscriminately for predictive testing in relatives. A negative test does not exclude a genetic contribution, especially when the phenotype or family history remains compelling. [3]

Some diagnostic problems are mechanism-specific rather than ejection-fraction-specific. CMR T2* addresses suspected iron overload; enzyme and genetic testing can investigate selected storage disorders; a monoclonal protein screen and appropriate tissue typing resolve amyloid questions; coronary and valve investigations assess loading and perfusion; and congenital disease requires anatomical expertise. The purpose is to shorten the route to a treatable cause, not to order an undirected panel in every patient. [3, 14, 81]

In cardio-oncology, the chronology of cancer treatment, baseline cardiovascular phenotype and serial imaging or biomarker changes are central. A new abnormality should be discussed within a risk-adapted pathway that considers both cardiovascular and oncological consequences. Generic heart-failure thresholds cannot replace definitions and surveillance schedules developed for particular treatment exposures. Exposure to cardiotoxic therapy is therefore a diagnostic clue that should be assessed within the dedicated 2022 ESC cardio-oncology framework. [48]

3.17. Longitudinal assessment and the diagnostic report

Heart failure is dynamic, but diagnostic reassessment should be driven by a question rather than by an automatic repetition of every baseline investigation. New symptoms, unexpected functional decline, arrhythmia, a change in murmur, suspected treatment toxicity or a decision about an intervention can justify additional imaging or biomarkers. A clinically stable patient with an adequate prior study does not necessarily benefit from another identical test performed without a decision to inform. [9]

Serial comparison should preserve method and context. The report should state whether image quality, rhythm, rate, loading, software or the imaging modality changed. The same caution applies to peptide assays and functional tests. A change that appears important numerically may not be interpretable if the methodology has changed substantially. Conversely, consistent small changes across several independent domains may be more persuasive than a dramatic isolated measurement.

Table 3.14. A diagnostic report that supports clinical decisions

Required element	Example of useful wording
Clinical question	"Progressive exertional dyspnoea; determine whether cardiac dysfunction or raised filling pressure explains limitation."
Current and previous phenotype	State the current LVEF, method and quality, and whether a previous reduced EF has been documented.
Objective evidence	Identify the relevant structural, functional, biochemical or invasive findings and the setting in which they were obtained.
Aetiological interpretation	Distinguish demonstrated disease from a suspected mechanism or an incidental abnormality.
Discordance and limitations	"Resting pressure indices are not diagnostic; exertional disease remains possible."
Action and reassessment	Specify the next investigation, the decision it will inform, and the clinical change that should trigger earlier review.

Improved ejection fraction should not erase the historical diagnosis. A patient whose ventricular function has recovered after treatment is different from a patient who has never had reduced function. The record should retain the previous lowest documented EF, treatment exposure and suspected cause, while describing the current state without automatically declaring cure. Similar care is needed after an acute episode: resolution of oedema describes a response to treatment, not necessarily disappearance of the underlying disease.

Communication with the patient is part of diagnostic quality. Explain what has been established, why further testing is proposed and what remains uncertain. A test should not be presented as a definitive exclusion when it has only lowered probability. Conversely, explaining that an abnormal imaging feature is not yet a complete diagnosis can reduce unnecessary fear and improve the quality of shared decisions. The practical goal is an accurate and intelligible account of the patient's problem.

3.18. Constructed clinical cases

Teaching status. The three cases below are deliberately constructed examples. They do not describe real patients and are not observational evidence. Numerical values are chosen to demonstrate diagnostic reasoning; the source references support the interpretive principles, not the fictional histories.

Case 3.1. Persistent dyspnea with a low peptide concentration

A 64-year-old woman with a body mass index of 38 kg/m² and treated hypertension reports progressive breathlessness when climbing stairs. She has no resting oedema, is in sinus rhythm and has an NT-proBNP concentration of 108 pg/mL. Echocardiography shows LVEF 61%, mild concentric remodelling, an average E/e′ of 10 and a left atrial volume index of 33 mL/m². The initial report describes preserved systolic function and no definite elevation of resting filling pressure.

The low peptide concentration reduces the likelihood of heart failure but does not settle the question in this phenotype. Obesity can lower natriuretic peptide concentrations, and the symptoms occur under a physiological condition not reproduced by resting measurements. Anaemia, pulmonary disease, deconditioning and other explanations should be assessed, but the label of “normal heart” would overstate the available information. A complete probability assessment and, if uncertainty persists, exercise evaluation are more defensible. [52, 112]

In the constructed continuation, technically adequate exercise haemodynamics show a rise in PCWP from 11 mmHg at rest to 28 mmHg during supine exercise. This supports exercise-induced elevation of left-sided filling pressure in the appropriate clinical setting. The result explains a mechanism; it should still be integrated with the underlying cardiometabolic phenotype and any coexisting pulmonary or peripheral limitation. The learning point is not that all obese patients with breathlessness require catheterization, but that a non-diagnostic resting study should not be relabelled as proof of absence of exertional disease. [110]

Case 3.2. An EF of 44% does not establish an ischemic cause

A 58-year-old man presents with declining exercise tolerance, an LVEF of 44% and elevated NT-proBNP. His ECG shows a left bundle branch block, and echocardiography describes global hypokinesia rather than a clear territorial pattern. He has diabetes and a family history of coronary disease, but no convincing acute coronary syndrome. The current clinical phenotype is HFrEF under the 2026 definition; the mechanism remains unresolved. [1]

The next steps should distinguish coronary disease, dyssynchrony, primary myocardial disease and possible mixed mechanisms. Coronary assessment is selected according to clinical probability and the potential consequences of the result; CMR may characterize injury or scar. Neither diabetes nor coronary calcium would prove that all ventricular dysfunction is ischemic, and a non-ischemic enhancement pattern would not remove the possibility of coexisting coronary disease. The final causal formulation must integrate the different domains. [3, 59]

The treatment discussion should also retain the historical evidence boundaries. A modern HFrEF label does not mean that every intervention studied only at an EF of 35% or less has been tested directly in this patient. Likewise, finding viable myocardium would not establish a prognostic indication for PCI. Diagnostic classification, trial eligibility and therapeutic indication are distinct steps in the reasoning process. [61]

Case 3.3. A positive bone scan with a monoclonal protein

A 77-year-old man has heart-failure symptoms, ventricular wall thickening, atrial enlargement and a history of bilateral carpal tunnel surgery. A bone-avid tracer scan shows grade 2 myocardial uptake confirmed with SPECT. Serum immunofixation also identifies a monoclonal protein. An initial interpretation proposes ATTR cardiomyopathy on the basis of age, phenotype and scintigraphy.

The non-biopsy ATTR pathway cannot be applied uncritically because the monoclonal screen is abnormal. A monoclonal protein does not by itself prove AL amyloidosis, but its presence prevents reliance on scintigraphy alone for amyloid typing. Specialist haematological assessment and tissue confirmation with accurate typing are required as indicated. Delay is particularly concerning when cardiac AL amyloidosis is plausible. [14, 80]

The learning point is conditional probability, not the unreliability of scintigraphy. The scan is highly informative within the correct biochemical and clinical context. Removing the condition of an appropriate monoclonal assessment changes what can safely be concluded from the same image. The report should make that dependency explicit rather than burying it in a generic recommendation for follow-up.

3.19. Implementation: an integrated diagnostic standard

The value of a diagnostic pathway is determined by whether it produces a coherent, actionable explanation of the patient's problem. A complete sequence is not necessarily a long sequence. In a patient with a clear syndrome, well-characterized cardiac disease and concordant findings, additional testing may add little. In a patient with persistent unexplained symptoms and discordant data, an apparently reassuring individual result may be insufficient. The difference lies in the unresolved decision.

For everyday practice, three transitions should be explicit. First, move from symptoms to a justified estimate of disease probability. Second, move from abnormal tests to a causal formulation. Third, move from that formulation to a defined management or reassessment decision. Problems arise when one transition is skipped: symptoms become a diagnosis, an incidental abnormality becomes an aetiology, or a sophisticated test is performed without a consequence for care.

Table 3.15. Frequent diagnostic errors and their corrective action

Error	Corrective action
Treating EF as the entire diagnosis	Add the clinical syndrome, trajectory, objective support and causal interpretation.
Using an acute peptide threshold in a stable outpatient	Match analyte, setting, age and intended rule-out or rule-in purpose.
Calling a grey-zone result negative	Preserve intermediate probability and specify the next investigation or reassessment.
Combining criteria from different HFpEF algorithms	Use one complete applicable framework; report complementary information separately.
Equating a normal resting study with normal exercise physiology	Investigate reserve when the clinical question remains exertional and unresolved.
Assuming a positive bone scan always establishes ATTR	Integrate monoclonal screening, tomographic confirmation and tissue typing when indicated.
Inferring therapeutic benefit directly from an imaging biomarker	Check the population, intervention and outcome evidence relevant to that decision.

A clinically useful diagnostic strategy should make uncertainty manageable. Measurements require technical context, thresholds require a population and a purpose, and diagnoses require clinical coherence. The final report should permit another clinician to understand what is known, what is inferred and what remains to be tested. This is the standard for a clinically interpretable diagnostic strategy.

4. Chronic HFrEF: Pharmacological Treatment and Optimization

4.1. Therapeutic objectives and the 2026 framework

The pharmacological treatment of chronic heart failure must address three different, complementary objectives: prolonging life, preventing deterioration that requires hospital care, and improving the patient's symptoms, function and lived experience. The treatment indication, supporting population, achievable dose and safety-monitoring plan should be considered together. Symptomatic improvement is not a sufficient reason to withhold disease-modifying treatment, and a long medication list is not, by itself, evidence of successful optimization. [1]

The 2026 ESC nomenclature defines HFrEF using LVEF <50%. This does not retrospectively change trial eligibility. The evidence below therefore retains each study's original EF range. Selected current recommendations are summarized in Table 4.1; the new B1/B2 evidence labels are preserved rather than converted into older grades. [1]

Table 4.1. Selected ESC 2026 pharmacological recommendations

Intervention / setting	Class / level
ACE inhibitor or ARNI; evidence-based beta-blocker in stable HFrEF	I / A
MRA; SGLT2 inhibitor in the indicated symptomatic HF population	I / A
Replace ACE inhibitor or ARB with sacubitril/valsartan in HFrEF	I / B1
Digoxin or digitoxin: symptomatic LVEF ≤40% despite foundational therapy	IIa / B1
Vericiguat: selected symptomatic LVEF <45% despite foundational therapy	IIb / B1
Continue foundational therapy after improvement of symptoms or LVEF	I / C

A recommendation, a randomized result and an authorised indication answer different questions. A guideline integrates evidence and clinical judgment; a trial estimates an effect within a defined population; a product label specifies conditions of use for a particular medicine. The three should be reconciled explicitly, not treated as interchangeable. The vericiguat starting-dose and ivabradine heart-rate distinctions later in this chapter illustrate why this matters.

> **Evidence boundary**
> This chapter concerns chronic pharmacological care. Cardiogenic shock, acute respiratory failure and unstable hypoperfusion require a different treatment setting. Device, revascularization and valve decisions are developed in their dedicated chapters, not replaced by drug escalation.

4.2. Reading therapeutic evidence without overstatement

Clinical interpretation begins with the prespecified primary endpoint. A reduction in a composite of cardiovascular death or heart-failure hospitalization does not prove a reduction in each component separately. Recurrent-event rate ratios, time-to-first-event hazard ratios and hierarchical win ratios also measure different effects. Their numerical values cannot be ranked as if they formed a head-to-head comparison. Table 4.2 deliberately retains these distinctions.

Table 4.2. Landmark and contemporary trials: population and principal result

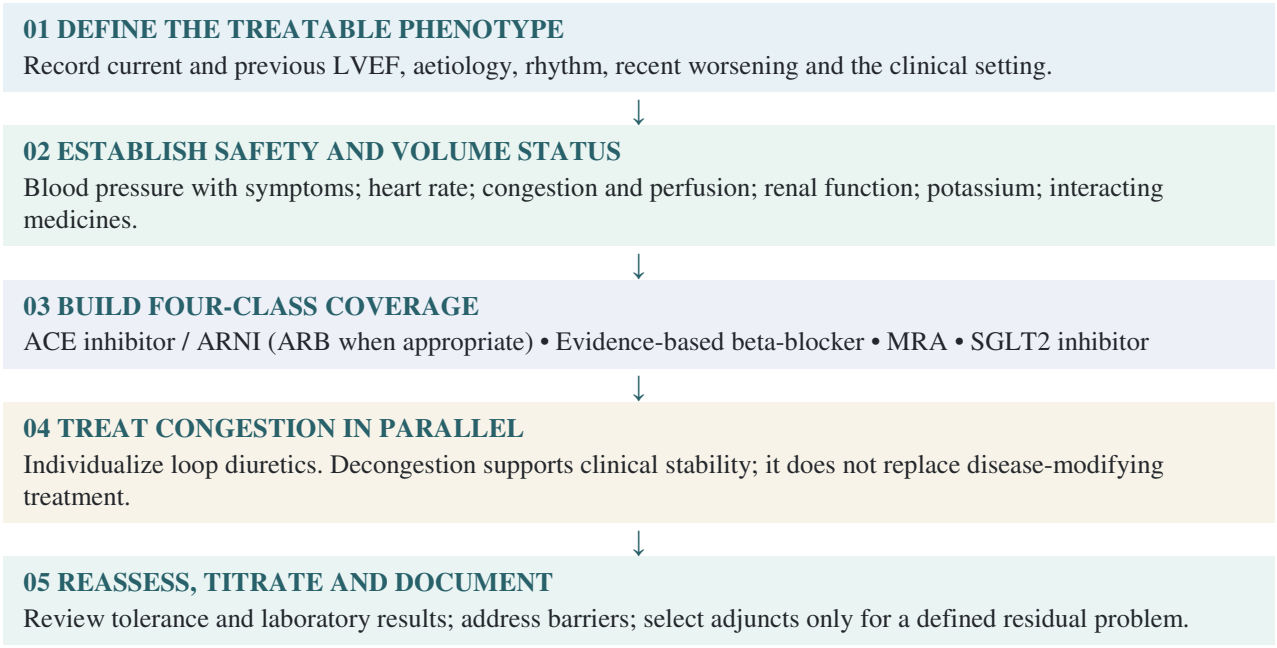
Trial / treatment	Population studied	Principal finding
PARADIGM-HF Sacubitril/valsartan [92]	LVEF ≤40%, later ≤35%; active comparator	CV death or HF admission: HR 0.80 (95% CI 0.73–0.87).
DAPA-HF Dapagliflozin [72]	LVEF ≤40%; with or without diabetes	Worsening HF or CV death: HR 0.74 (0.65–0.85).
EMPEROR-Reduced Empagliflozin [125]	LVEF ≤40%	CV death or HF admission: HR 0.75 (0.65–0.86); CV death alone not significant.
VICTORIA Vericiguat [126]	LVEF <45%; recent worsening	CV death or HF admission: HR 0.90 (0.82–0.98).
VICTOR Vericiguat [127]	LVEF ≤40%; no recent worsening	Same composite: HR 0.93 (0.83–1.04); primary endpoint neutral.
DIGIT-HF Digitoxin [128]	More symptomatic / lower-EF population	All-cause death or first HF admission: HR 0.82 (0.69–0.98).
DECISION Low-dose digoxin [129]	LVEF ≤50%; contemporary background	Total worsening-HF events or CV death: RR 0.81 (0.61–1.07); primary endpoint neutral.

Absolute benefit depends on baseline risk and observation time. The same relative effect may correspond to very different numbers of events prevented in a recently hospitalized patient and in a clinically stable outpatient. Conversely, a statistically neutral result does not prove that the true effect is exactly zero; it means that the trial did not establish the specified benefit under its design and analysis. A positive secondary signal cannot silently replace a neutral primary result.

4.3. A four-class architecture, not a four-step queue

The therapeutic framework places four disease-modifying classes in parallel: renin–angiotensin system inhibition with an ACE inhibitor or ARNI, an evidence-based beta-blocker, an MRA and an SGLT2 inhibitor. An ARB remains an alternative when the preferred renin–angiotensin options cannot be used. This is a framework for early coverage of complementary mechanisms, not a requirement to administer every medicine at the same visit regardless of stability. [130]

Figure 4.1. From treatment eligibility to durable multidrug therapy



A low starting dose in one class does not justify leaving the other classes absent for months. Equally, the wish to achieve a target dose must not override symptomatic hypotension, significant bradycardia, progressive organ dysfunction or uncontrolled hyperkalaemia. A useful prescription record distinguishes “not indicated”, “temporarily deferred”, “contraindicated”, “not tolerated” and “not yet attempted”. These categories imply different subsequent actions.

Optimization also requires an identified clinician responsible for reviewing each result. A laboratory request without ownership, or a planned dose increase without access to reassessment, is an incomplete treatment intervention. The practical sequence should be adapted to the dominant constraint rather than to an inflexible order of drug classes.

4.4. Angiotensin receptor–neprilysin inhibition

From mechanism to comparative clinical evidence

Sacubitril/valsartan combines augmentation of endogenous natriuretic-peptide signalling with angiotensin-receptor blockade. The therapeutic rationale is to attenuate maladaptive vasoconstrictor and sodium-retaining pathways while preserving beneficial counter-regulatory effects. Its role is therefore not simply that of a more potent diuretic. The evidence supporting treatment and the prescribing restrictions should be considered separately. [131]

PARADIGM-HF randomized 8,442 patients after a run-in phase demonstrating tolerance of both study regimens. Sacubitril/valsartan reduced the primary composite relative to enalapril, with benefits also reported for cardiovascular and all-cause mortality. The original eligibility threshold was LVEF ≤40%, subsequently amended to ≤35%; it was never ≤50%. Active comparison with enalapril supports substitution rather than combined use of the two treatments. Run-in selection limits direct extrapolation to unstable or markedly intolerant patients. [92]

Initiation around hospitalization

PIONEER-HF evaluated initiation after haemodynamic stabilization in patients hospitalized with decompensated HFrEF. Its primary outcome was the change in NT-proBNP, not mortality. The greater biomarker reduction with sacubitril/valsartan supports early biological efficacy; exploratory clinical outcomes are informative but should not be presented as a definitive survival trial. [132]

TRANSITION addressed a different question: whether starting sacubitril/valsartan before discharge or shortly afterwards was feasible in stabilized patients. Approximately half reached the target dose by ten weeks. This was a timing and tolerability comparison, not a placebo-controlled demonstration of mortality reduction. The findings of the initiation trials should therefore be interpreted according to their individual endpoints. [133]

> **Interpretation for the clinic**
> "Initiate early" means after appropriate stabilization and assessment, with a titration and monitoring plan. It does not mean starting a vasodilating regimen during shock, disregarding the prior ACE-inhibitor dose, or treating a trial renal exclusion criterion as a universal drug contraindication.

A patient whose symptoms remain mild may still merit comparative disease-modifying treatment. Conversely, persistent breathlessness should prompt reassessment for residual congestion, ischaemia, valve disease, anaemia and non-cardiac limitation rather than being attributed automatically to an insufficient ARNI dose. The decision is an integrated treatment judgment, not a symptom-only switch.

Sacubitril/valsartan: prescribing and titration

Table 4.3. Sacubitril/valsartan: adult chronic-HF prescribing essentials

Decision	Practical specification
Usual starting dose	49/51 mg twice daily.
Lower starting dose	24/26 mg twice daily in appropriate low-dose / treatment-naïve or vulnerable patients; assess blood pressure and renal status.
Target and interval	97/103 mg twice daily, increasing approximately every 2–4 weeks as tolerated.
Before initiation	Do not start with systolic BP <100 mmHg or potassium >5.4 mmol/L under the cited EU product information.
ACE-inhibitor transition	At least 36 hours between an ACE inhibitor and ARNI, in either direction. Do not coadminister.
ARB transition	Stop the separate ARB: valsartan is already contained in ARNI.
Renal impairment	eGFR <30 mL/min/1.73 m² requires particular caution and a lower starting dose, not an automatic universal contraindication.

A safer transition is a documented transition

Medication reconciliation should establish the exact time of the last ACE-inhibitor dose, the dose and formulation currently taken, and whether duplicate prescriptions remain active. A verbal instruction to "replace the previous tablet" is inadequate when the patient or caregiver manages several similar boxes. The written schedule should identify the medicine being stopped, the first permitted ARNI dose and the date of reassessment.

Before each increase, review the clinical trajectory rather than one isolated number. New dizziness, a fall, reduced oral intake, diarrhoea or an unintended diuretic increase may explain poor tolerance. Persistent

congestion with low blood pressure suggests a different problem from orthostatic symptoms in an over-diuresed patient. These states should not receive the same automatic dose reduction.

The target dose is a reference for optimization, not a test the patient must pass to receive benefit from the whole treatment programme. When escalation is not tolerated, document the limiting factor, preserve the tolerated regimen where appropriate, and revisit the decision after reversible causes have been addressed. This prevents a temporary limitation from becoming a permanent, unexplained omission. The distinction between a trial target and an individualized maintenance dose is developed further in the monitoring section.

> **Avoid a common reconciliation error**
> Do not list an ACE inhibitor, an ARB and sacubitril/valsartan together as three complementary "pillars". They occupy overlapping renin–angiotensin pathways; the intended treatment choice must be explicit.

4.5. ACE inhibitors and angiotensin-receptor blockers

ACE inhibitors retain an evidence-based role. SOLVD demonstrated a survival benefit of enalapril in symptomatic patients with LVEF ≤35%, establishing that neurohormonal treatment changes the natural history rather than merely reducing filling pressures. The historical evidence remains important even when ARNI is selected as the preferred replacement in an eligible patient. [134]

Table 4.4. Selected renin–angiotensin medicines: adult trial-based doses

Drug	Initial oral dose	Trial / guideline target
Enalapril	2.5 mg twice daily	10–20 mg twice daily
Lisinopril	2.5–5 mg daily	20–35 mg daily
Ramipril	1.25–2.5 mg twice daily	5 mg twice daily
Captopril	6.25 mg three times daily	50 mg three times daily
Candesartan	4 mg daily	32 mg daily
Losartan	25–50 mg daily; lower in selected patients	150 mg daily
Valsartan	40 mg twice daily	160 mg twice daily

CHARM-Alternative supports candesartan in patients with LVEF ≤40% who could not take an ACE inhibitor. The relevant result was reduction of cardiovascular death or heart-failure admission; it should not be rewritten as an independently established reduction in every mortality endpoint. An ARB is an alternative strategy for intolerance, not an additional agent to place alongside ARNI. [135]

HEAAL compared losartan 150 mg with 50 mg in patients with symptomatic systolic HF and ACE-inhibitor intolerance. The higher dose modestly improved the death-or-HF-admission composite but produced more renal impairment, hyperkalaemia and hypotension. This illustrates the need to pursue tolerated evidence-based doses while measuring the cost of escalation in the individual patient. [136]

Cough, angioedema, renal deterioration and hypotension require different decisions. The adverse effect should be characterized rather than recorded simply as "intolerance". A small haemodynamic creatinine change is not equivalent to angioedema, and the appropriate future treatment options differ substantially. Avoiding unnecessary dual renin–angiotensin blockade is as important as avoiding therapeutic omission.

4.6. Evidence-based beta-blockade

Beta-blocker therapy interrupts maladaptive sympathetic activation, but initiation requires clinical stability. CIBIS-II, MERIT-HF and COPERNICUS established benefits with specific agents and formulations; the evidence should not be generalized indiscriminately to every beta-blocker. In COPERNICUS, even patients with severe systolic dysfunction were clinically euvolaemic at enrolment. Severity of reduced LVEF is therefore not a reason to omit therapy, whereas active shock is not the setting in which to start or escalate it. [90, 137, 138]

Table 4.5. Beta-blockers used in chronic HF: dose and evidence distinctions [90, 137–139]

Agent	Starting → target oral dose	Clinical distinction
Bisoprolol	1.25 → 10 mg daily	CIBIS-II: mortality benefit in symptomatic systolic HF.
Carvedilol	3.125 → 25 mg twice daily	A 50 mg twice-daily target applies only to selected patients >85 kg; blood-pressure tolerance matters.
Metoprolol succinate CR/XL	12.5–25 → 200 mg daily	Do not substitute immediate-release metoprolol as though the trial formulation were irrelevant.
Nebivolol	1.25 → 10 mg daily	SENIORS: composite benefit in patients ≥70 years; death alone was not significantly reduced.

The relationship between heart rate and treatment benefit is not the same in every rhythm. Individual-patient trial analyses support beta-blockade most strongly in sinus rhythm, with supportive but less extensive evidence in the mildly reduced EF range. Atrial-fibrillation subgroup results did not establish the same mortality effect. This does not eliminate an indication for ventricular rate control, but the purpose of treatment should be stated accurately. [74]

When the next dose increase is inappropriate

Assess new bradycardia, conduction disease, symptomatic hypotension, worsening perfusion or recurrent congestion before escalating. Fatigue alone deserves a broader review: it may reflect deconditioning, iron deficiency, sleep disturbance or persistent HF rather than a drug effect. Abrupt, unnecessary withdrawal of an established regimen is different from cautious adjustment in haemodynamic compromise; both the reason and a reassessment plan should be documented. [130]

> **Practical synthesis**
>
> Treat the patient's rhythm and perfusion, not a target heart rate in isolation. A low pulse with dizziness and conduction disease, and a similar pulse in an asymptomatic stable patient, are not equivalent titration problems.

4.7. Mineralocorticoid-receptor antagonism

RALES established spironolactone in severe symptomatic systolic HF, whereas EMPHASIS-HF extended eplerenone evidence to patients with milder symptoms. Their effects are not explained solely by potassium-sparing diuresis. Antagonism of mineralocorticoid signalling addresses a persistent pathway of remodelling and sodium retention despite other neurohormonal treatment. EPHESUS provides a distinct post-infarction evidence base and should not be confused with a trial in all chronic-HF phenotypes. [89, 140, 141]

Table 4.6. Steroidal MRAs: initiating safely and responding to potassium

Treatment / finding	Dose or action
Spironolactone	Usually 12.5–25 mg daily initially; target up to 50 mg daily when tolerated.
Eplerenone: usual regimen	25 mg daily → 50 mg daily.
Eplerenone: creatinine clearance 30–60 mL/min	The cited SmPC starts at 25 mg on alternate days; titrate by potassium and tolerance.
Before eplerenone	Do not initiate if K >5.0 mmol/L; severe renal impairment is contraindicated.
K 5.5–5.9 mmol/L on eplerenone	Reduce one dose step under the product-specific schedule.
K ≥6.0 mmol/L	Withhold and arrange prompt clinical assessment; urgency depends on severity, ECG and clinical context.
Monitoring / restart	Baseline, within the first week, at one month and after adjustments; restart only when the relevant label criteria are met.

Endocrine adverse effects are more frequent with spironolactone; eplerenone is more receptor-selective. A switch may therefore preserve mineralocorticoid blockade when breast symptoms or sexual adverse effects make spironolactone difficult to continue. The response should address the actual adverse effect rather than abandoning the whole class automatically. [89, 142]

FINEARTS-HF studied finerenone in LVEF ≥40%, with a reduction in total worsening-HF events and cardiovascular death as a composite. It does not establish that finerenone is a dose-for-dose replacement for spironolactone or eplerenone throughout classic lower-EF HFrEF. Nor does it support simultaneous use of two MRAs. Phenotype, renal status and the specific authorised indication remain decisive. [73]

4.8. SGLT2 inhibition: benefit independent of diabetes

DAPA-HF and EMPEROR-Reduced established SGLT2 inhibition as HF treatment rather than merely glucose-lowering therapy. DAPA-HF enrolled 4,744 patients with LVEF ≤40% and demonstrated a reduction in worsening HF or cardiovascular death, with benefit in patients with and without diabetes. EMPEROR-Reduced enrolled 3,730 patients and reduced cardiovascular death or HF hospitalization; cardiovascular death alone was not significantly reduced in that trial. These differences should remain visible in academic writing. [72, 125, 143]

Table 4.7. SGLT2 inhibitors in adult HF: dose and regulatory limits

Feature	Dapagliflozin	Empagliflozin
HF dose	10 mg once daily	10 mg once daily
Dose titration for HF	No routine upward titration	No escalation to 25 mg solely for HF
Initiation: renal limit in cited EU label	Do not initiate below GFR 25 mL/min	Do not initiate below eGFR 20 mL/min/1.73 m²
Glucose-lowering versus HF effect	Diminished glycaemic action at low GFR does not erase the HF indication	The HF dose is distinct from higher-dose diabetes regimens
Temporary interruption	Consider acute serious illness, major surgery or important volume depletion	Consider acute serious illness, major surgery or important volume depletion

Counselling should distinguish genital fungal infection, symptoms of dehydration and ketoacidosis. Ketoacidosis can occur without marked hyperglycaemia; persistent nausea, vomiting, abdominal pain or unexplained breathlessness during an at-risk illness warrants assessment rather than reassurance based on glucose alone. Interruption and restart should be coordinated with the treating team, including ketone assessment where indicated. [144, 145]

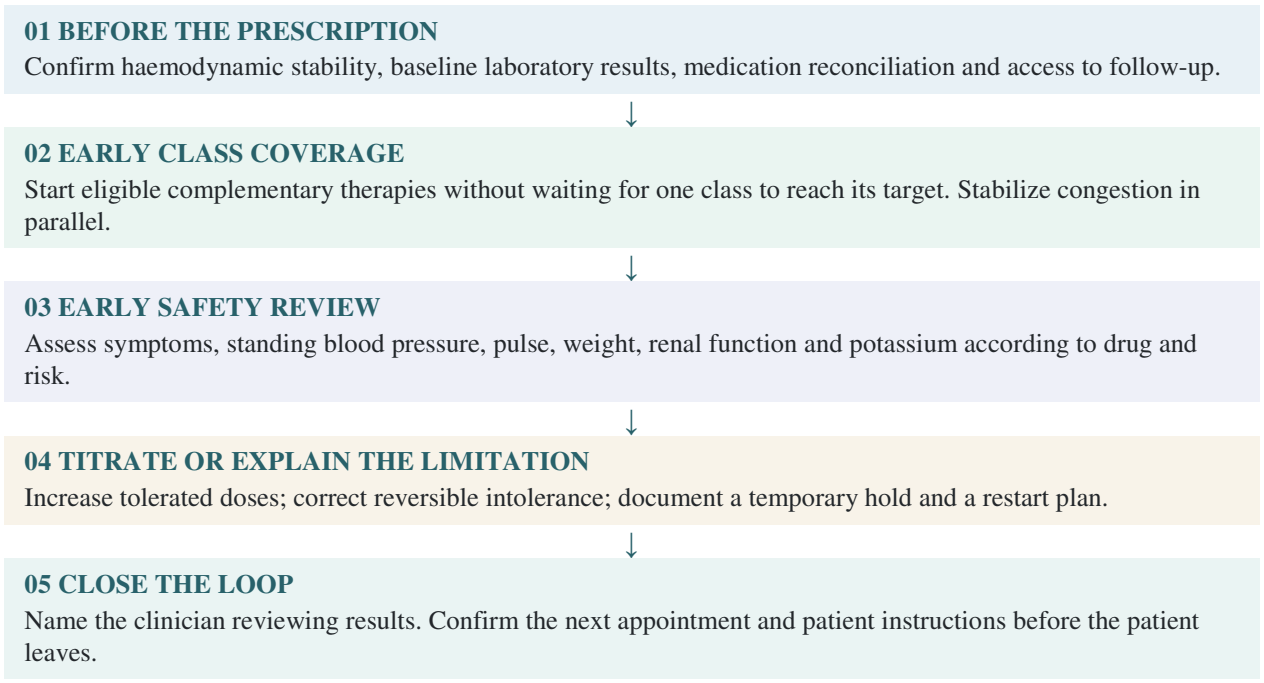
An early, modest reduction in filtration can accompany altered intraglomerular haemodynamics. This is not equivalent to progressive structural kidney injury, but it should not be used to dismiss hypotension, oliguria or significant volume loss. The clinical trajectory determines whether the change is an expected treatment effect or a signal to reassess the regimen. [33, 58, 125]

> **Prescribing distinction**
> The historical eGFR entry thresholds in DAPA-HF and EMPEROR-Reduced are trial characteristics. Contemporary initiation should follow the current product-specific label, not an uncritical copy of the older trial exclusion criterion.

4.9. Rapid implementation and the post-discharge window

STRONG-HF tested high-intensity care after an acute-HF admission: rapid titration combined with frequent structured reassessment. The 180-day risk of HF readmission or all-cause death was 15.2% versus 23.3%; adverse events were more frequent, although serious events were similar. The intervention was an organized care package, not an isolated instruction to increase doses. It should not be described as a randomized comparison of universal contemporary four-drug initiation sequences. [146]

Figure 4.2. An individualized initiation and reassessment cycle



EMPULSE supports empagliflozin after inpatient stabilization, using a hierarchical outcome that included clinical events and health status. Its favourable win ratio cannot be translated into a stand-alone mortality reduction. DAPA ACT HF–TIMI 68, by contrast, did not significantly reduce its two-month primary

endpoint: HR 0.86, 95% CI 0.68–1.08. Thus the inpatient evidence should not be presented as uniformly positive across every drug, endpoint and follow-up period. [147, 148]

The practical inference is to use hospitalization as an opportunity, while preserving the conditions that make initiation safe. Patients with unresolved hypoperfusion, unstable renal function or no feasible monitoring pathway need tailored decisions, not automatic implementation of a calendar.

4.10. Low blood pressure and treatment intolerance

Low blood pressure is a clinical state, not a diagnosis of drug intolerance. Distinguish an asymptomatic low measurement from reproducible orthostatic symptoms, and both from low-output failure with impaired perfusion. The clinical review should establish timing, posture, recent fluid loss, dosing errors and the contribution of medicines prescribed for other conditions. Expert algorithms in this area are useful but should be labelled as such rather than presented as randomized evidence. [149]

Table 4.8. Interpreting low blood pressure during optimization

Pattern	Priority assessment	Reasoned response
Low BP, no symptoms, stable perfusion	Repeat reliable measurements; review trajectory	Avoid reflex withdrawal solely because of one value.
Orthostatic dizziness, little congestion	Volume loss, intake, excess diuresis, other vasodilators	Correct reversible contributors before abandoning all disease-modifying classes.
Bradycardia with symptoms	ECG, conduction, other rate-slowing drugs	Reconsider the rate-slowing combination and its indication.
Hypotension with congestion or cold extremities	Possible advanced low-output HF / shock	Urgent clinical reassessment rather than routine outpatient titration.
Abrupt fall after a previously tolerated regimen	Intercurrent illness, bleeding, infection, new medicines	Investigate the new cause; do not assume chronic HF medicines suddenly became intrinsically unsuitable.

A useful distinction is between a treatment that caused symptoms and a treatment that unmasked limited circulatory reserve. Both may require adjustment, but only the latter may signal a need for more comprehensive HF assessment. Recurrent intolerance to several classes, particularly with escalating diuretic requirements and persistent congestion, should prompt reconsideration of disease severity rather than repeated medication cycling.

An individualized plan may preserve lower doses across several complementary classes instead of one maximally titrated class with all others omitted. This is a clinical implementation principle, not proof that every low-dose combination has been tested head-to-head. Record the limiting symptom, the selected adjustment and the criterion for revisiting it.

> **Safety boundary**
> Syncope, confusion, cold extremities, oliguria, chest pain or a sustained hypotensive deterioration require prompt assessment. A pathway for stable ambulatory intolerance must not delay recognition of an acute emergency.

4.11. Renal function and potassium: separate the problems

Renal dysfunction in HF reflects several processes: reduced perfusion, venous congestion, intrinsic kidney disease, intercurrent injury and medication-related haemodynamic change. Treating all creatinine increases as the same event encourages both unnecessary withdrawal and unsafe continuation. The assessment must connect the laboratory trajectory to weight, blood pressure, urine output, congestion, potassium and recent treatment changes. [33, 58]

Table 4.9. A renal-function change is interpreted in its clinical setting

Finding	Questions that change management
Small early filtration decline, otherwise stable	Was RAAS or SGLT2 treatment just started? Are perfusion, potassium and volume status acceptable?
Creatinine rise with effective decongestion	Has congestion improved without hypotension or oliguria? Is the change transient?
Progressive rise with persistent oedema	Is venous congestion unresolved? Is cardiac output inadequate? Is there intrinsic renal disease?
Rise with diarrhoea, poor intake or orthostasis	Is there volume depletion, infection, an interacting medicine or an incorrect dose?
Rise with hyperkalaemia	Verify the result and its urgency; examine the combination of renal reserve, RAAS therapy, supplements and intercurrent illness.

KDIGO advises continuing ACE-inhibitor or ARB treatment unless creatinine rises by more than 30% within four weeks of initiation or dose escalation, with a larger rise prompting evaluation. This is not a universal permission to ignore a smaller change in an unstable patient, nor a blanket command to withdraw all HF medicines at a numerical threshold. Correctable causes and the clinical context remain central. [33]

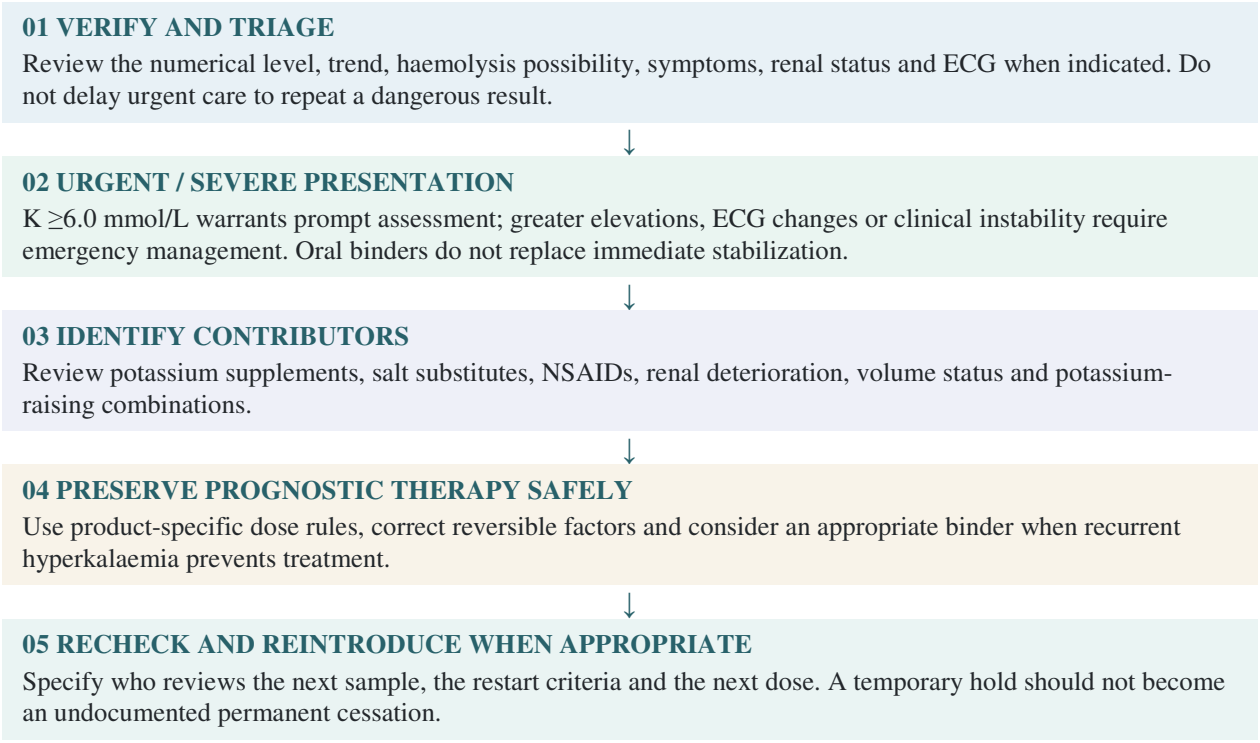
Preserve useful treatment without normalizing danger

A patient may be congested and have renal dysfunction simultaneously. Reducing diuretics simply to improve the creatinine value may leave the underlying venous congestion untreated. Conversely, aggressive diuresis in an already depleted patient may compound hypotension. The goal is not the lowest laboratory creatinine at any cost; it is effective circulation and safe, sustainable decongestion.

Before labelling a medicine permanently contraindicated, identify whether the limitation is reversible and whether an alternative dose, agent, timing or monitoring arrangement can preserve its intended benefit. This approach requires clinical judgment; it is not an instruction to maintain treatment during rapidly progressive acute kidney injury.

Hyperkalaemia: rescue, prevention and treatment preservation

Figure 4.3. A potassium result requires both a safety decision and a treatment plan



DIAMOND showed that patiromer can improve potassium control and facilitate maintenance of RAAS-directed treatment. Its findings should not be recast as proof that the binder itself reduces mortality. REALIZE-K likewise improved maintenance of normokalaemia during spironolactone optimization, but its exploratory cardiovascular-death or worsening-HF outcome was numerically more frequent with sodium zirconium cyclosilicate (11% versus 3%). The trial was small and not powered for that clinical endpoint; the signal warrants attention, not dismissal or a definitive causal conclusion. [150, 151]

Binder selection includes tolerability and administration burden. Patiromer requires attention to magnesium and separation from relevant oral medicines; sodium zirconium cyclosilicate requires attention to sodium load, oedema and pH-dependent drug interactions. These are different products, not interchangeable powders. Follow the current instructions for spacing and monitoring. [152, 153]

The reasoned objective is twofold: prevent potassium-related harm now and avoid avoidable loss of effective HF treatment later. Normalizing potassium without revisiting the withdrawn medicine leaves the second objective unfinished.

4.12. Diuretics and the maintenance of euvolaemia

Diuretics address a major cause of symptoms and instability, but their dose is a response to congestion rather than a fixed lifelong target. Use the lowest effective maintenance dose that prevents clinically important fluid retention. Disease-modifying medicines cannot substitute for timely decongestion, and symptomatic diuresis cannot substitute for neurohormonal and SGLT2 treatment. [1, 49]

Table 4.10. Interpreting the outpatient diuretic requirement

Clinical state	Therapeutic objective	What should be reviewed
Persistent pulmonary / systemic congestion	Achieve adequate relief and reassess response	Actual intake and adherence, dose delivery, renal function, perfusion and precipitating disease.
Euvolaemia after treatment optimization	Maintain stability with the necessary dose	Weight trend, orthostasis, renal function and whether the previous dose remains appropriate.
Inadequate response to a loop diuretic	Distinguish insufficient delivery from resistance	Timing, absorption, sodium exposure, interacting drugs and renal reserve.
Sequential nephron blockade	Use only for a defined insufficient response	Close surveillance for sodium, potassium and renal changes; avoid an unmonitored chronic add-on.
Rapid recurrent dose escalation	Recognize a high-risk trajectory	Consider unresolved aetiology, advanced HF and specialist reassessment.

TRANSFORM-HF randomized 2,859 patients after an HF admission to torsemide or furosemide and found no significant difference in all-cause mortality. The result argues against presenting one loop diuretic as universally prognostically superior. It does not mean that absorption, dosing frequency, individual response or access are irrelevant. A change of agent remains a practical intervention, not a guaranteed survival strategy. [154]

Self-adjustment can be appropriate only when the patient has an individualized written plan. It should identify the relevant change in weight or symptoms, the permitted action, the duration of any increase and the reason to contact the HF team. A general instruction to “take more when swollen” is not a sufficient safety framework. [53]

> **Do not infer a mortality trial from a recommendation grade**
> A strong recommendation for treating congestion does not establish that a particular loop-diuretic regimen independently reduces mortality. Indication, clinical effectiveness and randomized prognostic evidence should remain distinct.

4.13. Heart-rate selection and alternative vasodilatation

Ivabradine: trial, guideline and regulatory heart-rate thresholds

Ivabradine acts on sinus-node pacemaker current and is not an AF rate-control drug. SHIFT studied symptomatic LVEF ≤35%, sinus rhythm and resting heart rate ≥70 beats/min despite background therapy; the benefit was predominantly a reduction in HF events. The current EU HF indication uses ≥75 beats/min. The 2026 ESC recommendation table specifies >70 beats/min in the relevant sinus-rhythm, low-EF population. These thresholds should be attributed correctly rather than averaged into a new rule. [1, 155, 156]

Table 4.11. Selected adjuncts: indication must precede dose

Treatment	Reference regimen	Selection and limitations
Ivabradine	Usually 5 mg twice daily with meals; 2.5 mg twice daily may be appropriate in older patients; maximum 7.5 mg twice daily.	Sinus rhythm only. Reassess symptomatic bradycardia / persistent HR <50. Check interacting rate-slowing and CYP3A medicines.
Hydralazine + isosorbide dinitrate	Trial fixed combination: 37.5/20 mg three times daily → 75/40 mg three times daily.	Selected patients with a supported indication; hypotension, headache, complexity and nitrate interactions limit use.

Hydralazine–isosorbide dinitrate: population-specific evidence

A-HeFT enrolled 1,050 self-identified Black patients with advanced symptoms and demonstrated benefit from adding the fixed combination to background treatment. The trial supports treatment in an identified study population; it does not establish that race is a precise biological predictor or that its findings are a head-to-head comparison with contemporary ARNI therapy. Clinical selection should include the actual indication, other tolerated medicines and patient preferences. [157]

Hydralazine–nitrate treatment also has a role when ACE inhibitors, ARBs and ARNI cannot be used. This is a narrower alternative pathway, with a less extensive evidence base than universal use of foundational therapy. Check the reason for intolerance and whether it truly excludes all renin–angiotensin options. Organic nitrates must not be combined with PDE5 inhibitors because of hypotension risk. [9, 60]

4.14. Vericiguat: recent worsening, selection and new dosing

Vericiguat stimulates soluble guanylate cyclase and addresses a pathway distinct from conventional neurohormonal blockade. VICTORIA enrolled 5,050 patients with LVEF <45% and recent worsening HF. The primary composite of cardiovascular death or HF hospitalization was reduced, but the individual mortality results did not establish a survival benefit. Selection should therefore be driven by residual risk and the studied clinical setting, not by an assumption that vericiguat is a universal fifth foundational class. [126]

VICTOR tested a more stable LVEF ≤40% population without recent HF hospitalization or intravenous diuretic treatment. Its primary endpoint was neutral. Signals in secondary mortality analyses do not override this result; reporting them as a definitive positive primary trial would misrepresent the evidence. These two studies answer related but different clinical questions. [127]

Table 4.12. Vericiguat: distinguish the current EU label from the trial-dose table

Item	Current prescribing interpretation
Authorised clinical setting	Symptomatic chronic reduced-EF HF, stabilized after recent decompensation requiring intravenous therapy.
Usual EU starting dose	5 mg once daily with food.
Lower starting dose	2.5 mg daily when symptomatic hypotension occurred during the preceding four weeks.
Target	10 mg daily; dose increases approximately every two weeks according to tolerance.
Before initiation	Do not start at systolic BP <100 mmHg.
Important limitations	Other soluble-guanylate-cyclase stimulators are contraindicated; PDE5-inhibitor combination is not recommended. Check renal, hepatic and pregnancy restrictions.

Before selecting an adjunct, confirm that the apparent failure of standard treatment is not actually incomplete class coverage, persistent congestion, non-adherence, an untreated valve lesion or an unrecognized rhythm problem. A patient may need advanced-HF assessment more urgently than another tablet. The usefulness of an additional drug depends on a clinical problem that its evidence genuinely addresses.

4.15. Digitalis glycosides: revisiting the evidence

New glycoside evidence must not be reduced to a claim that all digitalis preparations improve survival. Drug identity, target concentration, background therapy and endpoint definition are critical. Digoxin and digitoxin should be discussed separately, not combined into a single interchangeable dose category.

Table 4.13. Three glycoside trials, three different questions

Study	Design / population	Interpretation
DIG [158]	Digoxin; predominantly sinus rhythm; older ACE-inhibitor / diuretic background.	All-cause mortality neutral; HF hospitalization reduced.
DIGIT-HF [128]	Digitoxin; LVEF ≤40% with NYHA III–IV, or ≤30% with NYHA II; contemporary care.	Death or first HF admission reduced; neither component was significantly reduced separately.
DECISION [129]	Low-dose digoxin; LVEF ≤50%; target 0.5–0.9 ng/mL; 29% with AF.	Prespecified primary recurrent-event / CV-death composite was not significantly reduced.

DIGIT-HF analysed 1,212 patients in its modified intention-to-treat population over a median of 36 months. The study used an initial digitoxin dose of 0.07 mg daily with concentration-guided adjustment. Its positive composite result is important but should be interpreted within the eligibility and monitoring conditions of the trial. Neither all-cause death nor first HF hospitalization alone was significantly reduced. [128]

DECISION included 1,001 patients and recorded 238 versus 291 primary-outcome events. The rate ratio was 0.81, but its confidence interval crossed unity and P=0.133. The correct conclusion is a neutral primary outcome, not a confirmed 19% reduction in clinical events. The study also provides randomized data including patients with AF; the older blanket statement that no such randomized evidence exists must therefore be retired. [129]

> **The clinical question is narrower than "Does digitalis work?"**
> Identify the intended purpose: residual symptomatic HF, selected prevention of worsening, or ventricular rate control. Then assess concentration-guided safety and alternatives. A potentially useful adjunct is not a substitute for foundational therapy.

Digitalis: concentration-guided use and preventable toxicity

Digoxin has a narrow therapeutic margin. The dose is influenced by renal function, lean body size, age and interacting medicines; a fixed "target dose" of 250 micrograms for every patient is inappropriate. Sample interpretation requires adequate distribution time: the cited product information specifies at least six hours after the preceding dose. An unexpectedly high early post-dose sample should not be interpreted as a stable trough concentration. [159]

Table 4.14. Digitalis: drug identity, units and monitoring

Feature	Digoxin	Digitoxin
Dose principle	Low maintenance regimens may use 62.5 or 125 micrograms daily; individualize for renal reserve, body size and interactions.	Use specialist, product- and concentration-guided dosing; do not convert directly from digoxin.
Concentration reference	DECISION target: 0.5–0.9 ng/mL.	DIGIT-HF target: 10.5–23.6 nmol/L, approximately 8–18 ng/mL.
Evidence interpretation	Older hospitalization benefit; contemporary DECISION primary outcome neutral.	Contemporary positive composite in a selected symptomatic population.
Major safeguards	Check sampling time, potassium, magnesium, renal function, ECG and relevant interactions.	Confirm local availability, formulation, assay, interactions and a monitoring service.

Nausea, anorexia, visual disturbance, confusion, bradycardia, conduction abnormalities or a new arrhythmia should prompt consideration of toxicity. A concentration within a laboratory reference interval does not rule it out, particularly when potassium or magnesium is low or renal function has deteriorated. The symptom pattern, ECG and biochemical context are more important than a number considered in isolation. [159]

A prescription should have an exit criterion

Before starting, define the clinical benefit expected and the circumstances in which the medicine will be reconsidered. Lack of symptomatic benefit, changing rhythm, renal deterioration, recurrent interaction problems or an inability to obtain interpretable concentrations may alter the benefit–risk balance. Routine dose escalation to force a laboratory value upward is not the objective.

Patients and caregivers should receive a medicine-specific written schedule, including the exact strength. This is especially important when microgram doses, split tablets or alternate-day administration are used. Medication reconciliation should distinguish glycoside therapy from beta-blockade and other rate-slowing treatment so that cumulative effects are recognized.

4.16. Iron, adjunctive strategies and avoidable harm

Iron deficiency should be sought rather than inferred from haemoglobin alone. The conventional HF framework uses ferritin <100 ng/mL, or 100–299 ng/mL with transferrin saturation <20%. Interpretation should include inflammation and the cause of deficiency. Intravenous iron is not a substitute for investigating occult blood loss or other relevant pathology. [9]

FAIR-HF established improvement in patient-reported status, symptoms and functional measures with ferric carboxymaltose, including in patients without anaemia. FAIR-HF2 did not meet its prespecified multiplicity-adjusted success criteria across its primary endpoints. A nominally favourable P value for one comparison must not be presented as proof of a mortality benefit. The therapeutic discussion should therefore distinguish symptomatic and hospitalization objectives from an unproven survival claim. [63, 160]

Table 4.15. Do not add treatment without identifying the problem

Situation	Why a review is needed
NSAIDs used for musculoskeletal pain	May promote fluid retention and interfere with renal and diuretic management.
Potassium supplements or potassium-containing salt substitutes	Can compound hyperkalaemia during RAAS / MRA treatment.
Several rate-slowing agents	Review cumulative bradycardia and conduction risk.
Nitrates plus a PDE5 inhibitor	Potential for severe hypotension; the combination is unsafe.
Unnecessary duplicate RAAS medicines or two MRAs	Overlap is not equivalent to complementary disease-modifying therapy.
Routine additional drug for every low LVEF	An EF value alone does not establish the indication for ivabradine, vericiguat or a glycoside.

GALACTIC-HF evaluated omecamtiv mecarbil in LVEF ≤35%. Its modest composite effect did not include a significant reduction in cardiovascular death alone. This evidence belongs in a discussion of additional and investigational approaches, not in an automatic replacement of the established treatment architecture. A trial signal is not, by itself, a local prescribing authorization. [161]

The broader clinical principle is disciplined addition. Before adding another therapy, ask which residual symptom, mechanism or risk is being targeted, whether that objective is supported by the evidence, and whether its monitoring burden is feasible for this patient.

4.17. LVEF 41–49%, improvement and treatment withdrawal

Terminology evolves more quickly than randomized populations. The historical HFmrEF group remains essential when interpreting earlier studies. SGLT2 evidence in EF >40%, including DELIVER, supports treatment across a broader EF spectrum. Beta-blocker evidence around 40–49% comes largely from individual-patient subgroup analyses. These are not equivalent evidentiary routes, even when contemporary nomenclature places the patients under one HFrEF heading. [74, 162]

Table 4.16. Four EF trajectories that should not be conflated

Trajectory	Interpretive priority
Persistently low LVEF	Optimize indicated therapy and reassess the aetiology, symptoms and need for non-pharmacological treatment.
Current LVEF 41–49% without previous severe reduction	Use current recommendations while retaining the original trial ranges and intervention-specific uncertainty.
Improved LVEF after previously documented HFrEF	Improvement is not automatically cure; historical dysfunction remains relevant to ongoing treatment.
Normal function after a corrected reversible cause	Any withdrawal discussion requires individualized assessment, objective recovery and a monitoring / restart plan.

TRED-HF randomized withdrawal in a highly selected recovered dilated-cardiomyopathy population: about 44% of those assigned to withdrawal relapsed within six months, compared with none initially continuing therapy. This directly challenges the assumption that normal EF permits routine discontinuation. The longer follow-up found relapse in 33 of 51 participants over a median of six years. That later observation was not a continuously randomized long-term comparison, but it reinforces persistent vulnerability. [5, 163]

A withdrawal discussion should distinguish treatment-related inconvenience from a genuine contraindication and should examine the original aetiology, ventricular volumes, biomarkers, rhythm and recurrent stressors. A patient with previous cardiomyopathy is not biologically equivalent to a person who has never had ventricular dysfunction. These distinctions should be explained before interpreting recovery as the end of care.

Default and exception

The default is continued disease-modifying therapy after improvement. Exceptional, specialist-supervised withdrawal in rigorously selected recovery is a separate decision; it must not become a generic instruction to stop treatment once LVEF exceeds a threshold.

4.18. Longitudinal optimization, adherence and follow-up

A pharmacological programme is a sequence of decisions, not a completed discharge prescription. Follow-up should establish whether each medicine is being taken, tolerated and used for its intended purpose. The clinical record should capture both objective observations and barriers reported by the patient, including adverse effects, cost, complexity, work schedules and difficulty obtaining laboratory tests. A prescription that is never dispensed is not equivalent to exposure in a randomized trial. [53]

Table 4.17. A practical monitoring record for chronic multidrug treatment

When / domain	Information to obtain	Decision to document
Before initiation	BP and symptoms, pulse / rhythm, weight / congestion, renal function, potassium, current medicines	Eligibility, starting dose, safety tests and named reviewer.
After starting or increasing RAAS / MRA therapy	Symptoms, renal function and potassium at a drug- and risk-appropriate interval	Continue, increase, reduce or temporarily hold, with explicit reasons.
After changing diuresis or during illness	Volume status, weight trend, intake, BP, renal and electrolyte changes	Maintenance dose and any individualized temporary-interruption instructions.
At each optimization review	Actual class coverage, dose, adherence, residual symptoms and planned tests	The next actionable change, or why no change is appropriate.
After sustained improvement	Trajectory, residual structural disease, patient goals and burden	Continue indicated therapy; reassess unnecessary adjuncts rather than withdrawing indiscriminately.

A review should end with a clear medication list and a next step. Separate the patient's instructions from the professional titration plan, and use teach-back to confirm the change. Where an agent has been deferred, record what must improve before initiation can be reconsidered. Where a drug has been held, specify who will decide about restarting it.

Success can be described through several complementary measures: appropriate class coverage, tolerated doses, symptom burden, congestion, functional capacity, laboratory safety, treatment persistence and fewer unplanned interruptions. A high target-dose percentage with repeated adverse events is not necessarily superior to a durable individualized regimen. Conversely, "maximally tolerated" should describe an assessed limitation, not substitute for an unattempted titration.

4.19. Clinical cases: applying the framework

Case 1 — Recently stabilized HFrEF with incomplete class coverage

A 61-year-old patient with LVEF 28% is euvolaemic after admission, with systolic BP 112 mmHg, potassium 4.4 mmol/L and eGFR 54 mL/min/1.73 m². The discharge list contains a low-dose ACE inhibitor, beta-blocker and loop diuretic, but no MRA or SGLT2 inhibitor. The issue is not simply how fast to maximize the ACE-inhibitor dose. It is to establish eligibility for complementary classes, decide whether ARNI substitution is appropriate, document any required washout and arrange early safety review.

Teaching point: early coverage and structured follow-up are linked. This example does not mean that every eligible medicine must be started simultaneously or that initiation during shock would be appropriate. [131, 132, 142, 144–146]

Case 2 — Potassium elevation during otherwise effective treatment

A 76-year-old patient taking an ARNI and MRA has potassium 5.7 mmol/L, a recent creatinine rise and increasing use of an over-the-counter NSAID. There are no reported palpitations or syncope, but the result requires timely clinical review. Confirm the context, inspect the interacting treatment and renal trajectory, and apply the MRA-specific dose rule. Consider whether recurrent hyperkalaemia will require a preventive strategy once the immediate problem is assessed.

Teaching point: neither ignoring the result nor permanently stopping every prognostic medicine is an adequate default. Reassessment and a documented restoration plan are part of the intervention. Binder-assisted maintenance is not proven independent mortality treatment. [142, 150–153]

Case 3 — Persistent symptoms despite tolerated foundational treatment

A 68-year-old patient with LVEF 32%, sinus rhythm at 82 beats/min and a recent intravenous-treated decompensation remains limited despite a documented optimized regimen. Reassess congestion, adherence, rhythm, ischaemia, valve disease and iron status before selecting an adjunct. Ivabradine, vericiguat and a glycoside address different selection questions; none should be added simply because the previous agent was ineffective.

Teaching point: match the clinical problem to the actual indication and endpoint evidence. For vericiguat, use the current product-label dose rather than copying an older table; for digitalis, neutral and positive trials must both be represented. [126–129, 155, 156, 158, 159, 164]

5. HFpEF: Diagnosis, Phenotypes and Treatment

5.1. Defining HFpEF without losing the clinical syndrome

Heart failure with preserved ejection fraction (HFpEF) is a symptomatic clinical syndrome, not an echocardiographic description. A left ventricular ejection fraction (LVEF) of at least 50% establishes the preserved-EF range, but the diagnosis also requires evidence that cardiac dysfunction and abnormal filling pressures account for the clinical presentation. Dyspnoea, fatigue and oedema are insufficient alone; conversely, a normal-looking LVEF does not exclude major haemodynamic impairment. The diagnostic task is therefore to connect symptoms, objective physiology and a plausible cardiac substrate. [2, 7]

The 2026 ESC classification retains HFpEF at LVEF ≥50% and groups symptomatic HF below 50% within HFrEF. This chapter uses that contemporary terminology while preserving the entry criteria and original names of historical studies. EMPEROR-Preserved and DELIVER enrolled LVEF >40%, FINEARTS-HF enrolled ≥40%, STEP-HFpEF enrolled ≥45%, and SUMMIT enrolled ≥50%. Their populations are not interchangeable, even when their results inform overlapping treatment decisions. [1, 73, 162, 165–167]

Longitudinal EF is equally important. The 2021 universal HFimpEF definition required an initial LVEF ≤40%, an increase of at least 10 percentage points and a subsequent value >40%. Other studies used their own operational criteria. A patient whose EF rises from 28% to 55% should not be relabelled as ordinary de novo HFpEF and lose the therapeutic history associated with ventricular recovery. The DELIVER HFimpEF analysis supports continued attention to residual risk after improvement. [2, 168]

A useful clinical formulation records four separate elements: the syndrome, its objective confirmation, its dominant aetiology or phenotype, and its current trajectory. For example, 'exercise-confirmed HFpEF with obesity, atrial fibrillation and recurrent congestion' conveys more clinically actionable information than 'diastolic heart failure' alone. This is a clinical formulation, not an additional diagnostic score.

Table 5.1. Distinctions that prevent misclassification

Finding	Interpretation
LVEF ≥50% alone	Preserved EF; not sufficient to establish HFpEF.
Diastolic dysfunction without HF symptoms	Preclinical abnormality; assess risk and underlying disease.
Symptoms plus objective raised filling pressures	Supports the HF syndrome after competing explanations are evaluated.
Recovered EF after prior systolic dysfunction	Preserve the longitudinal HFimpEF/recovery context.
Amyloidosis, severe valve disease or constriction	Identify and treat the specific cause, not merely an EF label.

5.2. A systemic disorder of cardiovascular reserve

The central haemodynamic abnormality in many patients is an excessive rise in left-sided filling pressure for the flow demanded by activity. Impaired relaxation, reduced ventricular compliance, arterial stiffening and restricted cardiac-output reserve can coexist. Resting compensation may conceal the disorder because daily

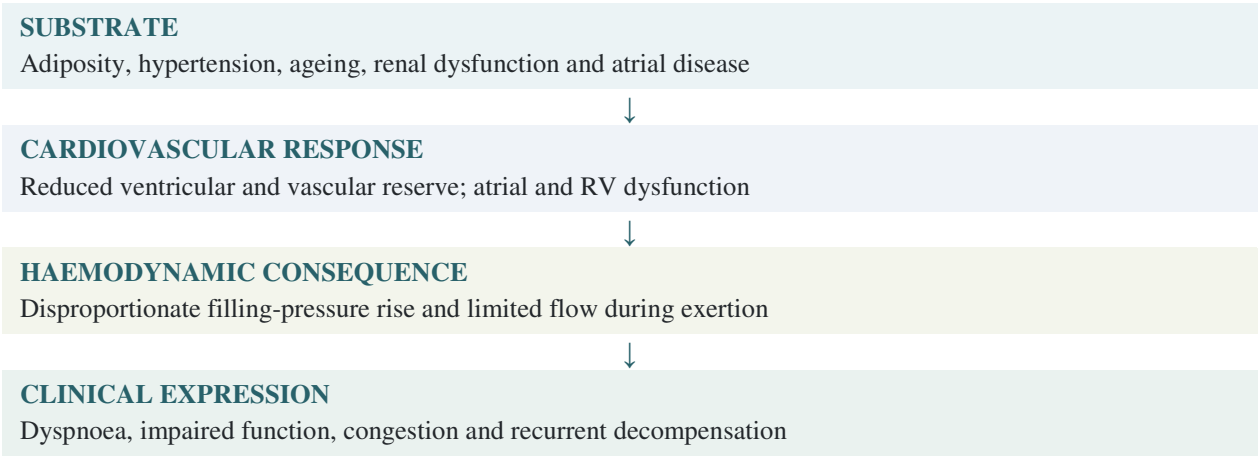
limitation emerges when venous return, heart rate and metabolic demand increase. An exercise abnormality is therefore biologically plausible even when resting examination and biomarkers are relatively reassuring. [111, 123]

The obesity-associated phenotype illustrates why HFpEF cannot be reduced to isolated diastolic dysfunction. In a detailed physiological study, obesity was associated with expanded plasma volume, altered ventricular interaction and greater haemodynamic impairment during exertion. Adiposity can influence both the disease and its recognition: a low natriuretic-peptide concentration or technically limited echocardiogram may obscure clinically significant HF. These observations identify mechanisms and diagnostic challenges; they do not mean that obesity alone establishes HFpEF. [52, 77]

The left atrium, pulmonary circulation and right ventricle are integral to the syndrome. Atrial dysfunction reduces the ability to buffer pulmonary venous pressure; atrial fibrillation adds rhythm irregularity and loss of coordinated contraction. Persistent pulmonary hypertension can increase right ventricular load, while intrinsic RV dysfunction further limits exercise flow and promotes systemic venous congestion. Invasive and imaging data link RV dysfunction with adverse prognosis, independently of the simplistic reassurance offered by preserved LVEF. [95]

Phenotyping should remain clinically useful rather than become a collection of labels. An individual may simultaneously have obesity-related haemodynamic stress, hypertensive remodelling, kidney disease and atrial myopathy. Treatment should address the dominant reversible contributors while retaining therapies supported across broader HF populations. Clustering studies demonstrate heterogeneity, but cluster membership is not itself a validated prescription algorithm. [169]

Figure 5.1. From systemic substrate to exercise limitation



[52, 95, 111, 123, 169]

5.3. Clinical assessment and competing explanations

Evaluation begins with the chronology and context of symptoms. Exertional dyspnoea should be distinguished from orthopnoea, episodic pulmonary oedema, wheeze, angina and fatigue without breathlessness. Establish the change from previous functional capacity, the relationship to weight gain or arrhythmia, prior HF admissions and response to diuretics. Improvement after diuresis is supportive but is not specific enough to establish the diagnosis independently. [7]

Clinical examination should assess congestion and perfusion, including jugular venous pressure, hepatojugular reflux, oedema, lung findings, heart rhythm and orthostatic blood pressure. The absence of obvious oedema does not exclude exertional HFpEF. Medication review is essential: negative chronotropic treatment, sodium-retaining drugs and excessive diuresis can create or amplify the same symptoms that are being attributed to HF. A resting consultation should also explore sleep, mobility, nutritional status and the patient's own functional priorities. [7, 170]

Diagnostic alternatives and coexisting disease require equal attention. Anaemia, obstructive lung disease, pulmonary vascular disease, obesity-related ventilatory limitation and physical deconditioning can explain dyspnoea, coexist with HFpEF, or both. Valvular disease, infiltrative cardiomyopathy and constrictive pericarditis require a specific diagnostic pathway because generic HFpEF treatment does not correct the underlying lesion. The aim is not to exclude every comorbidity before diagnosing HF, but to determine its relative contribution. [7, 14, 45]

A structured initial panel includes electrocardiography, comprehensive echocardiography, natriuretic peptides and laboratory assessment of blood count, renal function, electrolytes, metabolic status and relevant endocrine abnormalities. Subsequent testing should answer a defined question. Serial low-yield investigations without a change in diagnostic probability are less useful than a targeted exercise study or expert reassessment when clinical and resting-test findings disagree. [7, 113]

Table 5.2. Diagnostic alternatives and clues to reassessment

Pattern	Priority question
Wheeze, hypoxaemia or abnormal spirometry	Is pulmonary disease sufficient to explain limitation, or does cardiac congestion coexist?
Marked wall thickening, low voltage or carpal tunnel history	Is amyloid cardiomyopathy present?
Prominent murmur or disproportionate atrial enlargement	Is clinically important valve disease driving the syndrome?
Severe dyspnoea with low filling pressure	Consider ventilatory limitation, deconditioning or a low-preload state.
Exertional symptoms with reassuring resting tests	Is an exercise-induced cardiac filling-pressure abnormality being missed?

[7, 14, 123]

5.4. Natriuretic peptides and echocardiographic evidence

Natriuretic peptides change diagnostic probability rather than provide a binary definition of HFpEF. Their interpretation depends on rhythm, renal function, age, adiposity, timing and treatment. A high NT-proBNP concentration in atrial fibrillation and kidney disease is not specific for the cause of dyspnoea. Conversely, patients with invasively demonstrated HFpEF can have concentrations below customary ambulatory thresholds, particularly with obesity. A low value should not terminate evaluation when the clinical probability remains substantial. [77, 171]

Echocardiography must extend beyond EF. Assess LV mass and geometry, regional and longitudinal function, left atrial size, mitral inflow and annular velocities, pulmonary pressure estimates, RV function and valve disease. Findings should be interpreted together, with attention to image quality and loading conditions. A solitary E/e′ value is an imperfect estimate of filling pressure, and chamber enlargement can reflect mechanisms other than HFpEF. [7, 123]

The table below presents commonly used supportive variables; it is not a new diagnostic score. HFA-PEFF applies domain-specific major and minor criteria, including rhythm-dependent peptide thresholds; those should not be replaced by a mixture of values borrowed from unrelated algorithms. When values are borderline, the reliability of measurement and concordance with symptoms matter more than a small difference around a numerical boundary. [7, 113]

Decongestion can normalize filling-pressure estimates without eliminating the underlying disorder of reserve. Record whether the study was performed during decompensation, after intensive diuresis or during stable ambulatory care. Comparison over time is most informative when rhythm, volume status and measurement methods are documented. A normal resting study after successful treatment is not equivalent to proof that the original HF diagnosis was incorrect. [123]

Table 5.3. Common supportive findings: context matters

Variable	Typical supportive finding	Essential qualification
LAVI	>34 mL/m² in sinus rhythm; >40 in AF	Interpret valve disease, rhythm and body-size indexing.
E/e′	>9 increases suspicion	Not a stand-alone pressure measurement or definitive rule-in.
PASP / TR velocity	>35 mmHg / >2.8 m/s	Consider pulmonary and RV disease; assess signal quality.
LV mass / geometry	Increased mass or concentric remodelling	Absence of LV hypertrophy does not exclude HFpEF.
NT-proBNP / BNP	Ambulatory elevations support HF	Use the thresholds of the selected diagnostic pathway.

[7, 77, 123]

5.5. Using H□FPEF and HFA-PEFF appropriately

The H_2FPEF score was derived using invasive exercise assessment in patients with unexplained dyspnoea. It combines six readily available clinical and echocardiographic features into a 0–9 score. Its role is probability estimation and selection for further evaluation, not automatic treatment authorization. Because atrial fibrillation contributes three points and obesity two, the score is particularly sensitive to the clinical substrate in which it is applied. [109]

The HFA-PEFF pathway is organized differently. After pre-test assessment, functional, morphological and biomarker domains contribute up to two points each. A total of 0–1 suggests low probability, 2–4 requires further functional assessment, and 5–6 strongly supports HFpEF in the appropriate setting. Multiple

abnormalities within one domain do not simply accumulate without limit. The final aetiological step remains essential, even when the numerical score is high. [7]

The two systems are complementary, not interchangeable. In validation against invasive exercise haemodynamics, their discrimination and sensitivity were not identical. Discordance can arise because one score emphasizes comorbidities while the other depends more heavily on imaging and peptides. Averaging the scores, combining selected components or choosing whichever confirms a preferred diagnosis creates an unvalidated method. [113]

An intermediate result should trigger a question rather than an indefinite label: will diastolic stress echocardiography, cardiopulmonary exercise testing or invasive exercise haemodynamics resolve the uncertainty sufficiently to change management? The answer depends on symptoms, local expertise, procedural risk and the clinical consequences of a false-positive or false-negative diagnosis. Even with a high score, specific mimics such as amyloidosis or significant valve disease need consideration. [7, 123]

Table 5.4. H□FPEF components and practical score interpretation

Component	Criterion	Points
Heavy	Body mass index >30 kg/m²	2
Hypertensive	Treatment with at least two antihypertensive agents	1
Atrial fibrillation	Paroxysmal or persistent AF	3
Pulmonary hypertension	Estimated PASP >35 mmHg	1
Elderly	Age >60 years	1
Filling pressure	E/e′ >9	1

[7, 109]

5.6. Exercise physiology and invasive confirmation

Exercise testing becomes particularly valuable when symptoms are convincing but resting investigations remain nondiagnostic. Cardiopulmonary exercise testing objectively characterizes reduced capacity and may identify ventilatory limitation, abnormal chronotropic response or impaired circulatory reserve. However, a low peak oxygen uptake is not specific for HFpEF: age, obesity, skeletal-muscle dysfunction, anaemia and effort all influence the measurement. The test should establish the mechanism of limitation, not merely confirm that the patient performs poorly. [111, 122, 123, 170]

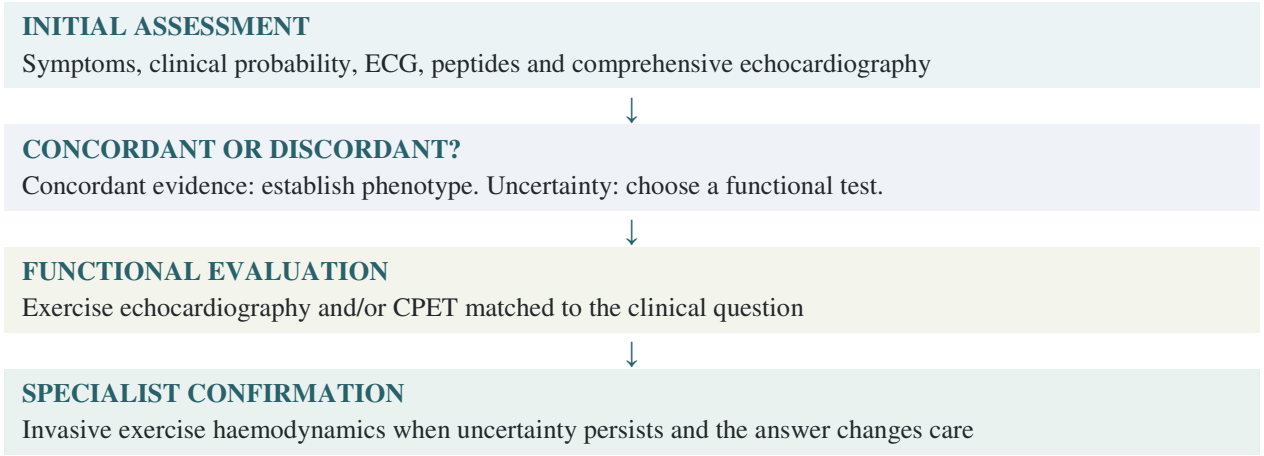
Diastolic stress echocardiography can demonstrate abnormal exercise filling-pressure surrogates, but technical feasibility and interpretative uncertainty increase at high heart rates. Exercise E/e′ and pulmonary pressure estimates should be integrated with the rest of the study; an isolated rise in TR velocity is insufficient. Simultaneous invasive–echocardiographic research shows why a negative or equivocal non-invasive test cannot always close the diagnostic pathway. [123]

In experienced centres, invasive exercise haemodynamics provides direct assessment of filling pressure and output. Commonly used reference criteria include PAWP ≥15 mmHg at rest or ≥25 mmHg during supine exercise. A PAWP/cardiac-output slope >2 mmHg per L/min can identify an abnormal pressure–flow

relationship. These measurements are sensitive to body position, respiratory swings, transducer reference, volume status and the method used to determine cardiac output; they are not portable numbers divorced from technique. [7, 111]

Interpretation should distinguish elevated absolute pressure, the pressure–flow response, and the clinical cause of that response. Obesity may increase intrathoracic pressure, and large respiratory variations can complicate wedge-pressure assessment. A specialist report should describe the protocol and explain whether the findings support HFpEF, pulmonary vascular disease, a low-preload state or mixed physiology. Clinical utility is greatest when the result resolves a decision rather than simply adds another abnormality to the record. [52, 111, 123]

Figure 5.2. Escalating diagnostic certainty in unexplained dyspnoea



[7, 111, 113, 123]

5.7. Phenotypes that change clinical priorities

A phenotype is useful when it changes what is measured, treated or monitored. Obesity-related HFpEF now has direct randomized evidence for incretin-based treatment, whereas a predominant amyloid phenotype requires protein typing and disease-specific management. A patient with extensive atrial disease may need a rhythm-focused evaluation, and one with severe pulmonary hypertension requires careful distinction between post-capillary pressure transmission and additional pulmonary vascular pathology. [14, 45, 166, 167, 172, 173]

The common hypertensive–vascular presentation is not defined solely by current office blood pressure. Years of pressure exposure can leave concentric remodelling and limited vascular reserve even when treatment has normalized the resting measurement. Conversely, low blood pressure in a patient previously labelled hypertensive can signal excessive medication, low stroke volume or an alternative infiltrative process. Historical exposure and present haemodynamics should both influence interpretation. [7, 14]

A cardiorenal presentation requires separation of chronic filtration impairment, acute haemodynamic change and congestion. Renal dysfunction can amplify peptide concentrations, complicate MRA dosing and alter tolerance of volume removal. It should prompt closer monitoring rather than reflex exclusion from effective therapy. Obesity, diabetes and CKD frequently coexist; assigning a patient to one phenotype should not obscure another treatable pathway. [16, 73, 144, 145, 174]

Prognostic enrichment is different from treatment-response enrichment. A phenotype with more events may have a larger absolute opportunity for benefit without a greater relative drug effect. Similarly, a statistically derived cluster can predict outcome yet fail to identify a uniquely effective therapy. This distinction protects against overinterpreting exploratory subgroup findings and allows phenotype-based care to remain anchored to clinical trials rather than attractive but untested biological narratives. [15, 169, 175]

Table 5.5. Phenotype-directed questions within a shared HF framework

Dominant feature	Assessment priority	Therapeutic emphasis
Obesity / metabolic burden	Confirm HF; distinguish adiposity from fluid	Weight-directed treatment plus nutrition and muscle preservation.
Atrial fibrillation / atrial myopathy	Rate, rhythm, embolic risk and valve disease	Individualized rhythm/rate control and anticoagulation.
Kidney disease / congestion	eGFR trajectory, potassium, perfusion and volume	Safe SGLT2/MRA implementation and adaptive diuresis.
Pulmonary hypertension / RV dysfunction	Define haemodynamics and contributing lung disease	Treat left-heart disease; avoid unselected PAH-drug use.
Infiltrative or valvular clues	Identify the specific aetiology	Specialist, disease-specific pathway.

[14, 45, 166, 167, 169, 172, 173, 175]

5.8. The contemporary treatment architecture

Treatment has evolved from an exclusively symptomatic approach to SGLT2-based disease modification. Subsequent evidence has broadened the treatment framework further: MRA therapy and obesity-directed treatment now require explicit discussion. This is not equivalent to transferring every HFrEF drug to every patient with preserved EF. The indication, expected endpoint and safety conditions of each intervention must remain distinct. [64, 73, 166, 167, 172]

The selected recommendations below were checked against the official ESC 2026 slideset, including its displayed evidence grades. They summarize the recommendation rather than reproduce the original table. The full guideline remains the definitive context for exceptions and related recommendations. In particular, a recommendation framed around HF hospitalization or cardiovascular death should not be rewritten as proof that each drug individually reduces cardiovascular mortality in an isolated HFpEF trial. [176]

Implementation combines shared foundations with patient-specific treatment. Relieve clinically important congestion, establish an SGLT2 inhibitor and a suitable MRA when appropriate, and address the dominant phenotype and comorbidities. The sequence depends on haemodynamic stability, renal function, potassium, current treatment and the feasibility of follow-up. A medication that is temporarily unsafe should have a documented reassessment plan rather than disappear from consideration indefinitely. [73, 144, 145, 162, 165, 174]

An evidence-based plan also states what is not expected. Diuresis can relieve congestion without reversing myocardial disease. Weight loss may improve symptoms and function without establishing a mortality effect.

A therapy chosen for hypertension or coronary disease may be appropriate despite neutral HFpEF-specific trials. Communicating these distinctions improves both scientific accuracy and shared decision-making.

Table 5.6. Selected ESC 2026 recommendations relevant to HFpEF

Intervention / setting	Intended benefit	Class / level
Dapagliflozin or empagliflozin; symptomatic HF	Lower HF hospitalization or CV death	I / A
MRA; steroidal or non-steroidal option in HFpEF	Lower HF hospitalization or CV death	I / A
Loop diuretic; clinical congestion	Symptoms, exercise capacity and HF hospitalization	I / A
ACE inhibitor, ARB or ARNI; symptomatic HFpEF	May reduce HF hospitalization	IIb / C
Semaglutide or tirzepatide; symptomatic HF, LVEF ≥45%, BMI ≥30	Weight, exercise capacity and quality of life	IIa / B1

[176]

5.9. SGLT2 inhibition: outcomes and clinical meaning

EMPEROR-Preserved randomized 5,988 patients with symptomatic HF and LVEF >40% to empagliflozin 10 mg daily or placebo. The primary composite of cardiovascular death or first HF hospitalization occurred in 13.8% versus 17.1% over a median 26.2 months (hazard ratio 0.79; 95% CI 0.69–0.90). The result was driven predominantly by fewer HF admissions and was not a demonstration of statistically significant cardiovascular mortality reduction in that trial alone. [165]

DELIVER randomized 6,263 patients with LVEF >40% to dapagliflozin 10 mg daily or placebo. Worsening HF or cardiovascular death occurred in 16.4% versus 19.5% over a median 2.3 years (hazard ratio 0.82; 95% CI 0.73–0.92). Worsening HF included hospitalization or an urgent visit requiring intravenous therapy. Benefit extended to patients without diabetes, reinforcing that these drugs are HF treatments rather than glucose-lowering options restricted to diabetic patients. [162]

The concordant results changed routine practice because they established a reproducible benefit in populations not confined to markedly reduced EF. Nevertheless, absolute benefit depends on baseline risk and the observation period. Neither the relative risk reduction nor the event rate should be transplanted unchanged to a low-risk patient with an uncertain HF diagnosis. Confirmation of the syndrome is part of appropriate treatment selection, not a bureaucratic prerequisite. [162, 165]

Patient-reported outcomes also matter. PRESERVED-HF demonstrated improvement in HF-related health status with dapagliflozin over a short treatment interval. Symptom benefit and event prevention answer different questions, and neither should be substituted for the other. A patient who reports little early symptomatic change may still merit continued preventive treatment, while a marked subjective response does not retrospectively validate an incorrect diagnosis. [177]

Table 5.7. Interpreting the pivotal SGLT2 trials

Study	Population and primary endpoint	Interpretative boundary
EMPEROR-Preserved	LVEF >40%; first HF admission or CV death	Main signal: fewer HF admissions; not isolated proof of reduced CV mortality.
DELIVER	LVEF >40%; worsening HF or CV death	Includes urgent IV-treated events; retain the study definition.
PRESERVED-HF	Symptomatic HF with preserved-range EF; health status	Supports functional benefit; not powered as a mortality trial.

[162, 165, 177]

SGLT2 inhibition — safe implementation

SGLT2 inhibitors do not require HF dose uptitration. Their practical advantage is therefore not merely ease of prescribing but the possibility of establishing therapy while other clinical problems are still being addressed. Before initiation, distinguish persistent congestion from volume depletion and review blood pressure, renal function, oral intake, diabetes treatment and previous ketoacidosis. Concurrent loop-diuretic requirements may change, but automatic diuretic withdrawal is inappropriate in a patient who remains congested. [144, 145]

Current EU information recommends empagliflozin 10 mg daily for HF and does not recommend initiation below eGFR 20 mL/min/1.73 m². Dapagliflozin is generally used at 10 mg daily and is not recommended for initiation below GFR 25 mL/min; severe hepatic impairment requires product-specific dose consideration. A lower glucose-lowering effect at reduced filtration does not negate an HF indication. Initiation thresholds should not be confused with an automatic discontinuation rule during subsequent treatment. [144, 145]

An early filtration change should be interpreted with the clinical trajectory. Small haemodynamic changes can coexist with useful treatment, whereas hypotension, oliguria, progressive creatinine elevation and clinical dehydration require reassessment. The decision is not 'continue regardless' versus 'stop for any creatinine rise'; it is a structured evaluation of volume, perfusion, intercurrent illness and other medicines. [144, 145]

Temporary interruption is appropriate during major surgery, prolonged fasting or serious acute illness in accordance with the current product information and local peri-procedural protocol. Explain symptoms of ketoacidosis, including nausea, abdominal pain, unusual fatigue and rapid breathing, which can occur without extreme hyperglycaemia. Genital infection and volume depletion require practical counselling. The written plan should identify when to contact the clinical team and who will review readiness to restart treatment. [144, 145]

Table 5.8. A practical SGLT2 treatment checklist

Stage	Clinical action
Before prescribing	Confirm HF and current authorised eligibility; record renal and volume status.
Medication review	Identify insulin/sulfonylurea-related hypoglycaemia risk and unnecessary diuresis.
Early review	Reassess symptoms, blood pressure, volume and renal trajectory according to risk.
Acute illness / fasting	Use a temporary-interruption and ketone-assessment plan when indicated.
Longitudinal care	Reconcile continuation, tolerance and the reason for any interruption.

[144, 145]

5.10. MRA therapy: from TOPCAT to FINEARTS-HF

TOPCAT was an important but inconclusive foundation for steroidal MRA treatment in preserved-range EF. It enrolled 3,445 patients with LVEF ≥45%; the primary composite of cardiovascular death, aborted cardiac arrest or HF hospitalization was not significantly reduced with spironolactone (hazard ratio 0.89; 95% CI 0.77–1.04). HF hospitalization was reduced, but the neutral primary outcome and regional concerns prevent a simple claim of unequivocal global trial success. [178]

FINEARTS-HF provided direct outcome evidence for the non-steroidal MRA finerenone in 6,001 patients with symptomatic HF and LVEF ≥40%. Over a median 32 months, total worsening-HF events plus cardiovascular deaths numbered 1,083 with finerenone and 1,283 with placebo (rate ratio 0.84; 95% CI 0.74–0.95). Cardiovascular death alone was not significantly reduced. Hyperkalaemia was more frequent, making laboratory surveillance integral to implementation rather than an optional precaution. [73]

The individual-patient meta-analysis of MRA trials supports benefit across the EF spectrum but also illustrates why the endpoints should remain separate. The magnitude and certainty of mortality effects differ between reduced- and preserved/mildly reduced-EF populations. A broad class recommendation is not equivalent to evidence that every MRA has been tested interchangeably in every phenotype. Selection should consider direct trial evidence, the authorised indication, renal and potassium eligibility, tolerability and access. [75]

Finerenone effects in FINEARTS-HF did not show evidence of material heterogeneity according to baseline SGLT2-inhibitor use. This supports compatibility of the approaches, but background SGLT2 treatment was not independently randomized. The analysis cannot establish the exact incremental benefit of every treatment combination or prove pharmacological synergy. Importantly, combination of an SGLT2 inhibitor with one MRA is different from combining two MRAs, which should not be treated as a routine intensification strategy. [174, 175]

Table 5.9. How the MRA evidence should be described

Evidence	Supported conclusion	Avoid claiming
TOPCAT	Reduced HF hospitalization; neutral overall primary composite	An unqualified mortality benefit in all HFpEF.
FINEARTS-HF	Fewer total worsening-HF/CV-death events with finerenone	A significant isolated CV-mortality reduction.
MRA pooled evidence	Benefit extends beyond traditional HFrEF populations	Equal evidence for every agent and every EF subgroup.
Finerenone with background SGLT2 inhibitor	No demonstrated loss of relative treatment effect	A factorial trial proving a precise synergistic benefit.

[73, 75, 175, 178]

5.11. Finerenone: an HF-specific prescribing framework

The current EU finerenone indication includes symptomatic chronic HF with LVEF ≥40%. The HF dosing scheme differs from its CKD-associated-with-diabetes scheme; therefore, the correct indication-specific table must be used. Start only when serum potassium is ≤5.0 mmol/L. Baseline eGFR ≥60 mL/min/1.73 m²

supports 20 mg daily initially and a 40 mg target; eGFR 25–<60 supports 10 mg initially and a 20 mg target. Do not initiate below 25. Recheck potassium and eGFR four weeks after initiation, restart or dose adjustment, and more often when clinically indicated. [174]

The 40 mg HF target should not be interpreted as a universal objective for every patient. It is tied to renal eligibility and subsequent tolerance. Equally, persistent use of a starting dose without reassessment may leave a potentially useful strategy incompletely implemented. The record should state the current dose, the reason for that dose and the next laboratory decision point. This operational discipline is especially important when more than one clinician adjusts diuretics, renin–angiotensin-system therapy or supplements.

Medication reconciliation should identify other MRAs, potassium-sparing treatment and interacting medicines. Strong CYP3A4 inhibitors are contraindicated; finerenone should not be combined with another MRA. An abrupt change in potassium must prompt assessment for acute kidney injury, dehydration, supplements and new prescriptions, as well as the finerenone dose itself. [174]

The concise potassium summary below highlights a clinically important feature of the current HF label: the action at 5.5–<6.0 mmol/L depends on the dose already being taken. It is not the same table as the diabetes/CKD pathway. Severe or symptomatic hyperkalaemia requires urgent clinical management; this maintenance table does not replace emergency treatment. Renal deterioration must also be considered, even when potassium is acceptable.

Table 5.10. Finerenone in HF: selected EU dose-adjustment instructions

Current potassium	Current dose and action
5.5–<6.0 mmol/L	10 mg: withhold; 20 mg: reduce to 10 mg; 40 mg: reduce to 20 mg.
≥6.0 mmol/L	Withhold at any dose.
Restart after interruption	10 mg when K <5.5; if repeatedly ≥5.5, wait until K <5.0.
Renal deterioration	An eGFR fall ≥40% warrants consideration of dose reduction or interruption.

[174]

IMPLEMENTATION SAFETY

Use one MRA, one clearly documented indication-specific regimen, and an explicit laboratory follow-up plan. A target dose is subordinate to the current potassium, renal trajectory and clinical state.

5.12. Semaglutide and obesity-related HFpEF

STEP-HFpEF changed the discussion of obesity from a background risk factor to a modifiable therapeutic component of symptomatic HF. The trial enrolled 529 patients with BMI ≥30 kg/m² and LVEF ≥45%, without diabetes, and compared once-weekly subcutaneous semaglutide 2.4 mg with placebo for 52 weeks. The placebo-adjusted improvement in KCCQ clinical summary score was 7.8 points; the between-group difference in body-weight change was −10.7 percentage points. Six-minute walk distance also improved. These were clinically relevant health-status, weight and functional findings, not a trial establishing a mortality benefit. [166]

STEP-HFpEF DM extended the approach to 616 patients with obesity-related HF and type 2 diabetes. At 52 weeks, the between-group improvement in KCCQ clinical summary score was 7.3 points and the difference in weight change was −6.4 percentage points. Functional improvement despite less weight reduction than in the non-diabetes trial reinforces the need to measure symptoms and performance directly rather than equate success with a predetermined number of kilograms lost. Cross-trial differences do not identify an individual patient's expected response. [172]

The 2026 ESC recommendation addresses semaglutide or tirzepatide in symptomatic HF with LVEF ≥45% and obesity, irrespective of diabetes, for weight, exercise capacity and quality of life. Its population and endpoints should be stated explicitly. It is not a recommendation for indiscriminate use in lean HFpEF, for substitution for decongestion, or for a proven survival effect in every preserved-EF phenotype. [176]

The semaglutide regimen carrying direct STEP-HFpEF evidence was subcutaneous 2.4 mg weekly after gradual escalation. Current EU weight-management product information contains other formulations and dosing options; these should not be assumed to reproduce the same HF-trial evidence. Formulation, indication, tolerability and the actual studied regimen must therefore remain visible in both prescribing and academic writing. [166, 172, 179]

Table 5.11. STEP-HFpEF evidence at 52 weeks

Outcome	Without diabetes	With type 2 diabetes
Participants / LVEF	529 / ≥45%	616 / ≥45%
KCCQ-CSS treatment difference	+7.8 points	+7.3 points
Body-weight treatment difference	−10.7 percentage points	−6.4 percentage points
6-minute walk treatment difference	+20.3 m	+14.3 m
Main interpretive boundary	Symptoms, weight and function	Not a mortality-powered comparison

[166, 172]

5.13. Tirzepatide: symptoms and worsening-HF events

SUMMIT provided outcome evidence in a specifically obese HFpEF population. It randomized 731 patients with BMI ≥30 kg/m² and LVEF ≥50% to tirzepatide, titrated to a maximum of 15 mg weekly, or placebo. Cardiovascular death or worsening HF occurred in 9.9% versus 15.3%, respectively, with a hazard ratio of 0.62 (95% CI 0.41–0.95). The benefit was driven by fewer worsening-HF events; cardiovascular mortality alone was not established as reduced. The health-status co-primary endpoint also favoured tirzepatide. [167]

Interpretation depends on the event definition. SUMMIT included clinically important worsening beyond hospitalization alone, including specified treatment intensification. Its composite should therefore not be renamed 'HF hospitalization and mortality' or compared numerically with the EMPEROR-Preserved and DELIVER primary outcomes as if the trials measured identical events. Trial population, follow-up, background treatment and statistical estimand also differed. [162, 165, 167]

A prespecified mechanistic analysis linked tirzepatide treatment to changes in circulatory overload and measures of end-organ stress. Such observations strengthen the biological rationale for treating obesity in

HFpEF, but changes in estimated volume or biomarkers cannot establish how much of the clinical effect is mediated by each pathway. Nor do they demonstrate that benefit is independent of weight loss. Mechanistic associations and randomized clinical endpoints answer related but distinct questions. [180]

Regulatory interpretation deserves separate treatment. In January 2026, EMA concluded that a separate HFpEF indication for Mounjaro was not warranted: the obesity indication already encompassed the studied patients, and the assessment did not establish an HF benefit independent of weight reduction. SUMMIT information was incorporated into the product information. Thus, a positive trial, a guideline recommendation and an authorised disease-specific indication are not synonymous. [181, 182]

Table 5.12. SUMMIT: an endpoint-aware reading

Feature	Finding and clinical meaning
Population	Obesity and symptomatic HF; LVEF ≥50%.
Clinical composite	CV death or worsening HF: HR 0.62 (95% CI 0.41–0.95).
KCCQ-CSS difference at 52 weeks	+6.9 points in favour of tirzepatide.
What is not established	An isolated CV-mortality benefit or superiority to semaglutide.
EU regulatory context	Prescribe within current authorised indications; HF data do not create a separate indication.

[167, 181, 182]

Implementing obesity treatment without losing muscle or volume control

A practical obesity-treatment pathway begins by confirming both the HF phenotype and the appropriateness of an authorised weight-management intervention. Record baseline symptoms, a functional measure, nutritional intake, mobility and the current congestion state. Body weight is an ambiguous outcome in HF: early loss may reflect decongestion, later loss may reflect adiposity reduction, and either can be accompanied by inadequate intake. The clinical record should therefore retain more than a weight curve. This pathway integrates implementation considerations from the trial programmes. [166, 167, 172, 180]

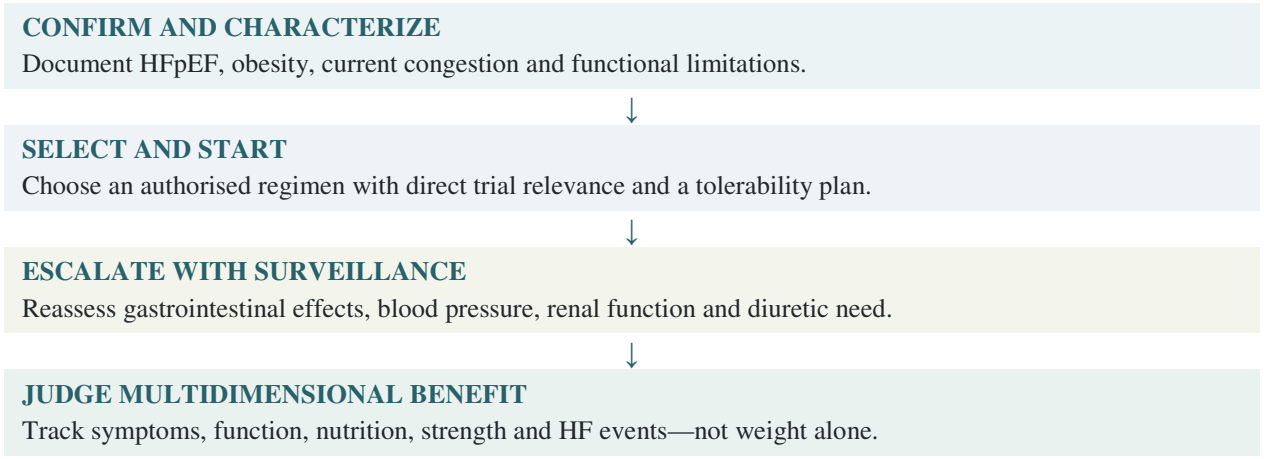
For the subcutaneous semaglutide regimen studied in STEP-HFpEF, escalation usually proceeds at four-week intervals through 0.25, 0.5, 1.0 and 1.7 mg weekly before 2.4 mg. Tirzepatide starts at 2.5 mg weekly, increases to 5 mg after four weeks, and can then increase in 2.5 mg steps after at least four weeks at the current dose, with a maximum of 15 mg weekly. Escalation should follow the current product information and may need delay for gastrointestinal intolerance. A calendar does not override clinical tolerance. [179, 181]

Nausea, vomiting or diarrhoea can reduce oral intake and destabilize volume and renal status, especially when an SGLT2 inhibitor, MRA and loop diuretic are also being used. Reassess blood pressure, congestion, renal function and the need for hypoglycaemia-producing diabetes medicines when relevant. Significant gastrointestinal symptoms, suspected pancreatitis or other serious adverse effects require prompt assessment rather than routine dose escalation. [179, 181]

Exercise and nutritional support should accompany weight management. Monitor strength, walking ability and independence as well as adiposity and symptoms. The aim is improved health and function, not rapid

weight loss at any cost. Shared decisions should address treatment burden, access, tolerability and the possibility that the best-maintained regimen differs from the maximum permitted dose. [97]

Figure 5.3. An integrated obesity–HFpEF treatment pathway



[97, 166, 167, 172, 179–181]

5.14. Other neurohormonal therapies and neutral trials

Earlier HFpEF trials remain essential because contemporary treatment should not erase the limitations of the evidence that preceded it. PARAGON-HF did not significantly reduce its primary recurrent-HF-hospitalization/CV-death endpoint in the overall population with LVEF ≥45%. CHARM-Preserved and I-PRESERVE likewise did not establish broad, unequivocal success for their primary outcomes. Subgroup and hospitalization signals can inform selection, but they should not be rewritten as mortality benefits in an unselected HFpEF population. [183–185]

The 2026 ESC framework allows ACE inhibitors, ARBs or ARNI to be considered in HFpEF to reduce HF hospitalization, with Class IIb, Level C evidence. Their use should still reflect blood pressure, renal function, potassium, competing indications and tolerance. A drug prescribed for hypertension or coronary disease may remain appropriate even when its HFpEF-specific outcome evidence is limited. Conversely, a preserved-EF label does not justify mechanically transferring every HFrEF target dose to every patient. [176]

Beta-blockers require a specific rationale, such as selected rate-control, ischaemic or other indications. Chronotropic limitation can contribute to exercise intolerance. PRESERVE-HR found improved functional capacity after short-term beta-blocker withdrawal in a selected population with HFpEF and chronotropic incompetence. The finding supports medication reassessment; it is not evidence for abrupt or universal withdrawal, particularly in patients with another compelling indication. [170]

Neutral trials define useful boundaries. RELAX did not demonstrate improved exercise capacity or clinical status with sildenafil; NEAT-HFpEF did not show a functional benefit from isosorbide mononitrate and observed lower activity with treatment. These results argue against prescribing the agents simply to improve HFpEF, without negating an independent indication in a properly assessed patient. In REDUCE LAP-HF II, an atrial shunt did not improve the overall primary outcome, so elevated atrial pressure alone is not sufficient justification for routine shunt implantation. [186–188]

Table 5.13. Avoiding therapeutic over-extrapolation

Strategy	Appropriate interpretation
ACE inhibitor / ARB / ARNI	Selected use; separate comorbidity indications from HF-specific evidence.
Beta-blocker	Review rhythm, ischaemia and chronotropic response before continuing or modifying.
Long-acting nitrate for HFpEF alone	No demonstrated routine functional benefit in NEAT-HFpEF.
PDE5 inhibition for HFpEF alone	No routine exercise or clinical-status benefit in RELAX.
Interatrial shunt	Overall neutral randomized evidence; not routine HFpEF care.

[170, 176, 183–188]

5.15. Decongestion and preservation of haemodynamic tolerance

Relief of congestion remains necessary even when disease-modifying therapies have been initiated. Individualized loop-diuretic treatment remains a priority; an SGLT2 inhibitor or MRA does not replace adequate diuresis. Assess pulmonary and systemic congestion, orthostatic symptoms, renal function and the trajectory of weight, not a single isolated measurement. [176]

In HFpEF, a small or relatively stiff ventricle may tolerate abrupt preload reduction poorly. Equally, persistent venous congestion can impair renal function and functional capacity. The practical objective is therefore adequate decongestion with preserved perfusion, followed by the lowest maintenance dose that prevents recurrence. A creatinine rise must be interpreted together with blood pressure, urine output and residual congestion; neither automatic diuretic withdrawal nor indiscriminate escalation is appropriate.

TRANSFORM-HF did not demonstrate an all-cause mortality advantage of torsemide over furosemide after hospitalization in a broad HF population. The trial does not imply that the agents are interchangeable milligram for milligram, nor that individual absorption, dosing practicality and response are irrelevant. It does argue against presenting the selection of torsemide itself as an established survival intervention for HFpEF. [154]

Sequential nephron blockade may be required for selected patients with persistent congestion, but it increases monitoring requirements. Sodium, potassium, renal function and volume status need close reassessment, particularly when combined with MRA and SGLT2 therapy. Acute pulmonary oedema, hypoperfusion or rapidly worsening organ function should prompt acute-care evaluation rather than repeated unsupervised outpatient adjustments. Detailed intravenous dosing belongs to the acute-HF chapter.

A written self-care plan can link symptom changes to timely contact with the HF team. It should define the patient's usual stable weight range, warning symptoms and any pre-agreed diuretic adjustment, rather than invite unrestricted self-prescribing. Nutritional and fluid advice should be individualized; severe restriction is not a substitute for understanding why congestion is recurring.

Table 5.14. Reassessing congestion before changing treatment

Clinical pattern	Reassessment priority
Weight gain, oedema and orthopnoea	Evaluate recurrent fluid retention, precipitant and diuretic response.
Weight loss with dizziness or poor intake	Consider excess diuresis, gastrointestinal losses or undernutrition.
Creatinine rise with persistent oedema	Integrate congestion and perfusion; do not interpret creatinine in isolation.
Creatinine rise with hypotension and dryness	Review volume depletion and interacting medicines promptly.
Recurrent instability despite adjustments	Reassess diagnosis, adherence, rhythm, valve disease and level of care.

5.16. Treating atrial, vascular and cardiorenal comorbidity

Comorbidity management is part of HFpEF treatment, not an optional addendum. Atrial fibrillation, hypertension, kidney disease, diabetes and coronary disease can influence both symptoms and the safety of treatment. Their interactions should be documented explicitly: for example, ventricular rate control may improve palpitations yet worsen chronotropic reserve, while simultaneous changes in diuresis and antihypertensive therapy may precipitate orthostatic symptoms. [173]

The 2024 ESC atrial-fibrillation framework uses CHA_2DS_2-VA to support thromboembolic risk assessment. Stroke prevention should not depend on whether symptoms improve after rhythm control. DOACs are generally preferred when appropriate, except in settings such as mechanical heart valves or moderate-to-severe mitral stenosis. Rhythm and rate strategies should be individualized according to symptoms, haemodynamics, AF duration, atrial disease and patient preferences. Evidence from selected HF ablation populations should not be generalized into a universal HFpEF mortality claim. [173]

Hypertension treatment should balance prevention of further vascular and ventricular injury against symptomatic hypotension. Consider seated and standing pressure, home measurements where feasible, existing HF medicines and the presence of valve or autonomic disease. Renal disease requires coordinated surveillance of filtration, potassium and albuminuria when relevant, with avoidance of unnecessary nephrotoxic exposure. The aim is to preserve useful therapy through informed monitoring rather than to withhold all treatment because CKD is present. [144, 145, 174]

In diabetes, the absence of a glucose-lowering need does not exclude HF-directed SGLT2 therapy. Conversely, improvement in glucose control during weight treatment may require reassessment of insulin or sulfonylurea exposure. Kidney, HF, glycaemic and obesity indications should be reconciled into one medication plan, with responsibility for laboratory testing and adverse-effect review assigned clearly. [144, 145, 179, 181]

Table 5.15. Comorbidity-directed care without therapeutic fragmentation

Domain	Decision to make explicit
Atrial fibrillation	Stroke prevention; symptom-directed rhythm/rate strategy; avoid excessive slowing.
Hypertension	Treat sustained hypertension while monitoring orthostatic and exertional tolerance.
CKD / diabetes	Reconcile HF and renal indications; coordinate potassium, eGFR and hypoglycaemia surveillance.
Coronary disease	Evaluate angina and ischaemia on their own merits; do not assume all dyspnoea is congestion.
Polypharmacy	Name the prescriber responsible for each change and the next safety review.

[144, 145, 173, 174, 179, 181, 182]

Pulmonary hypertension, right-heart disease and phenocopies

Pulmonary hypertension in HFpEF often reflects elevated left-sided filling pressure, but the pulmonary vascular contribution can become substantial. Right-heart catheterization is useful when it will clarify the mechanism and alter management, not simply to attach a pressure label. Interpreting pulmonary pressure without wedge pressure, flow and vascular resistance can misclassify pulmonary vascular disease and expose patients to inappropriate treatment. [45]

Right ventricular dysfunction should prompt assessment of congestion, pulmonary load, tricuspid regurgitation, rhythm and extracardiac organ function. It can identify a high-risk trajectory despite preserved LVEF. The appropriate response is not merely to repeat the EF measurement, but to investigate the cause of right-heart deterioration and determine whether specialist HF, pulmonary-hypertension or valve assessment is required. [45, 95]

Pulmonary arterial hypertension drugs should not be routinely transferred to PH associated with HFpEF. PASSION evaluated tadalafil in patients with combined postcapillary and precapillary PH; the prematurely terminated study did not support routine treatment and raised safety concerns. Together with neutral sildenafil evidence, this argues for careful mechanistic classification and specialist review rather than empirical vasodilator prescribing. [45, 186, 189]

Amyloidosis is a particularly important alternative aetiology in apparent HFpEF with unexplained wall thickening, conduction disease, neuropathy or characteristic musculoskeletal clues. Monoclonal-protein assessment requires serum free light chains plus serum and urine immunofixation. Bone-tracer scintigraphy with tomographic confirmation must be interpreted in that biochemical context. A positive scan in the presence of a monoclonal protein does not independently establish ATTR cardiomyopathy. Disease-specific typing and treatment take priority over automatic application of a generic HFpEF regimen. [14]

Severe valve disease, constriction and other specific cardiomyopathies require the same diagnostic discipline. Their haemodynamic consequences may resemble HFpEF, but the therapeutic opportunity can be fundamentally different. Advanced imaging or haemodynamics should therefore be selected because it can reveal a correctable mechanism, not because more testing is inherently better. [7, 14]

Table 5.16. Findings that justify a disease-specific pathway

Finding	Actionable question
Disproportionate pulmonary pressure / RV failure	Is this postcapillary PH, additional pulmonary vascular disease, or another cause?
Wall thickening with extracardiac red flags	Has AL been excluded correctly before interpreting bone scintigraphy?
Severe valve lesion	Can valve-specific treatment correct the haemodynamic driver?
Pericardial disease or discordant filling pattern	Is constriction or another restrictive mechanism present?

[7, 14, 45]

5.17. Exercise, nutrition, iron status and frailty

Functional limitation in HFpEF reflects both cardiovascular and peripheral reserve. Rehabilitation should therefore address endurance, strength, balance and confidence, with intensity adapted to congestion, rhythm, frailty and comorbidity. Exercise and weight management should be integrated within this multidimensional assessment rather than reduced to a uniform aerobic prescription.

In a randomized factorial study of older obese patients with HFpEF, caloric restriction and aerobic exercise each improved peak oxygen consumption, with additive effects when combined. These were functional findings, not evidence of reduced mortality. The programme also illustrates why nutritional change is best integrated with activity and monitoring rather than delivered as isolated advice to lose weight. [97]

OptimEx-Clin compared high-intensity interval training, moderate continuous training and guideline-based activity advice. Neither exercise strategy achieved the prespecified clinically important between-group peak-VO_2 difference versus control, and the trial did not establish a general superiority of high-intensity training. Exercise selection should therefore reflect feasibility, adherence, patient goals and safety rather than a claim that one intensity pattern is always optimal. [190]

Frailty and sarcopenia can coexist with obesity. Follow strength, mobility, food intake and unintended weight loss, particularly during incretin-based treatment or recurrent decompensation. A smaller body mass with worse strength and poorer independence is not an adequate definition of therapeutic success. Dietary plans should accommodate kidney disease, diabetes and appetite without producing avoidable undernutrition. [179, 181]

Iron deficiency deserves investigation, but the HFpEF-specific treatment evidence remains limited. FAIR-HFpEF stopped early after recruiting 39 rather than the planned 200 participants; ferric carboxymaltose improved six-minute walk distance at 24 weeks, but the study was too small to establish effects on hospitalization or mortality. Investigate the cause of iron deficiency and distinguish this exploratory functional signal from the larger outcome evidence in other HF populations. [191]

Table 5.17. A functional rather than weight-only follow-up

Domain	Practical observation
Endurance	Walking tolerance, exertional symptoms and an appropriate repeat functional test.
Strength / independence	Chair rise, mobility, falls and ability to perform usual daily activities.
Nutrition	Appetite, intake, unintended loss and signs of muscle depletion.
Iron status	Confirm deficiency and evaluate its cause; do not assume anaemia is obligatory.
Programme adherence	Identify transport, fear of exertion, cost, fatigue and caregiver barriers.

[97, 190, 191]

5.18. Longitudinal care and evaluation of treatment response

The follow-up plan should distinguish efficacy, safety and diagnostic reassessment. Efficacy includes symptoms, function, quality of life and HF events. Safety includes blood pressure, volume, renal function, potassium and treatment-specific adverse effects. Diagnostic reassessment asks whether an unexpected trajectory indicates a different or additional disease. These domains are related, but one cannot substitute for the others. A lower natriuretic-peptide concentration does not by itself demonstrate restored exercise capacity or adequate volume status. [77]

At treatment initiation, record a reproducible baseline: current medicines and indications, congestion signs, blood pressure including orthostatic symptoms, renal and electrolyte results, body weight and a functional or patient-reported measure. Repeat the same measure when feasible so that change can be interpreted. KCCQ and six-minute walk testing were useful trial endpoints, but their use in clinic must account for literacy, mobility limitations and testing consistency. [166, 167, 172, 177]

Review intensity should match the intervention and clinical vulnerability. Finerenone requires the indication-specific potassium/eGFR schedule, including review four weeks after initiation, restart or dose adjustment. Intercurrent illness, diuretic escalation, hypotension or poor intake may justify earlier assessment. After an HF hospitalization, early clinical contact should review residual congestion, treatment reconciliation, laboratory testing and the reason for any medication interruption. [174]

A coherent record also captures non-response. Persistent dyspnoea despite euvolaemia may warrant evaluation of AF, chronotropic limitation, pulmonary disease, anaemia, ischaemia or an alternative myocardial process rather than further diuresis. Recurrent admissions, progressive RV dysfunction, declining renal reserve or profound frailty should prompt specialist review even when LVEF remains preserved. [7, 95, 170]

Shared decision-making should address the outcomes the patient values, including independence and treatment burden. Document why a potentially useful therapy was not started, reduced or stopped, and whether that decision will be revisited. Such documentation turns 'maximally tolerated treatment' from an unexplained label into a reviewable clinical judgment. This is a quality-of-care principle rather than a separately validated HFpEF intervention.

Table 5.18. A minimum longitudinal HFpEF record

Question	Documented answer
Is the diagnosis still convincing?	Objective evidence, aetiology, competing explanations and trajectory.
Is congestion controlled?	Symptoms, examination, weight pattern, diuretic plan and perfusion.
Are therapies effective and tolerated?	Patient-reported change, function, HF events and adverse effects.
Are laboratory responsibilities clear?	Next test, responsible clinician and action thresholds.
What matters to the patient?	Functional priorities, feasibility, adherence and treatment preferences.

5.19. Three clinical cases

The following cases are teaching examples. Their observations and management discussions are constructed to illustrate reasoning; they are not patient records, trial participants or individualized prescriptions.

Case 5.1 • Obesity and apparently reassuring natriuretic peptides

A 62-year-old patient has obesity, hypertension and exertional dyspnoea. LVEF is 60%, NT-proBNP is 105 pg/mL, and resting echocardiography is equivocal. The low peptide concentration does not resolve the diagnosis because obesity can reduce diagnostic sensitivity. After evaluation for pulmonary disease, anaemia and other contributors, exercise haemodynamics show a supine exercise PAWP of 30 mmHg with technically adequate measurement. The pattern supports exercise-confirmed HFpEF. Treatment discussion should include congestion assessment, broad HF therapy when eligible, obesity management and rehabilitation, not an assertion that a normal EF or low peptide excludes HF. [7, 77, 123]

Case 5.2 • Finerenone and indication-specific potassium management

A 74-year-old patient with established HFpEF has recurrent congestion despite loop-diuretic and SGLT2 treatment. Baseline eGFR is 48 mL/min/1.73 m² and potassium is 4.6 mmol/L. For the current EU HF indication, finerenone would begin at 10 mg daily with a 20 mg target, not the 40 mg target used for higher baseline filtration. Four weeks after titration to 20 mg, potassium is 5.7 mmol/L. The current HF-specific maintenance table calls for reduction to 10 mg at that dose, together with review of renal function, intercurrent illness and interacting treatment. The example illustrates why the HF and diabetes/CKD dose-adjustment tables must not be confused. [174]

Case 5.3 • Weight reduction with emerging treatment intolerance

A 68-year-old patient with obesity-related HFpEF starts an incretin-based weight-management programme. Over follow-up, weight falls and breathlessness improves, but nausea, poor intake and postural dizziness develop while the loop-diuretic dose is unchanged. This is not a reason to celebrate weight loss without reassessment. Review congestion, standing pressure, renal function, nutrition and other glucose-lowering therapy; reconsider dose escalation and diuretic need according to findings. Judge benefit using function and health status as well as weight, and explain that the available HFpEF trials do not establish isolated mortality benefit for this individual. [166, 167, 172, 179–181]

Across the cases, the general lesson is to preserve the distinction between diagnosis, phenotype, trial eligibility and prescribing. Numerical thresholds gain meaning only within the appropriate clinical and

methodological context. Changes in symptoms, weight, potassium or EF should trigger a reasoned reassessment rather than an automatic treatment rule.

CLINICAL REASONING

Confirm the syndrome, identify the mechanism, select evidence with a matching population, and reassess the whole patient after every meaningful therapeutic change.

6. Rhythm, Devices, Coronary and Valvular Interventions

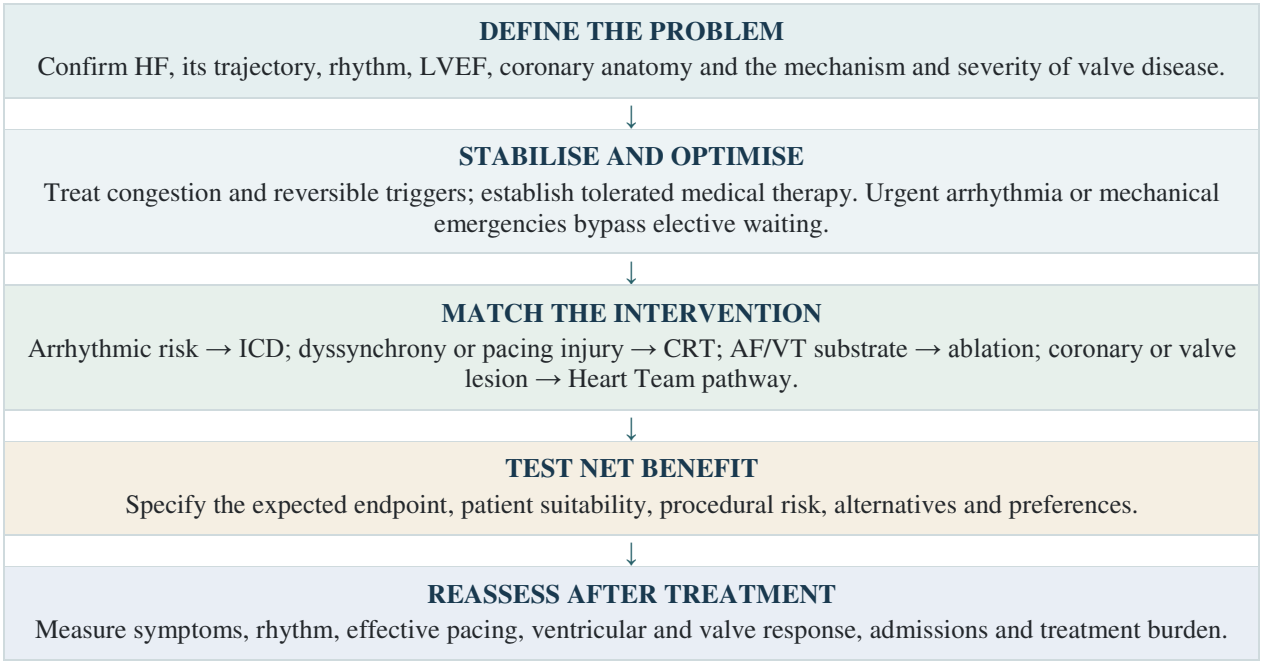
6.1. Integrating electrical and structural interventions

Heart failure is rarely a problem of contractility alone. Electrical instability, loss of atrioventricular coordination, coronary disease and abnormal valvular loading may each perpetuate the syndrome. Device, arrhythmia, coronary and valve interventions should therefore be considered within a connected therapeutic framework. The relevant question is which abnormality is a modifiable driver of this patient's deterioration, and which intervention has evidence for an outcome that matters to that patient.

An implantable cardioverter-defibrillator prevents selected arrhythmic deaths but does not reverse pump failure. Cardiac resynchronization can alter ventricular mechanics; ablation may remove an arrhythmia-mediated component; revascularization and valve intervention address different anatomical substrates. These mechanisms are complementary, but their benefits cannot simply be added or inferred from technical success. Each decision requires assessment of competing causes of death, reversibility, procedural burden and the opportunity to optimise foundational medical therapy. [10, 59, 173, 192, 193]

The 2026 ESC terminology groups symptomatic HF with LVEF <50% as HFrEF. It does not change the original enrolment criteria of ICD, CRT, ablation or revascularization trials. In particular, an LVEF of 45% is not, by itself, a conventional primary-prevention ICD indication. Recommendation grades reproduced in selected tables below are explicitly labelled by source year; the B1 labels in the 2026 HF material are not silently converted to the older B category. [1, 176]

Figure 6.1. A mechanism-directed interventional pathway



[10, 59, 173, 176, 192, 193]

This pathway deliberately separates referral from implantation. Early specialist assessment may be appropriate while treatment is being optimised, whereas the final procedure should follow a documented

indication and shared decision. Conversely, refractory shock, recurrent unstable ventricular arrhythmia or an acute mechanical lesion should not be delayed by a routine outpatient optimisation schedule. [10, 176, 192]

6.2. ICD therapy: indication, timing and competing risk

Secondary prevention begins with the event, not an isolated LVEF threshold. Resuscitated ventricular fibrillation or haemodynamically compromising ventricular tachycardia requires exclusion of an adequately reversible cause, assessment of neurological and overall prognosis, and discussion of ICD treatment. The routine three-month optimisation interval used in primary prevention is not a blanket reason to postpone secondary-prevention protection. Events during the first 48 hours of acute myocardial infarction require a different causal assessment. [176, 192]

For primary prevention, reduced LVEF is a practical risk-enrichment criterion rather than a complete measure of arrhythmic substrate. MADIT-II and SCD-HeFT established benefit in selected populations; their treatment eras, aetiological mix and entry thresholds remain important when estimating absolute benefit today. Modern medical therapy can improve LVEF and reduce both sudden and non-sudden mortality, so a recent measurement after meaningful treatment optimisation is essential. [194, 195]

Table 6.1. Selected ICD decisions in the 2026 ESC HF framework

Clinical setting	Decision boundary	2026 grade
Secondary prevention	Unstable ventricular arrhythmia without a reversible cause; meaningful survival >1 year; exclude early post-MI events as specified in guidance.	I / A
Ischaemic primary prevention	NYHA II–III; LVEF ≤35% despite ≥3 months of optimal foundational therapy; not within 40 days after MI; favourable >1-year prognosis.	I / B1
Non-ischaemic primary prevention	Comparable symptomatic, LVEF and treatment criteria; individualise substrate and competing risk.	IIa / B1
Early post-MI primary prevention	Routine implantation within 40 days is not recommended.	III / B1
Refractory NYHA IV	Do not implant routinely when CRT, LVAD or transplantation are not appropriate.	III / C

[176]

The qualifying optimisation period should represent an actual therapeutic attempt, including tolerance assessment, rather than merely elapsed calendar time. Persistent low LVEF despite this process differs from newly diagnosed dysfunction during rapid AF, myocarditis or another potentially reversible state. Review prior imaging, QRS morphology and pacing requirements before choosing ICD alone rather than a resynchronization system. [192, 193]

Expected survival must include functional status and patient goals. Severe frailty, advanced malignancy or irreversible organ failure may make non-arrhythmic death dominant even when arrhythmic risk is high. Equally, chronological age alone is insufficient to establish futility. A useful discussion distinguishes the likelihood of receiving a shock from the likelihood that an ICD will prolong a life the patient considers acceptable. [176, 192]

6.3. Risk beyond LVEF: scar, genotype and the DANISH legacy

Non-ischaemic cardiomyopathy is heterogeneous. A patient with ventricular dysfunction and a high-risk genetic substrate, conduction disease, syncope or myocardial fibrosis may differ substantially from a patient with an otherwise similar LVEF and extensive reverse remodelling. CMR and phenotype-directed genetic assessment refine risk, but an association with arrhythmia does not automatically establish the benefit of prophylactic ICD implantation. [3]

In the original DANISH trial, prophylactic ICD treatment reduced sudden cardiac death without a statistically significant reduction in all-cause mortality. The 2025 extended analysis, with median follow-up of 13.2 years, remained neutral for all-cause death (HR 0.96, 95% CI 0.82–1.13) while showing fewer sudden cardiovascular deaths (HR 0.54, 95% CI 0.36–0.80). This is a competing-risk result, not evidence that the device cannot terminate arrhythmias. [196, 197]

The extended follow-up did not identify an age interaction for all-cause mortality. An age-related difference in sudden cardiovascular death should therefore not be rewritten as proof of an all-cause survival benefit below age 70, nor as a universal prohibition above that age. The patient's substrate, non-arrhythmic risk and preferences remain central. [197]

Table 6.2. How to use additional risk information without over-interpreting it

Finding	Useful interpretation	Limit
LGE on CMR	Identifies scar and supports aetiological and arrhythmic assessment.	Scar is not a stand-alone universal ICD mandate.
Pathogenic variant	May justify a gene- and phenotype-specific pathway.	A variant of uncertain significance is not equivalent to a pathogenic result.
Unexplained syncope / NSVT	Increases concern in the relevant structural context.	Establish the mechanism; do not assume every syncope is ventricular tachycardia.
Improved LVEF	Suggests treatment response and changes absolute-risk assessment.	Prior arrhythmic substrate and previous appropriate therapies may persist.
Advanced comorbidity	Helps estimate competing death and treatment burden.	Neither an age label nor a single score replaces clinical judgement.

[3, 192]

CMR GUIDE, reported in 2026, specifically tested prophylactic ICD implantation in patients with LVEF 36–50% and CMR-detected scar. The primary endpoint of sudden cardiac death or haemodynamically significant ventricular arrhythmia occurred in 7.8% of ICD recipients and 9.2% of loop-recorder recipients; the difference was not statistically significant. A neutral overall result does not invalidate scar as a prognostic marker, but it prevents routine expansion of ICD eligibility to all scar-positive patients in this EF range. [198]

The practical synthesis is to retain established indications, recognise validated disease-specific exceptions and present unresolved decisions honestly. Risk prediction, treatment-effect prediction and patient preference answer different questions and should be documented separately. [3, 192, 198]

6.4. Device choice, programming and lifetime management

Device selection should start with the functions the patient needs. A transvenous ICD can provide bradycardia pacing and antitachycardia pacing; CRT-D adds resynchronization. A subcutaneous ICD avoids an intravascular lead but does not provide chronic bradycardia pacing, conventional antitachycardia pacing or CRT. Anticipated future pacing needs, vascular access, infection history and the likely ventricular arrhythmia pattern are therefore more informative than a preference for a particular hardware design. [192, 199]

Table 6.3. Matching device capabilities to the clinical problem

System / strategy	Principal advantage	Important limitation
Transvenous ICD	Defibrillation, pacing and antitachycardia pacing within one system.	Intravascular leads introduce lead- and infection-related lifetime issues.
Subcutaneous ICD	Avoids a transvenous lead in appropriately screened patients.	Not a substitute when chronic pacing, ATP or resynchronization is needed.
CRT-D	Combines resynchronization and defibrillation when both are justified.	The incremental defibrillator decision remains individualised.
CRT-P	Resynchronization without shock therapy.	Does not provide protection against ventricular tachyarrhythmic death.
Wearable defibrillator	Temporary protection in selected time-limited risk situations.	Effectiveness depends on wearing time; not a routine post-MI solution.
Generator replacement	Opportunity to renew protection where benefit persists.	Reassess prognosis, prior therapies, goals and complications; replacement is not automatic.

[176, 192, 193, 199, 200]

PRAETORIAN supported non-inferiority of subcutaneous versus transvenous ICD treatment for its composite of device complications and inappropriate shocks in patients without a pacing indication. It did not establish interchangeability for patients who require pacing or CRT. VEST did not significantly reduce its primary arrhythmic-death endpoint with routine wearable-defibrillator assignment after myocardial infarction; selected bridging use should not be described as proven universal benefit. [199, 200]

Programming is part of treatment, not an administrative afterthought. MADIT-RIT demonstrated the value of higher-rate detection or longer detection delays in reducing inappropriate therapy. Nevertheless, secondary-prevention patients with documented slower VT require tailored zones; one high-rate threshold is not appropriate for every patient. Review stored electrograms after therapy, distinguish supraventricular arrhythmia from VT and correct oversensing or lead problems. [201]

Longitudinal care includes wound and infection surveillance, lead and battery assessment, symptom review, remote alerts and explicit responsibility for responding to alerts. At generator depletion, reassess the original indication, ventricular function, previous appropriate shocks, competing mortality and the patient’s wishes. Discuss shock deactivation before terminal deterioration; deactivating defibrillation need not mean stopping bradycardia pacing or resynchronization. [176, 192, 193]

6.5. CRT: clinical benefit and the electrical phenotype

CRT treats a specific physiological problem: poorly coordinated ventricular activation that worsens mechanical efficiency, filling and functional mitral regurgitation. Benefit is most consistently established in symptomatic patients with substantial LVEF reduction and left bundle branch block with a markedly prolonged QRS. CARE-HF established improvement in important clinical outcomes; the results should not be diluted into the proposition that any patient with a low EF benefits from pacing. [202]

Table 6.4. Selected CRT indications: preserve the 2026 source grades

Rhythm / electrical setting	Core conditions	2026 grade
Sinus rhythm; LBBB ≥150 ms	Symptomatic; LVEF ≤35% despite optimal foundational treatment.	I / A
Sinus rhythm; LBBB 130–149 ms	Comparable symptoms, LVEF and treatment criteria.	IIa / C
Sinus rhythm; non-LBBB ≥150 ms	Comparable symptoms, LVEF and treatment criteria.	IIa / C
Sinus rhythm; non-LBBB 130–149 ms	Select carefully; expected benefit is less certain.	IIb / C
HFrEF with high-degree AV block	When ventricular pacing is required, consider CRT rather than isolated RV pacing.	IIa / B1
QRS <130 ms, no pacing indication	Do not implant CRT solely for HF or echocardiographic dyssynchrony.	III / A

[176]

Electrical and mechanical measurements should remain conceptually distinct. Septal flash, apical rocking and scar distribution can inform interpretation or lead strategy, but they do not override a narrow intrinsic QRS in a patient without a pacing indication. EchoCRT demonstrated that echocardiographic dyssynchrony does not rescue the indication in this setting. [203]

Assess the ventricular substrate, rhythm, QRS morphology and duration, anticipated pacing burden and meaningful survival together. A patient requiring pacing for advanced AV block is not the same population as a patient with a narrow QRS and intact conduction; evidence from BLOCK-HF should not be transferred indiscriminately between them. The decision between CRT-P and CRT-D requires a separate estimate of arrhythmic risk and competing mortality. [193, 196, 204]

The 2026 framework allows selected patients with severe dysfunction and LBBB ≥150 ms to have medical treatment initiation and CRT planning proceed together, with reassessment before implantation. This is a conditional pathway, not permission to omit assessment of reversibility or to implant every newly diagnosed patient immediately. In all recipients, evaluate effective resynchronization, ventricular response and residual symptoms rather than labelling response from a single echocardiographic percentage. [176, 193]

6.6. Pacing-related HF, upgrade and conduction-system pacing

Chronic RV pacing may reproduce an LBBB-like activation pattern and can contribute to ventricular dysfunction. Establish the temporal relationship between pacing and deterioration, quantify the paced burden

and exclude other causes, including ischaemia, progressive valve disease and uncontrolled arrhythmia. An existing device does not remove the need to investigate a new HF phenotype. [193, 205]

BLOCK-HF compared biventricular with RV pacing in patients with AV block and LVEF ≤50%. Its central lesson concerns the patient who requires frequent ventricular pacing. BUDAPEST-CRT Upgrade subsequently supplied direct randomized evidence for upgrading a selected symptomatic population with LVEF ≤35%, RV pacing ≥20% and a paced QRS ≥150 ms. [204, 206]

In BUDAPEST-CRT Upgrade, death or HF hospitalization occurred in 10% after CRT-D upgrade versus 32% with ICD treatment, corresponding to an HR of 0.27 (95% CI 0.16–0.47). The trial's separate primary composite also incorporated reverse remodelling; these two endpoints should not be conflated. Its findings support timely upgrade evaluation in a matching phenotype, not automatic upgrading of every pacemaker recipient. [206]

Table 6.5. Assessment before a CRT upgrade

Domain	Information needed	Decision relevance
Ventricular trajectory	LVEF before pacing, current LVEF, chamber size and HF course.	Distinguish pacing contribution from unrelated disease progression.
Electrical burden	Actual RV pacing percentage, paced QRS and intrinsic conduction.	Match the indication to the pacing-related substrate.
Existing system	Lead integrity, venous access, battery status and previous procedures.	Define procedural complexity and alternatives.
Clinical treatment	Symptoms, congestion, tolerated medical therapy and reversible triggers.	Avoid using upgrade as a substitute for fundamental care.
Risk / preference	Infection, frailty, anticoagulation, renal status and expected survival.	Balance clinical gain against an additional procedure.

[193, 206]

A high displayed biventricular percentage is not necessarily identical to effective resynchronization. Fusion, pseudofusion, intermittent capture failure, AF or frequent ventricular ectopy may reduce the physiological dose of CRT. Use electrocardiography, device electrograms and, where appropriate, ambulatory assessment to establish what is actually being delivered. Persistent symptoms should trigger structured troubleshooting rather than an immediate assumption that the underlying disease is unresponsive. [193]

Conduction-system pacing offers another way to recruit the intrinsic activation system. His-bundle pacing and left bundle branch area pacing are not identical techniques; documentation of conduction-system capture, thresholds, lead stability and the paced electrical pattern matters. The 2025 ESC consensus and the 2023 physiological-pacing guideline provide a framework, while newer randomized evidence requires additional qualification. [205, 207]

Conduction-system pacing: interpreting the 2026 trials

A physiological concept is not sufficient evidence of clinical superiority. Conduction-system pacing studies differ in operator experience, the method used to establish conduction capture, ventricular substrate, rescue

strategies, follow-up and endpoint composition. The 2026 evidence is particularly instructive because important randomized trials do not point in a single direction. [208, 209]

Table 6.6. Two randomized CSP comparisons that should not be collapsed into one claim

Trial / setting	Principal result	Interpretative boundary
PhysioSync-HF, 2026 173 participants; LVEF ≤35%, LBBB; 12-month assessment.	CSP was inferior to biventricular pacing for the hierarchical endpoint integrating death, HF events and LVEF; odds ratio 2.36 (95% CI 1.37–4.06).	The hierarchical result is not proof of a separately significant mortality increase.
HeartSync-LBBP, 2026 200 participants; six centres in China; median 36 months.	Death or HF hospitalization: 8% with LBB pacing versus 28% with biventricular pacing; HR 0.26 (95% CI 0.12–0.57).	Clinical benefit was driven mainly by fewer HF admissions; do not claim an independently proven mortality reduction.

[208, 209]

These findings argue against replacing established biventricular CRT with a universal CSP-first rule. They also argue against declaring every conduction-system technique ineffective. A defensible approach is to recognise the established CRT indication, identify whether conventional coronary-sinus lead placement is feasible, and select an alternative or rescue method according to the patient's substrate and the implanting centre's expertise. [193, 205, 208, 209]

The procedural report should identify what was achieved: His capture, left bundle capture or septal myocardial pacing, rather than treating all deep septal leads as equivalent. Follow-up should reassess thresholds, sensing, electrical correction, battery implications and clinical response. In a pacing-dependent patient, reliability and a contingency strategy have particular importance. These practical distinctions are integral to the intervention's biological plausibility and its long-term safety. [205, 207]

Observational comparisons of His-bundle pacing provide historical context but should be distinguished from later randomized evidence. The two 2026 trials are reported separately; their results do not, by themselves, establish a new ESC recommendation class. [208, 209]

A structured response to persistent HF after pacing

First determine whether the electrical intervention is being delivered effectively. Then reassess medical treatment, ischaemia, valve loading, atrial rhythm, ectopic burden, RV function and non-cardiac limitation. Improvement in one domain does not guarantee resolution of all others. Advanced-HF referral and rehabilitation may be appropriate alongside device troubleshooting, rather than after all technical options have been exhausted. [193, 205]

6.7. AF, thromboembolic prevention and cardioversion safety

AF and HF interact through atrial myopathy, loss of atrial contraction, irregular ventricular activation, tachycardia and shared comorbidities. The AF-CARE framework places comorbidity treatment, avoidance of stroke, reduction of symptoms and repeated evaluation within one continuing process. Restoration of sinus rhythm does not replace prevention of embolism, and rate control does not address the entire HF–AF syndrome. [173]

The 2024 ESC AF guideline uses CHA_2DS_2-VA rather than CHA_2DS_2-VASc for routine thromboembolic assessment, and the 2026 HF guidance adopts that framework. HF contributes one point; the total score and clinical circumstances determine treatment. Oral anticoagulation is recommended at a score ≥2 and should be considered at a score of 1. Bleeding risk should prompt correction of modifiable hazards and closer follow-up, not automatic withholding of treatment. [173, 176]

Table 6.7. Anticoagulation and cardioversion: prevent avoidable category errors

Situation	Clinical principle	Do not assume
AF with an OAC indication	Prefer a DOAC when eligible; use the agent's approved dose and reduction criteria.	Empirical underdosing is a safe solution to frailty or bleeding anxiety.
Mechanical valve or moderate-to-severe mitral stenosis	Use the appropriate VKA-based pathway.	A DOAC preference applies to every valvular condition.
Stable AF lasting >24 hours or uncertain duration	Before elective cardioversion, provide ≥3 weeks of therapeutic OAC or exclude atrial thrombus with TOE.	A 48-hour duration threshold remains the current ESC boundary.
Haemodynamic instability attributable to AF	Perform urgent electrical cardioversion and institute anticoagulation as soon as feasible.	Elective pre-cardioversion waiting rules justify delaying emergency treatment.
After cardioversion / catheter ablation	OAC generally ≥4 weeks after cardioversion and ≥2 months after ablation; longer-term treatment follows thromboembolic risk.	A successful procedure proves that stroke risk has disappeared.

[173, 176]

Before cardioversion, verify actual anticoagulant adherence and correct dosing, rather than accepting a prescription list as proof of uninterrupted protection. Unknown onset and missed doses are clinically important. In a patient with HF and additional risk factors, the short post-procedural minimum should not be confused with the appropriate duration of long-term treatment. [173]

The coexistence of coronary disease requires an explicit antithrombotic plan. Recent PCI may require a limited combination strategy, but indefinite addition of antiplatelet therapy to OAC without a separate indication increases treatment burden and bleeding risk. Record the indication and intended duration of each agent and reassess them after the coronary risk period changes. [59, 173]

Conversely, HF in sinus rhythm alone is not a routine indication for anticoagulation. WARCEF and COMMANDER-HF did not establish a favourable overall outcome strategy for indiscriminate anticoagulation in their studied populations. Documented LV thrombus, venous thromboembolism or another specific indication requires its own pathway. [210, 211]

Left atrial appendage closure: selection rather than substitution

Percutaneous left atrial appendage closure addresses a major anatomical source of AF-related embolism, but it does not remove every cause of stroke and does not eliminate procedural or subsequent antithrombotic risk.

Patient selection remains important despite new randomized data, because the risk balance changes with the population and the comparator. [173]

Table 6.8. The 2026 LAA-closure trials answer different questions

Evidence	Population / comparison	What the result supports
CHAMPION-AF	AF patients suitable for anticoagulation; device-based closure versus NOAC therapy.	Non-inferiority for the composite of cardiovascular death, stroke or systemic embolism, with less non-procedure-related bleeding at 3 years.
CLOSURE-AF	AF patients with high stroke and bleeding risk; closure versus physician-directed best medical care.	Non-inferiority was not established for the composite including stroke, systemic embolism, major bleeding and cardiovascular or unexplained death.
Application to HF	Assess HF severity, procedural tolerance, competing mortality, bleeding source and required post-procedure treatment.	Neither trial supplies a blanket HF-specific instruction to replace effective OAC with a device.

[212, 213]

The apparent contrast is not resolved by selecting the preferred headline. CHAMPION-AF enrolled anticoagulation-eligible patients and assessed an efficacy composite separately from non-procedural bleeding. CLOSURE-AF tested a higher-risk clinical setting and a broader composite that included major bleeding. Non-inferiority on one endpoint is not equivalence on every component, and a reduction in non-procedural bleeding should not be rewritten as absence of procedural harm. [212, 213]

For the individual patient, clarify why anticoagulation is problematic. A potentially treatable gastrointestinal bleeding source, a transient drug interaction, inappropriate dosing and an irreversible contraindication are not interchangeable. Evaluate the ability to tolerate whatever short-term antithrombotic regimen and follow-up imaging the proposed device requires. The procedural discussion should include pericardial complications, embolic events, device-related thrombus, residual leak and the possibility of renewed anticoagulation. [173]

Surgical appendage exclusion performed during another cardiac operation is a different decision from a stand-alone percutaneous procedure. Neither should be described as automatically permitting withdrawal of anticoagulation in a high-risk patient. Decisions belong within the relevant surgical or electrophysiological pathway and must account for the patient’s subsequent rhythm and thromboembolic risk. [10, 173]

For this chapter, appendage closure is consequently presented as a selected strategy with evolving evidence, not a routine response to the combination of HF and AF. The endpoint, population and treatment trade-off should be visible in the consultation record and in the way trial results are communicated to the patient. [173, 212, 213]

6.8. Rate control, rhythm control and AF catheter ablation

The first distinction is whether AF is a contributor to ventricular dysfunction or principally a marker of established atrial and myocardial disease. Recent-onset rapid AF with previously normal ventricular function creates a different opportunity from long-standing AF with severe atrial remodelling and advanced multisystem HF. Treat congestion, thyroid disease, infection and electrolyte abnormalities while considering the rhythm strategy; these tasks should proceed in parallel. [173]

Beta-blockers and digoxin are useful rate-control agents in the appropriate haemodynamic setting. Dose selection must reflect blood pressure, renal function, bradycardia risk and clinical stability. A resting rate below 110 beats/min may be an initial target in selected stable patients, but persistent symptoms, suspected tachycardia-mediated dysfunction or inadequate CRT delivery may require a different strategy. Ivabradine does not control AF. Non-dihydropyridine calcium-channel blockers are not suitable for substantial LV systolic dysfunction. [173]

Table 6.9. Randomized rhythm-control evidence in HF: keep the populations visible

Trial	Key setting	Interpretation
CASTLE-AF	363 patients; LVEF ≤35%, AF and an implanted defibrillator.	Ablation reduced death or HF hospitalization (28.5% versus 44.6%; HR 0.62); selected population.
RAFT-AF	411 patients with HF and substantial AF burden.	Primary death/HF-event result did not reach significance (HR 0.71, 95% CI 0.49–1.03), despite functional and ventricular improvements.
EAST-AFNET 4 HF analysis	Early rhythm control in recently diagnosed AF; HF across EF categories.	Supports early integrated rhythm treatment; not a trial of ablation alone.
CASTLE-HTx	End-stage HF with AF evaluated for transplantation at a specialist centre.	Ablation improved the composite of death, LVAD or urgent transplant; specialist selection limits broad extrapolation.

[214–217]

In the 2026 HF recommendation set, AF ablation in selected symptomatic HFrEF receives a IIa/C recommendation for improvement in quality of life and reduction of HF hospitalization or death. This source-specific grade should not be silently replaced with a different grade from the 2024 AF document. Arrhythmia-mediated cardiomyopathy is a particularly important reason for early electrophysiology assessment. [173, 176]

Ablation counselling should address the chance of recurrence, possible repeat procedures, antiarrhythmic exposure, anticoagulation and procedural risk. Improvement in LVEF is not identical to cure of the underlying cardiomyopathy. Continued HF treatment and reassessment remain important even when rhythm control is successful; persistent limitation may reflect valve disease, fibrosis, chronotropic impairment or non-cardiac comorbidity. [173, 214, 216]

6.9. AV-node ablation and effective resynchronization in AF

AV-node ablation controls ventricular activation by creating pacing dependence; it does not restore atrial contraction or eliminate AF. It is therefore fundamentally different from pulmonary-vein isolation. The intended pacing system must be selected before ablation, particularly when ventricular function is impaired or a high lifelong pacing burden is inevitable. [173, 193]

The relevant clinical problems include persistent rapid ventricular rates despite tolerated treatment, intolerable drug effects and failure to deliver effective biventricular pacing. A device counter alone may not establish reliable resynchronization. Confirm capture and investigate fusion, ectopy or lead issues before attributing all ineffective pacing to AV conduction. [193]

Table 6.10. Why APAF-CRT and CAAN-AF should not be treated as interchangeable

Question	Evidence	Clinical meaning
Does an ablate-and-CRT strategy outperform drugs in a highly symptomatic permanent-AF population?	APAF-CRT: narrow QRS, prior HF hospitalization; all-cause mortality 11% versus 29%, HR 0.26.	Supports a selected combined strategy; not a conventional narrow-QRS CRT indication in patients with intact rate control.
Does routine AV-node ablation improve outcomes in patients already receiving CRT-D?	CAAN-AF, 2026: 143 patients; no significant reduction in death/nonfatal HF events, incidence-rate ratio 1.16 (95% CI 0.60–2.24).	The trial stopped for futility; do not ablate all AF patients simply because they have CRT.
What should prompt individual review?	Persistent symptoms, inadequate rate control or demonstrably ineffective resynchronization.	Compare AF ablation, drug adjustment and AV-node ablation within the individual pacing strategy.

[218, 219]

The 2026 ESC HF table supports considering AV-node ablation with CRT in severely symptomatic permanent AF with poor rate control and previous HF hospitalization. Application requires the specified clinical setting rather than a broad inference from AF alone. An already well-controlled CRT recipient and a patient with repeated decompensation caused by uncontrolled AF are not the same treatment question. [176]

Before proceeding, explain irreversible pacing dependence and discuss the reliability of the pacing system, future generator replacement and the consequences of lead failure. Reassess ventricular function, symptoms and medication requirements after rate regularisation. A successful ablation does not automatically justify stopping anticoagulation because the atrial arrhythmia and its thromboembolic substrate remain present. [173, 193]

The two trials provide complementary randomized perspectives. The resulting recommendation is selective and mechanism-based: correct a demonstrable problem with rate or effective pacing, rather than adding an ablation procedure by default. [218, 219]

6.10. Ventricular arrhythmias, ectopy and catheter ablation

Ventricular arrhythmia management has three distinct objectives: terminating an immediately dangerous rhythm, preventing sudden death and reducing recurrent arrhythmia or shocks. These objectives may require different interventions. An ICD can terminate VT without preventing recurrence; ablation can reduce arrhythmia burden without necessarily replacing an established ICD indication. [192]

Initial assessment includes electrolytes, ischaemia, HF decompensation, QT-prolonging or pro-arrhythmic drugs and device recordings. Polymorphic VT during acute ischaemia differs from recurrent scar-related monomorphic VT. Revascularization should address active coronary indications, but it is not a universal treatment for the stable scar substrate sustaining monomorphic VT. [59, 192]

Table 6.11. A practical ventricular-arrhythmia framework

Presentation	Priority	Subsequent pathway
Unstable sustained VT / VF	Immediate resuscitation or cardioversion/defibrillation and treatment of reversible factors.	Evaluate secondary-prevention protection and the underlying substrate.
Recurrent ICD therapy or electrical storm	Confirm appropriate therapies; stabilise haemodynamics and reduce arrhythmic triggers.	Urgent specialist assessment, tailored drugs, programming and consideration of ablation.
Post-MI clinically significant monomorphic VT	Define scar, coronary status and procedural risk.	Discuss early ablation as well as drug therapy; do not require endless ineffective drug escalation.
Frequent PVCs with LV dysfunction	Quantify burden and morphology; examine temporal relationship and CMR findings.	Consider PVC-induced or aggravated cardiomyopathy and a suppression/ablation strategy.

[192, 220]

VANISH2 randomized 416 patients with prior myocardial infarction, clinically significant VT and an ICD to initial ablation or antiarrhythmic drugs. The composite of death, VT storm, appropriate ICD shock or medically treated sustained VT occurred in 50.7% versus 60.6% (HR 0.75, 95% CI 0.58–0.97). This supports earlier consideration of ablation in a matching ischaemic substrate; it does not establish an independent mortality benefit or a universal strategy for non-ischaemic VT. Procedural and drug-related harms remain part of the comparison. [220]

Frequent PVCs may be the cause, an aggravator or a consequence of cardiomyopathy. A sustained burden around 10% or higher raises suspicion in the appropriate setting, but no single percentage establishes causality. Assess day-to-day variability, morphology, scar and competing aetiologies. Improvement after suppression supports the causal formulation, while persistence of dysfunction should prompt reconsideration of the myocardial disease. [192]

Amiodarone can be useful when clinically indicated, but its pulmonary, thyroid, hepatic and other toxicities require surveillance. Successful ablation should be followed by device review, continued HF treatment and reassessment of residual risk rather than an assumption that all electrical and structural disease has resolved. [192]

6.11. Coronary disease: defining the reason for intervention

Coronary disease may be the cause of ventricular injury, an active source of ischaemia or an incidental anatomical finding in a patient whose dominant HF mechanism lies elsewhere. The distinction matters because an obstructive lesion does not by itself establish that revascularization will improve ventricular function or survival. Indications for intervention should distinguish acute coronary disease, refractory symptoms and selected prognostic revascularization. [59]

Assess symptom pattern, previous infarction, ECG, regional wall motion, scar and coronary anatomy. Exertional dyspnoea can represent ischaemia, elevated filling pressure or both. Coronary CT angiography, functional imaging and invasive angiography should be selected according to the clinical probability of

disease, the question being asked and whether the result can change management. Advanced testing is not an end in itself. [59]

Table 6.12. Separate the coronary questions in a patient with HF

Question	Relevant clinical setting	Decision focus
Is urgent coronary treatment required?	Acute coronary syndrome, ongoing ischaemia or haemodynamic compromise attributable to acute coronary disease.	Follow the acute coronary pathway; stable-HF revascularization trials do not justify delay.
Is revascularization needed for symptoms?	Persistent angina or an angina equivalent with obstructive CAD despite appropriate medical therapy.	Balance symptom relief, anatomy, feasibility and procedural risk.
Is prognostic revascularization appropriate?	Selected ischaemic LV dysfunction with surgically amenable coronary disease.	Discuss CABG evidence, life expectancy and early operative risk; do not substitute a general PCI survival claim.
Is the lesion incidental to the HF mechanism?	Scarred myocardium, non-ischaemic disease or symptoms explained predominantly by another process.	Optimise HF and vascular prevention; avoid procedures without a defined therapeutic objective.

[59, 61, 62]

Medical care should not be reduced to anti-anginal treatment alone. Disease-modifying HF therapy, lipid lowering for established atherosclerotic disease, smoking cessation, rehabilitation and an appropriate antithrombotic regimen address different risks. Beta-blockers may serve both HF and anti-anginal purposes, whereas other anti-anginal agents should be selected according to blood pressure, rhythm, renal function and drug interactions. [59]

Amlodipine or other haemodynamically suitable agents may relieve symptoms in selected patients, but symptom improvement is not evidence of a disease-modifying HF effect. Verapamil and diltiazem are inappropriate in significant systolic dysfunction. Nitrate-associated hypotension and the interaction with phosphodiesterase-5 inhibitors require particular attention. The pharmacological chapter provides the wider optimisation framework. [59]

Document the intended outcome before coronary intervention: relief of angina, prevention of events in a defined anatomy, or treatment of an acute coronary syndrome. This makes later assessment more meaningful and prevents a technically successful PCI from being misrepresented as successful treatment of every component of the HF syndrome. [59, 61, 62]

6.12. CABG, PCI and the limitations of viability-based selection

The main randomized evidence for CABG and PCI in severe ischaemic LV dysfunction comes from different trials, populations and treatment eras. Their findings should be compared critically, not presented as a direct randomized contest between procedures. A Heart Team must integrate coronary complexity, the feasibility of durable revascularization, surgical risk, comorbidity, expected survival and the patient’s priorities. [59, 61, 62]

Table 6.13. What the principal revascularization trials actually tested

Study	Design / population	Main interpretation
STICH / STICHES	CABG plus medical therapy versus medical therapy in surgically amenable CAD with LVEF ≤35%.	Initial all-cause mortality result was neutral; extended follow-up demonstrated lower mortality with CABG. At about 10 years: 58.9% versus 66.1%.
REVIVED-BCIS2	PCI plus optimal medical therapy versus optimal medical therapy; stable ischaemic dysfunction, LVEF ≤35%, viability required.	Death or HF hospitalization was not reduced (HR 0.99, 95% CI 0.78–1.27); there was no sustained advantage in LVEF.
REVIVED viability analysis	Prespecified assessment of viability and non-viable myocardium.	Viability did not identify a subgroup deriving prognostic benefit from PCI; scar burden provided prognostic information.

[61, 62, 221]

STICHES demonstrates why follow-up duration matters. An operation can impose an early hazard while providing a later advantage. The potential gain is therefore less persuasive when severe frailty or non-cardiac disease markedly limits life expectancy. Conversely, a younger suitable patient with extensive coronary disease and a long horizon may have a materially different balance of risk and benefit. [62]

REVIVED-BCIS2 does not mean that PCI is never appropriate in HF. It means that adding PCI to medical treatment did not improve the tested death/HF-hospitalization endpoint in that stable, viability-selected population. It does not address emergency reperfusion in acute myocardial infarction, every possible coronary anatomy or all patients with refractory angina. Its early quality-of-life effects also should not be converted into a survival claim. [61]

Viability imaging can explain dysfunctional myocardium, quantify scar and clarify the likelihood of regional recovery. However, demonstrating viable tissue is not equivalent to demonstrating that a specific revascularization strategy improves survival. The absence of a treatment interaction in REVIVED should prevent the use of viability as a simple gatekeeper that automatically sends a patient to PCI. [221]

The 2026 HF recommendations favour CABG when revascularization is selected for a suitable patient with multivessel CAD and LVEF ≤35% after Heart Team discussion. Persistent angina despite treatment supplies a separate indication for considering revascularization. Shared decision-making should disclose both the expected endpoint and the uncertainty about ventricular recovery. [59, 176]

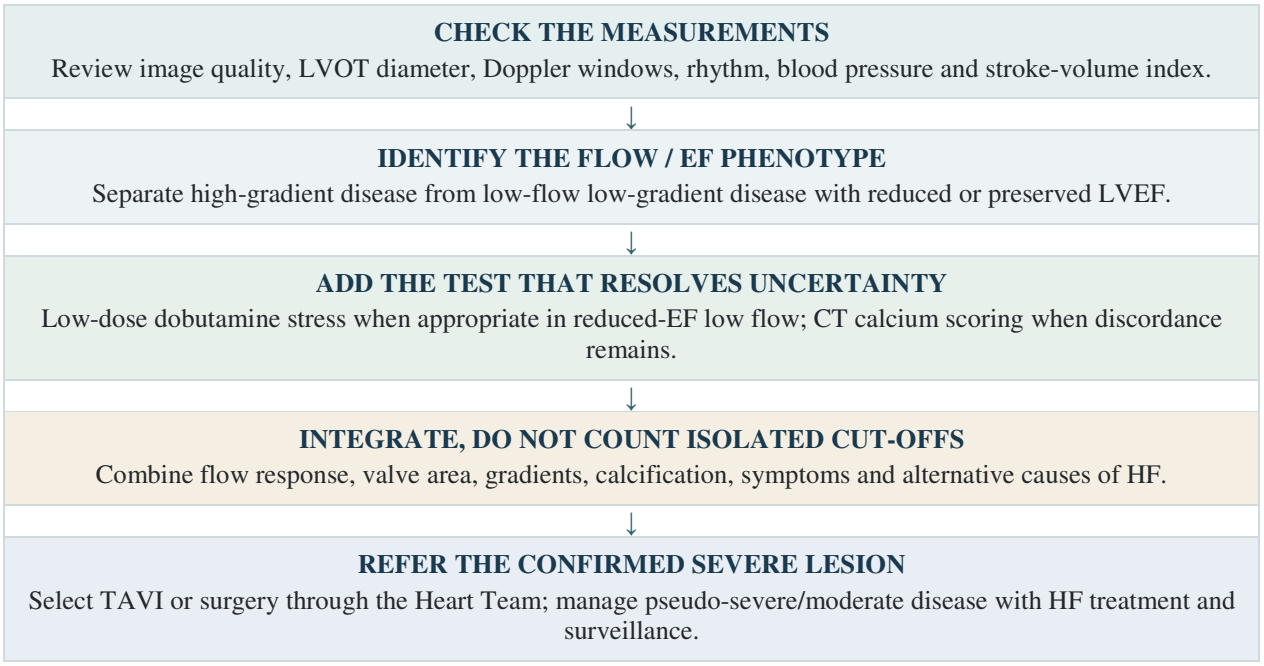
6.13. Aortic stenosis: establishing severity in low-flow HF

Aortic stenosis adds a fixed outflow load to a ventricle already operating with limited reserve. Severe disease may cause or aggravate HF, but gradients depend on flow. A small calculated valve area with a low gradient therefore requires reconciliation rather than immediate classification as either severe obstruction or harmless moderate disease. Verify blood pressure, Doppler alignment, LV outflow tract measurement and stroke volume before advancing the diagnostic pathway. [10]

Concordant high-gradient severe AS is supported by a peak velocity ≥4.0 m/s or mean gradient ≥40 mmHg in the appropriate anatomical context. In discordant low-gradient disease, a valve area ≤1.0 cm² and stroke-volume index ≤35 mL/m² raise the question of low-flow severe AS. Reduced LVEF and preserved LVEF

low-flow phenotypes require different physiological interpretation, even though both may have clinically important obstruction. [10]

Figure 6.2. Resolving discordant aortic-stenosis measurements



[10]

With dobutamine, an increase in flow can distinguish fixed obstruction from a valve that opens more fully when stroke volume improves. Persistently small valve area with a rise in gradient supports true severe AS; enlargement of valve area suggests pseudo-severe disease. Absence of flow reserve should not, by itself, end assessment or establish futility. CT valve calcification can provide flow-independent support. [10]

Sex-specific CT calcium interpretation is important: values above approximately 2000 Agatston units in men or 1200 in women support severe AS in the relevant setting, but must be integrated with the complete assessment. Marked symptoms may also arise from coronary disease, amyloidosis, pulmonary disease or a second valve lesion. A technically plausible valve measurement is not sufficient evidence that the valve is the sole cause of the patient's limitation. [10]

6.14. TAVI, surgery and the boundary of moderate-AS intervention

Once severe AS is confirmed and symptoms are attributable to the lesion, definitive valve intervention should not be postponed simply because diuretics temporarily improve dyspnoea. Medical therapy cannot remove the fixed obstruction. The route of treatment is a Heart Team decision incorporating anatomy, age, procedural risk, concomitant surgical disease, life expectancy and the likely sequence of future interventions. [10]

The 2025 ESC/EACTS framework moved the age-based preference toward TAVI to age 70 in suitable patients with tricuspid AS, subject to anatomical and transfemoral feasibility. This is not an instruction to perform TAVI in every patient aged 70 or older, particularly when anatomy or associated disease favours surgery. Bicuspid valves, aortopathy and the need for concomitant CABG require specific consideration. [10]

Table 6.14. Valve-route selection and the meaning of the TAVR UNLOAD result

Situation	Factors that matter	Interpretation
Severe symptomatic tricuspid AS	Age, transfemoral feasibility, anatomy, life expectancy and patient preference.	TAVI or SAVR according to the contemporary Heart Team pathway.
Associated surgical disease	Aortic pathology, complex coronary disease or another valve requiring surgery.	The optimal combined operation may outweigh an isolated transcatheter preference.
Low-flow severe AS	Confirmation of true severity, ventricular reserve and competing disease.	Low LVEF alone should not be equated with futility.
Moderate AS with systolic HF	HF optimisation, repeated imaging and progression surveillance.	TAVR UNLOAD did not establish superiority of routine early TAVI on its primary hierarchical endpoint.
Very limited meaningful survival	Irreversible comorbidity, severe frailty, expected functional gain and patient goals.	Symptom-directed or palliative care may be more appropriate than a futile procedure.

[10, 222, 223]

TAVR UNLOAD enrolled 178 patients with systolic HF and moderate AS. The primary hierarchical endpoint was not significantly improved by early TAVI (win ratio 1.31, 95% CI 0.91–1.88), although a quality-of-life advantage was observed at one year. A favourable symptomatic signal is not equivalent to proof that intervening on all moderate stenoses improves survival or HF events. [223]

The lifetime plan includes prosthesis durability, coronary access, possible future valve-in-valve treatment, paravalvular regurgitation, pacemaker risk and the consequences of an eventual reintervention. A single operative-risk score does not capture these considerations. Explain what each route is expected to achieve and which important uncertainties remain for that individual. [10]

After intervention, persistent HF deserves a renewed assessment of prosthetic function, residual valve lesions, ventricular and atrial disease, rhythm, ischaemia and non-cardiac limitation. Valve replacement removes an obstruction; it does not necessarily erase myocardial fibrosis or every component of the pre-existing HF syndrome. [10]

6.15. Aortic regurgitation and primary mitral regurgitation

Severe regurgitant lesions produce volume overload but are not interchangeable with functional regurgitation caused by ventricular disease. Primary MR originates in the valve apparatus, whereas AR commonly involves leaflet disease, the aortic root or both. When a severe primary lesion causes HF, medical treatment is supportive and should not become a reason to defer assessment for definitive correction. [10]

Table 6.15. Primary regurgitant lesions: connect mechanism to definitive treatment

Lesion / setting	Principal pathway	Key qualification
Symptomatic severe AR	Aortic valve surgery when appropriate, irrespective of LVEF.	Assess aortic dimensions, mechanism, coronary disease and overall operability.
Severe AR without symptoms	Use ventricular dimensions, systolic function and aortic criteria to time intervention.	Waiting for overt HF can miss the opportunity to prevent irreversible dysfunction.
Severe AR, ineligible for surgery	Selected transcatheter treatment where anatomy and specialist assessment support it.	Not an automatic extension of standard calcific-AS TAVI practice.
Symptomatic severe primary MR	Surgery, preferably durable repair when feasible and appropriate.	Mechanism, repairability and centre expertise determine the optimal procedure.
Primary MR with high/prohibitive surgical risk	Consider a transcatheter repair pathway if anatomy and expected benefit are favourable.	Secondary-MR trials do not establish equivalence to surgery in all primary MR.

[10]

In AR, forward output and regurgitant volume depend on loading conditions and diastolic time. Treat hypertension and congestion carefully, but do not interpret haemodynamic improvement as correction of the lesion. The 2025 guidance retains surgery for symptomatic severe AR; for asymptomatic severe AR, marked ventricular enlargement or systolic impairment can justify intervention before symptoms develop. A transcatheter option in an inoperable patient requires device- and anatomy-specific expertise. [10]

In primary MR, a seemingly normal LVEF may conceal impaired myocardial function because part of ejection occurs into the relatively low-pressure left atrium. Progressive ventricular enlargement, declining systolic performance, AF and pulmonary-pressure consequences therefore require active surveillance. Symptoms, quantitative MR severity and the probability of durable repair should be reviewed together rather than waiting for an unequivocally low EF. [10]

The mitral mechanism must be defined carefully. Prolapse, flail, rheumatic restriction, calcification and endocarditic destruction imply different repairability, procedural risk and therapeutic priorities. Severe acute MR with haemodynamic compromise is not an elective chronic-HF optimisation problem and requires urgent specialist management. [10]

These distinctions also guide interpretation of newer studies. MATTERHORN compared TEER with surgery in secondary MR; it must not be cited as proof that transcatheter repair has replaced durable surgical repair for primary degenerative disease. After any procedure, reassess residual regurgitation, stenosis, ventricular response and the need for continuing HF treatment. [10, 224]

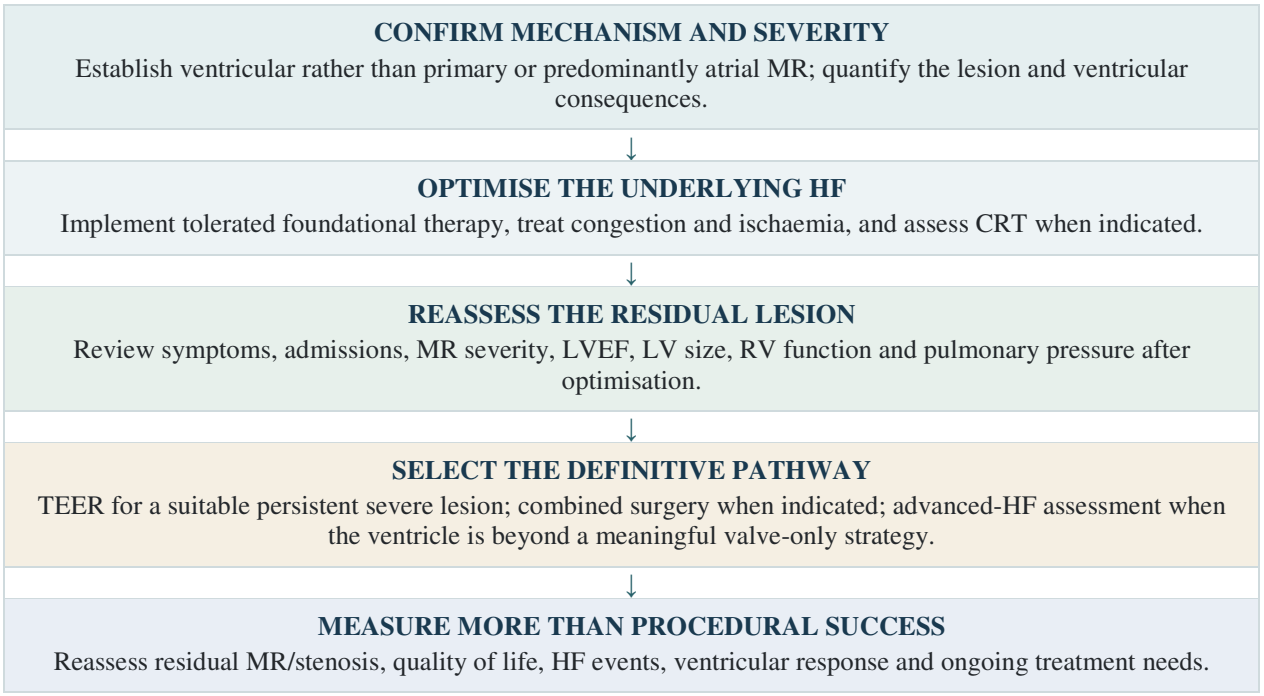
6.16. Secondary MR: optimising the ventricle before the valve

Secondary MR is usually a consequence of altered ventricular or atrial geometry rather than a primary leaflet lesion. In ventricular secondary MR, papillary-muscle displacement, tethering and annular enlargement impair coaptation. Atrial secondary MR reflects a different geometry, often associated with AF and marked

atrial or annular dilatation. The mechanism influences both the opportunity for medical or electrical improvement and the choice of intervention. [10]

Assess regurgitation under interpretable loading conditions and use an integrated echocardiographic evaluation. EROA, regurgitant volume, jet characteristics, pulmonary-vein flow, chamber size and ventricular function should be reconciled rather than reduced to one number. An EROA threshold alone is insufficient to reproduce the full selection process used in COAPT. [10, 225]

Figure 6.3. A coordinated pathway for ventricular secondary MR



[10, 176, 225–227]

The 2026 HF guidance gives mitral TEER a Class I/B1 recommendation in stable, persistently symptomatic patients with severe ventricular secondary MR despite medical treatment and CRT when indicated, when the specified suitability criteria are met. Its wording emphasises HF hospitalization and quality of life; it should not be paraphrased as a guaranteed mortality benefit for every patient with functional MR. [176]

Favourable selection includes LVEF 20–50%, LV end-systolic diameter ≤70 mm, systolic pulmonary artery pressure ≤70 mmHg and suitable valve anatomy. Symptoms, recent HF hospitalization or elevated natriuretic peptides, absence of advanced Stage D disease and the lack of severe RV or competing valve disease also matter. A coronary lesion requiring revascularization or an infiltrative/restrictive cardiomyopathy can change the pathway. [176]

Early referral to a combined HF and valve team need not await the end of every titration step. However, proceeding directly to TEER without establishing tolerated treatment and assessing resynchronization may miss a reversible component of MR. Conversely, refractory advanced disease requires timely LVAD or transplantation assessment rather than serial low-yield valve procedures. [10]

Secondary-MR trials: reconciling benefit, neutrality and selection

The divergent early trials are best understood as evidence that the context of the lesion matters. Differences in ventricular size, severity assessment, optimisation, procedural performance and follow-up can affect the incremental value of repairing MR. The concept of MR severity relative to ventricular remodelling is useful for discussion, but it should not be used as a single retrospectively derived rule that replaces a complete clinical evaluation. [225, 228]

Table 6.16. Randomized secondary-MR evidence and its limits

Trial	Comparison / population	Main message
COAPT and 5-year follow-up	TEER plus medical therapy versus medical therapy in a carefully selected symptomatic HF population.	Lower HF hospitalization and mortality in the studied population; durable benefit does not remove the selection requirements.
MITRA-FR	Percutaneous repair plus medical therapy versus medical therapy in secondary MR with LV dysfunction.	No significant improvement in the main death/HF-hospitalization outcome; not every secondary-MR phenotype benefits.
RESHAPE-HF2	505 patients with HF and moderate-to-severe functional MR; TEER versus medical therapy.	Total HF hospitalizations or cardiovascular death: rate ratio 0.64 (95% CI 0.48–0.85); quality of life also improved.
MATTERHORN	TEER versus mitral surgery in selected secondary MR.	Non-inferiority for the one-year composite outcome; not proof of equivalence for all mechanisms or long-term durability.

[224–228]

RESHAPE-HF2 broadened the evidence base beyond the original COAPT population. Its lower event rate for recurrent HF hospitalization or cardiovascular death was accompanied by better health status, but should not be described as a separately proven reduction in cardiovascular mortality. The trial does not justify intervention for mild MR or eliminate the need to optimise the underlying HF syndrome. [227]

MATTERHORN addresses a different comparison: whether TEER can be an alternative to surgery in selected patients with secondary MR. This cannot be merged with comparisons against medical therapy, because the clinical question and competing risks differ. A shorter, less invasive procedure may have advantages, while residual MR, repeat intervention and long-term durability remain relevant. [224]

Atrial secondary MR deserves its own mechanism-directed discussion. Rhythm management and treatment of HFpEF-associated loading may be important; surgical and transcatheter pathways should follow the dedicated valve framework. Applying ventricular COAPT-like criteria uncritically to every patient with atrial annular dilatation would obscure the different substrate. [10]

After TEER, persistent dyspnoea should prompt assessment of residual regurgitation, transmitral gradient, RV function, pulmonary pressure, rhythm and non-cardiac limitation. Technical reduction of the jet is necessary but not sufficient to establish patient benefit. Continue medical therapy and longitudinal HF care; the device corrects a lesion within a continuing myocardial disease process. [10]

6.17. Tricuspid regurgitation: from symptoms to HF-event evidence

TR can be both a consequence and a driver of HF. Define whether the dominant mechanism is leaflet disease, atrial annular dilatation, RV remodelling, pulmonary vascular disease or interaction with an intracardiac lead. Severe systemic congestion should not be accepted as an inevitable terminal manifestation without a mechanism-based valve assessment, but advanced irreversible RV or end-organ disease may narrow the benefit of intervention. [10]

Table 6.17. The evolving randomized evidence for transcatheter TR treatment

Trial	Treatment tested	Interpretative message
TRILUMINATE Pivotal	Tricuspid TEER versus medical therapy.	The one-year benefit was predominantly health-status driven; two-year data subsequently showed fewer HF hospitalizations.
Tri.Fr	TEER plus optimised therapy versus therapy alone.	Improved the trial's clinical composite and patient-reported outcomes; not proof of isolated survival benefit.
TRISCEND II	Transcatheter valve replacement versus medical therapy.	Hierarchical benefit, mainly symptoms and health status; bleeding and pacemaker risks must be considered.
TRIC-I-HF, 2026	Transcatheter repair plus therapy versus therapy alone in symptomatic severe TR with elevated HF-event risk.	Positive hierarchical one-year result and lower three-year death/HF-hospitalization composite.

[229–233]

TRIC-I-HF randomized 360 patients. Its first hierarchical endpoint favoured repair (win ratio 2.42, 95% CI 1.76–3.33). The prespecified subsequent comparison of death or HF hospitalization through three years was also positive (HR 0.40, 95% CI 0.29–0.55). These 2026 results do not establish a separately significant mortality effect from the composite alone. [233]

The 2025 valve guidance supports considering transcatheter treatment in suitable high-risk patients with symptomatic severe TR despite medical therapy, without severe RV dysfunction or pre-capillary pulmonary hypertension. This recommendation should remain labelled by source year. New TRIC-I-HF evidence is discussed separately rather than assigned an invented updated ESC class. [10, 233]

Pre-procedural evaluation should establish RV reserve, pulmonary haemodynamics, hepatic and renal status, leaflet anatomy, coaptation gap and any lead–valve interaction. Neither a single TAPSE value nor visible oedema alone decides candidacy. Lead extraction, repair and replacement require coordinated electrophysiology and valve expertise; removing a lead is not a routine remedy for every device-associated TR. [10]

The aim is earlier appropriate referral before severe irreversible organ dysfunction, followed by an explicit discussion of symptom relief, HF events, procedural complications and uncertain individual survival gain. Continue decongestion and treatment of the underlying HF after intervention. [10, 233]

6.18. Additional devices and haemodynamic monitoring

Residual symptoms despite medical treatment and appropriate conventional device therapy create interest in additional technologies. Their clinical value must be judged by the outcome actually tested. Improvement in exercise capacity or a symptom score is meaningful, but it is not equivalent to lower mortality. Established treatments and adjunctive devices should be distinguished on the basis of their randomized evidence.

Table 6.18. Adjunctive technologies: benefit claims should match the evidence

Technology	Evidence-based role under discussion	What should not be claimed
Cardiac contractility modulation	Selected symptomatic systolic HF without an established CRT indication; FIX-HF-5C assessed functional capacity and health status.	A substitute for indicated CRT or a definitively established survival therapy.
Baroreflex activation therapy	Selected HFrEF with symptomatic limitation; BeAT-HF showed durable symptom and functional improvements.	The long-term primary cardiovascular mortality/HF-morbidity endpoint was significantly reduced.
Pulmonary-artery pressure monitoring	Selected patients within a structured HF service; MONITOR-HF supported better health status and fewer HF admissions.	A sensor alone improves care irrespective of adherence or a clinical response system.
Remote ICD / CRT surveillance	Earlier recognition of device problems, arrhythmia and actionable alerts.	Every available physiological alert has proven benefit for HF mortality or hospitalization.

[193, 234–237]

CCM applies non-excitatory signals during the myocardial refractory period. The rationale differs from resynchronization, and a narrow QRS is not itself evidence that CCM is indicated. Patient selection should begin with confirmation that fundamental HF therapy is genuinely optimised and that an established pacing or CRT indication has not been overlooked. The functional outcomes of FIX-HF-5C should be described without adding an unproven mortality claim. [236]

Long-term BeAT-HF results did not significantly improve the primary cardiovascular-death/HF-morbidity endpoint (rate ratio 0.94, 95% CI 0.57–1.57), despite sustained improvements in patient-centred outcomes. A favourable secondary hierarchical analysis does not overturn the neutral primary result. This distinction is important for balanced counselling about an implanted autonomic therapy. [237]

Pulmonary-artery pressure monitoring is a management strategy rather than an isolated measurement. MONITOR-HF and GUIDE-HF should be considered together: the former showed benefit in its care setting, whereas the overall GUIDE-HF result was neutral and was affected by the pandemic-era context. Patients and teams need reliable transmission, interpretation and medication-adjustment pathways; otherwise, an early warning does not become an effective intervention. [234, 235]

For all adjunctive technologies, identify the intended outcome, the supporting population, procedural risk, follow-up burden and an objective reassessment plan. Referral should not distract from disease-specific treatment, rehabilitation or timely advanced-HF evaluation when those are more appropriate. [193, 234, 236, 237]

6.19. Clinical cases

Case 1. Persistent systolic dysfunction with LBBB and secondary MR

A 64-year-old patient has ischaemic HF, NYHA III symptoms, LVEF 28%, sinus rhythm, LBBB with QRS 166 ms and severe ventricular secondary MR. Tolerated medical treatment has been optimised for four months; there is no coronary lesion requiring revascularization. The immediate elective question is not simply whether to perform TEER. The marked electrical dyssynchrony establishes a strong reason to evaluate CRT, while the ischaemic substrate also prompts an ICD discussion. Valve-team referral can occur in parallel.

After effective CRT and continued treatment, reassess symptoms and MR under stable loading conditions. Persistent severe MR then requires review of LV size, RV function, pulmonary pressure, anatomy and recent HF events before TEER. The teaching point is sequencing: a potentially reversible electrical contribution should be addressed without delaying multidisciplinary assessment. The case does not guarantee that CRT will abolish MR. [10, 176, 193]

Case 2. Permanent AF in a patient already receiving CRT-D

A 77-year-old patient with permanent AF, LVEF 32% and a CRT-D reports worsening fatigue. Device interrogation displays 94% biventricular pacing. The surface ECG and ambulatory recording show intermittent fusion and frequent ventricular ectopy; resting ventricular rate is not persistently rapid. Automatic AV-node ablation would treat an assumed rather than an established mechanism. Review capture, ectopic burden, lead function, congestion and tolerated rate-control treatment first.

If effective resynchronization remains inadequate because of conducted AF despite an appropriate strategy, AV-node ablation may become reasonable. If pacing is already effective and another limitation dominates, the neutral CAAN-AF result cautions against routine ablation. Continue risk-based anticoagulation irrespective of the pacing strategy. The teaching point is to measure effective therapy before adding an irreversible procedure. [173, 193, 218, 219]

Case 3. Recurrent right-sided HF with severe TR

An 80-year-old patient has repeated congestion admissions, severe TR, a dilated annulus and persistent symptoms despite careful diuresis. LVEF is 55%. A preserved LV EF does not establish low risk or remove the need for valve assessment. Determine the TR mechanism, RV reserve, pulmonary haemodynamics, end-organ status and anatomical feasibility; assess whether an intracardiac lead contributes to the lesion.

A high-risk but otherwise suitable patient should be discussed by the valve team before irreversible RV and organ dysfunction develops. Counselling can now include the positive death/HF-hospitalization composite from TRIC-I-HF, while distinguishing that trial from an individual survival prediction and considering procedural risk. The teaching point is neither “intervene on every severe TR” nor “TR therapy is only cosmetic”: select the patient and state the endpoint accurately. [10, 229, 232, 233]

7. Decompensated Heart Failure, Pulmonary Oedema and Cardiogenic Shock

The acute deterioration of heart failure requires more than relief of breathlessness. This chapter connects the recognition of congestion, respiratory failure and hypoperfusion with response-guided decongestion, selective circulatory support and the transition to sustained disease-modifying treatment.

7.1. The decompensated-heart-failure continuum

Decompensated heart failure is a clinical deterioration that exceeds the patient's current circulatory reserve and requires prompt reassessment or intensification of treatment. It may develop abruptly, as in pulmonary oedema or infarct-related shock, or over days to weeks through progressive sodium retention and congestion. The temporal pattern, the severity of organ dysfunction and the setting of care are related but are not equivalent concepts. New-onset disease should be distinguished from deterioration of established heart failure.

The 2026 ESC framework uses decompensated heart failure rather than restricting the discussion to an apparently sudden "acute" event. Historical trial names and eligibility criteria nevertheless retain AHF or ADHF. The change in terminology must not reclassify a haemodynamically unstable patient as suitable for ambulatory care or imply that every episode requires admission. The decision depends on respiratory status, perfusion, renal reserve, reversible precipitants and the reliability of the proposed care pathway. [1, 176, 238]

Management has three overlapping objectives: immediate stabilisation, correction of the dominant haemodynamic disturbance and prevention of the next deterioration. The first two cannot be replaced by long-term disease-modifying therapy; equally, successful diuresis alone does not complete the treatment episode. A coherent plan begins at first contact and continues through the vulnerable transition after discharge. [146]

Table 7.1. Selected ESC 2026 recommendations relevant to this chapter

Clinical action — concise paraphrase	Class / level
IV loop diuretic for admitted DHF with fluid overload.	I / A
Short-term acetazolamide or HCTZ added in appropriate congested chronic loop users.	IIa / B1
Early urinary-sodium-guided adjustment to improve natriuresis and diuresis.	IIb / B1
In-hospital SGLT2 inhibitor after initial stabilisation.	I / B1
Shock-team assessment for potential temporary MCS.	I / C
Selected STEMI-related shock: consider microaxial support; not unselected MCS.	IIa / B1; III / B1
Rapid FMT implementation and frequent follow-up in the first six weeks.	I / B2

[176]

Clinical priorities should be recorded as explicit problems rather than a single label: pulmonary congestion, systemic congestion, respiratory failure, hypoperfusion, precipitating disease and treatment gaps. This problem-oriented formulation allows therapies to proceed in parallel without confusing a short-term physiological response with a demonstrated survival benefit.

7.2. Congestion, redistribution and clinical phenotypes

Congestion reflects increased filling pressures and may involve the pulmonary circulation, systemic venous circulation or both. Total-body fluid accumulation is only one mechanism. An abrupt shift of blood from the splanchnic reservoir, a rise in afterload or acute mitral regurgitation can produce severe pulmonary oedema before a large change in weight occurs. Conversely, extensive peripheral oedema may coexist with relatively little breathlessness at rest. The bedside examination should therefore establish the distribution and likely mechanism of congestion.

The interaction between forward flow and venous pressure is especially important in cardiorenal dysfunction. Renal filtration depends not only on arterial perfusion but also on the opposing pressure transmitted through the venous circulation. An observational study in advanced decompensated HF linked venous congestion with worsening renal function; it does not prove that a single central venous pressure target improves outcomes. The practical implication is to assess both perfusion and congestion rather than attributing every creatinine rise to inadequate cardiac output. [57]

The traditional warm–cold and wet–dry profiles remain useful clinical shorthand. They are provisional assessments, not definitive haemodynamic measurements, and the same patient may change category after vasodilation, diuresis, ventilation or deterioration. “Warm” does not guarantee adequate organ perfusion, and a patient without obvious oedema may still have markedly elevated filling pressures.

Table 7.2. Bedside profiles: dominant problem and immediate implications

Profile	Typical interpretation	Clinical emphasis
Warm and wet	Congestion with apparently maintained peripheral perfusion.	Decongestion; assess blood pressure, triggers and treatment gaps.
Cold and wet	Congestion plus suspected low forward flow.	Confirm hypoperfusion; restore perfusion while managing venous pressure; early escalation if worsening.
Cold and dry	Low-output physiology with little visible congestion; underfilling is possible but not assured.	Use echo and, when necessary, invasive assessment before a fluid challenge.
Warm and dry	No obvious congestion or hypoperfusion.	Reconsider the cause of symptoms or document a successful treatment response.

Phenotyping should also specify left-, right- or biventricular involvement, the rhythm and the underlying substrate. A preserved ejection fraction does not exclude decompensation, severe pulmonary oedema or shock. A low ejection fraction, in isolation, is not an indication for inotropes. Treatment is selected for the current physiological problem and its cause, not merely for the numerical ejection fraction.

7.3. First medical contact and reversible precipitants

The initial assessment is a simultaneous diagnostic and therapeutic process. Record respiratory rate, oxygen saturation, blood pressure, heart rate and rhythm, mental status, skin perfusion and urine output when measurable. Establish intravenous access and electrocardiographic monitoring in unstable patients. An immediate ECG and focused echocardiography may identify a cause requiring a procedure rather than further

escalation of nonspecific HF treatment. Investigations must not postpone life-saving respiratory or circulatory support.

A rapid history should establish symptom onset, previous ventricular function, recent admissions, medication changes and adherence, renal disease and exposure to drugs that promote fluid retention. The examination should actively seek pulmonary congestion, systemic congestion and hypoperfusion. The CHAMPIT framework is a memory aid; it is not an exhaustive list and its components may coexist.

Table 7.3. CHAMPIT: causes that alter the immediate treatment pathway

Trigger	What must be established rapidly	Treatment consequence
C — Coronary syndrome	Ischaemic symptoms, ECG changes, dynamic troponin and wall-motion findings.	Urgent coronary assessment/reperfusion when indicated; do not label all troponin release as infarction.
H — Hypertensive emergency	Acute pressure-related organ injury and pulmonary oedema.	Controlled afterload reduction and respiratory support, with repeated perfusion assessment.
A — Arrhythmia	Tachyarrhythmia, severe bradycardia or high-grade block.	Restore a tolerated rhythm or rate; urgent cardioversion/pacing when instability is attributable to it.
M — Mechanical cause	Acute valve failure, septal rupture or other structural emergency.	Immediate imaging and surgical/interventional discussion.
P — Pulmonary embolism	RV strain and the clinical probability of pulmonary vascular obstruction.	PE-specific diagnostic and reperfusion pathway where appropriate.
I — Infection	Pulmonary/systemic infection; myocarditis as a primary cardiac process.	Treat infection; distinguish distributive or mixed shock and myocarditis-specific needs.
T — Tamponade	Effusion with clinically significant haemodynamic compromise.	Urgent drainage and cause-directed management.

[13, 60, 239]

Disposition is itself a therapeutic decision. Persistent hypoxaemia, ventilatory support, vasoactive infusions, major arrhythmia or evolving organ injury generally require an appropriately monitored hospital environment. An outpatient escalation pathway is reasonable only when it includes prompt reassessment, access to blood tests and a clear route back to urgent care; it is not simply discharge with a larger diuretic dose. [238]

7.4. Diagnosis, biomarkers and bedside imaging

The diagnosis should answer three questions: is the current syndrome cardiac, what mechanism is responsible, and how unstable is the patient? Symptoms, examination, ECG, natriuretic peptides and imaging provide complementary information. No individual measurement can reliably answer all three questions. Diagnostic testing should be directed towards decisions that can change management rather than a uniform extensive panel in every patient.

In the acute presentation, low natriuretic peptide concentrations help exclude HF: BNP <100 pg/mL, NT-proBNP <300 pg/mL or MR-proANP <120 pmol/L. These are acute rule-out thresholds, not outpatient thresholds, treatment targets or proof that a higher value confirms HF. Obesity and some abrupt presentations can lower sensitivity; renal impairment, atrial fibrillation and age reduce specificity. [9]

Table 7.4. A decision-oriented initial diagnostic panel

Investigation	Question answered	Important limitation
12-lead ECG	Ischaemia, arrhythmia, conduction disease.	A tracing alone neither confirms nor excludes the entire HF syndrome.
BNP / NT-proBNP	Does biomarker evidence support or weaken the HF diagnosis?	Interpret with rhythm, age, renal function, adiposity and previous values.
Troponin with serial testing when indicated	Myocardial injury and possible acute infarction.	An elevation alone is not type 1 myocardial infarction.
Creatinine, urea, Na, K, chloride	Renal reserve and treatment safety.	Interpret a change with congestion, perfusion, medications and urine output.
Blood count, liver tests; selected thyroid tests	Anaemia, infection and extracardiac contributors.	Abnormalities may be causes, consequences or coincident disease.
Blood gas and lactate in severe illness	Gas exchange, acid–base disturbance and systemic stress.	Lactate also depends on adrenergic stimulation and clearance.
Echocardiography	Ventricular function, valve disease, pericardium and major structural causes.	Loading conditions influence findings; focused imaging does not replace a comprehensive study.
Lung ultrasound / chest radiography	Congestion, effusions and alternative pulmonary disease.	B-lines are not unique to cardiogenic oedema; a normal radiograph does not exclude HF.

[100]

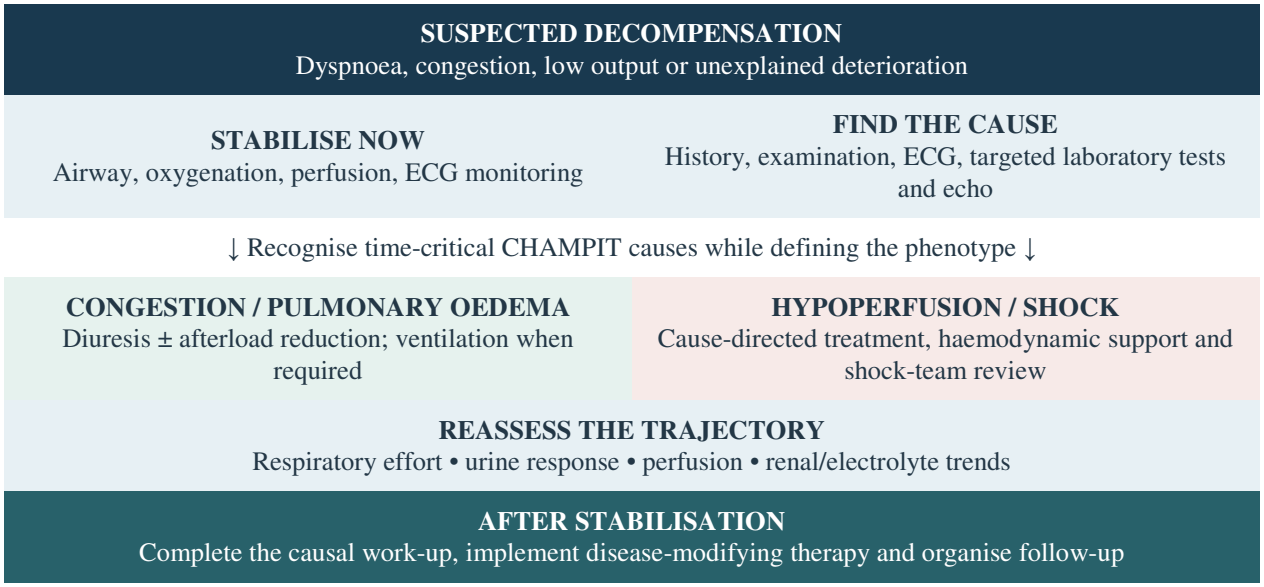
D-dimer, procalcitonin, cultures, toxicology and advanced imaging should be selected according to the differential diagnosis. A procalcitonin concentration should not become an automatic antibiotic rule, particularly when clinical infection is already evident or when shock requires immediate treatment. The cause of deterioration should be revisited if the expected response does not occur.

Diagnostic integration and serial reassessment

Echocardiography is particularly urgent in shock, a new murmur, suspected mechanical complications, marked RV failure or possible tamponade. Assess chamber size and function, regional abnormalities, valve severity and the pericardium. A technically limited focused examination is still useful for urgent questions, but unresolved findings should prompt expert imaging rather than false diagnostic certainty.

Lung ultrasound adds a repeatable assessment of pulmonary interstitial involvement and pleural fluid. The distribution of B-lines, pleural abnormalities and consolidation must be interpreted with the clinical picture. Inferior vena cava dimensions may support assessment of right-sided pressure but do not independently establish fluid responsiveness. Serial examinations are most useful when comparable technique is used and the findings influence an explicit therapeutic decision. [100]

Figure 7.1. Parallel diagnosis, stabilisation and phenotype-directed care



Persistent symptoms despite an apparently successful diuresis warrant reconsideration of the diagnosis and the haemodynamic model. Examples include pneumonia superimposed on HF, pulmonary embolism, severe valvular disease, RV-predominant failure, anaemia and low output. Likewise, improved oxygen saturation after supplemental oxygen does not establish resolution of pulmonary oedema, and reduced peripheral oedema does not guarantee normal filling pressures.

A useful daily record states the dominant problem, the intervention, the expected response and the observed response. This makes disagreement between symptoms, imaging, biomarkers and renal indices visible, supports handover and reduces the risk of continuing an ineffective strategy simply because it is familiar.

7.5. Pulmonary oedema and respiratory support

Acute cardiogenic pulmonary oedema often represents an abrupt rise in pulmonary capillary pressure with fluid redistribution rather than a large increase in total-body water. Severe hypertension, acute mitral regurgitation, ischaemia or rapid arrhythmia may dominate. The therapeutic response therefore depends on the mechanism: respiratory support and carefully controlled afterload reduction may relieve distress before substantial diuresis has occurred. Congestion and excess volume should still be treated when present.

Oxygen is indicated for hypoxaemia, not routinely for every dyspnoeic patient. The ESC threshold is SpO_2 <90% or PaO_2 <60 mmHg. Non-invasive positive-pressure ventilation is appropriate to consider early in marked respiratory distress; hypotension, impaired consciousness, vomiting or inability to protect the airway change its suitability. A deteriorating patient should not remain on an unsuccessful non-invasive strategy while intubation is delayed. [9, 176]

Table 7.5. Respiratory support selected by the clinical problem

Modality	Potential role	Safety and reassessment
Supplemental oxygen	Correct documented hypoxaemia.	Titrate to an individualised oxygenation goal; assess hypercapnia risk rather than giving unlimited oxygen.
CPAP	Pulmonary oedema with significant respiratory distress and a protected airway.	Check blood pressure, work of breathing and tolerance soon after initiation.
Bilevel NIV	Selected patients needing additional ventilatory assistance.	Follow respiratory effort, gas exchange, consciousness and mask tolerance.
Endotracheal intubation	Progressive failure, exhaustion, inability to protect the airway or failed NIV.	Anticipate peri-intubation hypotension; experienced airway and circulatory support are essential.
Positive-pressure caution	RV failure, low preload reserve or shock.	Avoid an uncritical increase in airway pressure; reassess venous return and circulation.

In the 3CPO randomized trial, non-invasive ventilation improved early respiratory and metabolic distress but did not demonstrate a short-term mortality advantage over standard oxygen. CPAP and bilevel treatment should therefore not be portrayed as established competing survival therapies. Their immediate value lies in unloading respiratory effort and improving gas exchange in appropriately selected patients. [240]

Positive intrathoracic pressure can reduce LV afterload but also reduces venous return; its effect is not uniformly favourable. In shock or RV-predominant disease, circulatory deterioration may follow otherwise effective oxygenation. Respiratory and haemodynamic management must be coordinated. Treat acute coronary or mechanical causes simultaneously, and reassess whether pulmonary oedema is resolving rather than judging success from the monitor alone.

7.6. Intravenous loop diuretics: dose and delivery

Intravenous loop diuretics remain the principal initial decongestive treatment for patients admitted with fluid overload. The dose must reach an effective tubular concentration; an insufficient dose may produce little natriuresis despite repeated administration. Oral absorption, prior loop exposure and renal function influence the response. Initial treatment should therefore be followed promptly by measurement of effect rather than left unchanged until the next day. [49]

The 2026 ESC decongestion figure begins with 40 mg IV furosemide in a diuretic-naïve patient or double the daily oral dose in a chronic user. This is a starting framework, not a rule that overrides perfusion, extreme renal impairment or the need to clarify drug equivalence and administration frequency. The complete daily regimen must be written unambiguously; a dose and a total daily dose are not interchangeable. [176]

Table 7.6. Writing and evaluating an initial loop-diuretic prescription

Step	Required information	Reason
Before treatment	Current congestion; blood pressure/perfusion; renal function/electrolytes; actual home drug and daily dose.	Avoid underdosing, duplication and treatment of a misclassified underfilled patient.
Prescription	Drug, route, each dose, frequency, daily total and intended time of reassessment.	Prevents ambiguity when changing from oral to IV administration.
Early evaluation	Urine output and, where available, spot urinary sodium at the specified interval.	Distinguishes an effective dose from apparent treatment without natriuresis.
During treatment	Symptoms, weight, intake/output, orthostasis, renal/electrolyte trends and perfusion.	Ensures fluid removal remains clinically useful and tolerable.
Before oral transition	Improving congestion and an oral regimen capable of maintaining stability.	A lower weight alone does not establish readiness for discharge.

DOSE randomized 308 patients using bolus versus continuous infusion and a lower-dose versus 2.5-times-home-dose strategy. It did not establish superiority for the primary symptom or creatinine endpoints. Higher dosing achieved greater fluid and weight loss with more transient renal-function change. The trial's 2.5-fold comparison is not the same as the current guideline's introductory dosing illustration. [241]

Continuous infusion is not automatically more effective than appropriately repeated boluses. When response is inadequate, first check dose delivery, urine collection, perfusion and ongoing sodium exposure; then adjust the regimen. Very high doses should not be presented as routine targets. The objective is effective, monitored decongestion with an eventual reduction to the lowest maintenance dose that preserves euvolaemia.

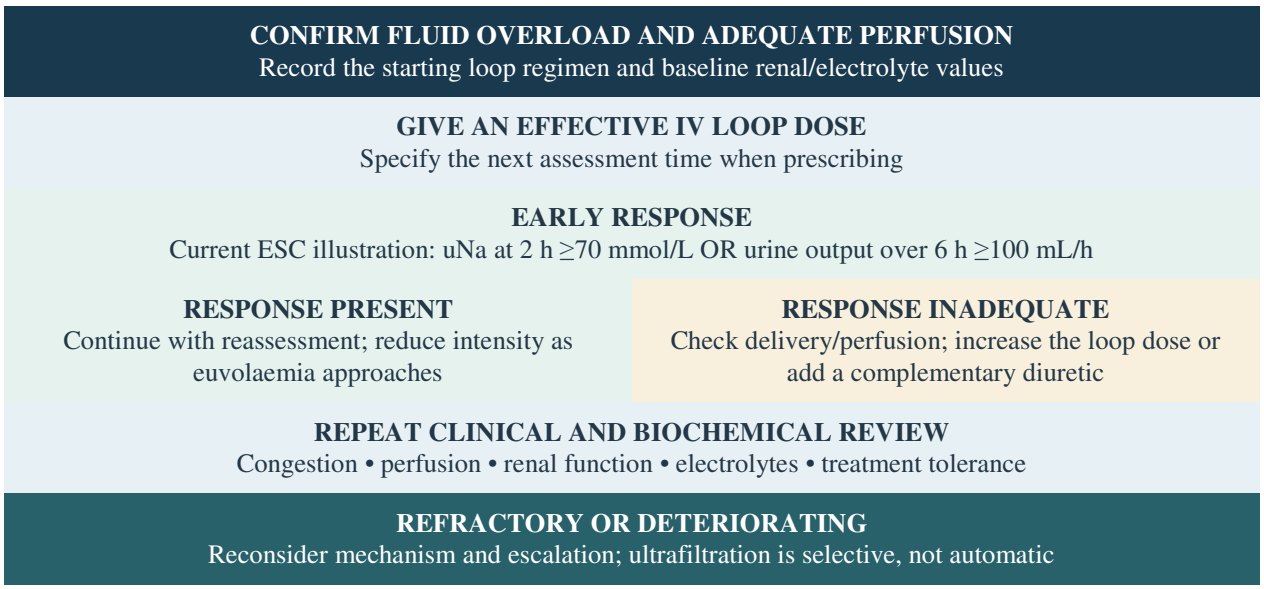
TRANSFORM-HF found no significant all-cause mortality advantage of torsemide over furosemide after discharge. Selection of a maintenance loop should therefore reflect reliable delivery, individual response and access rather than a claim that one agent has proven universal survival superiority. [154]

7.7. Early response assessment and natriuresis-guided therapy

An early urine response provides information that symptom change and daily weight may not yet capture. Spot urinary sodium is a concentration, whereas total sodium excretion also depends on urine volume; the two should not be confused. A sample taken before the diuretic, after an undocumented interval or from old urine cannot be interpreted as the intended post-dose measurement. Discordant sodium and urine-volume findings should prompt review of sampling and the overall clinical response.

PUSH-AHF randomized 310 patients to a sodium-guided strategy or usual care. Twenty-four-hour natriuresis was greater with guidance (409 versus 345 mmol), but the 180-day death/HF-rehospitalization endpoint was not improved. ENACT-HF subsequently reported better diuretic response using a standardized protocol in a nonrandomized, multicentre before–after design. These studies support implementation and physiological response, not a proven survival effect from pursuing a numerical urinary sodium value. [242, 243]

Figure 7.2. A response-guided decongestion cycle



[176]

A protocol requires an operational system: staff who know when samples are due, a reliable urine measurement, laboratory turnaround and authority to respond to the result. Measuring sodium without changing an ineffective treatment is not a sodium-guided strategy. Conversely, escalation should stop when new hypotension, worsening perfusion or major electrolyte disturbance makes the previous goal unsafe.

The response should be interpreted against baseline congestion and the intended daily fluid balance. A low value after substantial decongestion does not automatically require more medication, and a high value does not remove the need to examine a patient who remains breathless or hypoperfused.

7.8. Sequential nephron blockade and combination diuretics

Chronic loop exposure and the sodium-avid state of HF can increase sodium reclamation at other nephron sites. Combining agents with different tubular actions can therefore improve decongestion, but also narrows the safety margin. Before calling a patient “diuretic resistant”, verify adherence, actual dose delivery, intestinal absorption before admission, renal perfusion and avoidable sodium or nephrotoxic exposure.

ADVOR tested acetazolamide 500 mg IV daily with standardized IV loop treatment in 519 patients with volume overload. Successful decongestion within three days occurred in 42.2% versus 30.5% with placebo. The trial did not establish a mortality benefit and excluded patients receiving SGLT2 inhibitors and those with eGFR <20 mL/min/1.73 m². Its short-course protocol is not evidence for indefinite acetazolamide treatment or every contemporary combination. [96]

CLOROTIC randomized 230 patients to HCTZ or placebo alongside IV furosemide. HCTZ improved weight loss and diuretic response, but not patient-reported dyspnoea, and impaired renal function occurred more often. HCTZ dosing was adjusted to renal function in the trial; this should not be converted uncritically into a universal ward prescription. [244]

Table 7.7. Combination treatment: mechanism, evidence and limits

Agent / approach	Potential rationale	Clinical and evidentiary boundary
Acetazolamide	Proximal sodium/bicarbonate blockade; relevant when an insufficient loop response persists.	ADVOR supports short-term decongestion. Review renal function, bicarbonate, acid–base status and electrolytes.
HCTZ / thiazide-type addition	Reduces distal sodium reabsorption and augments loop natriuresis.	CLOROTIC supports response improvement, with renal safety concerns. Monitor sodium and potassium closely.
Metolazone	Alternative distal blockade used in selected resistant cases.	Do not infer identical dosing or trial-level outcome evidence from HCTZ studies.
SGLT2 inhibitor	Disease-modifying therapy with additional effects on congestion after stabilisation.	Not a substitute for adequate IV loop treatment or a rescue therapy for shock.
Multiple-agent escalation	May overcome persistent sodium retention.	More drugs require closer monitoring; stop escalation if the physiological assumptions fail.

[96, 147, 244]

Combination therapy should be linked to a documented response and an exit plan. As congestion resolves, additional short-term agents may no longer be necessary. A fall in blood pressure, progressive oliguria, metabolic acidosis or clinically important electrolyte depletion should trigger reassessment, not merely another increase in loop dose. Evidence for a specific short-term combination cannot be assumed to establish long-term superiority or safety in excluded populations.

7.9. Cardiorenal deterioration, electrolytes and ultrafiltration

A change in creatinine during decongestion must be interpreted, not merely noticed. Effective fluid removal may coexist with a transient functional fall in filtration, whereas persistent congestion with worsening renal indices may reflect treatment failure. Clinical interpretation should integrate blood pressure, perfusion, urine output, congestion trajectory, exposure to nephrotoxins and the rate and magnitude of biochemical change. [245]

In a mechanistic analysis of patients undergoing aggressive diuresis, worsening renal function was not associated with increased tubular-injury biomarkers. This finding challenges the assumption that every creatinine rise represents structural injury; it does not establish that all rises are benign, nor justify ignoring oliguria, severe hypotension or progressive multiorgan dysfunction. [246]

Table 7.8. Interpreting deterioration during decongestion

Observed pattern	Possible interpretation	Appropriate reassessment
Creatinine rises; congestion improves; perfusion maintained	A functional haemodynamic change may contribute.	Review magnitude, trajectory, medications and residual congestion before withdrawing beneficial treatment.
Creatinine rises; congestion persists; urine response poor	Venous congestion, inadequate delivery or low-output physiology.	Reassess the mechanism, diuretic strategy and need for haemodynamic expertise.
Oliguria with hypotension, rising lactate or altered mentation	Potential systemic hypoperfusion or evolving shock.	Urgent escalation; do not manage as isolated diuretic resistance.
Falling Na/K/chloride or major acid–base disturbance	Treatment-related depletion, dilution or another process.	Define the mechanism; adjust contributing agents and use monitored correction.
Refractory hyperkalaemia, acidosis, uraemia or fluid overload	A conventional urgent renal-support indication may exist.	Joint renal/critical-care assessment; do not delay necessary RRT while pursuing a diuretic algorithm.

CARRESS-HF compared ultrafiltration with stepped pharmacological treatment in 188 patients with persistent congestion and worsening renal function. Ultrafiltration produced less favourable renal preservation, similar weight loss and more serious adverse events. The tested fixed-rate approach should not become routine first-line treatment for this syndrome. The result also does not prohibit individualized ultrafiltration or RRT for a clear refractory or urgent indication. [247]

Fluid removal must remain proportionate to circulatory tolerance and plasma refill. Hyponatraemia requires distinction between dilution and depletion; excessive correction can cause neurological injury. Potassium and magnesium disturbances may amplify arrhythmic risk, especially during inotropic treatment. These problems require monitored, locally approved correction protocols rather than rigid electrolyte replacement instructions applied to all patients.

7.10. Vasodilators, adjunctive treatment and avoidable harm

Intravenous vasodilation may rapidly improve pulmonary congestion when high afterload and fluid redistribution dominate, provided arterial pressure and perfusion permit it. Nitrates and nitroprusside differ in their balance of venous and arterial effects, but both can cause clinically important hypotension. In the source framework, SBP >110 mmHg identifies a setting in which IV vasodilators may be considered; blood pressure alone does not establish suitability. Acute valve pathology and preload-dependent physiology require specialist assessment.

GALACTIC did not show that an early, intensive and sustained vasodilator strategy reduced the 180-day composite of death or HF rehospitalization in unselected AHF. This neutral trial does not negate symptom-directed vasodilation in a hypertensive pulmonary-oedema phenotype. It does prevent a plausible haemodynamic mechanism being presented as a general survival intervention. [248]

Table 7.9. Adjuncts: use a defined indication rather than a routine order set

Intervention	Reasonable role	Avoidable error
IV nitrate / nitroprusside	Selected high-afterload congestion with adequate pressure.	Indiscriminate boluses, rapid pressure overshoot or use without close monitoring.
Opiate	Exceptional severe pain or a carefully defined supportive-care indication.	Routine morphine for every episode of pulmonary oedema.
VTE prophylaxis	Hospitalized patients at thrombotic risk without contraindication or existing therapeutic anticoagulation.	Duplicate anticoagulation or failure to reassess bleeding and renal function.
Digoxin / rhythm treatment	Selected AF rate-control problems; urgent cardioversion for instability attributable to AF.	Treating a dangerous rhythm only with escalating diuretics; ignoring renal clearance and interactions.
“Renal-dose” dopamine	No established routine renal-protection role in DHF.	Confusing a possible haemodynamic effect with proven decongestive or renal benefit.

[249]

ROSE-AHF found that low-dose dopamine or low-dose nesiritide did not improve decongestion or renal function in the studied patients with AHF and renal dysfunction. Neither should be added simply to protect the kidney during diuresis. [249]

Routine opiates can worsen respiratory drive, consciousness and haemodynamic stability. Equally, therapeutic anticoagulation for AF or another indication does not imply that another prophylactic anticoagulant should be added. Medication reconciliation should include nonprescription NSAIDs, duplicate vasoactive therapy and recent changes that may have precipitated congestion. The safest adjunctive strategy is one in which every agent has a documented purpose, a monitoring plan and a criterion for withdrawal.

7.11. Cardiogenic shock: recognition, staging and haemodynamics

Cardiogenic shock is primarily a failure of effective tissue perfusion caused by cardiac dysfunction. Hypotension is common but not obligatory: intense vasoconstriction or ongoing vasopressor treatment may maintain measured pressure despite inadequate flow. Cold extremities, altered mentation, oliguria, worsening acidosis and lactate trends therefore matter alongside arterial pressure. A normal or restored pressure cannot be treated as proof of successful resuscitation.

The SCAI classification describes the severity and trajectory of shock, from risk through extremis. It is distinct from chronic HF stages and from INTERMACS profiles. Repeated staging after treatment is more informative than one admission label. Arrest-related neurological uncertainty and the dominant ventricular phenotype should be described separately; one lactate result is not sufficient to assign the entire clinical state. [250]

Table 7.10. SCAI shock stages: a concise clinical interpretation

Stage	Clinical meaning	Operational consequence
A — At risk	Risk of shock without current instability or hypoperfusion.	Identify the cause and monitor for deterioration.
B — Beginning	Haemodynamic instability without clear tissue hypoperfusion.	Increase vigilance; correct reversible causes before progression.
C — Classic	Hypoperfusion requiring intervention beyond simple volume assessment.	Active circulatory support and cause-directed treatment.
D — Deteriorating	Failure to improve or worsening despite the initial intervention.	Reassess diagnosis, haemodynamics, support and escalation promptly.
E — Extremis	Actual or impending circulatory collapse.	Immediate resuscitative intervention and assessment of reversibility.

[250]

Invasive haemodynamic assessment can resolve uncertainty about left- versus right-sided failure, filling pressures and the adequacy of output in selected complex or refractory patients. A pulmonary artery catheter should answer a management question, not merely produce numbers. Measurements require appropriate zeroing, waveform interpretation and consideration of ventilation and valve disease. Their value depends on a team capable of acting on the findings. [251]

Where measured, cardiac index, wedge pressure, right atrial pressure and mixed venous oxygen saturation are integrated with the clinical trajectory. A low cardiac power output or disproportionate right-sided pressure can support a haemodynamic formulation but should not be a stand-alone device trigger. Reassess the level of support, organ function and the intended destination at each escalation; the goal is restoration of a sustainable circulation, not correction of a single displayed variable.

7.12. Vasoactive treatment: supporting pressure and flow

Vasoactive agents buy time for definitive treatment; they do not correct an occluded artery, ruptured valve apparatus or irreversible pump failure. A vasopressor may be necessary when perfusion pressure is inadequate, while an inotrope may be added for insufficient forward flow. More vasoconstriction can raise pressure while worsening afterload. Every dose change should therefore be judged by organ perfusion and overall haemodynamics, not pressure alone.

The dosing examples refer to three product-specific summaries of product characteristics (SmPCs). They are not a universal shock protocol. Formulation, concentration, salt-versus-base expression, renal adjustment, vascular access and local authorisation must be checked before prescription. An infusion rate in millilitres per hour cannot be inferred without the exact prepared concentration. [252–254]

Table 7.11. Selected vasoactive agents: dose examples and clinical limitations

Agent	Dose context	Main constraint
Norepinephrine	Example SmPC initial dose: 0.05–0.15 micrograms/kg/min of noradrenaline base. [252]	The consulted product specifies adults >50 kg; check base/salt strength and access. Titrate to perfusion, not pressure alone.
Dobutamine	Most adult patients respond to 2.5–10 micrograms/kg/min in the consulted SmPC. [253]	Individual titration; tachycardia, arrhythmia and oxygen demand. This is not a universal upper limit.
Milrinone	SmPC maintenance infusion: 0.375–0.75 micrograms/kg/min, with renal dose reduction. [254]	Hypotension, renal accumulation and loading-dose risk. The consulted label does not recommend immediate post-AMI use.
Levosimendan	Specialist, formulation-specific dosing; no universal regimen specified here.	Vasodilation and sustained metabolite effects; no established general superiority in shock.
Epinephrine	Use a resuscitation or shock-specific local protocol rather than a generic HF dose.	Tachycardia and adrenergic lactate generation; not generally the preferred initial cardiogenic-shock agent.

[251–254]

SOAP II, conducted across shock syndromes, found more arrhythmias with dopamine; its cardiogenic-shock subgroup should not be mistaken for an independently powered trial. OPTIMA-CC, a small randomized infarct-related shock study, was stopped early because refractory shock was more frequent with epinephrine than norepinephrine. [255, 256]

DOREMI randomized 192 patients to milrinone or dobutamine and found no significant difference in the primary composite outcome. Drug choice consequently remains conditional on pressure, rhythm, renal function, prior treatment and local expertise rather than an established universal survival advantage. Prolonged or escalating requirements should prompt a new haemodynamic and support assessment, not a presumption that a higher infusion rate is the definitive solution. [257]

7.13. Infarct-related shock and mechanical emergencies

When acute myocardial infarction causes cardiogenic shock, rapid reperfusion and treatment of mechanical complications are central. Haemodynamic stabilisation should facilitate rather than replace coronary diagnosis and reperfusion. Bedside echocardiography may identify a mechanical cause, but a necessary transfer or procedure should not be delayed by a lengthy diagnostic sequence that cannot alter the immediate decision. [60]

CULPRIT-SHOCK studied the extent of initial PCI in infarction with shock and multivessel disease. A culprit-lesion-only strategy, allowing staged treatment, reduced the 30-day composite of death or severe renal failure compared with immediate multivessel PCI. It did not test withholding reperfusion, nor establish a policy of never treating other vessels later. The acute procedure and the subsequent complete revascularisation plan are separate decisions. [258]

Table 7.12. Mechanical and coronary emergencies in a deteriorating patient

Clinical problem	Diagnostic priority	Definitive pathway
Acute infarction with shock	ECG, urgent coronary definition and ventricular assessment.	Culprit reperfusion with coordinated shock care; reassess residual anatomy after stabilisation.
Papillary muscle rupture / acute severe MR	Urgent echo, often expert transoesophageal imaging.	Immediate surgical/interventional assessment; support is a bridge, not valve treatment.
Post-infarction ventricular septal rupture	Identify shunt, ventricular function and haemodynamic consequences.	Urgent multidisciplinary planning; timing and bridging individualized to anatomy and instability.
Free-wall rupture / tamponade	Rapid identification of pericardial blood and haemodynamic collapse.	Emergency surgical and drainage strategy appropriate to the cause.
Acute prosthetic or native valve failure	Mechanism, severity, infection or thrombosis where relevant.	Cause-specific urgent structural or surgical treatment.

[60]

Mechanical support may preserve perfusion during assessment or transfer, but its physiology must fit the lesion. An intervention that increases LV afterload may worsen pulmonary congestion in some settings. The balance among support, ventricular unloading, bleeding, anticoagulation and the urgency of repair cannot be reduced to one device for every mechanical complication. [251]

Fulminant myocarditis is a distinct cause of rapid pump failure and electrical instability. Early discussion with a centre offering advanced HF, biopsy expertise and temporary support is appropriate when deterioration is severe. Disease-specific treatment depends on the mechanism and, in selected cases, tissue diagnosis; the chapter does not recommend indiscriminate immunosuppression for every suspected myocarditis. [13]

The clinical record should identify the precipitating lesion, the immediate definitive intervention, the support being used to reach it and the anticipated next reassessment. This avoids a common conceptual error: equating a more stable monitor with correction of the disease that caused the shock.

7.14. Temporary mechanical circulatory support: selection and evidence

Temporary MCS can restore flow or support oxygen delivery while recovery, definitive repair or a durable strategy is assessed. Its immediate physiological effectiveness is not synonymous with improved survival. Contemporary trials distinguish strategies that have improved clinical outcomes from those that provide physiological support without a demonstrated outcome benefit. Patient selection, timing and the planned exit are inseparable from the device itself.

The distinction between infarct-related and HF-related shock is particularly important. A selected patient with STEMI and predominant LV failure is not the same population as a patient with progressive chronic

biventricular failure, a mechanical complication or uncertain neurological recovery after arrest. Evidence must remain attached to the population that generated it.

Table 7.13. Randomized evidence: circulatory support is not one uniform intervention

Trial / population	Principal finding	Interpretive boundary
IABP-SHOCK II: infarct-related shock	Routine IABP did not reduce 30-day mortality. [259]	Do not infer benefit from haemodynamic plausibility alone.
ECLS-SHOCK: infarct-related shock	Early routine ECLS did not lower 30-day mortality; bleeding and vascular complications increased. [260]	Not a trial of every rescue indication, myocarditis or mechanical complication.
DanGer-Shock: selected STEMI-related shock	Microaxial support reduced 180-day mortality: 45.8% vs 58.5%; HR 0.74. Major safety events increased. [261]	Selection and expertise are essential; not evidence for unselected shock or hypoxic brain injury.
Altshock-2: HF-related shock eligible for advanced therapies	Early IABP did not significantly improve 60-day survival or successful bridge; trial stopped for futility. [262]	Do not extrapolate a positive STEMI microaxial-pump trial to routine IABP in HF shock.

[259–262]

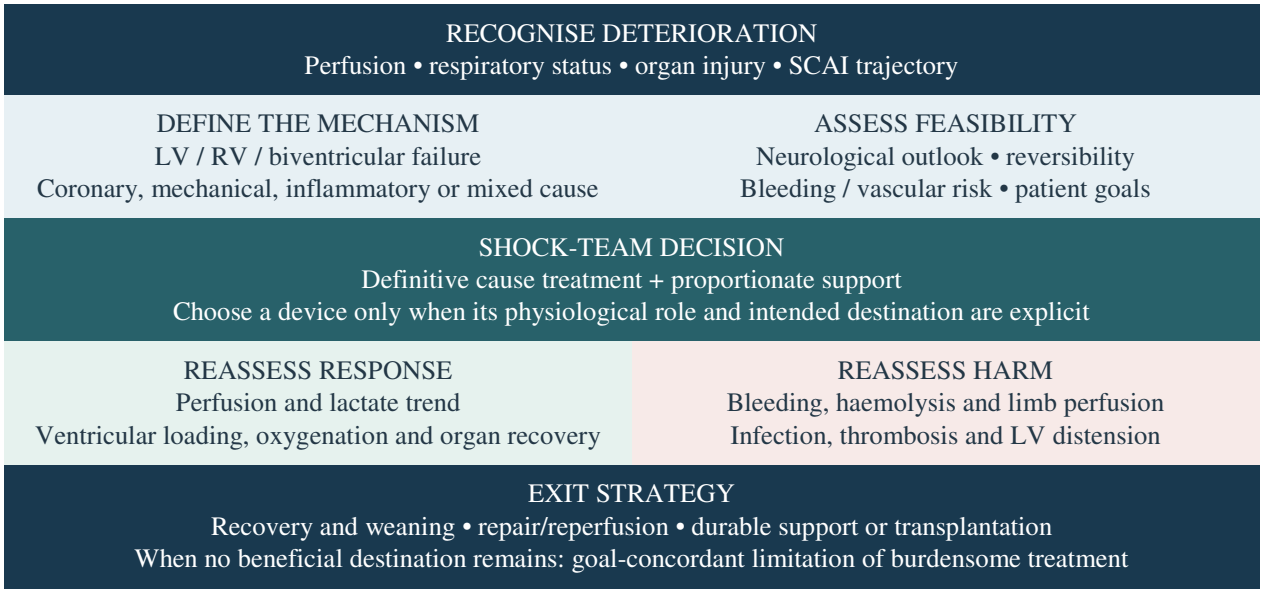
In DanGer-Shock, the survival signal was accompanied by a substantially higher composite safety-event rate, including bleeding, limb ischaemia and other device complications. Benefit and harm must both be represented in consent and selection; neither a device's capacity to generate flow nor one favourable endpoint removes its procedural burden. [261]

The practical conclusion is selective, team-based deployment, not indiscriminate escalation. A meaningful decision records the haemodynamic failure being treated, why the proposed support fits it, which harms are acceptable and what will happen if the heart does not recover. Evidence against routine implantation is compatible with a carefully justified bridge in an individual patient.

Temporary support: matching physiology to a feasible destination

An LV microaxial pump unloads the left ventricle and depends on adequate right-sided delivery and suitable anatomy. VA-ECMO supports systemic circulation and gas exchange but may raise LV afterload, causing distension or pulmonary congestion. A right-sided support strategy addresses a different physiological failure. No device is simply "stronger" without reference to ventricular function, oxygenation, vascular access and the underlying lesion. [251]

Figure 7.3. A shock-team pathway with an explicit exit strategy



[251]

Monitoring must include device function as well as patient physiology. Restored pressure with persistent acidosis, oliguria or rising vasoactive requirements may indicate inadequate support, a wrong diagnosis, a mechanical problem or irreversible injury. Bleeding and haemolysis can themselves impair oxygen delivery and renal function. VA-ECMO-associated LV distension requires assessment for unloading; adding another device carries additional access and bleeding risks.

Weaning is a structured reassessment of native circulatory reserve, not simply a reduction in pump speed. Conversely, escalation should not occur automatically because a device is available. When irreversible neurological injury or multiorgan failure makes meaningful recovery or a durable bridge unattainable, continued support may conflict with the patient's goals. Such decisions require repeated multidisciplinary review and clear communication with the patient or surrogate.

7.15. Right ventricular failure and mixed circulatory states

Acute RV failure requires identification of the cause of excessive afterload, impaired contractility or adverse loading. RV infarction, pulmonary embolism, pulmonary hypertension, postoperative dysfunction and severe valve disease cannot be treated as one mechanism. Systemic venous congestion may coexist with inadequate LV filling because RV dilatation and septal displacement impair ventricular interaction. More intravenous fluid can therefore worsen, rather than restore, effective output.

The immediate priorities are adequate oxygenation, a tolerated rhythm, correction of reversible increases in pulmonary vascular resistance and a carefully judged preload. Hypoxaemia, hypercapnia, acidosis and excessive intrathoracic pressure can amplify RV stress. In a congested patient, cautious decongestion may improve ventricular interaction and renal venous pressure; a fluid challenge should be reserved for convincing underfilling with repeated response assessment.

Table 7.14. Predominant RV or mixed failure: avoid a generic LV-shock pathway

Mechanism	Targeted assessment	Management emphasis
RV infarction	Coronary anatomy, RV function, rhythm and LV filling.	Reperfusion and AV synchrony; cautious, responsive preload assessment rather than routine large-volume loading.
High-risk pulmonary embolism	Haemodynamic instability, RV strain and feasibility of urgent confirmation.	PE-specific reperfusion and anticoagulation decisions, with specialist support when required. [239]
Pulmonary vascular decompensation	Precipitant, RV–pulmonary vascular interaction and baseline therapy.	Specialist pulmonary-hypertension input; do not abruptly substitute conventional LV-HF treatment.
Mixed cardiogenic/distributive state	Infection, vascular tone, cardiac output, congestion and perfusion.	Treat infection and circulatory dysfunction together; avoid reflexive fluid or vasopressor escalation.
Severe TR / biventricular failure	Valve mechanism, venous congestion and both ventricles.	Consider the entire circulation and advanced-care pathway before isolated LV support.

[239, 251]

An inodilator may improve RV performance but can worsen systemic hypotension; a vasopressor may support coronary perfusion while increasing systemic vascular resistance. The combination must be selected from actual haemodynamics rather than an assumption that any RV failure requires the same drug. Persistent instability should prompt specialist haemodynamic assessment and discussion of support appropriate to right-sided or biventricular failure. [251]

Mixed shock is a diagnosis to establish, not a label that explains away uncertainty. Repeated examination, echocardiography, laboratory trends and, in selected cases, invasive measurements help distinguish ongoing low output from vasoplegia or a competing process. The absence of pulmonary oedema does not imply preserved circulation in severe RV failure. Equally, a high right atrial pressure does not establish a safe fixed volume-removal target.

7.16. Disease-modifying treatment after initial stabilisation

Hospitalization should be used to establish a durable treatment strategy once the immediate respiratory and circulatory emergency has been controlled. Congestion relief and foundational medical therapy address different aspects of the illness. Oral disease-modifying treatment is not a substitute for resuscitation, but waiting for a remote outpatient visit may leave a vulnerable patient undertreated. Continuation, reintroduction and early optimization of indicated treatment should be considered once the patient is clinically stable.

Initial stabilisation means that the patient can tolerate the proposed intervention; it does not require every measurement to be normal. Assess blood pressure and perfusion, vasoactive requirements, oral intake, renal function, potassium and the direction of clinical change. Eligibility thresholds from one trial are useful context, not automatic rules for all drugs or all patients. Drug-specific and product-specific restrictions remain essential.

Table 7.15. A phenotype- and safety-based inpatient treatment review

Treatment domain	Clinical opportunity	Reason to defer, adjust or reassess
SGLT2 inhibitor	Consider in-hospital initiation after initial stabilisation across the appropriate HF spectrum.	Shock, ketoacidosis risk, major fasting/critical illness or product-specific renal restrictions require assessment. [147, 148]
ARNI / ACE inhibitor / ARB	Introduce or restore an appropriate RAAS-directed agent in eligible systolic HF.	Symptomatic hypotension, severe evolving renal dysfunction or hyperkalaemia; observe ACE inhibitor-to-ARNI washout. [132]
Evidence-based beta-blocker	Preserve when tolerated; initiate or retitrate when haemodynamically stable.	Profound shock, severe bradycardia or major instability may require temporary modification.
MRA	Correct an omitted indication when potassium and renal function permit.	Do not initiate or titrate without a laboratory-monitoring plan. [146]
Maintenance diuretic	Establish an oral regimen that sustains the achieved congestion status.	Avoid both residual congestion and excessive volume depletion; reassess after other therapies change.

Medication withdrawal should be a deliberate, documented decision. A temporary contraindication during shock does not necessarily remain after recovery. Before discharge, record what has been withheld, why, what must improve and who will reconsider it. This is particularly important when renal changes or low blood pressure have led to the discontinuation of several beneficial classes at once.

The four-class framework developed for chronic HFrEF must not be applied indiscriminately to every patient with HFpEF or a disease-specific cardiomyopathy. Conversely, in a patient with improved EF, present-day EF alone does not erase the historical indication for treatment. This chapter concentrates on the transition from instability to appropriate long-term care, not on replacing the phenotype-specific chapters.

Hospital initiation trials: benefit, neutrality and applicability

The evidence for initiating treatment during or immediately after hospitalization is heterogeneous. Trials differ in stabilization requirements, ejection-fraction ranges, diabetes status, treatment timing and outcome hierarchy. A positive hierarchical composite may reflect health-status improvement as well as clinical events; a biomarker endpoint does not establish an independent mortality benefit. These distinctions are necessary for an academically accurate treatment narrative.

Table 7.16. Selected trials informing treatment around a hospitalization

Trial	Population and intervention	What the result supports — and does not
EMPULSE	530 stabilized patients; empagliflozin 10 mg daily, irrespective of EF or diabetes.	90-day hierarchical clinical benefit, win ratio 1.36. Not a 36% mortality reduction. [147]
DAPA ACT HF–TIMI 68	2401 hospitalized HF patients; dapagliflozin after stabilisation.	Two-month CV death/worsening HF: 10.9% vs 12.7%; HR 0.86, 95% CI 0.68–1.08, P=0.20. Primary result neutral. [148]
DICTATE-AHF	Early dapagliflozin during IV-diuretic treatment.	Primary diuretic-efficiency endpoint not significantly improved; secondary findings inform feasibility, not proven survival benefit. [263]
SOLOIST-WHF	Type 2 diabetes and recent worsening HF; sotagliflozin before or shortly after discharge.	Fewer total CV deaths and HF events in the composite. Do not present CV mortality alone as independently proven. [264]
PIONEER-HF	Stabilized hospitalized HFrEF; sacubitril/valsartan versus enalapril.	Greater NT-proBNP reduction; clinical-event analyses are not equivalent to a mortality-powered primary trial. [132]

EMPULSE provides evidence for a clinically useful hospital-start strategy in a stabilized population. DAPA ACT HF–TIMI 68 should nevertheless be reported as neutral for its own primary endpoint, even when considered alongside broader SGLT2-inhibitor evidence. A pooled analysis and an individual trial answer related but distinct questions. The current recommendation is not a licence to convert every point estimate below one into a positive trial. [147, 148]

Clinical implementation should connect the first dose with an achievable continuation plan. The patient needs to understand the purpose of treatment, warning symptoms and circumstances requiring medical advice or temporary interruption. The discharge prescription, laboratory appointments and access to medication should agree. Starting an appropriate agent without these arrangements leaves the transition incomplete.

7.17. Discharge readiness and the first six weeks

Discharge is a transition in the treatment setting, not proof that the pathophysiological episode has ended. Residual congestion, unstable renal function, treatment gaps and inadequate follow-up are major vulnerabilities. Symptom improvement should be corroborated by a multidimensional assessment of congestion, perfusion, functional capacity and tolerance of the intended oral regimen. A lower weight alone does not prove euvolaemia. [40]

The decision should also include the patient's capacity to implement care. Cognitive impairment, reduced mobility, treatment affordability and lack of support can turn a physiologically plausible discharge plan into an unsafe one. Conversely, a reliable specialist outpatient pathway may permit earlier reassessment and treatment adjustment in selected patients. These are individual decisions; there is no single biomarker concentration that certifies readiness.

Table 7.17. A structured discharge-readiness review

Domain	Questions that require a documented answer
Congestion and perfusion	Are orthopnoea, oedema, jugular venous pressure and pulmonary findings improving? Is there unresolved hypoperfusion?
Oral treatment	Has the maintenance diuretic plan been tested where feasible? Which indicated therapies have been started, withheld or scheduled for reconsideration?
Laboratory and rhythm safety	Are renal function and electrolytes sufficiently stable? Is the rhythm tolerated, and is an arrhythmic or device issue unresolved?
Precipitating cause	Has the trigger been treated or a definitive procedure arranged? Are outstanding investigations assigned to a responsible clinician?
Function and support	Can the patient obtain and take medication, mobilize safely and communicate deterioration? Is caregiver involvement agreed?
Transition and access	Is early review booked, with required tests and contact details? Does the receiving team have the actual inpatient course and treatment rationale?

The written handover should describe the presumed cause, current phenotype, residual problems, discharge weight and relevant trends, rather than reproduce a medication list without explanation. Include changes in renal function and the reason for treatment modification. For each unresolved issue, specify the next action and the clinician or team responsible. [40]

In COACH, a risk-guided strategy linked to rapid outpatient follow-up improved short-term outcomes compared with usual care. The intervention was a care pathway, not a single risk score used in isolation. Its practical lesson is to pair risk assessment with the resources needed to act on it. Discharging a high-risk patient without an operational follow-up pathway does not reproduce the tested strategy. [238]

The first six weeks: rapid optimization with active surveillance

STRONG-HF tested a structured high-intensity approach after an acute HF admission: rapid optimization of guideline-directed treatment with repeated visits, examination and laboratory surveillance. At 180 days, HF readmission or all-cause death occurred in 15.2% of the high-intensity group and 23.3% with usual care. The benefit belongs to an integrated titration-and-follow-up strategy, not to unsupervised rapid dose escalation. [146]

The trial's principal dose-optimization framework concerned RAAS-directed therapy, beta-blockers and MRAs. It should not be retold as a trial in which every patient received a fully contemporary four-class regimen from the first day. A present-day pathway may incorporate SGLT2 inhibitors, but the added component and its evidence must be identified separately. The 2023 focused update already incorporated intensive early follow-up, and ESC 2026 retains an explicitly early implementation approach. [64, 146]

Table 7.18. An implementable follow-up sequence after discharge

Time point	Clinical work	Safety and continuity
Before discharge	Agree the treatment trajectory, baseline laboratory values and residual congestion assessment.	Book the first review and tests; communicate withheld therapies and reasons.
Early review, often within 1–2 weeks	Reassess symptoms, weight, congestion, pressure, rhythm and adherence.	Check renal function and electrolytes; review tolerability before further titration.
Repeated visits during weeks 1–6	Adjust disease-modifying therapy and diuretics according to the evolving clinical profile.	Use closer follow-up for instability; do not force target doses despite adverse physiology.
After early optimization	Review function, rehabilitation needs, unresolved aetiology and device/advanced-care questions.	Provide long-term ownership and an escalation pathway rather than ending support at week six.

[146]

Surveillance should respond to symptoms as well as scheduled dates. Dizziness, worsening breathlessness, reduced urine output, palpitations or inability to maintain intake may require earlier contact. Laboratory testing without a system to review and act on results is not adequate follow-up. The responsibility for a dose change and its subsequent safety check should be unambiguous.

A flexible plan may prioritise tolerable doses across appropriate classes rather than maximize one agent while leaving others absent. Yet rapid implementation should not conceal uncertainty about diagnosis, persistent hypoperfusion or access to medication. Failure to tolerate multiple indicated therapies, recurrent congestion or repeated admission should prompt reassessment for advanced disease rather than endless repetition of the same discharge cycle.

7.18. Comorbidity, rehabilitation and supportive care

Treatment of decompensation should preserve the patient's ability to live and function after the admission. Iron deficiency, malnutrition, frailty, immobility, sleep disturbance and psychological distress can limit recovery even when congestion improves. Their recognition belongs within the hospitalization-to-home pathway, but interventions should be matched to evidence and clinical stability rather than added to an indiscriminate checklist.

AFFIRM-AHF supported a reduction in HF hospitalizations with IV ferric carboxymaltose after a stabilized admission in iron-deficient patients; its primary composite narrowly missed conventional significance and CV mortality was not reduced independently. FAIR-HF2 subsequently failed to meet its prespecified multiplicity-adjusted primary efficacy criteria. Iron treatment should not therefore be presented as an established mortality intervention. [160, 265]

Table 7.19. Recovery-focused care beyond the main drug and device pathway

Issue	Appropriate clinical emphasis	Evidence boundary
Iron deficiency	Check ferritin and transferrin saturation, investigate cause and select treatment for an appropriate phenotype.	Distinguish symptom/HF-event evidence from an unproven mortality claim. [160, 265]
Frailty and physical function	Assess mobility, strength, balance and endurance; introduce individualized rehabilitation after stabilisation.	REHAB-HF improved physical function; it did not establish a mortality benefit. [266]
Pleural effusion	Treat HF congestion; investigate atypical effusions or persistent severe symptoms.	TAP-IT did not support routine upfront drainage for every qualifying HF effusion. [267]
Nutrition and self-care	Address poor intake, medication access, health literacy and caregiver needs.	Avoid rigid restriction that worsens nutrition or an unsupported self-adjustment plan.
Palliative/supportive needs	Relieve distress, clarify goals and discuss burdens of invasive treatment where relevant.	Supportive care can accompany active HF treatment; it is not synonymous with abandoning care.

REHAB-HF used a multidomain rehabilitation intervention in older hospitalized patients and improved physical function. Its relevance is not that exercise should begin at any intensity during instability, but that post-hospital disability is a modifiable treatment target. Programme content and monitoring should reflect the patient's functional reserve. [266]

TAP-IT found no advantage of routine upfront thoracentesis for its primary 90-day days-alive-out-of-hospital outcome. Very large effusions were excluded, and the result does not remove indications for diagnostic aspiration or individualized drainage of refractory symptomatic effusions. [267]

Supportive discussions should address what recovery means to the patient, the likely treatment burden and acceptable alternatives if further deterioration occurs. Such conversations are most useful before another crisis makes communication and shared decision-making difficult.

7.19. Clinical cases

Case 1 — Abrupt pulmonary oedema with severe hypertension

A 72-year-old woman develops marked breathlessness over two hours. SBP is 195 mmHg, respiratory rate 34/min and SpO_2 84%. She is distressed but alert, with diffuse bilateral B-lines and no major peripheral oedema. The immediate problem is respiratory failure with probable high-afterload pulmonary congestion, not a requirement to wait for a large weight gain or a natriuretic-peptide result.

Monitoring, oxygenation and early positive-pressure support are considered alongside ECG and urgent echocardiographic assessment. Afterload reduction requires careful pressure surveillance; a loop diuretic is selected according to congestion and previous exposure. Acute coronary disease, severe valve regurgitation and arrhythmia are actively sought. A rapid improvement in breathing does not remove the need to establish the cause and a long-term plan. The case illustrates redistribution-dominant congestion and parallel rather than sequential care.

Case 2 — Persistent congestion with a creatinine rise

A 68-year-old man with chronic systolic HF and CKD is admitted with oedema, orthopnoea and elevated jugular venous pressure. After an initial IV loop dose, uNa at two hours is 35 mmol/L and urine output averages 60 mL/h. SBP is 118 mmHg, mentation is normal and there are no signs of peripheral hypoperfusion. The poor early response prompts review of dose, delivery and congestion rather than waiting passively until the next day.

Treatment is intensified with monitored reassessment; combination diuresis is considered if appropriate. A subsequent modest creatinine rise is interpreted with the entire trajectory. Improving congestion with maintained perfusion is different from oliguria with hypotension or rising lactate. The case does not imply that any creatinine rise is harmless or that ultrafiltration is the automatic next step. Before discharge, the oral regimen, indicated disease-modifying therapies and laboratory follow-up must be coherent. [96, 242, 246, 247]

Case 3 — STEMI, shock and a selective support decision

A 59-year-old man with anterior STEMI has SBP 78 mmHg, cool extremities, oliguria and increasing lactate. Echocardiography shows severe LV dysfunction without a mechanical complication. He has no out-of-hospital arrest or evidence of hypoxic neurological injury. Urgent culprit reperfusion proceeds with vasoactive support and shock-team involvement; support decisions must not replace treatment of the infarction.

A microaxial pump may be considered in a suitable patient after assessment of anatomy, vascular and bleeding risk, reversibility and expertise. DanGer-Shock informs this selected scenario; ECLS-SHOCK does not support routine VA-ECMO for all infarct-related shock. The team documents the intended bridge, reassessment and exit strategy. Neither trial allows a guarantee of survival, and the presence of profound irreversible organ injury would change the balance. [258, 260, 261]

8. Advanced Heart Failure, Mechanical Support and Transplantation

Advanced heart failure is not simply a lower ejection fraction or a higher diuretic dose. It is a narrowing therapeutic window in which disease trajectory, reversibility of organ dysfunction and the patient's goals must be assessed together.

8.1. Recognizing advanced heart failure

Advanced HF is persistent severe disease despite appropriate medical, device and surgical treatment, rather than as a diagnosis established by LVEF alone. The syndrome may occur with severe LV systolic dysfunction, isolated RV failure, restrictive physiology, complex congenital disease or a non-correctable valve lesion. End-organ injury strengthens the impression of severity but is not required before referral. [20]

The 2026 ESC definition retains four complementary domains. The distinction between repeated congestion and a single low-output episode requiring vasoactive support is clinically important: the latter can reveal a dangerous trajectory without a long history of recurrent admissions. Functional limitation must be attributable substantially to cardiac disease, after considering lung disease, frailty, anaemia and musculoskeletal disability. [1, 176]

Table 8.1. Operational domains of advanced HF: a clinical framework

Domain	Findings supporting the definition
Severe symptoms	Persistent NYHA III–IV limitation despite appropriately implemented and tolerated treatment.
Severe cardiac dysfunction	LVEF ≤30%, severe isolated RV failure, non-correctable structural disease, or severe diastolic/structural abnormalities with high natriuretic peptides in a compatible phenotype.
Clinical instability	At least two unplanned visits/admissions for congestion or malignant arrhythmia within 12 months, or at least one low-output episode requiring inotropic/vasoactive support.
Marked functional impairment	Inability to exercise; 6-minute walk distance <300 m; or cardiac limitation with pVO□ <12–14 mL/kg/min (12 on beta-blockade) or <50% predicted.

[1, 20].

Definitions serve different purposes. A population study estimates disease burden, a referral registry enriches for high-risk patients, and a transplant programme selects people expected to benefit from a scarce resource. Their event rates are not interchangeable. The population-based analysis by Dunlay and colleagues and the HELP-HF registry both demonstrate the seriousness of advanced disease, but neither supplies an individual survival clock. [21, 268]

The practical diagnosis should state the dominant mechanism, trajectory and remaining therapeutic options: for example, "progressive low-output biventricular HF with worsening hepatic congestion despite treatment," rather than simply "EF 20%." This formulation makes disease trajectory and potentially reversible mechanisms explicit.

8.2. Early referral and integrated care networks

Referral is not synonymous with listing or device implantation. Its immediate value is to preserve choices while the patient still has enough neurological, renal, hepatic and functional reserve for a meaningful assessment. Waiting for refractory shock, cachexia or fixed pulmonary vascular disease may eliminate an option that was feasible earlier. Contemporary referral guidance therefore addresses both clinical recognition and structural barriers to access. [22]

The “I NEED HELP” framework is a screening aid, not a points-based transplant eligibility score. One concerning feature can justify discussion with an advanced-HF team, particularly when it is new, progressive or clustered with others. The HELP-HF analyses support the prognostic relevance of these warning features, but referral should not depend on reaching an arbitrary total. [24]

Table 8.2. Referral signals and the question they should trigger

Signal	Action-oriented interpretation
Inotropes or hypoperfusion	Is temporary haemodynamic support concealing dependence or loss of organ reserve?
NYHA III–IV symptoms / high peptides	Are symptoms persistent after decongestion and appropriate aetiology-directed treatment?
End-organ deterioration	Is kidney or liver dysfunction reversible with improved perfusion and lower venous pressure?
Very low LVEF / poor RV function	Is advanced assessment needed before further instability? EF alone is insufficient.
ICD therapies / repeated admissions	Is electrical or haemodynamic instability becoming recurrent despite treatment?
Escalating diuretics / low pressure	Is congestion resistant, or is tolerance of disease-modifying treatment narrowing?
Treatment intolerance	Has hypotension, renal dysfunction or another barrier prevented sustainable therapy?

[22, 24]

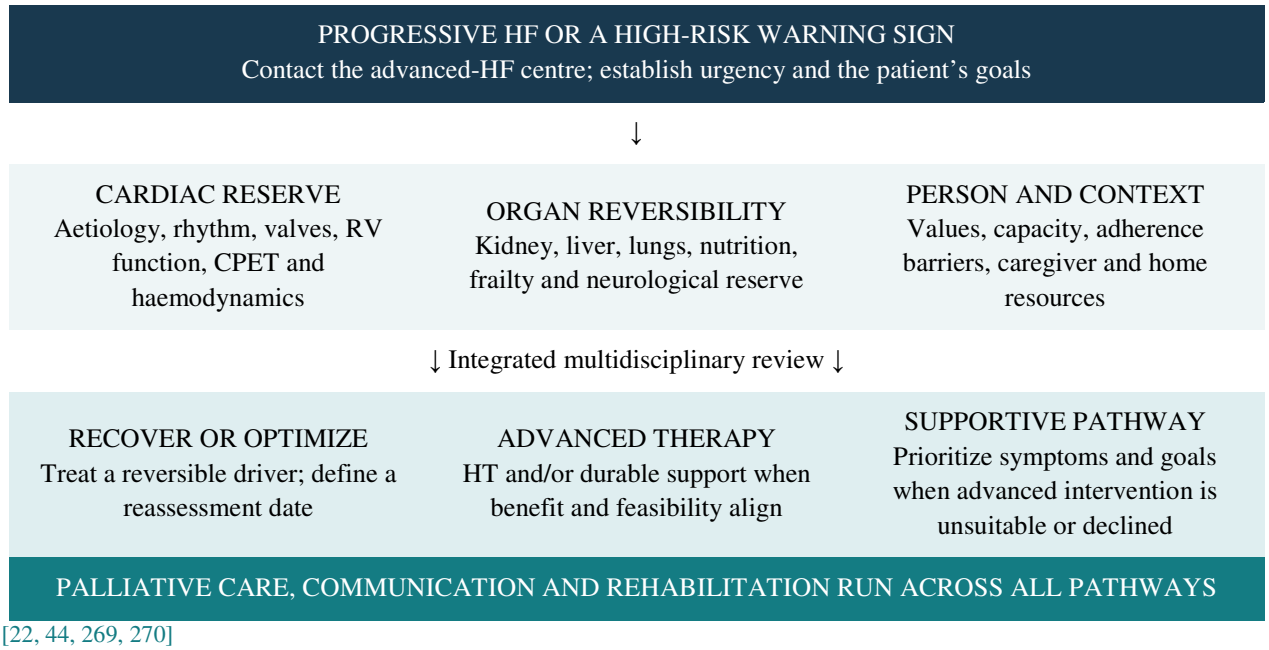
A hub-and-spoke network should make escalation operational: a named contact, a minimum referral dataset, a route for urgent transfer and a plan for shared follow-up. The referring team continues decongestion and treatment of precipitating factors while the hub determines the urgency and scope of investigation. Transfer should not wait for completion of every outpatient test when deterioration is active. [269]

The 2026 ESC guideline recommends early specialist consultation for potentially eligible and interested patients at risk of, or with, advanced HF when no absolute contraindication is established (Class I, level A). This is a recommendation to evaluate promptly—not a guarantee of transplantation or LVAD benefit. [1]

Referral assessment: parallel work, not serial delay

A referral can fail even when every individual investigation is appropriate if the investigations occur too slowly or without an agreed decision point. A useful programme separates immediately reversible problems from longer-term eligibility questions and conducts the cardiac, extracardiac and psychosocial assessments in parallel. The model below organizes these parallel assessments around a common multidisciplinary decision point. [22]

Figure 8.1. Early referral and parallel assessment



[22, 44, 269, 270]

The referral dossier should summarize trajectory rather than reproduce an entire electronic record: admissions and inotropic exposure, tolerated therapies and reasons for dose reduction, current congestion, recent echocardiography, laboratory trends, major comorbidities and the patient's understanding of the proposed assessment. Missing CPET or invasive data should be noted explicitly, not replaced by estimated values.

Shared care remains bidirectional. After stabilization or advanced intervention, parts of surveillance may return to the local team, but responsibility for anticoagulation, device alarms, immunosuppression and urgent escalation must remain explicit. A technically successful implant cannot compensate for an unsafe transition home. [271, 272]

Equity is a clinical responsibility: transport, medication access, language, caregiving and health-literacy barriers should prompt support and remediation. They should not be silently converted into biological contraindications. [270]

8.3. INTERMACS profiles and clinical trajectory

INTERMACS describes the clinical state of advanced-HF patients being considered for mechanical support. It complements, but does not replace, the definition of advanced HF, transplant assessment or shock staging. A profile is a time-dependent description: the same person may move from recurrent ambulatory congestion to inotrope dependence within days. [273]

Table 8.3. INTERMACS profiles: clinical meaning and practical urgency

Profile	Clinical state	Planning implication
1	Critical shock with rapidly progressive hypoperfusion.	Immediate stabilization and an exit-strategy discussion; durable implantation in unassessed collapse is not automatic.
2	Progressive decline despite inotropes.	Urgent advanced-team reassessment, organ rescue and consideration of temporary or durable support.
3	Stable only with continuous inotropic or temporary support.	Dependence remains high risk; plan a definitive strategy rather than interpreting stability as recovery.
4	Symptoms at rest or with daily activities, often recurrent congestion.	Evaluate durable options before further organ dysfunction; assess correctable causes and treatment feasibility.
5	Comfort at rest but predominantly housebound.	Measure objective cardiac limitation, nutrition and organ reserve; apparent resting comfort can be misleading.
6	Exertion-limited ambulatory patient.	Clarify cardiac versus non-cardiac limitation and follow the trajectory closely.
7	Advanced NYHA III symptoms without recent major instability.	Continue optimization and surveillance; advanced intervention depends on the total risk–benefit assessment.

[271, 273]

Modifiers—temporary support, recurrent ventricular arrhythmias and frequent decompensations—add information that a single profile can miss. Document the actual events and treatment requirements rather than only the label. Likewise, a patient on temporary support needs a description of ventricular involvement, gas-exchange failure, vasoactive exposure and neurological status. [269, 273]

SCAI shock stages address the presence and progression of shock, whereas INTERMACS emphasizes advanced-HF severity and support dependence. They overlap in unstable patients but are not one-to-one equivalents. A rising lactate, deteriorating perfusion or escalating support should trigger reassessment even if the recorded INTERMACS profile has not yet been changed. [250]

8.4. Prognostic assessment and exercise testing

Prognostic assessment asks three different questions: how likely deterioration is without advanced intervention, whether the patient can survive and rehabilitate after it, and what life with the intervention is expected to be like. CPET provides an integrated measure of cardiovascular, pulmonary and skeletal-muscle function, while risk models summarize selected population-level predictors. Neither should replace the multidisciplinary decision. [43, 274]

In a clinically stable patient, a technically adequate CPET helps distinguish severe circulatory limitation from deconditioning or other causes of poor exercise tolerance. Interpretation includes achieved effort, pVO_2, percentage predicted, ventilatory efficiency, blood pressure, rhythm and the reason for stopping. A low weight-indexed pVO_2 in obesity requires particular caution because adipose mass increases the denominator. [1, 23]

Table 8.4. A structured interpretation of prognostic and functional data

Measure	What it adds	Important limitation
pVO□	Objective functional reserve and longitudinal change.	Thresholds near 12–14 mL/kg/min depend on beta-blockade, effort, age, sex and clinical context.
% predicted pVO□	Context for age- and sex-related expected capacity.	Prediction equations and testing modality matter; <50% is a warning, not an isolated listing order.
VE/VCO□ relationship	Ventilatory inefficiency and pulmonary-circulatory burden.	Interpret alongside lung disease, oscillatory ventilation and test quality.
6-minute walk	Practical submaximal function; useful when maximal testing is unsuitable.	Frailty, arthritis, neurological disease and learning effects may dominate.
Risk model / trajectory	Structured survival discussion plus admissions, organ trends and treatment intolerance.	Calibration may be poor in shock, new therapies or populations unlike the derivation cohort.

[1, 43, 274]

A favourable score must not cancel repeated admissions or progressive organ injury. Conversely, a poor functional result caused mainly by a remediable non-cardiac problem should prompt treatment and reassessment rather than an irreversible exclusion. Repeat measurements are most useful when the clinical condition and testing method are sufficiently comparable.

A submaximal test does not yield the same information as a well-performed maximal CPET. Interpret the respiratory exchange ratio, symptoms and exercise termination before comparing a pVO_2 value with a threshold. Severe chronotropic limitation, anaemia or an early non-cardiac stopping reason can alter the apparent result. A change between studies is most credible when measurement quality, medication state and volume status are comparable. [23, 274]

The clinician should communicate ranges and uncertainty, and distinguish risk on current therapy from anticipated perioperative risk. “High risk” is not equivalent to “benefit from any available device”: advanced interventions can fail to improve a prognosis dominated by irreversible extracardiac disease. [43, 271]

8.5. Haemodynamics and reversibility of organ dysfunction

Right-heart catheterization informs advanced-therapy assessment by characterizing filling pressures, cardiac output and pulmonary vascular load. Measurements are only as reliable as acquisition and interpretation: transducer position, respiratory phase, a credible wedge tracing, oxygen consumption assumptions and the presence of shunts or significant regurgitation can materially affect the result. Record whether measurements were obtained during congestion, inotropic therapy or mechanical support. [271]

RAP and PAWP describe congestion in different circulations; CI describes indexed forward flow. Pulmonary vascular resistance is calculated as (mean pulmonary artery pressure − PAWP)/CO, expressed in WU. PAPi is (systolic − diastolic pulmonary artery pressure)/RAP. These derived variables are not substitutes for the source waveforms or the whole clinical picture. [275, 276]

Table 8.5. Haemodynamic questions that change advanced-therapy planning

Finding	Clinical question / response
High filling pressures with preserved flow	Can decongestion restore function and clarify the true degree of organ impairment?
Low CI with hypoperfusion	Is inotropic or temporary mechanical support required while a definitive strategy is evaluated?
High RAP, low PAPi, RV dysfunction	Is isolated LV support feasible, or would it expose inadequate RV reserve? Interpret after volume optimization.
Elevated PVR	Is the pulmonary vascular burden reversible with lower left-sided pressure and improved flow? Persistent elevation increases donor-RV risk.
Improvement after treatment	Does a repeat study show a durable response, not merely an acceptable pressure obtained at the cost of systemic hypotension?

[271, 275, 276], [1]

The key distinction is between dysfunction and irreversibility. Venous congestion, low perfusion, diuretic exposure and intrinsic kidney disease can all contribute to a low eGFR. Similarly, congestive cholestasis differs from established cirrhosis with clinically important portal hypertension. Assessment should integrate serial laboratory results, imaging, prior history and organ-specialist advice. [277]

The equations also explain why derived indices are condition dependent. PVR may fall when measured flow increases even if the transpulmonary pressure difference changes little, while PAPi changes with both pulsatile pulmonary pressure and RAP. An apparently improved number should therefore be checked against its components, systemic pressure and the patient's perfusion. Venous congestion can remain clinically important even when cardiac output appears acceptable. [275, 276]

Pulmonary vasodilator testing or reassessment after unloading may clarify transplant feasibility, but no single PVR result is an absolute verdict. The ability to lower resistance while maintaining systemic pressure, the chronicity of pulmonary vascular disease and the overall recipient risk matter. Evaluation of combined heart–kidney or heart–liver transplantation is considered separately in Section 8.14. [23, 277]

8.6. Medical therapy while advanced options are evaluated

Advanced assessment should proceed alongside treatment, not after every pharmacological possibility has been exhausted. Continue disease-modifying therapy at tolerated doses while correcting congestion, infection, arrhythmia, ischaemia and other reversible drivers. Treatment intolerance has particular prognostic and practical importance: falling blood pressure or worsening renal function may indicate a narrowing haemodynamic reserve rather than a simple failure to titrate medication. [9]

The LIFE trial illustrates the limits of extrapolating from ambulatory HFrEF trials to advanced disease. Sacubitril/valsartan did not significantly improve the trial's NT-proBNP primary outcome compared with valsartan in the studied advanced-HF population, and tolerability was important. This result does not erase the established benefits of ARNI in broader eligible HFrEF; it argues against assuming identical tolerance or efficacy in every end-stage presentation. [278]

Table 8.6. Preserving benefit while recognizing haemodynamic intolerance

Problem	Reasoned response
Congestion with stable perfusion	Review adherence and absorption; individualize loop-diuretic delivery and sequential blockade; assess response rather than dose alone.
Modest creatinine rise during decongestion	Interpret with perfusion, urine output, congestion and the overall trend; do not equate every rise with structural kidney injury.
Symptomatic hypotension	Identify over-diuresis, infection, bleeding or other causes; review non-essential vasodilators and the balance of prognostic treatment.
Persistent organ hypoperfusion	Reassess urgency, rate-slowing treatment and need for support. Selected beta-blocker/ivabradine down-titration is not a rule for stable patients.
Apparent treatment resistance	Reconsider aetiology, significant valve disease, electrical dyssynchrony, RV failure and adherence barriers; define a reassessment deadline.

[1, 278]

In ESC 2026, selected reduction or withdrawal of beta-blocker or ivabradine treatment can be considered when organ hypoperfusion persists despite initial measures (IIa C). This narrow scenario should not be translated into routine withdrawal after a low LVEF measurement or during uncomplicated congestion. [1]

Repeatedly adjusting a regimen without revisiting advanced options can create false reassurance. A written plan should identify what improvement would justify continued medical management, what deterioration would trigger transfer and when the team will reassess transplant or mechanical-support eligibility. [22]

8.7. Inotropes, renal support and therapeutic intent

Inotropic treatment can improve forward flow and perfusion, but physiological improvement is not synonymous with longer survival. Its purpose should be named at initiation: rescue from hypoperfusion, a bridge to decision or advanced therapy, or symptom-focused support when definitive intervention is unsuitable or declined. Repeated failure to wean indicates dependence and should prompt reconsideration of the treatment destination. [269]

Table 8.7. Supportive therapies must have an explicit goal and reassessment point

Strategy	Potential role	Principal limitations
Continuous inotrope	Low-output organ hypoperfusion while evaluating HT, durable MCS or reversibility.	Arrhythmia, hypotension or ischaemia; line infection; drug-specific renal handling and tachyphylaxis.
Ambulatory inotrope	Selected bridge or symptom-focused programme with reliable infrastructure.	Infusion and access burden; caregiver training; repeated review of benefit and harms.
Intermittent levosimendan	Selected programme based on limited trial and service experience.	Small-study signals do not establish routine mortality benefit or a universal schedule.
Kidney replacement therapy	Conventional renal indications or severe refractory volume overload with kidney failure.	Haemodynamic tolerance, access and whether renal injury is reversible influence the larger plan.
Ultrafiltration	Selected congestion unresponsive to an optimized diuretic strategy.	Not a routine superior substitute for stepped pharmacological treatment.

[247, 269, 279]

LION-HEART investigated intermittent outpatient levosimendan in a small randomized programme and supports further interest in selected patients. Biomarker and hospitalization findings should not be presented as proof of a mortality benefit, nor generalized to every advanced-HF phenotype or infusion regimen. [279]

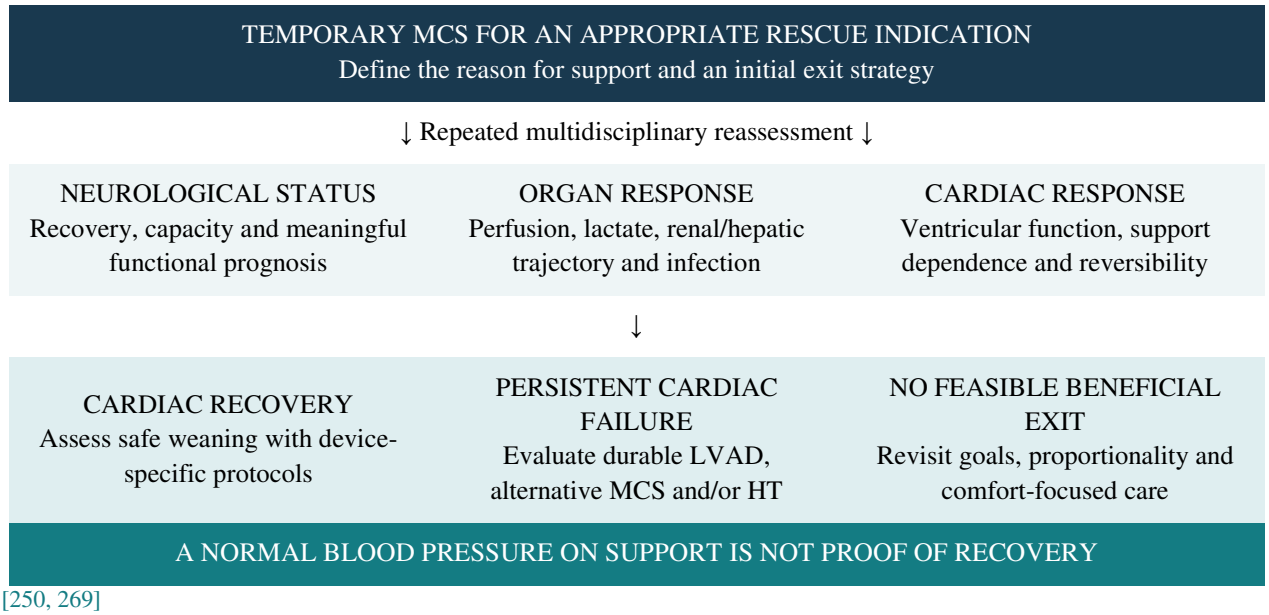
CARRESS-HF found that ultrafiltration, as delivered in that trial, did not offer superior decongestion with renal safety compared with stepped pharmacological care in patients with cardiorenal deterioration and persistent congestion. The lesson is not that extracorporeal fluid removal is never appropriate, but that indication, rate of removal and haemodynamic context matter. [247]

ESC 2026 assigns continuous inotropic support for selected low-output hypoperfusion as a bridge a IIa C recommendation; kidney replacement for refractory volume overload with end-stage kidney failure is IIa C, whereas ultrafiltration after failed diuretic escalation is IIb C. These recommendations describe different clinical problems and should not be merged. [1]

8.8. Temporary support and the bridge-to-decision pathway

Temporary MCS may preserve circulation while neurological recovery, organ reversibility and long-term candidacy become clearer. It is not a durable plan in itself. Device choice depends on LV, RV or biventricular involvement, respiratory failure, vascular access and the intended duration and destination of support. Acute shock protocols and trial evidence are developed in Chapter 7; this section focuses on the transition to advanced therapy. [269]

Figure 8.2. Temporary support: recovery and exit strategies



[250, 269]

Improved blood pressure may coexist with inadequate native cardiac recovery or continued dependence on high levels of support. Assessment includes neurological status, infection, bleeding, limb and organ perfusion, RV function, pulmonary congestion and the ability to reduce support. The duration of acceptable bridging is individualized; neither a fixed day count nor an isolated lactate value determines candidacy. [269]

Veno-arterial ECMO can increase LV afterload, whereas an LV unloading device cannot by itself correct every form of RV or respiratory failure. Biventricular failure may require a different configuration from

isolated LV failure. Escalation or de-escalation therefore belongs to an experienced team and should never be inferred solely from pump-flow display values. [269, 271]

When no feasible beneficial exit emerges, continued support is reassessed with the patient or surrogate. Communication should make clear that withdrawal of a burdensome treatment and active provision of comfort are compatible clinical responsibilities. [44]

8.9. Durable LVAD: indication and strategic intent

A durable LVAD is considered when severe LV failure persists despite appropriate treatment and the expected benefit exceeds the risks of surgery and long-term device dependence. It may bridge a patient to transplantation, restore eligibility by improving a reversible barrier, permit recovery in selected disease, or provide long-term support without a transplant plan. These labels describe strategic intent and can change over time. [271]

Table 8.8. Durable-support strategies and essential selection questions

Strategy	Clinical purpose	What must be clarified
Bridge to transplantation	Protect an eligible candidate from deterioration while awaiting a donor.	Waiting-list risk, donor access, sensitization and the likely support interval.
Bridge to candidacy	Allow improvement of a potentially reversible contraindication.	Which barrier is expected to change, how it will be measured and when candidacy is reassessed.
Bridge to recovery	Support myocardium while unloading and aetiology-directed treatment permit recovery.	A recovery protocol and objective evidence of adequate function off substantial support.
Long-term / destination support	Offer survival and functional benefit when HT is not an option or is not chosen.	Daily device burden, anticoagulation, expected complications, caregiver capacity and patient goals.

[271, 280, 281].

ESC 2026 recommends durable LVAD support in selected patients with advanced HFrEF despite foundational and indicated interventional therapy, after integrated evaluation (I C). Stronger recommendation language does not remove the need to select patients or transform observational selection evidence into a modern LVAD-versus-GDMT randomized comparison. [1]

INTERMACS 2–4 patients commonly form the core population considered, while some stabilized patients previously in critical shock and selected ambulatory patients may also be appropriate. Conversely, irreversible neurological or major extracardiac disease, uncontrolled infection, inability to receive essential anticoagulation, or severe RV dysfunction incompatible with isolated LV support may outweigh the expected benefit. [271]

Selected patients with HFpEF, restrictive or hypertrophic disease may have advanced HF but unsuitable LV anatomy for conventional LVAD implantation. Small cavities, biventricular disease and complex congenital circulations require separate expert strategies. A diagnosis of advanced HF is therefore not equivalent to eligibility for an isolated durable LVAD. [271]

8.10. Right ventricular reserve and operative planning

Durable LV support changes the loading conditions of both ventricles. LV unloading can reduce pulmonary venous pressure, but increased venous return and altered septal geometry may expose inadequate RV reserve. Severe RV failure can prevent effective LVAD filling even when the pump is functioning normally. This is why isolated-LVAD candidacy cannot be determined from LVEF and cardiac index alone. [271]

Table 8.9. Pre-implant assessment beyond the left ventricle

Domain	What to assess	Why it changes the plan
RV and pulmonary circulation	RV size/function, tricuspid regurgitation, RAP, pulmonary pressures, PVR and PAPi.	Identifies risk of early or late RV failure; may require an alternative or planned additional support strategy.
Valves and shunts	Aortic regurgitation, other significant valve lesions, intracardiac shunts and prostheses.	Aortic regurgitation can create recirculation; anatomy may require treatment at implantation.
Anatomy and access	LV cavity, thrombus, prior surgery, aorta and vascular disease.	Determines inflow/outflow feasibility, surgical complexity and embolic risk.
Organs and haemostasis	Renal/hepatic function, lung disease, infection, neurological reserve and bleeding history.	Differentiates recoverable congestion from a risk that support cannot reverse.
Function and support system	Nutrition, frailty, cognition, capacity, learning and practical home arrangements.	Determines rehabilitation potential and whether safe long-term management can be achieved.

[270, 271, 275, 282]

EUROMACS-RHF and indices such as PAPi provide structured risk information. Their calibration and discrimination depend on the population, the definition of RV failure and contemporary device practice. A low PAPi during marked congestion or changing vasoactive support must be interpreted in that setting; it is not an immutable biological characteristic or a single-number veto. [275, 282]

Volume optimization and reassessment can be informative when time permits. More than mild aortic regurgitation requires specific operative consideration because an LVAD can drive blood through the aorta back into the LV without providing effective systemic perfusion. Significant valve disease should be discussed before implantation, not discovered only during low-flow follow-up. [271]

The operative plan also includes pathology. Examination of an apical core or explanted heart may clarify an unrecognized non-ischaemic aetiology and implications for relatives; the ESC 2026 recommendation supports this assessment in the relevant setting (IIa C). [1]

8.11. Interpreting contemporary LVAD outcomes

Historical evidence, device-comparison trials and registries answer different questions. REMATCH established a survival advantage of an earlier-generation device over then-current medical treatment in a selected end-stage population. Its event rates do not predict contemporary magnetically levitated-pump outcomes, and its medical comparator predates today's foundational HF therapy. [283]

Table 8.10. LVAD evidence: what the main studies do and do not establish

Study	Key finding / design	Interpretive boundary
MOMENTUM 3 final report	Fully magnetically levitated versus axial-flow LVAD; 2-year survival free of disabling stroke or reoperation was 76.9% versus 64.8%.	Composite freedom from events is not overall survival; the comparator was another pump, not modern GDMT or HT.
MOMENTUM 3 extended follow-up	Five-year overall survival estimates were 58.4% versus 43.7% for magnetically levitated versus axial-flow support.	Extended follow-up of an originally randomized cohort has follow-up and selection limitations; not a direct comparison with transplantation.
STS Intermacs annual report	Large real-world assessment of device outcomes and evolving magnetically levitated-device practice.	Registry case mix, era and competing outcomes differ from randomized trials and individual-centre practice.
ARIES-HM3	Aspirin avoidance in HeartMate 3 recipients receiving VKA met non-inferiority for the primary haemocompatibility outcome and reduced bleeding.	Device-specific antiplatelet evidence; not permission to withdraw anticoagulation or generalize to every pump.

[284–287]

The full MOMENTUM 3 report and the 2026 ESC discussion should be distinguished from earlier, smaller cohorts. The earlier 84.5% two-year survival figure should not be substituted for the final-trial population. The two-year primary composite and overall survival are different endpoints, and numerical similarity across cohorts does not establish equivalence to HT. [1, 284]

Outcome communication should also describe time at home, functional independence, bleeding, stroke, driveline infection and caregiver workload. Better pump haemocompatibility does not eliminate the morbidity of advanced disease or long-term device support. A realistic account of both benefit and burden is essential to informed choice. [281, 286]

8.12. Long-term LVAD care and complications

Long-term LVAD management integrates pump surveillance with treatment of the patient’s residual cardiovascular disease. Review congestion, perfusion, RV function, aortic-valve behaviour, blood pressure, rhythm, renal function, haemolysis markers and functional status. Changes in displayed flow or power are interpreted alongside the clinical state and the device’s validated parameters, not used as stand-alone diagnoses. [271]

Continuous-flow support alters the relation between palpable pulse, cuff measurements and arterial pressure. The team should specify how blood pressure is measured and interpreted for that device and patient. Avoiding excessive afterload is important, but aggressive blood-pressure reduction can impair perfusion; a number obtained by a particular method must not be relabelled automatically as mean pressure. [271]

Table 8.11. Antithrombotic management: separating evidence from overgeneralization

Issue	Practical interpretation
Baseline anticoagulation	VKA remains the established anticoagulant framework for many durable continuous-flow devices; follow device- and centre-specific targets and monitoring.
ARIES-HM3 regimen	The trial compared aspirin with placebo in HeartMate 3 recipients receiving VKA with an INR target of 2.0–3.0.
Meaning of aspirin avoidance	Supports reduction of antiplatelet-related bleeding in the studied device context; it does not remove the need for anticoagulation.
Other indications / devices	Recent coronary intervention, another vascular indication or another pump requires a separate risk–benefit decision.
Bleeding or thrombosis	Urgent multidisciplinary assessment determines interruption, reversal and resumption. There is no safe universal schedule.
Direct oral anticoagulants	Do not substitute routinely on the assumption that AF evidence applies to durable LVAD support.

[287, 288]

ARIES-HM3 informs antithrombotic management after HeartMate 3 implantation. Both trial groups received anticoagulation; the randomized difference concerned aspirin. Reporting the trial as showing that “blood thinners are unnecessary” would be a serious clinical error. [287]

Echocardiographic follow-up should consider LV size, septal position, RV performance, aortic-valve opening and regurgitation, not merely report an EF. Aortic regurgitation can create a recirculating volume that makes apparent pump flow misleading. Conversely, excessive unloading can promote suction and adverse ventricular interaction. Speed optimization is therefore a physiological assessment coordinated by the LVAD team, sometimes supplemented by invasive haemodynamics. [271]

Safe outpatient support requires an emergency contact, a medication and INR plan, education about bleeding and neurological symptoms, reliable power arrangements and a device-specific response to alarms. Persistent difficulty with these tasks should lead to practical support and retraining before it is labelled non-adherence. [270, 271]

Complications: recognize the patient’s problem before changing the pump

A low-flow alarm is a warning, not a diagnosis. Possible mechanisms include low preload, RV failure, tamponade, excessive afterload, inflow or outflow obstruction and pump-related complications. Reflex fluid administration may worsen a congested patient, while increasing speed can aggravate suction or adverse septal position. Assessment should involve the implanting or designated LVAD service. [271]

Table 8.12. Common late problems and the first interpretive priorities

Presentation	Important possibilities	Assessment priority
Low-flow alarm / presyncope	Hypovolaemia, RV failure, arrhythmia, tamponade, high afterload, inflow/outflow obstruction.	Assess perfusion and volume state; interrogate the device and obtain targeted imaging. Avoid blind fluid or speed changes.
Congestion / declining exercise capacity	RV failure, aortic regurgitation, inadequate unloading, renal dysfunction or another comorbidity.	Reassess biventricular function, valve disease, haemodynamics and the broader HF regimen.
Dark urine / rising haemolysis markers	Haemolysis from pump or flow-path pathology; consider other causes of anaemia.	Prompt LVAD-team review with device trends, laboratory confirmation and imaging as appropriate.
Gastrointestinal or other bleeding	Antithrombotic exposure, vascular lesions, acquired haemostatic changes.	Stabilize; localize bleeding; coordinate anticoagulant decisions with pump-thrombosis risk.
Fever / driveline drainage	Local or systemic device-associated infection, or unrelated infection.	Cultures and assessment of depth/systemic involvement; do not assume a superficial exit-site problem.
Focal neurology / altered consciousness	Ischaemic or haemorrhagic stroke, embolism or another acute neurological illness.	Emergency stroke and LVAD-team assessment; urgent imaging before antithrombotic changes.

[271, 288]

The competing risks of bleeding and thrombosis are dynamic. A previous bleed does not eliminate embolic risk, and a normal device interrogation does not exclude a non-device neurological emergency. Decisions about reversal or resumption require a documented rationale and communication between cardiology, surgery, neurology or gastroenterology as relevant. [288]

Repeated infection, recurrent stroke, progressive RV failure or loss of functional independence should reopen the discussion of transplant eligibility and goals of support. “Destination therapy” should not mean that the destination is never reconsidered. [281]

8.13. Recovery, rehabilitation and life with a device

Reverse remodelling during LVAD support is not equivalent to recovery sufficient for device removal. A recovery programme combines unloading with medical and aetiology-directed therapy, then tests whether adequate function persists during carefully controlled reduction of support. The protocol is device-specific and must assess both ventricles, filling pressures and the durability of improvement. [271, 280]

RESTAGE-HF demonstrated the feasibility of structured recovery assessment in a selected non-ischaemic population supported with an axial-flow device. Its results should not be generalized to all implant recipients, ischaemic disease, long-standing fibrosis or a different pump using the same speed settings. Successful explantation also requires continued surveillance because remission can relapse. [280]

Table 8.13. Recovery and rehabilitation: complementary but different objectives

Objective	What the programme should establish
Myocardial recovery	Repeated objective improvement; low-support testing under an expert protocol; acceptable biventricular and haemodynamic reserve.
Functional recovery	Mobility, strength, balance, endurance and ability to perform valued daily activities, even when the device remains necessary.
Nutritional recovery	Correct malnutrition and deficiencies while recognizing oedema, obesity and sarcopenia; individualize dietary support.
Self-management	Demonstrated competence with alarms, power, driveline care and medication organization; accessible reinforcement and backup.
Social recovery	A feasible home plan, caregiver support, psychological care and realistic discussion of work, travel and relationships.

[270, 271, 280, 289]

Exercise rehabilitation is not simply a test of cardiac recovery. In Ex-VAD, supervised exercise did not significantly improve the prespecified peak-VO_2 primary endpoint, while benefits in submaximal function and physical quality of life were observed. These findings support measured expectations: improvements important to patients are possible without proof of a mortality benefit or a positive maximal-exercise primary outcome. [289]

Training must account for device stability, wound and driveline protection, arrhythmias, blood pressure, falls risk and anticoagulation. Education should include the caregiver without assuming unlimited caregiver capacity. A sustainable programme can prevent the appearance of “technical success” from obscuring severe daily treatment burden. [270, 271]

ESC 2026 supports exercise-based rehabilitation for LVAD recipients (I B1). Implementation nevertheless requires a programme adapted to advanced-HF physiology and device-related precautions, not unrestricted exercise advice. [1, 290]

8.14. Heart-transplant candidacy and multidisciplinary selection

HT offers a potential survival and functional advantage to selected patients whose advanced cardiac disease is not adequately treatable by other means. Selection balances the risk without transplantation against operative risk, expected long-term benefit, rehabilitation potential and the responsibilities of lifelong treatment. A severe LVEF reduction is neither required in every eligible phenotype nor sufficient by itself. [23]

Candidacy is a multidisciplinary judgement, not a checklist scored mechanically. The assessment integrates CPET when feasible, invasive haemodynamics, RV and pulmonary vascular disease, renal and hepatic reserve, infection, malignancy, frailty, psychosocial circumstances and the patient’s priorities. Criteria also depend on centre expertise and the applicable allocation system. [23, 270]

Table 8.14. Core transplant-selection questions

Domain	Question that must be answered
Cardiac indication	Is the disease advanced despite appropriate treatment, and is a meaningful alternative available?
Pulmonary vascular load	Could donor-RV failure be precipitated by persistent pulmonary vascular disease, and how reversible is that burden?
Extracardiac prognosis	Will irreversible renal, hepatic, pulmonary, neurological or malignant disease dominate outcome despite a new heart?
Functional reserve	Can the patient survive the operation and regain a level of independence consistent with their goals?
Infection and immunological risk	Is infection controlled? What are the sensitization, donor-specific antibody and matching implications?
Treatment feasibility and preferences	Can lifelong immunosuppression and surveillance be sustained with appropriate support, and does the patient accept the trade-offs?

[1, 23, 270, 272]

Age boundaries used in historical programme practice are not universal biological rules. Chronological age interacts with comorbidities, frailty and expected benefit; highly selected older candidates require especially careful assessment. Severe obesity should prompt a structured weight and risk strategy rather than an isolated label without context. [1, 291]

Contraindications should be described as irreversible, potentially reversible or uncertain. Active infection, active substance use or an unresolved adherence problem may require treatment before reassessment; controlled psychiatric illness, disability or limited finances alone should not be conflated with inability to benefit. [270]

Renal, hepatic, frailty and psychosocial assessment

Renal and hepatic dysfunction often reflect both HF and intrinsic organ disease. Establishing reversibility avoids two errors: denying isolated HT to someone with recoverable congestion-related dysfunction, and exposing a recipient with irreversible multiorgan disease to a strategy that cannot address the full burden. Serial assessment after haemodynamic optimization is usually more informative than a single laboratory value. [277]

Table 8.15. Selection barriers: characterization, remediation and reassessment

Problem	Assessment emphasis	Interpretive safeguard
Kidney dysfunction	Prior eGFR trajectory, proteinuria, renal structure, diabetes/vascular disease and response to decongestion or support.	Marked persistent dysfunction or documented intrinsic CKD may justify heart–kidney evaluation; transient AKI is not equivalent to irreversible CKD.
Hepatic dysfunction	Congestion versus cirrhosis, synthetic function, portal-hypertension features and hepatology assessment.	Abnormal liver tests alone do not establish a need for combined heart–liver transplantation.
Pulmonary vascular disease	Repeat haemodynamics, appropriate reversibility testing and response to LV unloading.	An isolated PVR value or hypotensive response should not be treated as definitive eligibility evidence.

Problem	Assessment emphasis	Interpretive safeguard
Frailty / malnutrition	Physical, cognitive and nutritional domains; disease-related versus less reversible limitations.	Frailty predicts risk but can be heterogeneous; assess whether rehabilitation or haemodynamic recovery is feasible.
Psychosocial difficulty	Capacity, knowledge, adherence history, substance use, caregiver resources and practical barriers.	Offer remediation and support; distinguish a treatable barrier from an unresolved inability to deliver safe care.
Malignancy / infection	Disease-specific prognosis, recurrence or dissemination risk, and specialist advice.	Avoid universal waiting intervals or blanket decisions detached from the actual disease.

[270, 277, 291]

The AHA dual-organ statement provides a framework for assessing severe renal disease, including very low eGFR and selected intermediate reductions accompanied by evidence of intrinsic CKD. Those clinical considerations must be separated from any jurisdiction's organ-allocation eligibility rules. The present chapter does not reproduce US administrative thresholds as Romanian or European policy. [277]

A psychosocial assessment should identify what safe treatment requires and which barriers can be changed. Teach-back, simplified regimens, transport assistance, caregiver respite and mental-health or addiction services may alter feasibility. The final decision should document both the clinical concern and the support attempted, rather than merely record "poor compliance." [270]

8.15. Waiting-list care, donors and emerging alternatives

Listing is the beginning of another high-risk phase. Reassess symptoms, perfusion, organ function, arrhythmias, infection, nutrition and the adequacy of bridging. Changes in sensitization, device complications or comorbidity may alter both waiting-list risk and donor compatibility. A patient who deteriorates on the list needs active re-evaluation, not passive continuation of the original plan. [23]

Table 8.16. Donor and waiting-list developments: scope of the evidence

Development	Potential value	Boundary of interpretation
Donation after circulatory death	Expands a donor pathway when procurement and preservation expertise are available.	The randomized DCD trial established six-month non-inferiority in its protocol; not equivalence across all techniques or long-term outcomes.
HCV-viraemic donors with antiviral therapy	Selected protocols can use organs previously avoided in uninfected recipients.	Requires explicit consent, reliable direct-acting antiviral access and infection/transplant expertise.
Contemporary registry surveillance	Describes changes in transplantation activity, recipient selection and outcomes over time.	US registry findings are not individual predictions or local allocation rules.
Cardiac xenotransplantation	A regulated investigational field discussed in the 2026 ISHLT consensus.	Not routine replacement for allotransplantation, durable LVAD or established supportive care.

[292–295]

In the DCD heart-transplant trial, risk-adjusted six-month survival was 94% with the DCD strategy and 90% with the conventional donor strategy, meeting a prespecified non-inferiority criterion. The margin was 20

percentage points, an important context when interpreting the result. The finding supports feasibility in the studied setting; it is not evidence that every DCD procurement approach has identical safety. [293]

The donor discussion should explain expected benefit and uncertainty in language the recipient can use. Donor age, size, ischaemic or preservation time, immunological compatibility and infection risks are considered together; acceptance is not governed by a single “ideal donor” characteristic. [23, 272]

National allocation systems and centre-level availability change. Waiting times, priority categories and the availability of specific technologies in Romania should be confirmed with the relevant transplant authority and programme.

8.16. Transplantation, early graft dysfunction and immunosuppression

Transplantation replaces the failing heart, not the need for specialist care. Early instability may reflect primary graft dysfunction, RV failure related to pulmonary vascular load, tamponade, bleeding, vasoplegia, ischaemia or rejection. These mechanisms can coexist and require rapid integration of echocardiography, haemodynamics, laboratory findings and operative information. Rescue support may be necessary while the cause is treated. [272]

Table 8.17. Early post-transplant care: mechanism and responsibility

Clinical domain	Core priorities
Graft function and circulation	Identify LV/RV or biventricular dysfunction; distinguish graft dysfunction from loading, mechanical and vascular causes; support perfusion.
Immunosuppression	Use a centre-defined regimen with therapeutic drug monitoring, organ-function assessment and adjustment for rejection and infection risk.
CNI-associated toxicity	Monitor renal function, potassium, magnesium, blood pressure and metabolic effects; review CYP3A-mediated interactions.
Antimetabolite / steroid effects	Assess cytopenia, gastrointestinal tolerance, infection, hyperglycaemia, muscle and bone consequences.
Infection prevention	Risk-adapted prophylaxis and surveillance, including CMV and Pneumocystis strategies; vaccination planning and education.
Discharge preparation	Demonstrated medication knowledge, laboratory and biopsy/clinic schedule, urgent-contact pathway, transport and caregiver support.

[272]

Tacrolimus or another CNI, an antimetabolite and corticosteroids commonly form the initial maintenance framework, with induction and subsequent modifications individualized. This is not a universal prescription: renal dysfunction, sensitization, rejection, malignancy, infection and intolerance change the balance. Abrupt unsupervised withdrawal of immunosuppression can place the graft at risk. [272]

Drug interactions are clinically consequential. Azole antifungals, macrolides and other inhibitors or inducers can alter CNI exposure; apparently minor new prescriptions may therefore require rapid monitoring and dose adjustment. Adherence discussions should explore affordability, side effects and regimen complexity rather than assume the patient understands every change. [270, 272]

Immunological surveillance should track pre-existing sensitization and donor-specific antibodies as well as newly developing donor-specific antibodies after HT. Neither antibody detection alone nor a drug trough concentration fully describes the balance between rejection and toxicity. The treatment history, adherence, graft function and relevant biopsy findings must be integrated before escalating immunosuppression, because intensified treatment carries an immediate infectious and haematological cost. [272]

The patient and family should understand that a denervated graft may not produce conventional warning symptoms. Unexplained fatigue, reduced exercise tolerance, oedema, arrhythmia or systemic illness can be significant even without angina or a typical heart-rate response. [272]

8.17. Long-term allograft surveillance and prevention

Long-term care balances prevention of rejection against infection, malignancy, renal dysfunction and metabolic toxicity. Acute cellular and antibody-mediated rejection are distinct processes requiring integration of graft function, histology and immunological information. A reassuring screening result should not delay investigation of new graft dysfunction. [272]

Table 8.18. Post-transplant surveillance: what each tool can establish

Tool / target	Role	Caution
Clinical review and echocardiography	Detect functional change, congestion, rhythm disturbance and structural complications.	Normal resting function does not exclude every form of rejection or CAV.
Endomyocardial biopsy / DSA	Histological and immunological assessment when indicated by time since HT or clinical risk.	Interpret biopsy findings, antibodies and graft function together.
Gene-expression profiling	Can reduce biopsy burden in selected low-risk recipients within validated surveillance settings.	Not a stand-alone exclusion of all rejection, particularly AMR or unexplained graft dysfunction.
Donor-derived cell-free DNA	Non-invasive indicator of graft injury with useful rule-out characteristics in studied populations.	Injury is not synonymous with a specific rejection mechanism; performance depends on context.
CAV and cardiovascular risk	Programme-directed coronary surveillance, blood pressure/metabolic care and statin therapy where appropriate.	Symptoms may be atypical; interactions and renal function affect preventive treatment.
Infection, cancer, function	Risk-adapted prophylaxis/screening, skin and other cancer surveillance, vaccination and rehabilitation.	Survival alone misses toxicity, disability and quality-of-life burden.

[272, 296–298]

IMAGE evaluated gene-expression-based surveillance in a selected population, not every newly transplanted or unstable recipient. Prospective cell-free-DNA studies similarly support an additional surveillance tool rather than an infallible diagnosis. Programmes should specify when non-invasive testing is appropriate and when symptoms, graft dysfunction or immunological risk require biopsy and invasive assessment. [297, 298]

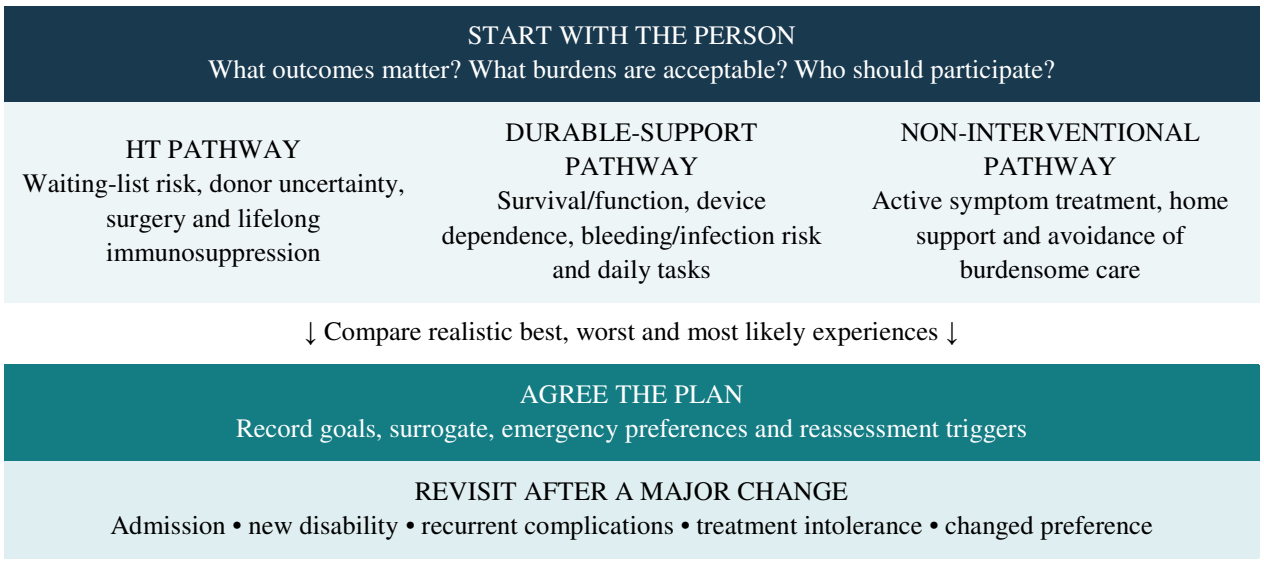
Statin therapy after adult HT has a transplant-specific rationale, including CAV prevention; it should not be confused with the absence of an indication to initiate a statin solely for non-ischaemic HF. The early pravastatin trial and recipient-care guidance support its role, with attention to interactions and tolerability. [272, 296]

Reported transplant survival depends on era, age, diagnosis, donor factors and whether survival is conditioned on the early postoperative period. A historical cohort median should not be presented as the life expectancy of a new individual recipient; contemporary registry reporting should be consulted for the relevant population. [292]

8.18. Palliative care, communication and shared decisions

Palliative care addresses symptoms, uncertainty and the practical burden of serious illness; it is not restricted to patients who are dying or ineligible for advanced therapy. PAL-HF demonstrated improvements in patient-centred outcomes with a structured palliative intervention, without establishing a mortality benefit. Such support can accompany assessment, bridging, LVAD care and transplantation.

Figure 8.3. Shared decisions across three care pathways



[44, 281]

DECIDE-LVAD emphasizes decision quality rather than persuading every eligible patient to accept a device. Information should explain survival and functional possibilities, but also anticoagulation, alarms, driveline care, caregiver workload and the possibility of stroke or recurrent admission. Declining an intervention after an informed discussion is not failure of care. [281]

Advance care planning should distinguish decisions that are often conflated. A do-not-resuscitate decision does not automatically mean stopping an LVAD. Deactivating ICD shocks does not necessarily mean withdrawing pacing or CRT. Any withdrawal of life-sustaining support requires a deliberate consent process, specialist coordination and anticipatory symptom management under applicable ethical and legal standards. [271]

Symptom-focused treatment remains active treatment. Congestion relief, management of breathlessness and anxiety, rehabilitation adapted to capacity, and practical support at home may remain appropriate alongside advanced support. The care plan should specify whom the family contacts during deterioration and which burdens the patient wishes to avoid; these details are often more useful than a nonspecific label of “palliative.” [44]

ESC 2026 supports goals-of-care discussions and advance planning (I B1), and integrated palliative care (I B2). These recommendations reinforce a parallel component of treatment rather than a last-minute substitute after all other plans fail. [1, 176]

8.19. Clinical cases

Case 1 — Recurrent congestion before irreversible organ failure

A 56-year-old patient with non-ischaemic cardiomyopathy has three admissions for congestion in nine months. LVEF is 22%; systolic pressure is 92–100 mmHg. Renal function has fallen during recurrent congestion, loop-diuretic requirements are increasing and the patient can no longer climb one flight of stairs. There is no inotrope requirement, and the patient is comfortable while sitting.

Interpretation. Resting comfort does not negate a high-risk trajectory. Repeated admissions, declining function, escalating diuretics and restricted treatment tolerance justify advanced-centre referral now. The working question is not "which pump should be implanted?" but "what is the reversible burden, what reserve remains and which options are feasible?" [22, 24]

Next assessment. Reassess congestion and aetiology, verify tolerated therapy, obtain CPET if stable, characterize haemodynamics and RV function, and investigate whether renal impairment is predominantly congestive or intrinsic. Begin the psychosocial and goals-of-care assessment in parallel. A potentially favourable response to decongestion should have a defined reassessment date rather than cancelling the referral. [271, 277]

Case 2 — Stability on inotropes is not recovery

A 62-year-old patient with ischaemic cardiomyopathy improves after treatment of low-output HF. Lactate normalizes and renal indices begin to recover, but attempts to stop the inotrope repeatedly produce symptomatic hypotension and oliguria. Echocardiography shows severe LV dysfunction with moderate RV dysfunction; the patient wishes to return home and values independence.

Interpretation. This pattern is compatible with support dependence rather than stable compensated HF. INTERMACS profiling communicates severity, but selection still requires examination of neurological and organ reserve, RV risk, anatomy, transplant feasibility and the patient's tolerance for device-related burden. A normal pressure during infusion is not proof of an adequate native circulation. [269, 273]

Decision focus. An integrated team considers HT, durable support or another bridge only after establishing a credible exit strategy. If isolated LVAD is contemplated, the RV findings and response to decongestion are central; a single favourable CI on inotropes cannot establish suitability. Palliative involvement should begin during this evaluation, not after it. [44, 282]

Case 3 — A complication changes the balance of benefit and burden

A 70-year-old HeartMate 3 recipient has recurrent gastrointestinal bleeding despite coordinated care. The pump is functioning, but the patient has lost strength, the caregiver is exhausted and another admission is feared. The medication list includes VKA and aspirin. There is no stated recent coronary intervention, although the vascular history requires confirmation.

Interpretation. Device success and patient success have diverged. Review the bleeding source, anticoagulant control, haemocompatibility risk and any independent antiplatelet indication. ARIES-HM3 supports a discussion of aspirin avoidance in the studied HeartMate 3/VKA context; it does not justify unsupervised withdrawal of VKA or identical management for another device. [287, 288]

Care plan. Reassess rehabilitation, nutrition, caregiver support and goals alongside treatment of the bleed. Explore what degree of recurrence or loss of independence would lead the patient to reconsider burdensome interventions. This is an update to shared decision making, not evidence that palliative care and ongoing LVAD support are mutually exclusive. [270, 281, 289]

Table 8.19. Readiness questions before committing to an advanced-therapy plan

Question	A satisfactory answer should include
Why now?	A documented trajectory and explanation of why current treatment is insufficient or unsafe to defer.
What is reversible?	Cardiac, pulmonary vascular and organ findings reassessed under defined treatment conditions.
Which treatment fits?	Ventricular anatomy and reserve, procedural risk, transplant eligibility and alternatives.
What does the patient value?	An informed comparison of likely benefit, uncertainty and treatment burden, with a named surrogate when appropriate.
Can the plan be delivered?	Medication, device or immunosuppression management; education, transport, caregiving and emergency access.
When will it be reconsidered?	Specific triggers for escalation, reassessment, recovery testing or a change in goals.

[22, 270, 271, 281]

Across all three cases, the recurring principle is to avoid a false binary between “continue medication” and “implant or transplant.” Advanced-HF care is a sequence of reassessments in which treatment, reversibility, eligibility and preferences change together.

9. Comorbidities, Rehabilitation and Longitudinal Care

9.1. Multimorbidity and the whole-person assessment

Heart failure is managed within a network of interacting diseases rather than in isolation. Kidney dysfunction, diabetes, pulmonary disease, iron deficiency, obesity, frailty and psychological distress can contribute to breathlessness, fatigue and recurrent hospitalisation independently of left ventricular function. They also modify tolerance of disease-modifying treatment. A patient with apparently stable congestion may nevertheless be deteriorating because of progressive anaemia, loss of muscle strength, cognitive impairment or inability to obtain medicines. Conversely, a rise in creatinine during successful decongestion need not represent irreversible kidney injury. The central clinical task is to identify the dominant, treatable mechanisms behind the patient's present limitation. [9]

Prevention, multidisciplinary care and self-management complement pharmacological and device treatment. Assessment is longitudinal: the same domains are revisited after hospitalisation, a major treatment change, an intercurrent illness or a decline in function. The resulting plan should specify what matters to the patient, which problems require action now, who will act, and how the response will be checked. Recording ten diagnoses without defining priorities is not equivalent to managing multimorbidity. [53]

Table 9.1. A multidimensional review that leads to an action plan

Domain	Minimum clinical question	Action-oriented interpretation
Cardiac stability	Is congestion, hypoperfusion, arrhythmia or a new structural problem present?	Treat instability first; do not attribute all deterioration to chronic comorbidity.
Organ reserve	What is changing in kidney function, electrolytes, haemoglobin, iron status or pulmonary function?	Distinguish a reversible contributor from a treatment effect or progressive disease.
Function and nutrition	Can the patient walk, rise from a chair, eat adequately and perform usual activities?	Identify rehabilitation, balance, nutritional or social-care needs.
Treatment feasibility	Are medicines understood, affordable, available and taken as intended?	Reconcile the actual regimen; resolve barriers before declaring treatment failure.
Psychological and social context	Are mood, cognition, isolation or caregiver strain interfering with care?	Agree on support, simplified instructions and a named contact.

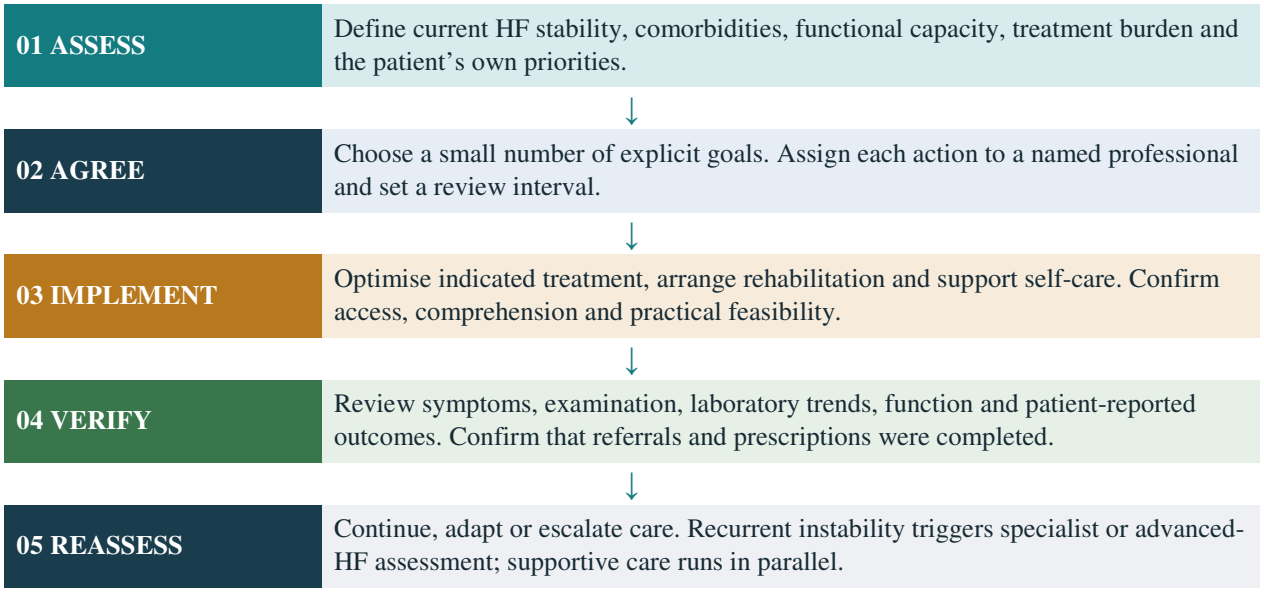
[53]

Prioritisation should consider both expected benefit and treatment burden. An additional intervention is less attractive when it conflicts with an essential therapy, imposes disproportionate monitoring, or has little chance of improving the patient's goals. Decisions should nevertheless avoid therapeutic nihilism: advanced age or multiple diagnoses alone does not justify withholding treatments likely to preserve independence or reduce heart-failure events. Shared decisions are revisited as the trajectory changes. [44]

9.2. Multidisciplinary care: coordination, responsibility and access

The heart-failure programme should connect specialist assessment with the everyday care delivered in the community. A clinic appointment, home visit or telephone call is a delivery method, not the intervention itself. Clinical value depends on continuity, access to treatment adjustment and the ability to close the loop after an abnormal finding. In a patient-centred model, cardiology, specialist nursing, primary care, pharmacy, rehabilitation, dietetics, mental-health services and other specialties contribute according to need rather than through a mandatory identical sequence for every patient. [1, 67]

Figure 9.1. A coordinated longitudinal care cycle



[53]

In the selected 2026 ESC HF recommendations, multidisciplinary programmes carry Class I, Level B1; self-care and education carry Class I, Level A; adherence assessment, including health literacy and polypharmacy, carries Class I, Level B2. These labels apply to the specified interventions, not to every locally proposed staffing configuration. [1]

Care coordination is particularly important when advice appears contradictory. A nephrology recommendation to preserve renal perfusion, a cardiology recommendation to remove excess fluid and a rehabilitation recommendation to increase activity may all be appropriate. The team must reconcile the current physiology and document a common plan instead of leaving the patient to choose between separate instructions. [54]

From a multidisciplinary meeting to accountable delivery

The practical output of a multidisciplinary review should be a shared care record: active diagnoses, current medicines and doses, the latest relevant investigations, agreed goals, pending decisions and clear escalation arrangements. The responsible clinician remains identifiable even when care crosses organisational boundaries. A discharge letter that lists medication changes but omits the laboratory follow-up owner creates a predictable safety gap. The same applies to an exercise referral without a statement of clinical stability or device-related precautions. These are practical requirements for continuity of care.

Table 9.2. Core functions and a suggested accountable output

Function	Usual contributors	Documented output
Clinical integration	HF clinician and primary-care clinician	Phenotype, stability, priorities, treatment decisions and criteria for re-referral.
Surveillance and education	HF nurse with the patient and caregiver	Written action plan, symptom review, teach-back and rapid-contact arrangements.
Medication safety	Pharmacist and prescribing clinician	Reconciled regimen; interaction, affordability and adherence review; laboratory plan.
Functional restoration	Rehabilitation team and physiotherapist	Baseline function, individual prescription, monitoring needs and progression criteria.
Nutrition and metabolic care	Dietitian; diabetes or kidney team when needed	Nutrition strategy that reconciles congestion, glycaemia, kidney disease and muscle preservation.
Psychosocial and supportive care	Mental-health, social-care and palliative-care professionals	Support for distress, practical barriers, caregiver needs and goal-concordant decisions.

[53]

Referral is not complete when a request is sent. The receiving service should acknowledge the request, communicate its assessment and identify what remains with the referring team. Likewise, home-based and hybrid programmes require a route back to in-person evaluation when symptoms cannot be safely interpreted remotely. Digital access should supplement, not become a prerequisite for, essential care. Telephone, written or caregiver-supported alternatives are necessary for people with sensory, cognitive or technological barriers. [299]

Quality measurement should examine both delivery and outcomes. Useful local indicators include completion of early post-discharge review, medicines reconciliation, timely laboratory checks, rehabilitation referral and attendance, patient understanding, preventable treatment interruption and the handling of abnormal results. Readmission and mortality rates require interpretation in relation to case mix and competing illness. A high-risk service should not be penalised for accepting complex patients, nor should an apparently low readmission rate conceal poor access or disengagement. These indicators are proposed for audit and are not a validated outcome-prediction model. [70]

9.3. Education, self-care and medication safety

Self-care is a practical skill set rather than a test of patient compliance. It includes taking medicines, observing symptoms, interpreting meaningful changes and knowing when professional help is required. Education should begin with what the patient already understands and should use clear language, demonstration and teach-back. The patient's own medication containers or treatment list often reveal discrepancies that a prescribed list misses. Repetition is essential after hospitalisation, cognitive change or introduction of a complex therapy. With the patient's agreement, a caregiver can share tasks without displacing the patient's autonomy. [53]

Table 9.3. An individualised self-care and escalation plan

Situation	Agreed patient action	Professional responsibility
Usual stable state	Take the agreed regimen; observe breathlessness, swelling, activity and weight when useful.	Specify the person's usual range and how to contact the team.
Increasing congestion	Report increasing oedema, orthopnoea or rapid weight change; follow only a previously agreed diuretic plan.	Assess severity, precipitant, kidney function and the need for urgent examination.
Dizziness, poor intake or diarrhoea	Seek advice about volume status and temporary medicine changes; avoid unsupervised wholesale withdrawal.	Decide which drugs to pause, when to recheck and exactly when to restart.
Severe breathlessness at rest, chest pain, syncope or confusion	Use emergency services rather than waiting for a routine clinic response.	Make emergency versus routine contact routes unambiguous.
Missed doses or unavailable medicines	Discuss the problem openly; do not double doses indiscriminately.	Resolve supply, cost, schedule or adverse-effect barriers without blame.

[53]

A gain of more than about 2 kg over 3 days is a useful warning example, but weight alone neither confirms nor excludes decompensation. It must be interpreted with symptoms and the patient's usual trajectory. A person losing muscle can become congested without net weight gain. Conversely, intentional nutritional recovery may increase weight without fluid overload. Diuretic self-adjustment requires a written, patient-specific protocol and a route to reassessment; it is not permission to change all heart-failure medicines.

Medication review should distinguish necessary multidrug treatment from avoidable complexity. Check duplicated RAAS agents, non-prescription NSAIDs, potassium supplements, salt substitutes, sedatives, herbal products and drugs added by another service. Simplifying administration, using a pill organiser or aligning refills can be more effective than another explanation of prognosis. A temporary interruption should always have a documented reason, review date and restart plan so that a short illness does not become permanent loss of beneficial therapy. [33]

9.4. Follow-up across the vulnerable and stable phases

Follow-up intensity should follow clinical risk and therapeutic activity. The first weeks after discharge, changes in diuretics or RAAS-active treatment, recurrent electrolyte disturbance and new functional decline require closer surveillance than stable long-term care. At each review, symptoms, examination, blood pressure, rhythm, volume status, renal function and treatment tolerance should be interpreted together. A visit that records only whether the patient feels better may miss residual congestion, orthostatic hypotension or a failure to start the intended regimen.

STRONG-HF tested a structured strategy of rapid treatment optimisation with repeated early visits after acute HF. It reduced the 180-day composite of death or HF readmission compared with usual care, while non-serious adverse events increased. The result supports organised optimisation with surveillance; it does not justify reproducing the speed of titration without the trial's clinical selection and safety checks. Nor did the study establish a universal sequence for all contemporary foundational agents. [146]

Table 9.4. A risk-adapted follow-up framework

Clinical phase	Suggested focus	Timing principle
Before discharge	Congestion, actual medicines, laboratory plan, education and rehabilitation referral.	The next contact and its owner should be identified before the patient leaves.
Early transition	Symptoms, BP, weight trend, electrolytes, kidney function and treatment implementation.	Early clinical review, commonly within 1–2 weeks; earlier when risk requires.
Active optimisation	Adverse effects, congestion and opportunities to initiate or titrate therapy.	Short intervals matched to the drug and clinical risk; intensified review in the first 6 weeks after admission.
Established stability	Comorbidities, function, adherence, wellbeing and prevention.	Use an individual stable-care schedule; do not apply it to new deterioration.
Change in trajectory	New dyspnoea, falls, loss of independence, arrhythmia or recurrent admission.	Prompt reassessment and escalation rather than waiting for the next scheduled visit.

[146]

The 2026 ESC stable-care illustration gives broad intervals of 6–12 months for stage C and 3–6 months for stage D. These are not intervals for laboratory monitoring after medication changes, and a patient's instability takes precedence. Follow-up frequency should therefore reflect the patient's phase of illness. [1]

Echocardiography is repeated when it will answer a clinical question, including reassessment after treatment optimisation or new deterioration, rather than automatically at every visit. Natriuretic peptides remain useful diagnostically and prognostically, but GUIDE-IT did not establish superiority of targeting a specific NT-proBNP concentration over high-quality usual care. A laboratory target should not substitute for clinical judgement or become a reason to intensify treatment beyond tolerance. [108]

9.5. Kidney dysfunction and the cardiorenal interface

The interaction between HF and kidney disease is bidirectional. Venous congestion, reduced perfusion, neurohormonal activation, diabetes and hypertension may coexist, while diuretic or RAAS-related haemodynamic changes complicate interpretation of laboratory results. Assessment should therefore establish the baseline, the rate of change and the accompanying volume and perfusion state. A diagnosis of CKD requires evidence of chronicity, generally at least 3 months; a single inpatient creatinine value cannot establish it. eGFR and urine albumin-to-creatinine ratio provide complementary information. [33, 54]

Table 9.5. Interpreting a change in kidney function during HF care

Pattern	Clinical interpretation	Response
Small early eGFR decrease after therapy	May reflect a haemodynamic effect rather than structural injury.	Assess BP, volume, potassium and the subsequent trajectory before stopping treatment.
Creatinine rise with improving congestion	May accompany effective fluid removal.	Reassess perfusion and residual congestion; do not reflexively replace diuresis with fluid.
Creatinine rise with hypotension or poor intake	Possible volume depletion, drug interaction or acute illness.	Urgently review the regimen, intake, infection and other reversible causes.
Progressive dysfunction with persistent congestion	May indicate unresolved cardiorenal disease or advanced HF.	Escalate clinical assessment; coordinate HF and kidney expertise.
Unexpected result or disproportionate drug toxicity	Measurement error, low muscle mass, obstruction or an alternative kidney disorder may contribute.	Confirm the result and investigate the specific clinical discrepancy.

[33, 54]

KDIGO advises checking BP, creatinine and potassium within 2–4 weeks of starting or increasing an ACE inhibitor or ARB, with earlier testing appropriate when clinical risk is higher. A creatinine rise exceeding 30% within 4 weeks is a trigger for investigation and reassessment, not a universal instruction to tolerate any lesser rise irrespective of the patient's condition. Persistent symptomatic hypotension, uncontrolled hyperkalaemia or acute illness may require treatment modification. [33]

DAPA-CKD and EMPA-KIDNEY established kidney-protective benefits of SGLT2 inhibition in selected CKD populations, including patients without diabetes. Their entry criteria and kidney endpoints differ from those of HF trials. The practical implication is to recognise overlapping indications while verifying the appropriate product-specific initiation threshold and monitoring plan. Advanced CKD, dialysis and transplantation are not interchangeable populations. Creatinine-based estimates can also mislead when muscle mass is very low; confirmatory assessment may be appropriate when a treatment decision depends on precision. [54, 300, 301]

9.6. Electrolyte disorders and preservation of essential therapy

Electrolyte disorders are both clinical hazards and obstacles to maintaining treatment. The combination of CKD, an MRA, RAAS inhibition, a potassium supplement or an intercurrent illness can destabilise potassium balance quickly. Conversely, aggressive loop or thiazide diuresis may lower potassium and magnesium. The clinical response must distinguish an immediately dangerous disturbance from a manageable chronic barrier. A single unexpected potassium result should be checked for sampling problems when the situation permits, but confirmation must not delay emergency treatment when the ECG or clinical presentation is concerning. [33]

Table 9.6. A practical electrolyte assessment matrix

Disturbance	Important contributors	Priority
Hyperkalaemia	CKD, RAAS-active drugs, supplements, potassium-based salt substitutes, acidosis and interacting medicines.	Assess urgency and ECG; identify reversible factors and plan repeat testing.
Hypokalaemia	Loop/thiazide diuretics, gastrointestinal loss, poor intake and associated magnesium depletion.	Correct deficits and review the cause; consider arrhythmic risk and digitalis exposure.
Hyponatraemia	Dilutional congestion, diuretic-associated depletion or non-HF causes.	Establish tonicity, symptoms and volume state before selecting treatment.
Hypochloraemia / alkalosis	Diuretic exposure, vomiting and neurohormonal sodium retention.	Interpret with sodium, potassium, bicarbonate, renal function and response to decongestion.
Phosphate depletion	Malnutrition, refeeding or repeated ferric carboxymaltose exposure.	Investigate unexplained weakness or bone symptoms; monitor at-risk iron recipients.

[302]

In severe hyperkalaemia, intravenous calcium stabilises the cardiac membrane: **it does not lower potassium and does not move potassium into cells**. Insulin with glucose when required and beta-adrenergic treatment

promote intracellular redistribution; definitive removal relies on renal excretion, gastrointestinal binding or dialysis as indicated. Emergency doses and monitoring must follow the local acute-care protocol, with special attention to hypoglycaemia, recurrent hyperkalaemia and the limitations of the ECG as a measure of risk. [33]

The long-term objective is not merely to normalise a number but to maintain a safe, effective treatment combination. Remove unnecessary potassium exposure and review competing medicines before abandoning prognostically important drugs. Where persistent hyperkalaemia prevents appropriate RAAS or MRA treatment, a potassium binder may be considered within a monitored plan. It must not be represented as a substitute for emergency stabilisation or as an intervention with independently established HF survival benefit. [33, 150, 151]

From correction to prevention of recurrence

DIAMOND showed that patiromer can facilitate potassium control and maintenance of MRA treatment in selected patients with HFrEF and current or previous RAAS-related hyperkalaemia. Its principal findings concern potassium and treatment enablement, not a demonstrated reduction in mortality. REALIZE-K similarly improved maintenance of normokalaemia on spironolactone with sodium zirconium cyclosilicate. However, more HF events occurred in its SZC arm, in a trial not powered to establish clinical-outcome differences. This signal deserves attention to congestion and sodium burden rather than an assumption that successful potassium control necessarily improves every outcome. [150, 151]

Table 9.7. A monitoring plan when potassium limits treatment

Step	Clinical task	Safety endpoint
Establish context	Review trend, kidney function, ECG when indicated, volume status and the actual medicine list.	Urgent disturbances have been separated from chronic treatment barriers.
Remove avoidable contributors	Stop unnecessary supplements or interacting drugs; review salt substitutes and constipation.	A modifiable cause is not being mistaken for unavoidable MRA intolerance.
Individualise the HF regimen	Consider appropriate temporary adjustment, binder use and specialist input.	The decision balances immediate safety with preservation of indicated therapy.
Recheck after intervention	Specify laboratory timing, who reads the result and the next action.	Abnormal potassium cannot remain unreviewed between services.
Reintroduce and maintain	Reassess paused therapy once the precipitant resolves.	A temporary safety measure does not become unintentional permanent undertreatment.

[33, 150, 151]

Hyponatraemia requires a different diagnostic sequence. In a congested patient it is commonly dilutional, but depletion from diuretics or gastrointestinal loss demands another approach. Severe neurological symptoms require urgent monitored treatment; the correction rate must be controlled to avoid osmotic demyelination. A correction ceiling of approximately 8 mmol/L over 24 hours is a safety concept rather than a universal therapeutic target; patients at high risk may need stricter limits under an acute-care protocol. Tolvaptan can produce aquaresis and raise sodium in selected circumstances, but correction of sodium must not be equated with a proven survival effect in HF. [9]

Dietary potassium restriction should be proportionate and dietitian-supported. A blanket ban on fruit, vegetables and adequate nutrition may aggravate frailty without addressing the main cause of hyperkalaemia. Similarly, escalating diuretics solely to lower potassium can cause volume depletion when congestion is absent. Each adjustment requires a plan to reassess symptoms, orthostasis, kidney function and the overall treatment burden. Electrolyte management is consequently inseparable from the broader cardiorenal and nutritional assessment. [33]

9.7. Diabetes, blood pressure and cardiometabolic risk

Diabetes care in HF should be judged by more than HbA1c. Prevention of hypoglycaemia, preservation of kidney function, avoidance of fluid retention and reduction of cardiovascular risk are integral objectives. Conversely, a drug that improves glycaemia does not necessarily improve HF outcomes. The distinction between glucose-lowering classes is important: thiazolidinediones promote fluid retention, saxagliptin has an adverse HF-hospitalisation signal, and insulin requirements should be assessed alongside nutrition and volume status. Metformin is generally used in stable patients within its kidney-function and acute-illness restrictions; it is not a treatment for decompensated HF. [9]

Table 9.8. Reconciling metabolic and HF indications

Therapeutic issue	Interpretation	Practical safeguard
SGLT2 inhibition	Benefits may arise from HF and/or CKD indications, independently of glucose lowering.	Check the individual drug's renal threshold, volume status and temporary-withholding advice.
Finerenone	CKD with type 2 diabetes and HF with LVEF ≥40% are distinct evidence pathways.	Do not routinely combine MRAs; monitor potassium and kidney function.
Incretin-based treatment	Obesity-related HFpEF, diabetes and CKD trials address different populations and outcomes.	Avoid transferring a trial dose or endpoint to another indication without verification.
Glycaemic targets	Frailty, cognition, renal function and hypoglycaemia risk may be more important than a rigid HbA1c goal.	Coordinate medication changes with intake and exercise progression.
Blood pressure and lipids	Treat the underlying cardiovascular and renal risk, while preserving tolerated HF therapy.	Assess orthostasis; do not add or remove drugs solely to satisfy an isolated clinic reading.

[54, 73, 300, 301, 303]

The 2026 ESC cardiovascular–kidney recommendations explicitly integrate SGLT2 inhibitors and finerenone with CKD risk stratification. Their thresholds depend on diabetes, eGFR and albuminuria. HF itself may provide a separate reason for SGLT2 treatment; therefore, absence of marked albuminuria should not be used automatically to deny a valid HF indication. FLOW demonstrated kidney and cardiovascular benefit of semaglutide in its selected type 2 diabetes and CKD population. This is not proof that every GLP-1 receptor agonist is interchangeable for every HF phenotype. [33, 54, 303]

FINEARTS-HF showed fewer total worsening-HF events and cardiovascular deaths as a composite with finerenone in patients with LVEF ≥40%; cardiovascular mortality alone was not significantly reduced. Treatment selection should preserve that distinction and incorporate potassium safety. During prolonged

fasting, surgery or critical illness, SGLT2 inhibitors may need temporary withholding because of ketosis risk, followed by explicit reassessment and restart. A mild infection in an otherwise stable, eating patient is not an automatic reason to stop every beneficial medicine. [33, 73]

9.8. Obesity, frailty, sarcopenia and cachexia

Body weight can reflect adiposity, fluid retention, nutritional depletion or a mixture of all three. The obesity paradox described in observational HF cohorts should not be interpreted as a recommendation to gain fat. Confounding, reverse causation, smoking, disease severity and muscle mass complicate those associations. Equally, indiscriminate weight reduction in a frail patient may worsen strength and independence. The clinical target is a favourable body composition and functional trajectory rather than the lowest achievable BMI.

Table 9.9. Distinguishing overlapping nutritional and functional syndromes

Syndrome	What should be established?	Management emphasis
Obesity-related limitation	Adiposity, congestion, sleep-disordered breathing, diabetes and the dominant HF phenotype.	Combine an appropriate weight strategy with strength-preserving activity and nutritional review.
Frailty	Vulnerability across physical, cognitive, psychological and social domains.	Identify reversible drivers; use multidomain rehabilitation and practical support.
Sarcopenia	Low muscle strength, with confirmation by low muscle quantity or quality; impaired performance indicates greater severity.	Progressive resistance and functional training with appropriate nutrition.
Cachexia	Unintentional oedema-free weight loss and systemic disease burden, after excluding alternative causes.	Address HF severity, intake, inflammation and reversible disease; avoid intentional caloric restriction.
Sarcopenic obesity	High adiposity accompanied by low strength or muscle reserve.	Do not let BMI conceal nutritional or functional vulnerability.

[304]

STEP-HFpEF demonstrated substantial improvement in symptoms, physical limitations and body weight with semaglutide in obesity-related HFpEF. SUMMIT extended the evidence with tirzepatide, reducing a composite of cardiovascular death or worsening HF and improving health status in patients with HFpEF and obesity. The events benefit was not a separately established cardiovascular mortality effect. These findings support phenotype-specific treatment, not universal use for advanced lean HFrEF, cachexia or every cause of preserved-EF breathlessness. [166, 167]

Function should be assessed serially using feasible measures such as chair rise, gait speed, grip strength or SPPB. A falling weight accompanied by poorer chair-rise performance is not necessarily therapeutic success. Gastrointestinal adverse effects, reduced intake and changes in diuretic requirement deserve attention during weight-loss treatment. Nutrition must be reconciled with kidney disease: a standard high-protein instruction can conflict with CKD guidance, while overly restrictive diets may be inappropriate in malnutrition or metabolic instability. Joint dietetic and renal assessment is preferable to a single protein target for all patients. [33, 304]

9.9. Iron deficiency and anaemia: diagnosis and clinical purpose

Iron deficiency and anaemia are related but distinct problems. Iron depletion may impair skeletal-muscle energetics and exercise tolerance before haemoglobin falls. Anaemia can additionally arise from kidney disease, bleeding, inflammation, nutritional deficiency, marrow disease or a combination of mechanisms. Labelling every low haemoglobin concentration as "cardiac anaemia" risks missing a treatable cause. Screening should therefore include a blood count, ferritin and TSAT, followed by cause-directed investigation when abnormalities are found.

Table 9.10. Interpreting iron and haemoglobin in the HF clinic

Finding	Meaning and limitation	Next step
Low haemoglobin	A syndrome, not an aetiological diagnosis.	Review indices, kidney function, bleeding, nutrition and other clinical clues.
Ferritin <100 ng/mL	Part of the conventional iron-deficiency eligibility definition in many HF trials.	Assess TSAT and clinical context; investigate why iron is low.
Ferritin 100–299 ng/mL with TSAT <20%	Another commonly used trial definition; inflammation can elevate ferritin.	Do not interpret ferritin alone as proof of adequate available iron.
Low TSAT with discordant ferritin	May indicate restricted iron availability; definitions differ among trials and guidance.	Avoid treating a trial cut-off as a universal biological gold standard.
Persistent fatigue after iron administration	Residual HF, anaemia, frailty, pulmonary disease or phosphate depletion may remain.	Reassess the symptom mechanism rather than repeating iron empirically.

[160, 265, 302, 305]

Treatment objectives must be explicit. In the selected 2026 ESC HF table, intravenous iron for symptomatic HFrEF with iron deficiency is recommended to improve symptoms and quality of life (I B1), and should be considered to reduce HF hospitalisation (IIa B1). This does not establish an independent mortality benefit, nor does it make every low ferritin result an indication for intravenous therapy. Trial-specific EF boundaries and the patient's current phenotype remain important. [1]

The formulation, total dose, interval and repeat-treatment criteria should follow the applicable product information and clinical protocol. Infusion reactions require appropriate facilities. With ferric carboxymaltose, symptomatic hypophosphataemia can occur; phosphate monitoring is particularly relevant for repeated high-dose exposure, prolonged treatment or pre-existing risk factors. Persistent or worsening fatigue and new musculoskeletal symptoms should not automatically be attributed to recurrent iron deficiency. The 2026 MHRA clarification applies this risk to all ferric carboxymaltose products, not only one brand. [302]

Reading the iron trials without overstating their endpoints

Early trials established a symptomatic role for intravenous iron, but later event-driven studies produced a more nuanced picture. FAIR-HF improved patient-reported status and functional measures. Subsequent trials differed in recent hospitalisation, LVEF, iron eligibility, formulation and endpoint construction. A statistically favourable secondary outcome or sensitivity analysis cannot be presented as a positive prespecified primary result. [63, 160, 265, 305, 306]

Table 9.11. Selected iron trials and the inference supported

Trial / population	Principal result	Clinical interpretation
FAIR-HF; symptomatic systolic HF	Improved global assessment, NYHA status and functional outcomes.	Supports symptom/function treatment; not a mortality trial.
AFFIRM-AHF; stabilised after acute HF, LVEF <50%	Primary recurrent-HFH/CV-death composite narrowly missed statistical significance; HFH was reduced.	Preserve the primary/secondary endpoint distinction.
IRONMAN; LVEF ≤45%, iron deficiency	Primary recurrent-HFH/CV-death outcome was not conventionally significant; COVID-sensitive analysis differed.	Does not establish a universal mortality effect.
HEART-FID; ambulatory HFrEF	Hierarchical outcome did not meet the prespecified significance threshold.	A nominal P value must be judged against the trial's analysis plan.
FAIR-HF2; LVEF ≤45%	No prespecified primary endpoint met the multiplicity-adjusted criteria.	Do not call the trial positive solely because one nominal P value was <0.05.
IRONOUT-HF; oral iron in HFrEF	No improvement in peak exercise capacity over 16 weeks.	High-dose oral iron is not an evidence-equivalent substitute for intravenous HF protocols.

[63, 160, 265, 305–307]

The conventional clinical approach is consequently to identify genuine deficiency, clarify the therapeutic aim and discuss the expected benefit without promising longer survival. Failure to feel better after treatment requires reassessment of the diagnosis, residual congestion, comorbid illness and functional limitation. Iron therapy should be embedded in a wider rehabilitation and nutrition plan rather than treated as an isolated correction of a laboratory result.

Erythropoiesis-stimulating treatment has a different evidence base. RED-HF did not improve clinical outcomes with darbepoetin alfa in systolic HF and anaemia, and thromboembolic events increased. Raising haemoglobin is therefore not, by itself, a valid HF treatment target. Decisions about erythropoiesis-stimulating agents for a separate renal or haematological indication belong within the relevant specialty pathway; the HF trial should neither be ignored nor misapplied to every other indication. [308]

9.10. Pulmonary disease and sleep-disordered breathing

COPD, sleep-disordered breathing and HF share symptoms but require different diagnostic and therapeutic decisions. Breathlessness should not be assigned to COPD solely because the patient smokes, or to HF solely because LVEF is reduced. Spirometry is best interpreted when congestion has been controlled, since pulmonary oedema can alter measured airflow. Inhaler technique, oxygenation, infection, deconditioning and respiratory-muscle weakness may all contribute to persistent limitation. Cardioselective beta-blockers can be used when a valid cardiac indication exists, with individual monitoring rather than automatic exclusion because of COPD.

Table 9.12. Respiratory phenotypes and therapeutic boundaries

Clinical problem	Assessment priority	Key limitation
COPD with HF	Confirm obstruction in a stable state; assess inhaler use, hypoxaemia and exacerbations.	Do not withdraw an indicated beta-blocker reflexively or prescribe one simply to prevent COPD exacerbations.
Obstructive sleep apnoea	Clarify obstructive events and symptoms through an appropriate sleep assessment.	Treatment may improve sleep and symptoms; an HF survival benefit is not established by that improvement alone.
Predominant central sleep apnoea	Identify HF phenotype and distinguish central from obstructive events before choosing equipment.	The selected ESC 2026 table retains a Class III A recommendation against ASV in HFrEF with predominant CSA.
Fatigue despite apparent respiratory improvement	Review congestion, iron status, mood, frailty and other non-respiratory contributors.	An improved apnoea index is not a complete measure of clinical recovery.

[1, 65, 66, 309]

BLOCK COPD tested metoprolol in patients without an established indication for beta-blockade and found more hospitalised exacerbations. That population does not justify withholding evidence-based beta-blocker therapy from a patient with a clear HF indication. The distinction between testing a drug to prevent pulmonary events and prescribing it for a cardiac disease must remain explicit. [309]

SERVE-HF demonstrated excess mortality with the studied ASV strategy in HFrEF and predominant CSA. ADVENT-HF, using a different system in sleep-disordered breathing, improved apnoea control but did not reduce its cardiovascular composite or mortality and did not reproduce the same mortality signal. The discordance must be acknowledged; it does not authorise a silent reversal of the current ESC recommendation. Device selection and management require specialist sleep and HF review, with the patient's type of apnoea and clinical objective documented. [1, 65, 66]

The sleep history should include information from the patient and, where appropriate, the partner. Snoring, witnessed pauses, nocturnal dyspnoea, insomnia and daytime sleepiness should lead to an appropriate differential diagnosis, not an empirical device prescription.

9.11. Psychological health, cognition and caregiver wellbeing

Depression, anxiety, fear of exertion and cognitive difficulty can affect self-care, participation in rehabilitation and interpretation of symptoms. They should be assessed without assuming that distress is an inevitable consequence of chronic illness or that poor adherence reflects unwillingness. Screening identifies a need for further evaluation; a positive questionnaire is not, by itself, a psychiatric diagnosis. Assessment should include the patient's own account, functional impact, sleep, substance use, available support and the possibility that hypoperfusion, medication effects or acute illness are contributing. [310]

Table 9.13. Integrating psychological and cognitive assessment

Finding	Clinical response	Avoid
Depressive or anxiety symptoms	Assess severity, functional effects and safety; arrange psychological or psychiatric care when indicated.	Assuming that all distress will disappear after decongestion.
Fear of exercise or of ICD shocks	Explain the safety plan, agree on graded activity and involve the rehabilitation/device team.	Using reassurance alone without addressing the feared event.
Memory or executive difficulties	Reconcile medicines, simplify instructions and assess capacity for self-management.	Confusing a complex regimen with an inability to participate in decisions.
Caregiver strain	Ask about workload, sleep, distress and practical support; agree on shared responsibilities.	Treating unpaid caregiving as an unlimited resource.
Persistent symptom burden or uncertainty about goals	Offer supportive and palliative expertise alongside active HF treatment.	Reserving goal-setting and symptom support for the final days of life.

[44, 310]

The 2026 ESC HF source supports assessment of anxiety, depression and frailty to inform individual care plans (IIa C). The purpose is actionable care rather than screening for its own sake. A positive finding should lead to an identified professional, agreed intervention and reassessment. Communication methods should accommodate sensory impairment, language barriers and fatigue, while preserving privacy and the patient's preferences for caregiver involvement. [1, 310]

MOOD-HF did not show that escitalopram improved death or hospitalisation, or depression outcomes relative to placebo, in the studied HF population. This does not mean depression should go untreated. It means an antidepressant should not be prescribed as a prognostic HF therapy. Treatment requires psychiatric reasoning, attention to adverse effects and interactions, and access to psychological approaches rather than an expectation that one drug will resolve the entire care problem. [311]

PAL-HF demonstrated better quality of life and psychological/spiritual outcomes with an interdisciplinary palliative intervention, without a demonstrated reduction in mortality or rehospitalisation. Supportive care therefore has value beyond survival endpoints. It can assist with breathlessness, uncertainty, family communication and decisions about treatment burden while disease-modifying therapy and rehabilitation continue. [44]

9.12. Thyroid disease, gout, pain, lipids and sexual health

Common conditions outside the principal HF pathways can cause substantial morbidity or introduce preventable treatment hazards. Management of thyroid disease, gout, arthritis, dyslipidaemia and sexual dysfunction should account for the specific indication, kidney function and formulation. A symptom-focused review is more useful than indiscriminate testing or treatment based solely on a comorbidity label.

Table 9.14. Frequently overlooked clinical interfaces

Problem	Useful approach	Important caution
Thyroid abnormality	Interpret TSH with free hormone concentrations, symptoms, acute illness and amiodarone exposure.	An isolated low T3 or mild TSH rise does not establish an indication for HF-directed thyroid treatment.
Gout / arthritis	Treat the cause of pain and use a renal- and interaction-appropriate strategy.	NSAIDs and COX-2 inhibitors may worsen HF; glucocorticoids also require attention to fluid and glucose effects.
Colchicine	Check the specific label, renal/hepatic function and interacting drugs.	Avoid a universal claim that all colchicine is contraindicated in dialysis; restrictions differ by formulation and indication.
Dyslipidaemia	Use established atherosclerotic or kidney-disease indications for lipid lowering.	Do not start a statin solely as treatment for HF, or stop one simply because HF is present.
Sexual dysfunction	Discuss symptoms, exercise tolerance, vascular disease, medications and psychological factors.	PDE5 inhibitors must not be combined with nitrates; clinical stability and product-specific precautions remain essential.

[54, 312–314]

TRUST found no symptomatic benefit of routine levothyroxine in older adults with subclinical hypothyroidism. It was not a trial of severe overt hypothyroidism or a general HF-treatment study. Persistent biochemical abnormality should therefore be interpreted in its endocrine context rather than converted into a universal age-independent treatment threshold. Hyperthyroidism associated with atrial fibrillation or tachycardia-mediated deterioration requires a different, cause-specific pathway. [314]

For gout, the ACR guideline supports allopurinol as a preferred first-line urate-lowering therapy, including in CKD, with a low starting dose and subsequent titration. Urate lowering treats gout; it has not become a disease-modifying HF therapy. Colchicine has clinically important CYP3A4/P-glycoprotein interactions. The US COLCRYS label contains specific reduced regimens for dialysis but prohibits important combinations in renal or hepatic impairment. It cannot be substituted for the locally applicable formulation’s prescribing information. [312, 313]

Pain, mobility and sexual health affect adherence and quality of life. Stable patients may be reassured and supported to resume appropriate activities, while new angina, syncope or severe breathlessness requires evaluation. These subjects should be invited sensitively, not left unaddressed because the consultation focuses on ventricular function.

9.13. Cardiac rehabilitation: indication and evidence

Cardiac rehabilitation is a structured, multidisciplinary treatment rather than a generic instruction to exercise. It integrates assessment, physical training, risk-factor management, education, nutrition and psychological support. The evidence should nevertheless be described according to the intervention and population studied: a programme improving peak oxygen uptake or SPPB has not necessarily demonstrated fewer deaths, and an exercise trial cannot validate every component of a complex rehabilitation service. [56, 315, 316]

Table 9.15. What major rehabilitation trials do—and do not—show

Study	Principal message	Application boundary
HF-ACTION	Exercise training was safe in selected stable HFrEF; the unadjusted primary composite was not statistically significant.	Adjusted and secondary findings should not be reported as unequivocal mortality reduction.
REHAB-HF	Early multidomain rehabilitation improved physical function after HF hospitalisation in older adults.	The study did not establish a reduction in 6-month rehospitalisation or mortality.
SMARTEX-HF	High-intensity intervals were not superior to moderate continuous training on the principal remodelling endpoint.	Adherence and achieved intensity matter; HIIT is not the default superior prescription.
REACH-HF	A facilitated home-based programme improved disease-specific quality of life.	Home delivery can expand access but is not unsupervised exercise for every risk category.
TELEREH-HF	Hybrid telerehabilitation improved short-term function; long-term days alive and out of hospital were not improved.	Technical feasibility and early functional gain do not guarantee long-term event reduction.

[266, 299, 317–319]

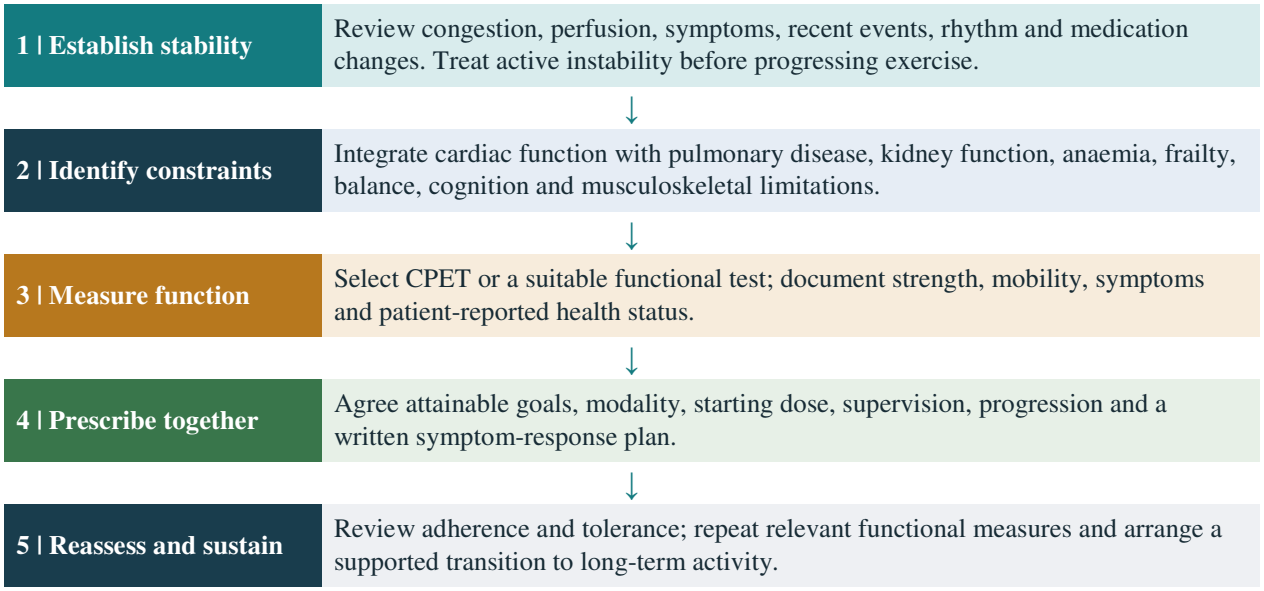
The 2026 ESC CR recommendations support rehabilitation for chronic HFrEF, HFpEF, LVAD and transplant populations, with the specific goals of each recommendation kept distinct. The selected table gives Class I B1 for HFrEF hospitalisation/function/quality-of-life outcomes and for HFpEF function/quality of life; the HFpEF hospitalisation recommendation is IIa B1. Initiation after decompensation requires clinical stability and individual assessment. [56]

The correct clinical question is not only whether exercise is beneficial, but how to make an evidence-based programme feasible and safe for this patient. Recurrent admissions, frailty, anxiety, transport problems and kidney disease may increase the need for adaptation rather than eliminate eligibility. The programme should begin from the patient's attainable baseline and should judge success by participation, function, symptoms and the ability to sustain activity after formal supervision ends. [266, 299]

9.14. Assessment before rehabilitation

Rehabilitation begins with a clinical and functional assessment, not with an exercise intensity copied from a generic schedule. The clinician should establish whether symptoms reflect stable limitation or active deterioration, identify the dominant cardiac and extracardiac constraints, and determine whether the proposed setting can manage them safely. A recent hospitalisation is a reason for reassessment and graded recovery; it is not a reason either for prolonged immobility or for immediate vigorous training. [56, 266]

Figure 9.2. Assessment-to-prescription rehabilitation pathway



[56, 266]

The baseline assessment should include exertional symptoms, orthostatic symptoms, resting blood pressure and rhythm, volume status, recent laboratory results and the therapeutic plan. Uncontrolled arrhythmia, ongoing ischaemia, decompensated congestion or clinically important hypoperfusion requires medical evaluation rather than a routine training session. Equipment, staff competencies and emergency procedures should match the patient's risk. [56]

CPET can distinguish limitations in cardiovascular reserve, ventilation and conditioning and can inform intensity where available. A walk test, chair-rise performance, gait speed and the SPPB provide complementary information, especially in frailty. They are not interchangeable measurements. Select the assessment that can be performed reliably and repeated meaningfully, rather than excluding a patient because maximal testing is impractical. [56, 266, 304]

An initial goal such as walking to a nearby shop, climbing the home staircase or transferring independently can make rehabilitation relevant. Record both the physiological starting point and the activity the person wants to regain; improvement in one does not guarantee improvement in the other. [56]

9.15. Exercise prescription and progression

An exercise prescription specifies frequency, intensity, duration, modality and progression, together with supervision and stopping criteria. It should be adjusted to current function rather than determined by LVEF alone. Perceived exertion and symptom response are particularly useful when beta-blockade, atrial fibrillation, pacing or chronotropic incompetence makes heart-rate targets unreliable. [56, 320]

Table 9.16. A practical, individualised exercise prescription

Component	Starting approach and progression	Clinical qualification
Endurance	Walking or cycling in tolerable bouts. ESC chronic-HF guidance describes progression from 2–3 to 3–5 days/week and from 15–30 to 45–60 minutes/session.	These are progression ranges, not an entry requirement. Shorter bouts may be necessary in severe deconditioning.
Intensity	Begin at an assessed, symptom-tolerated intensity; moderate training is a practical reference, with lower intensity in selected patients.	Do not prescribe vigorous work solely because the resting examination is reassuring. Integrate functional testing and recovery.
Resistance	Begin with safe technique and low load; progressively approach at least 2 days/week, at least 2 sets of 8–15 repetitions and 40–60% of 1RM when appropriate.	Avoid breath-holding and straining. Adapt to frailty, joint disease, sternotomy precautions and device-related restrictions.
Balance and mobility	Include gait, transfers, chair rises and balance practice when deficits are present.	Falls risk and functional dependence may be more urgent targets than aerobic intensity.
Inspiratory muscle work	Consider supervised instruction and an assessed prescription for selected patients with respiratory muscle limitation.	This is complementary training, not a substitute for diagnosing pulmonary disease or treating congestion.
Recovery and review	Include warm-up and cool-down, symptom review and graded progression of one or a few components at a time.	Stop and assess new chest pain, presyncope, disproportionate dyspnoea or sustained symptomatic palpitations.

[56, 266]

The objective is a sustainable dose of exercise, not rapid achievement of every nominal target. Progression may first increase the accumulated duration or number of tolerable bouts, then increase workload. Recovery between sessions, fatigue the following day and the ability to continue ordinary activities are useful checks against excessive prescription. [56]

High-intensity interval training is an option for selected, assessed patients, not the default standard for all HF. SMARTEX-HF did not establish superiority over moderate continuous training for its principal remodelling comparison; difficulty achieving assigned intensities also limits simple interpretation of training labels. [318]

9.16. Programme adaptation and long-term maintenance

A rehabilitation programme should be modified when the patient's constraints change, not abandoned because the standard format is unsuitable. Frailty, comorbidities and access inform the exercise prescription, including the choice of setting, training content, contact frequency and the plan after formal supervision ends. [56]

Table 9.17. Adapting rehabilitation without losing its therapeutic purpose

Clinical context	Programme emphasis	Practical safeguard
HFpEF and obesity	Combine aerobic activity, strength preservation, nutritional support and management of dominant comorbidities.	Do not equate weight loss with muscle recovery; assess function and nutritional adequacy.
Frailty after decompensation	Use low-burden, progressive balance, mobility, strength and endurance work.	Stabilise active HF and reassess falls risk; functional benefit does not imply proven mortality reduction.
Kidney disease or diabetes	Coordinate exercise with volume status, laboratory surveillance, meals and glucose-lowering treatment.	Avoid dehydration and assess hypoglycaemia risk where relevant; adapt during intercurrent illness.
AF, pacing or ICD	Use symptom- and test-informed targets and review device settings and arrhythmic history.	Arrange device-team input when exercise may approach programmed therapy zones; rate targets depend on clinical assessment and device settings.
LVAD or transplantation	Use specialist rehabilitation with education, equipment handling and procedure-specific precautions.	Account for anticoagulation, driveline or wound protection, infection risk and altered haemodynamic responses.
Home or hybrid programme	Provide an explicit prescription, scheduled support, monitoring and a route for clinical escalation.	Choose the delivery model around clinical safety, patient capability and access, not technology availability alone.

[56, 266, 299, 319]

Home-based care is not synonymous with unsupervised care. REACH-HF supports a facilitated home programme in an HFrEF population, with benefit in disease-specific health status. TELEREH-HF showed that short-term gains during a structured hybrid intervention do not automatically translate into better long-term clinical outcomes. Programme duration and the maintenance system must therefore be made explicit. [299, 319]

At reassessment, compare function with the same method, enquire about participation and adverse symptoms, and examine whether the programme remains achievable. Missed sessions may reflect transport, caregiving demands, low mood or treatment burden rather than unwillingness. A shorter, supported programme that the patient completes may be more useful than an ambitious prescription that cannot be implemented. [56]

Formal discharge from rehabilitation should transfer an activity plan, a named contact, review triggers and maintenance goals to the continuing-care team. Lifelong activity is a longitudinal treatment task rather than a certificate of programme completion. [56]

9.17. Remote monitoring and digital care

Remote monitoring is a clinical service with a measurement component. Data transmission alone cannot improve congestion, correct medication errors or provide reassurance: those effects depend on interpretation and action. Continuous treatment optimisation should be distinguished from indiscriminate emergency alerts, and trial evidence should be interpreted according to the reported outcomes. [235]

Table 9.18. Remote-care evidence: the intervention is more than the device

Study or modality	Supported interpretation	Important boundary
TIM-HF2	Structured remote patient management reduced the primary measure of days lost to unplanned cardiovascular admission or death.	A staffed, protocol-based service was tested; this is not proof for every home application or wearable.
GUIDE-HF	The overall primary comparison of haemodynamic-guided care was neutral.	A prespecified pre-COVID analysis suggested benefit; it does not replace the overall randomised result.
MONITOR-HF	PA-pressure-guided management improved health status and reduced HF hospitalisations in the studied population.	Participants were selected, symptomatic patients with prior HF hospitalisation, cared for within an organised service.
TELEREH-HF	Hybrid telerehabilitation produced short-term functional benefits but no significant improvement in its long-term primary outcome.	An exercise intervention and an implanted haemodynamic-monitoring strategy are different clinical interventions.
Device surveillance	Interrogation can identify technical problems and arrhythmic events relevant to clinical care.	Technical surveillance should not be presented as interchangeable with proven HF-event prevention.
Consumer measurements	Symptoms, weight, activity and blood pressure can support clinical review when reliable and actionable.	Accuracy, adherence, digital access and a response pathway must be established; more measurements are not necessarily better care.

[234, 235, 319, 321]

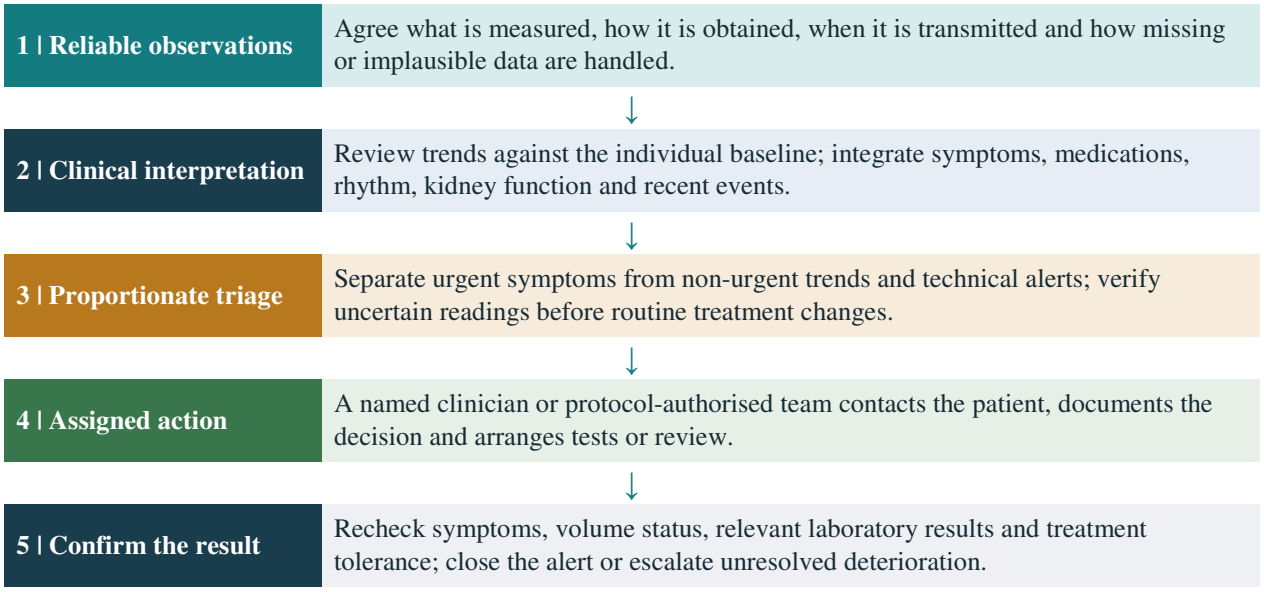
The selected 2026 ESC HF recommendation supports considering remote PA-pressure monitoring in symptomatic NYHA III patients with an HF admission within the preceding 12 months (IIa, B1). Non-invasive telemonitoring has a weaker recommendation (IIb, B1). These are not equivalent endorsements, and neither implies universal implantation or routine distribution of a particular commercial product. [1]

Selection should establish whether the patient and service can act on the information. Practical considerations include the ability to transmit measurements, clinical capacity to respond, laboratory access after treatment changes and a realistic plan for holidays or out-of-hours deterioration. A patient must understand that routine remote transmission is not an emergency-response system. [53]

Making a remote-monitoring service clinically accountable

A useful implementation model links each measurement to a defined decision and each decision to reassessment. The design below is a conceptual service model, not a validated prediction model or a reproduction of a guideline algorithm. It can be adapted to non-invasive monitoring or an implanted haemodynamic system, but the thresholds and response protocols must remain modality- and patient-specific. [234, 321]

Figure 9.3. A closed-loop remote-monitoring service



[234, 321]

For example, a rise in body weight without breathlessness or oedema may warrant verification and dietary or medication enquiry, rather than automatic diuretic escalation. Conversely, worsening orthopnoea, hypotension or reduced urine output should not be dismissed because weight is unchanged. PA pressure and weight reflect different aspects of the clinical state and should not be treated as interchangeable measurements. [53, 234, 235]

Alert burden is a safety issue. Services should audit the proportion of actionable alerts, time to review, unresolved events and unintended consequences of treatment changes. False reassurance and excessive intervention are both potential failures. Patients with limited connectivity, language barriers or cognitive impairment need a supported alternative rather than exclusion from effective follow-up. [53]

The programme should specify consent, appropriate access to clinical information, data stewardship and communication with the primary-care and specialist teams. Where an intervention changes a diuretic or RAAS-active medicine, the feedback loop must include blood pressure, symptoms and laboratory surveillance, not just a graph showing that the original alert has disappeared. [33, 53]

9.18. Nutrition, fluid intake and prevention of intercurrent illness

Lifestyle advice should reduce risk without creating avoidable thirst, malnutrition, inactivity or treatment fatigue. Advice should be individualized rather than based on uniform restriction. The task of the continuing-care team is to translate that principle into a feasible plan and to revise it when congestion, renal function, appetite, weather, illness or goals of care change. [53]

Table 9.19. Individualising lifestyle and prevention advice

Domain	Clinical purpose	Avoid an automatic rule
Dietary pattern and salt	Support a balanced, affordable diet; identify excessive salt intake and protect nutritional adequacy.	Do not promise fewer events from severe sodium restriction in every patient.
Fluid intake	Tailor advice to congestion, sodium, renal function, thirst and environmental conditions.	Do not prescribe the same daily limit indefinitely to every stable patient.
Body composition	Track appetite, unintentional weight loss, strength and function alongside weight.	A falling scale reading may represent decongestion, fat loss or muscle loss; the implications differ.
Vaccination and infection	Review influenza and pneumococcal protection and other indicated vaccines under applicable national guidance.	Do not equate observational associations with a proven universal mortality benefit.
Tobacco, alcohol and drugs	Offer cessation support; advise abstinence in alcohol-related cardiomyopathy and avoidance of harmful drug exposure.	Education without support is often insufficient; use a non-judgemental discussion.
Travel and daily living	Plan medicines, access to care, activity, temperature exposure and device needs around clinical stability.	Recent instability or a new functional decline should prompt review rather than a generic reassurance.

[53, 322–324]

SODIUM-HF did not demonstrate a significant reduction in its primary clinical-event composite with the lower-sodium intervention. FRESH-UP, in stable chronic HF, did not show a statistically significant between-group improvement in the primary KCCQ outcome with liberal intake; restriction produced more thirst. Neither trial supports indiscriminate excess intake, and neither establishes the correct strategy for severe hyponatraemia or refractory congestion. [322, 323]

IVVE did not significantly reduce its overall co-primary cardiovascular outcomes with influenza vaccination, although selected secondary and seasonal analyses were favourable. Vaccination should therefore be discussed as infection prevention within guideline-based care, not as a guaranteed HF mortality treatment. During significant acute illness, review intake, perfusion, renal function and medication safety; SGLT2 inhibition may require temporary interruption during critical illness or prolonged fasting. [1, 33, 324]

9.19. Constructed teaching cases: integrating competing priorities

Case 1 | Kidney dysfunction, potassium and preventable undertreatment

A 68-year-old patient with chronic HFrEF and CKD returns after an MRA dose change. Potassium is 5.6 mmol/L, creatinine has risen and blood pressure is stable. The patient is not breathless but has started a potassium-containing salt substitute and an over-the-counter anti-inflammatory for knee pain. The immediate task is to establish urgency, verify the result where appropriate and assess ECG findings and symptoms, rather than label all prognostic therapy permanently intolerable. Medication reconciliation, volume assessment and review of the renal trajectory identify potentially reversible contributors. The team determines any temporary dose modification, laboratory reassessment and longer-term potassium-control strategy. A binder may help maintain indicated treatment, but DIAMOND and REALIZE-K do not establish a mortality benefit from that

strategy. The plan must name who reviews the repeat result and when treatment is reconsidered. [9, 33, 150, 151]

Case 2 | HFpEF, obesity and frailty after hospitalization

A 76-year-old patient with HFpEF and obesity is euvolemic after admission but struggles to rise from a chair and is afraid to walk outside. A purely weight-centered assessment would miss an important functional deficit. The review includes nutrition, strength, mobility, balance, mood, comorbidities and the patient's own goal of resuming independent shopping. A supervised, graded programme initially prioritises safe transfers, balance and tolerable walking, with resistance work and nutritional support as appropriate. Weight-directed treatment is assessed separately from muscle recovery. REHAB-HF supports improvement in physical function in a recently hospitalized older population, while STEP-HFpEF and SUMMIT inform selected obesity-related HFpEF treatment. These findings do not justify promising an identical response or substituting weight loss for rehabilitation. Follow-up records function, symptoms, adherence and nutritional tolerance, not only kilograms lost. [166, 167, 266, 304]

Case 3 | A digital alert that requires a clinical response

A 72-year-old patient with NYHA III HF and a recent admission transmits a sustained upward PA-pressure trend. Weight has changed little. The team first confirms reliable acquisition, contacts the patient and reviews symptoms, adherence, recent medicines, renal function and potential infection. Any therapeutic adjustment is linked to blood-pressure and laboratory reassessment. A technical alert is not closed merely because a message was sent: the response and its clinical effect must be documented. MONITOR-HF supports benefit in a selected population managed within a structured service, whereas the overall GUIDE-HF primary result was neutral. The case therefore illustrates selection and a closed feedback loop, not universal device efficacy. If symptoms indicate acute deterioration, direct assessment takes precedence over waiting for the next routine transmission. [234, 235]

Bibliography

1. Køber L, Adamo M, Ruwald AC, et al. 2026 ESC Guidelines for the management of heart failure. Eur Heart J. 2026;47(38):5346–5457. doi:10.1093/eurheartj/ehag100.

2. Bozkurt B, Coats AJS, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the HFSA, HFA of the ESC and JHFS. Eur J Heart Fail. 2021;23:352–380. doi:10.1002/ejhf.2115.

3. Arbelo E, Protonotarios A, Gimeno JR, et al. 2023 ESC Guidelines for the management of cardiomyopathies. Eur Heart J. 2023;44:3503–3626. doi:10.1093/eurheartj/ehad194.

4. Docherty KF, Lam CSP, Rakisheva A, et al. Heart failure diagnosis in the general community—who, how and when? A clinical consensus statement of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur J Heart Fail. 2023;25(8):1185-1198. doi:10.1002/ejhf.2946.

5. Halliday BP, Wassall R, Lota AS, et al. 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. doi:10.1016/S0140-6736(18)32484-X.

6. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28:1–39.e14. doi:10.1016/j.echo.2014.10.003.

7. Pieske B, Tschöpe C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm. A consensus recommendation from the Heart Failure Association of the ESC. Eur Heart J. 2019;40:3297–3317. doi:10.1093/eurheartj/ehz641.

8. Mueller C, McDonald K, de Boer RA, et al. 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. doi:10.1002/ejhf.1494.

9. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42:3599–3726. doi:10.1093/eurheartj/ehab368.

10. Praz F, Borger MA, Lanz J, et al. 2025 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2025;46:4635–4736. doi:10.1093/eurheartj/ehaf194.

11. Tsutsui H, Albert NM, Coats AJS, et al. Natriuretic peptides: role in the diagnosis and management of heart failure: a scientific statement from the Heart Failure Association of the European Society of Cardiology, Heart Failure Society of America and Japanese Heart Failure Society. Eur J Heart Fail. 2023;25(5):616-631. doi:10.1002/ejhf.2848.

12. Nagueh SF, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography and for Heart Failure With Preserved Ejection Fraction Diagnosis: an update from the American Society of Echocardiography. J Am Soc Echocardiogr. 2025;38:537–569. doi:10.1016/j.echo.2025.03.011.

13. Schulz-Menger J, Collini V, Gröschel J, et al. 2025 ESC Guidelines for the management of myocarditis and pericarditis. Eur Heart J. 2025;46:3952–4041. doi:10.1093/eurheartj/ehaf192.

14. Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2021;42:1554–1568. doi:10.1093/eurheartj/ehab072.

15. Peters AE, Tromp J, Shah SJ, et al. Phenomapping in heart failure with preserved ejection fraction: insights, limitations, and future directions. Cardiovasc Res. 2023;118(18):3403–3415. doi:10.1093/cvr/cvac179.

16. Anker SD, Usman MS, Anker MS, et al. Patient phenotype profiling in heart failure with preserved ejection fraction to guide therapeutic decision making. A scientific statement of the Heart Failure Association, the European Heart Rhythm Association of the European Society of Cardiology, and the European Society of Hypertension. Eur J Heart Fail. 2023;25(7):936-955. doi:10.1002/ejhf.2894.

17. Folsom AR, Yamagishi K, Hozawa A, Chambless LE. Absolute and attributable risks of heart failure incidence in relation to optimal risk factors. Circ Heart Fail. 2009;2(1):11–17. doi:10.1161/CIRCHEARTFAILURE.108.794933.

18. SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med. 1992;327(10):685–691. doi:10.1056/NEJM199209033271003.

19. Caraballo C, Desai NR, Mulder H, et al. Clinical implications of the New York Heart Association classification. J Am Heart Assoc. 2019;8(23):e014240. doi:10.1161/JAHA.119.014240.

20. Crespo-Leiro MG, Metra M, Lund LH, et al. 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. doi:10.1002/ejhf.1236.

21. Pagnesi M, Lombardi CM, Chiarito M, et al. Prognostic impact of the updated 2018 HFA-ESC definition of advanced heart failure: results from the HELP-HF registry. Eur J Heart Fail. 2022;24:1493–1503. doi:10.1002/ejhf.2561.

22. Baudry G, Crespo-Leiro MG, Delmas C, et al. Identifying and overcoming barriers to referral in advanced heart failure. A scientific statement of the Heart Failure Association of the ESC. Eur J Heart Fail. 2025;27:3312–3325. doi:10.1002/ejhf.70003.

23. Peled Y, Ducharme A, Kittleson M, et al. ISHLT Guidelines for the Evaluation and Care of Cardiac Transplant Candidates—2024. J Heart Lung Transplant. 2024;43(10):1529–1628.e54. doi:10.1016/j.healun.2024.05.010.

24. Pagnesi M, Ghiraldin D, Vizzardi E, et al. Detailed Assessment of the “I Need Help” Criteria in Patients With Heart Failure: Insights From the HELP-HF Registry. Circ Heart Fail. 2023;16:e011003. doi:10.1161/CIRCHEARTFAILURE.123.011003.

25. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res. 2023;118(17):3272–3287. doi:10.1093/cvr/cvac013.

26. Emmons-Bell S, Johnson C, Roth G. Prevalence, incidence and survival of heart failure: a systematic review. Heart. 2022;108(17):1351–1360. doi:10.1136/heartjnl-2021-320131.

27. Seferović PM, Polovina M, Savarese G, et al. Insights into the European heart failure epidemiology. Eur J Heart Fail. 2025;27(11):1950–1960. doi:10.1002/ejhf.3710.

28. Christiansen MN, Køber L, Weeke P, et al. Age-specific trends in incidence, mortality, and comorbidities of heart failure in Denmark, 1995 to 2012. Circulation. 2017;135(13):1214–1223. doi:10.1161/CIRCULATIONAHA.116.025941.

29. Conrad N, Judge A, Tran J, et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. Lancet. 2018;391(10120):572–580. doi:10.1016/S0140-6736(17)32520-5.

30. Lecoeur E, Domengé O, Fayol A, Jannot AS, Hulot JS. Epidemiology of heart failure in young adults: a French nationwide cohort study. Eur Heart J. 2023;44(5):383–392. doi:10.1093/eurheartj/ehac651.

31. Vasan RS, Xanthakis V, Lyass A, et al. Epidemiology of left ventricular systolic dysfunction and heart failure in the Framingham Study: an echocardiographic study over 3 decades. JACC Cardiovasc Imaging. 2018;11(1):1–11. doi:10.1016/j.jcmg.2017.08.007.

32. Stolfo D, Uijl A, Vedin O, et al. Sex-based differences in heart failure across the ejection fraction spectrum: phenotyping, and prognostic and therapeutic implications. JACC Heart Fail. 2019;7(6):505–515. doi:10.1016/j.jchf.2019.03.011.

33. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024;105(4S):S117–S314. doi:10.1016/j.kint.2023.10.018.

34. Vitale C, Jankowska E, Hill L, et al. Heart Failure Association of the European Society of Cardiology position paper on frailty in patients with heart failure. Eur J Heart Fail. 2019;21(11):1299–1305. doi:10.1002/ejhf.1611.

35. Garred CH, Malmborg M, Malik ME, et al. Age-specific mortality trends in heart failure over 25 years: a retrospective Danish nationwide cohort study. Lancet Healthy Longev. 2024;5(5):e326–e335. doi:10.1016/S2666-7568(24)00029-1.

36. Lindberg F, Benson L, Dahlström U, Lund LH, Savarese G. Trends in heart failure mortality in Sweden between 1997 and 2022. Eur J Heart Fail. 2025;27(2):366–376. doi:10.1002/ejhf.3506.

37. Shah KS, Xu H, Matsouaka RA, et al. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. J Am Coll Cardiol. 2017;70(20):2476–2486. doi:10.1016/j.jacc.2017.08.074.

38. Arulmuruganantha vadivel A, Holt A, Parveen S, et al. Importance of diagnostic setting in determining mortality in patients with new-onset heart failure: temporal trends in Denmark from 1997 to 2017. Eur Heart J Qual Care Clin Outcomes. 2022;8(7):750–760. doi:10.1093/ehjqcco/qcab073.

39. Lindmark K, Boman K, Stålhammar J, et al. Recurrent heart failure hospitalizations increase the risk of cardiovascular and all-cause mortality in patients with heart failure in Sweden: a real-world study. ESC Heart Fail. 2021;8(3):2144–2153. doi:10.1002/ehf2.13296.

40. Metra M, Adamo M, Tomasoni D, et al. Pre-discharge and early post-discharge management of patients hospitalized for acute heart failure: a scientific statement by the Heart Failure Association of the ESC. Eur J Heart Fail. 2023;25(7):1115–1131. doi:10.1002/ejhf.2888.

41. Gulati A, Jabbour A, Ismail TF, et al. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. JAMA. 2013;309:896–908. doi:10.1001/jama.2013.1363.

42. Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite outcomes in randomized trials: greater precision but with greater uncertainty? JAMA. 2003;289(19):2554–2559. doi:10.1001/jama.289.19.2554.

43. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation. 2006;113:1424–1433. doi:10.1161/CIRCULATIONAHA.105.584102.

44. Rogers JG, Patel CB, Mentz RJ, et al. Palliative Care in Heart Failure: The PAL-HF Randomized, Controlled Clinical Trial. J Am Coll Cardiol. 2017;70(3):331–341. doi:10.1016/j.jacc.2017.05.030.

45. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43:3618–3731. doi:10.1093/eurheartj/ehac237.

46. Gorter TM, van Veldhuisen DJ, Bauersachs J, et al. 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(1):16–37. doi:10.1002/ejhf.1029.

47. Mukherjee M, Rudski LG, Addetia K, et al. Guidelines for the Echocardiographic Assessment of the Right Heart in Adults and Special Considerations in Pulmonary Hypertension: recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr. 2025;38:141–186. doi:10.1016/j.echo.2025.01.006.

48. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the EHA, ESTRO and IC-OS. Eur Heart J. 2022;43:4229–4361. doi:10.1093/eurheartj/ehac244.

49. Mullens W, Damman K, Harjola VP, et al. 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(2):137–155. doi:10.1002/ejhf.1369.

50. Larsson SC, Tektonidis TG, Gigante B, Åkesson A, Wolk A. Healthy lifestyle and risk of heart failure: results from 2 prospective cohort studies. Circ Heart Fail. 2016;9(4):e002855. doi:10.1161/CIRCHEARTFAILURE.115.002855.

51. SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373(22):2103–2116. doi:10.1056/NEJMoa1511939.

52. 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. doi:10.1161/CIRCULATIONAHA.116.026807.

53. Jaarsma T, et al. 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(1):157–174. doi:10.1002/ejhf.2008.

54. Damman K, ter Maaten JM, Mayne KJ, et al. 2026 ESC Guidelines for the management of cardiovascular disease and chronic kidney disease, in collaboration with the European Renal Association (ERA). Eur Heart J. Published online 28 August 2026. doi:10.1093/eurheartj/ehag098.

55. McEvoy JW, McCarthy CP, Bruno RM, et al. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. Eur Heart J. 2024;45(38):3912–4018. doi:10.1093/eurheartj/ehae178.

56. Bäck M, Wilhelm M, Marcin T, et al. 2026 ESC Guidelines on cardiac rehabilitation. Eur Heart J. 2026;47(39):5631–5729. doi:10.1093/eurheartj/ehag099.

57. Mullens W, Abrahams Z, Francis GS, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol. 2009;53:589–596. doi:10.1016/j.jacc.2008.05.068.

58. Mullens W, Martens P, Testani JM, et al. Renal effects of guideline-directed medical therapies in heart failure: a consensus document from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2022;24(4):603–619. doi:10.1002/ejhf.2471.

59. Vrints C, Andreotti F, Koskinas KC, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes. Eur Heart J. 2024;45:3415–3537. doi:10.1093/eurheartj/ehae177.

60. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J. 2023;44:3720–3826. doi:10.1093/eurheartj/ehad191.

61. Perera D, Clayton T, O'Kane PD, et al. Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction. N Engl J Med. 2022;387:1351–1360. doi:10.1056/NEJMoa2206606.

62. Velazquez EJ, Lee KL, Jones RH, et al. Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy. N Engl J Med. 2016;374:1511–1520. doi:10.1056/NEJMoa1602001.

63. Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med. 2009;361:2436–2448. doi:10.1056/NEJMoa0908355.

64. McDonagh TA, Metra M, Adamo M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2023;44:3627–3639. doi:10.1093/eurheartj/ehad195.

65. Cowie MR, et al. Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. N Engl J Med. 2015;373:1095–1105. doi:10.1056/NEJMoa1506459.

66. Bradley TD, et al. Adaptive servo-ventilation for sleep-disordered breathing in patients with heart failure with reduced ejection fraction (ADVENT-HF): a multicentre, multinational, parallel-group, open-label, phase 3 randomised controlled trial. Lancet Respir Med. 2024;12:153–166. doi:10.1016/S2213-2600(23)00374-0.

67. Takeda A, Martin N, Taylor RS, Taylor SJC. Disease management interventions for heart failure. Cochrane Database Syst Rev. 2019;2019(1):CD002752. doi:10.1002/14651858.CD002752.pub4.

68. Van Spall HGC, Rahman T, Mytton O, et al. 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(11):1427–1443. doi:10.1002/ejhf.765.

69. Jonkman NH, Westland H, Groenwold RHH, et al. 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(11):861–871. doi:10.1016/j.cardfail.2016.06.422.

70. Aktaa S, Polovina M, Rosano G, et al. European Society of Cardiology quality indicators for the care and outcomes of adults with heart failure. Developed by the Working Group for Heart Failure Quality Indicators in collaboration with the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2022;24(1):132–142. doi:10.1002/ejhf.2371.

71. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. BMJ. 1999;319(7223):1492–1495. doi:10.1136/bmj.319.7223.1492.

72. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019;381:1995–2008. doi:10.1056/NEJMoa1911303.

73. Solomon SD, McMurray JJV, Vaduganathan M, et al. Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2024;391:1475–1485. doi:10.1056/NEJMoa2407107.

74. Cleland JGF, Bunting KV, Flather MD, et al. 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. doi:10.1093/eurheartj/ehx564.

75. Jhund PS, Talebi A, Henderson AD, et al. Mineralocorticoid receptor antagonists in heart failure: an individual patient level meta-analysis. Lancet. 2024;404:1119–1131. doi:10.1016/S0140-6736(24)01733-1.

76. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ. 2010;340:c117. doi:10.1136/bmj.c117.

77. Verbrugge FH, Omote K, Reddy YNV, et al. Heart failure with preserved ejection fraction in patients with normal natriuretic peptide levels is associated with increased morbidity and mortality. Eur Heart J. 2022;43:1941–1951. doi:10.1093/eurheartj/ehab911.

78. Borbély A, van der Velden J, Papp Z, et al. Cardiomyocyte stiffness in diastolic heart failure. Circulation. 2005;111:774–781. doi:10.1161/01.CIR.0000155257.33485.6D.

79. Borlaug BA, Olson TP, Lam CSP, et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2010;56:845–854. doi:10.1016/j.jacc.2010.03.077.

80. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation. 2016;133:2404–2412. doi:10.1161/CIRCULATIONAHA.116.021612.

81. Anderson LJ, Holden S, Davis B, et al. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. Eur Heart J. 2001;22:2171–2179. doi:10.1053/euhj.2001.2822.

82. Herman DS, Lam L, Taylor MRG, et al. Truncations of titin causing dilated cardiomyopathy. N Engl J Med. 2012;366:619–628. doi:10.1056/NEJMoa1110186.

83. Ware JS, Li J, Mazaika E, et al. Shared Genetic Predisposition in Peripartum and Dilated Cardiomyopathies. N Engl J Med. 2016;374:233–241. doi:10.1056/NEJMoa1505517.

84. Beuckelmann DJ, Näbauer M, Erdmann E. Intracellular calcium handling in isolated ventricular myocytes from patients with terminal heart failure. Circulation. 1992;85:1046–1055. doi:10.1161/01.CIR.85.3.1046.

85. van Heerebeek L, Hamdani N, Falcão-Pires I, et al. Low myocardial protein kinase G activity in heart failure with preserved ejection fraction. Circulation. 2012;126:830–839. doi:10.1161/CIRCULATIONAHA.111.076075.

86. Greenberg B, Butler J, Felker GM, et al. Calcium upregulation by percutaneous administration of gene therapy in patients with cardiac disease (CUPID 2): a randomised, multinational, double-blind, placebo-controlled, phase 2b trial. Lancet. 2016;387:1178–1186. doi:10.1016/S0140-6736(16)00082-9.

87. Neubauer S, Horn M, Cramer M, et al. Myocardial phosphocreatine-to-ATP ratio is a predictor of mortality in patients with dilated cardiomyopathy. Circulation. 1997;96:2190–2196. doi:10.1161/01.CIR.96.7.2190.

88. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987;316:1429–1435. doi:10.1056/NEJM198706043162301.

89. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med. 1999;341:709–717. doi:10.1056/NEJM199909023411001.

90. Packer M, Coats AJS, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344:1651–1658. doi:10.1056/NEJM200105313442201.

91. Bristow MR, Ginsburg R, Minobe W, et al. Decreased catecholamine sensitivity and beta-adrenergic-receptor density in failing human hearts. N Engl J Med. 1982;307:205–211. doi:10.1056/NEJM198207223070401.

92. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993–1004. doi:10.1056/NEJMoa1409077.

93. Mann DL, McMurray JJV, Packer M, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Circulation. 2004;109:1594–1602. doi:10.1161/01.CIR.0000124490.27666.B2.

94. Shah SJ, Lam CSP, Svedlund S, et al. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. Eur Heart J. 2018;39:3439–3450. doi:10.1093/eurheartj/ehy531.

95. Melenovsky V, Hwang SJ, Lin G, Redfield MM, Borlaug BA. Right heart dysfunction in heart failure with preserved ejection fraction. Eur Heart J. 2014;35:3452–3462. doi:10.1093/eurheartj/ehu193.

96. Mullens W, Dauw J, Martens P, et al. Acetazolamide in Acute Decompensated Heart Failure with Volume Overload. N Engl J Med. 2022;387:1185–1195. doi:10.1056/NEJMoa2203094.

97. Kitzman DW, Brubaker P, Morgan T, et al. 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. doi:10.1001/jama.2015.17346.

98. Prabhu S, Taylor AJ, Costello BT, et al. Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction: the CAMERA-MRI Study. J Am Coll Cardiol. 2017;70:1949–1961. doi:10.1016/j.jacc.2017.08.041.

99. Drazner MH, Hellkamp AS, Leier CV, et al. Value of clinician assessment of hemodynamics in advanced heart failure: the ESCAPE trial. Circ Heart Fail. 2008;1:170–177. doi:10.1161/CIRCHEARTFAILURE.108.769778.

100. Gargani L, Girerd N, Platz E, et al. Lung ultrasound in acute and chronic heart failure: a clinical consensus statement of the European Association of Cardiovascular Imaging (EACVI). Eur Heart J Cardiovasc Imaging. 2023;24:1569–1582. doi:10.1093/ehjci/jead169.

101. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med. 2002;347:161–167. doi:10.1056/NEJMoa020233.

102. Bayes-Genis A, Docherty KF, Petrie MC, et al. Practical algorithms for early diagnosis of heart failure and heart stress using NT-proBNP: a clinical consensus statement from the Heart Failure Association of the ESC. Eur J Heart Fail. 2023;25:1891–1898. doi:10.1002/ejhf.3036.

103. Maisel A, Mueller C, Nowak R, et al. 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. doi:10.1016/j.jacc.2010.02.025.

104. Gohar A, Rutten FH, den Ruijter H, et al. Mid-regional pro-atrial natriuretic peptide for the early detection of non-acute heart failure. Eur J Heart Fail. 2019;21:1219–1227. doi:10.1002/ejhf.1495.

105. Taylor CJ, Taylor KS, Jones NR, et al. Age-adjusted natriuretic peptide thresholds for a diagnosis of heart failure in the community: diagnostic accuracy study. ESC Heart Fail. 2025;12(5):3552-3568. doi:10.1002/ehf2.15383.

106. Myhre PL, Vaduganathan M, Claggett B, et al. B-Type Natriuretic Peptide During Treatment With Sacubitril/Valsartan: The PARADIGM-HF Trial. J Am Coll Cardiol. 2019;73:1264–1272. doi:10.1016/j.jacc.2019.01.018.

107. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J. 2019;40:237–269. doi:10.1093/eurheartj/ehy462.

108. Felker GM, Anstrom KJ, Adams KF, et al. 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. doi:10.1001/jama.2017.10565.

109. 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. doi:10.1161/CIRCULATIONAHA.118.034646.

110. Borlaug BA, Nishimura RA, Sorajja P, Lam CSP, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail. 2010;3:588–595. doi:10.1161/CIRCHEARTFAILURE.109.930701.

111. Eisman AS, Shah RV, Dhakal BP, et al. Pulmonary Capillary Wedge Pressure Patterns During Exercise Predict Exercise Capacity and Incident Heart Failure. Circ Heart Fail. 2018;11:e004750. doi:10.1161/CIRCHEARTFAILURE.117.004750.

112. Harada T, Sorimachi H, Obokata M, et al. Echocardiographic Diastolic Function Grading in Heart Failure With Preserved Ejection Fraction: Testing the Updated 2025 ASE Criteria. J Am Coll Cardiol. 2026;87:1261–1275. doi:10.1016/j.jacc.2025.11.024.

113. Reddy YNV, Kaye DM, Handoko ML, et al. Diagnosis of Heart Failure With Preserved Ejection Fraction Among Patients With Unexplained Dyspnea. JAMA Cardiol. 2022;7:891–899. doi:10.1001/jamacardio.2022.1916.

114. Selvaraj S, Myhre PL, Vaduganathan M, et al. Application of diagnostic algorithms for heart failure with preserved ejection fraction to the community. JACC Heart Fail. 2020;8(8):640-653. doi:10.1016/j.jchf.2020.03.013.

115. Paterson DI, Wells G, Erthal F, et al. OUTSMART HF: a randomized controlled trial of routine versus selective cardiac magnetic resonance for patients with nonischemic heart failure (IMAGE-HF 1B). Circulation. 2020;141(10):818-827. doi:10.1161/CIRCULATIONAHA.119.043964.

116. Messroghli DR, Moon JC, Ferreira VM, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: a consensus statement by the SCMR endorsed by the EACVI. J Cardiovasc Magn Reson. 2017;19:75. doi:10.1186/s12968-017-0389-8.

117. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation: Expert Recommendations. J Am Coll Cardiol. 2018;72:3158–3176. doi:10.1016/j.jacc.2018.09.072.

118. Baggiano A, Boldrini M, Martinez-Naharro A, et al. Noncontrast magnetic resonance for the diagnosis of cardiac amyloidosis. JACC Cardiovasc Imaging. 2020;13(1):69-80. doi:10.1016/j.jcmg.2019.03.026.

119. Becker MAJ, Cornel JH, van de Ven PM, et al. The prognostic value of late gadolinium-enhanced cardiac magnetic resonance imaging in nonischemic dilated cardiomyopathy: a review and meta-analysis. JACC Cardiovasc Imaging. 2018;11(9):1274–1284. doi:10.1016/j.jcmg.2018.03.006.

120. Chareonthaitawee P, Beanlands RS, Chen W, et al. Joint SNMMI–ASNC Expert Consensus Document on the Role of 18F-FDG PET/CT in Cardiac Sarcoid Detection and Therapy Monitoring. J Nucl Med. 2017;58:1341–1353. doi:10.2967/jnumed.117.196287.

121. Guazzi M, Arena R, Halle M, Piepoli MF, Myers J, Lavie CJ. 2016 Focused Update: Clinical Recommendations for Cardiopulmonary Exercise Testing Data Assessment in Specific Patient Populations. Circulation. 2016;133:e694–e711. doi:10.1161/CIR.0000000000000406.

122. Guazzi M, Wilhelm M, Halle M, et al. Exercise testing in heart failure with preserved ejection fraction: an appraisal through diagnosis, pathophysiology and therapy—a clinical consensus statement of the Heart Failure Association and European Association of Preventive Cardiology of the European Society of Cardiology. Eur J Heart Fail. 2022;24(8):1327-1345. doi:10.1002/ejhf.2601.

123. Obokata M, Kane GC, Reddy YNV, Olson TP, Melenovsky V, Borlaug BA. Role of Diastolic Stress Testing in the Evaluation for Heart Failure With Preserved Ejection Fraction: a simultaneous invasive–echocardiographic study. Circulation. 2017;135:825–838. doi:10.1161/CIRCULATIONAHA.116.024822.

124. Seferović PM, Tsutsui H, McNamara DM, et al. Heart Failure Association of the ESC, Heart Failure Society of America and Japanese Heart Failure Society position statement on endomyocardial biopsy. Eur J Heart Fail. 2021;23:854–871. doi:10.1002/ejhf.2190.

125. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383:1413–1424. doi:10.1056/NEJMoa2022190.

126. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. N Engl J Med. 2020;382:1883–1893. doi:10.1056/NEJMoa1915928.

127. Butler J, McMullan CJ, Anstrom KJ, et al. Vericiguat in patients with chronic heart failure and reduced ejection fraction (VICTOR): a double-blind, placebo-controlled, randomised, phase 3 trial. Lancet. 2025;406:1341–1350. doi:10.1016/S0140-6736(25)01665-4.

128. Bavendiek U, Großhennig A, Schwab J, et al. Digitoxin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2025;393:1155–1165. doi:10.1056/NEJMoa2415471.

129. van Veldhuisen DJ, Rienstra M, Mosterd A, et al. Low-dose digoxin in patients with heart failure with reduced or mildly reduced ejection fraction: a randomized controlled trial. Nat Med. 2026;32:2647–2653. doi:10.1038/s41591-026-04406-6.

130. Maddox TM, Januzzi JL Jr, Allen LA, et al. 2024 ACC Expert Consensus Decision Pathway for treatment of heart failure with reduced ejection fraction. J Am Coll Cardiol. 2024;83:1444–1488. doi:10.1016/j.jacc.2023.12.024.

131. European Medicines Agency. Entresto (sacubitril/valsartan): EU product information. Accessed 15 October 2026. Available from: https://www.ema.europa.eu/en/documents/product-information/entresto-epar-product-information_en.pdf

132. Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin–neprilysin inhibition in acute decompensated heart failure. N Engl J Med. 2019;380:539–548. doi:10.1056/NEJMoa1812851.

133. Wachter R, Senni M, Belohlavek J, et al. 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. doi:10.1002/ejhf.1498.

134. The SOLVD Investigators. 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. doi:10.1056/NEJM199108013250501.

135. Granger CB, McMurray JJV, Yusuf S, et al. 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. doi:10.1016/S0140-6736(03)14284-5.

136. Konstam MA, Neaton JD, Dickstein K, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. Lancet. 2009;374:1840–1848. doi:10.1016/S0140-6736(09)61913-9.

137. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353:9–13. doi:10.1016/S0140-6736(98)11181-9.

138. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure. Lancet. 1999;353:2001–2007. doi:10.1016/S0140-6736(99)04440-2.

139. Flather MD, Shibata MC, Coats AJS, et al. 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. doi:10.1093/eurheartj/ehi115.

140. Zannad F, McMurray JJV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011;364:11–21. doi:10.1056/NEJMoa1009492.

141. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348:1309–1321. doi:10.1056/NEJMoa030207.

142. Electronic Medicines Compendium. Eplerenone 25 mg film-coated tablets: Summary of Product Characteristics. Accessed 15 October 2026. Available from: https://www.medicines.org.uk/emc/product/13347/smpc

143. Zannad F, Ferreira JP, Pocock SJ, et al. 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(10254):819–829. doi:10.1016/S0140-6736(20)31824-9.

144. European Medicines Agency. Forxiga (dapagliflozin): EU product information. Accessed 15 October 2026. Available from: https://www.ema.europa.eu/en/documents/product-information/forxiga-epar-product-information_en.pdf

145. European Medicines Agency. Jardiance (empagliflozin): EU product information. Accessed 15 October 2026. Available from: https://www.ema.europa.eu/en/documents/product-information/jardiance-epar-product-information_en.pdf

146. Mebazaa A, Davison B, Chioncel O, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised trial. Lancet. 2022;400:1938–1952. doi:10.1016/S0140-6736(22)02076-1.

147. Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nat Med. 2022;28:568–574. doi:10.1038/s41591-021-01659-1.

148. Berg DD, Patel SM, Haller PM, et al. Dapagliflozin in patients hospitalized for heart failure: primary results of the DAPA ACT HF–TIMI 68 randomized clinical trial and meta-analysis of sodium-glucose cotransporter-2 inhibitors in patients hospitalized for heart failure. Circulation. 2025;152:1411–1422. doi:10.1161/CIRCULATIONAHA.125.076575.

149. Cautela J, Tartiere JM, Cohen-Solal A, et al. Management of low blood pressure in ambulatory heart failure with reduced ejection fraction patients. Eur J Heart Fail. 2020;22:1357–1365. doi:10.1002/ejhf.1835.

150. Butler J, Anker SD, Lund LH, et al. Patiromer for the management of hyperkalemia in heart failure with reduced ejection fraction: the DIAMOND trial. Eur Heart J. 2022;43:4362–4373. doi:10.1093/eurheartj/ehac401.

151. Kosiborod MN, Cherney DZI, Desai AS, et al. Sodium zirconium cyclosilicate for management of hyperkalemia during spironolactone optimization in patients with heart failure. J Am Coll Cardiol. 2025;85:971–984. doi:10.1016/j.jacc.2024.11.014.

152. European Medicines Agency. Veltassa (patiromer): EU product information. Accessed 15 October 2026. Available from: https://www.ema.europa.eu/en/documents/product-information/veltassa-epar-product-information_en.pdf

153. European Medicines Agency. Lokelma (sodium zirconium cyclosilicate): EU product information. Accessed 15 October 2026. Available from: https://www.ema.europa.eu/en/documents/product-information/lokelma-epar-product-information_en.pdf

154. Mentz RJ, Anstrom KJ, Eisenstein EL, et al. Effect of torsemide vs furosemide after discharge on all-cause mortality in patients hospitalized with heart failure: the TRANSFORM-HF randomized clinical trial. JAMA. 2023;329:214–223. doi:10.1001/jama.2022.23924.

155. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376:875–885. doi:10.1016/S0140-6736(10)61198-1.

156. European Medicines Agency. Procoralan (ivabradine): EU product information. Accessed 15 October 2026. Available from: https://www.ema.europa.eu/en/documents/product-information/procoralan-epar-product-information_en.pdf

157. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in Blacks with heart failure. N Engl J Med. 2004;351:2049–2057. doi:10.1056/NEJMoa042934.

158. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med. 1997;336:525–533. doi:10.1056/NEJM199702203360801.

159. Electronic Medicines Compendium. Digoxin tablets: Summary of Product Characteristics, sections 4.2–4.5. Accessed 15 October 2026. Available from: https://www.medicines.org.uk/emc/product/5465/smpc

160. Anker SD, Friede T, Butler J, et al. Intravenous ferric carboxymaltose in heart failure with iron deficiency: the FAIR-HF2 DZHK05 randomized clinical trial. JAMA. 2025;333:1965–1976. doi:10.1001/jama.2025.3833.

161. Teerlink JR, Diaz R, Felker GM, et al. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. N Engl J Med. 2021;384:105–116. doi:10.1056/NEJMoa2025797.

162. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med. 2022;387:1089–1098. doi:10.1056/NEJMoa2206286.

163. Cheng L, Hammersley D, Ragavan A, et al. Long-term follow-up of the TRED-HF trial: implications for therapy in patients with dilated cardiomyopathy and heart failure remission. Eur J Heart Fail. 2025;27:113–123. doi:10.1002/ejhf.3475.

164. European Medicines Agency. Verquvo (vericiguat): EU product information. Accessed 15 October 2026. Available from: https://www.ema.europa.eu/en/documents/product-information/verquvo-epar-product-information_en.pdf

165. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385:1451–1461. doi:10.1056/NEJMoa2107038.

166. Kosiborod MN, Abildstrøm SZ, Borlaug BA, et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. N Engl J Med. 2023;389:1069–1084. doi:10.1056/NEJMoa2306963.

167. Packer M, Zile MR, Kramer CM, et al. Tirzepatide for heart failure with preserved ejection fraction and obesity. N Engl J Med. 2025;392:427–437. doi:10.1056/NEJMoa2410027.

168. Vardeny O, Fang JC, Desai AS, et al. Dapagliflozin in heart failure with improved ejection fraction: a prespecified analysis of the DELIVER trial. Nat Med. 2022;28:2504–2511. doi:10.1038/s41591-022-02102-9.

169. Shah SJ, Katz DH, Selvaraj S, et al. Phenomapping for novel classification of heart failure with preserved ejection fraction. Circulation. 2015;131:269–279. doi:10.1161/CIRCULATIONAHA.114.010637.

170. Palau P, Seller J, Domínguez E, et al. Effect of β-blocker withdrawal on functional capacity in heart failure and preserved ejection fraction. J Am Coll Cardiol. 2021;78:2042–2056. doi:10.1016/j.jacc.2021.08.073.

171. Reddy YNV, Tada A, Obokata M, et al. Evidence-based application of natriuretic peptides in the evaluation of chronic heart failure with preserved ejection fraction in the ambulatory outpatient setting. Circulation. 2025;151(14):976-989. doi:10.1161/CIRCULATIONAHA.124.072156.

172. Kosiborod MN, Petrie MC, Borlaug BA, et al. Semaglutide in patients with obesity-related heart failure and type 2 diabetes. N Engl J Med. 2024;390:1394–1407. doi:10.1056/NEJMoa2313917.

173. Van Gelder IC, Rienstra M, Bunting KV, et al. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2024;45:3314–3414. doi:10.1093/eurheartj/ehae176.

174. European Medicines Agency. Kerendia (finerenone): EU product information. Accessed 15 October 2026. Available from: https://www.ema.europa.eu/en/documents/product-information/kerendia-epar-product-information_en.pdf

175. Vaduganathan M, Claggett BL, Kulac IJ, et al. Effects of the nonsteroidal MRA finerenone with and without concomitant SGLT2 inhibitor use in heart failure. Circulation. 2025;151:149–158. doi:10.1161/CIRCULATIONAHA.124.072055.

176. European Society of Cardiology. 2026 ESC Guidelines for the management of heart failure: official slide set. 2026. Accessed 15 October 2026. Available from: https://dam-assets.escardio.org/download/b2e587389baa11f185de06bdfb3e4be9

177. Nassif ME, Windsor SL, Borlaug BA, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. Nat Med. 2021;27:1954–1960. doi:10.1038/s41591-021-01536-x.

178. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014;370:1383–1392. doi:10.1056/NEJMoa1313731.

179. European Medicines Agency. Wegovy (semaglutide): EU product information. Accessed 15 October 2026. Available from: https://www.ema.europa.eu/en/documents/product-information/wegovy-epar-product-information_en.pdf

180. Borlaug BA, Zile MR, Kramer CM, et al. Effects of tirzepatide on circulatory overload and end-organ damage in heart failure with preserved ejection fraction and obesity: a secondary analysis of the SUMMIT trial. Nat Med. 2025;31:544–551. doi:10.1038/s41591-024-03374-z.

181. European Medicines Agency. Mounjaro (tirzepatide): EU product information. Accessed 15 October 2026. Available from: https://www.ema.europa.eu/en/documents/product-information/mounjaro-epar-product-information_en.pdf

182. European Medicines Agency. Questions and answers on the outcome of the assessment of the use of Mounjaro in HFpEF in adults with obesity. 30 January 2026. Available from: https://www.ema.europa.eu/en/documents/medicine-qa/questions-answers-outcome-assessment-use-mounjaro-treatment-heart-failure-preserved-ejection-fraction-adults-obesity_en.pdf

183. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med. 2019;381:1609–1620. doi:10.1056/NEJMoa1908655.

184. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. Lancet. 2003;362:777–781. doi:10.1016/S0140-6736(03)14285-7.

185. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008;359:2456–2467. doi:10.1056/NEJMoa0805450.

186. Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA. 2013;309:1268–1277. doi:10.1001/jama.2013.2024.

187. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. N Engl J Med. 2015;373:2314–2324. doi:10.1056/NEJMoa1510774.

188. Shah SJ, Borlaug BA, Chung ES, et al. Atrial shunt device for heart failure with preserved and mildly reduced ejection fraction (REDUCE LAP-HF II): a randomised, multicentre, blinded, sham-controlled trial. Lancet. 2022;399:1130–1140. doi:10.1016/S0140-6736(22)00016-2.

189. Hoeper MM, Oerke B, Wissmüller M, et al. Tadalafil for treatment of combined postcapillary and precapillary pulmonary hypertension in patients with heart failure and preserved ejection fraction: a randomized controlled phase 3 study. Circulation. 2024;150:600–610. doi:10.1161/CIRCULATIONAHA.124.069340.

190. Mueller S, Winzer EB, Duvinage A, et al. Effect of high-intensity interval training, moderate continuous training, or guideline-based physical activity advice on peak oxygen consumption in patients with heart failure with preserved ejection fraction: a randomized clinical trial. JAMA. 2021;325:542–551. doi:10.1001/jama.2020.26812.

191. von Haehling S, Doehner W, Evertz R, et al. Ferric carboxymaltose and exercise capacity in heart failure with preserved ejection fraction and iron deficiency: the FAIR-HFpEF trial. Eur Heart J. 2024;45:3789–3800. doi:10.1093/eurheartj/ehae479.

192. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2022;43:3997–4126. doi:10.1093/eurheartj/ehac262.

193. Glikson M, Nielsen JC, Kronborg MB, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J. 2021;42:3427–3520. doi:10.1093/eurheartj/ehab364.

194. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346:877–883. doi:10.1056/NEJMoa013474.

195. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352:225–237. doi:10.1056/NEJMoa043399.

196. Køber L, Thune JJ, Nielsen JC, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med. 2016;375:1221–1230. doi:10.1056/NEJMoa1608029.

197. Butt JH, Doi SN, Thune JJ, et al. Long-term effect of ICDs in nonischemic heart failure with reduced ejection fraction: extended follow-up analysis of DANISH. J Am Coll Cardiol. 2025;86:2402–2414. doi:10.1016/j.jacc.2025.08.089.

198. Selvanayagam JB, Cleland JGF, Hillis GS, et al. Cardiovascular magnetic resonance to guide defibrillator implantation for LVEF of 36% to 50%: the CMR GUIDE randomized clinical trial. JAMA. Published online 28 August 2026. doi:10.1001/jama.2026.17078.

199. Knops RE, Nordkamp LRAO, Delnoy PPHM, et al. Subcutaneous or transvenous defibrillator therapy. N Engl J Med. 2020;383:526–536. doi:10.1056/NEJMoa1915932.

200. Olgin JE, Pletcher MJ, Vittinghoff E, et al. Wearable cardioverter-defibrillator after myocardial infarction. N Engl J Med. 2018;379:1205–1215. doi:10.1056/NEJMoa1800781.

201. Moss AJ, Schuger C, Beck CA, et al. Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med. 2012;367:2275–2283. doi:10.1056/NEJMoa1211107.

202. Cleland JGF, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005;352:1539–1549. doi:10.1056/NEJMoa050496.

203. Ruschitzka F, Abraham WT, Singh JP, et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med. 2013;369:1395–1405. doi:10.1056/NEJMoa1306687.

204. Curtis AB, Worley SJ, Adamson PB, et al. Biventricular pacing for atrioventricular block and systolic dysfunction. N Engl J Med. 2013;368:1585–1593. doi:10.1056/NEJMoa1210356.

205. Glikson M, et al. European Society of Cardiology clinical consensus statement on indications for conduction system pacing. Europace. 2025;27:euaf050. doi:10.1093/europace/euaf050.

206. Merkely B, Hatala R, Wranicz JK, et al. Upgrade of right ventricular pacing to cardiac resynchronization therapy in heart failure: a randomized trial. Eur Heart J. 2023;44:4259–4269. doi:10.1093/eurheartj/ehad591.

207. Chung MK, Patton KK, Lau CP, et al. 2023 HRS/APHRS/LAHRS guideline on cardiac physiologic pacing for the avoidance and mitigation of heart failure. Heart Rhythm. 2023;20:e17–e91. doi:10.1016/j.hrthm.2023.03.1538.

208. Zimerman A, dal Forno A, Rohde LE, et al. Conduction system vs biventricular pacing in heart failure: the PhysioSync-HF randomized clinical trial. JAMA Cardiol. 2026;11:360–368. doi:10.1001/jamacardio.2026.0101.

209. Chen X, Liu X, Li R, et al. Long-term outcomes of left bundle-branch pacing vs biventricular pacing in heart failure: the HeartSync-LBBP randomized clinical trial. JAMA Cardiol. 2026;11:352–359. doi:10.1001/jamacardio.2026.0083.

210. Homma S, Thompson JLP, Pullicino PM, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med. 2012;366:1859–1869. doi:10.1056/NEJMoa1202299.

211. Zannad F, Anker SD, Byra WM, et al. Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease. N Engl J Med. 2018;379:1332–1342. doi:10.1056/NEJMoa1808848.

212. Doshi SK, Kar S, Nair DG, et al. Left atrial appendage closure or anticoagulation for atrial fibrillation. N Engl J Med. 2026;394(21):2083–2094. doi:10.1056/NEJMoa2517213.

213. Landmesser U, Skurk C, Kirchhof P, et al. Left atrial appendage closure or medical therapy in atrial fibrillation. N Engl J Med. 2026;394:1270–1280. doi:10.1056/NEJMoa2513310.

214. Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med. 2018;378:417–427. doi:10.1056/NEJMoa1707855.

215. Sohns C, Fox H, Marrouche NF, et al. Catheter ablation in end-stage heart failure with atrial fibrillation. N Engl J Med. 2023;389:1380–1389. doi:10.1056/NEJMoa2306037.

216. Parkash R, Wells GA, Rouleau J, et al. Randomized ablation-based rhythm-control versus rate-control trial in patients with heart failure and atrial fibrillation: results from the RAFT-AF trial. Circulation. 2022;145:1693–1704. doi:10.1161/CIRCULATIONAHA.121.057095.

217. Rillig A, Magnussen C, Ozga AK, et al. Early rhythm control therapy in patients with atrial fibrillation and heart failure. Circulation. 2021;144:845–858. doi:10.1161/CIRCULATIONAHA.121.056323.

218. Brignole M, Pentimalli F, Palmisano P, et al. AV junction ablation and cardiac resynchronization for patients with permanent atrial fibrillation and narrow QRS: the APAF-CRT mortality trial. Eur Heart J. 2021;42:4731–4739. doi:10.1093/eurheartj/ehab569.

219. Sanders P, Ariyaratnam JP, Stiles MK, et al. Cardiac resynchronization therapy with or without atrioventricular node ablation in atrial fibrillation: the CAAN-AF trial. Eur Heart J. 2026;47:5128–5138. doi:10.1093/eurheartj/ehag206.

220. Sapp JL, Tang ASL, Parkash R, et al. Catheter ablation or antiarrhythmic drugs for ventricular tachycardia. N Engl J Med. 2025;392:737–747. doi:10.1056/NEJMoa2409501.

221. Perera D, Ryan M, Morgan HP, et al. Viability and outcomes with revascularization or medical therapy in ischemic ventricular dysfunction: a prespecified secondary analysis of the REVIVED-BCIS2 trial. JAMA Cardiol. 2023;8:1154–1161. doi:10.1001/jamacardio.2023.3803.

222. Corrigendum to: 2025 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2026;47(38):5507. doi:10.1093/eurheartj/ehag625.

223. Van Mieghem NM, Elmariah S, Spitzer E, et al. Transcatheter aortic valve replacement in patients with systolic heart failure and moderate aortic stenosis: TAVR UNLOAD. J Am Coll Cardiol. 2025;85:878–890. doi:10.1016/j.jacc.2024.10.070.

224. Baldus S, Doenst T, Pfister R, et al. Transcatheter repair versus mitral-valve surgery for secondary mitral regurgitation. N Engl J Med. 2024;391:1787–1798. doi:10.1056/NEJMoa2408739.

225. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med. 2018;379:2307–2318. doi:10.1056/NEJMoa1806640.

226. Stone GW, Abraham WT, Lindenfeld J, et al. Five-year follow-up after transcatheter repair of secondary mitral regurgitation. N Engl J Med. 2023;388:2037–2048. doi:10.1056/NEJMoa2300213.

227. Anker SD, Friede T, von Bardeleben RS, et al. Transcatheter valve repair in heart failure with moderate to severe mitral regurgitation. N Engl J Med. 2024;391:1799–1809. doi:10.1056/NEJMoa2314328.

228. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med. 2018;379:2297–2306. doi:10.1056/NEJMoa1805374.

229. Sorajja P, Whisenant B, Hamid N, et al. Transcatheter repair for patients with tricuspid regurgitation. N Engl J Med. 2023;388:1833–1842. doi:10.1056/NEJMoa2300525.

230. Kar S, Makkar RR, Whisenant BK, et al. Two-year outcomes of transcatheter edge-to-edge repair for severe tricuspid regurgitation: the TRILUMINATE Pivotal randomized controlled trial. Circulation. 2025;151:1630–1638. doi:10.1161/CIRCULATIONAHA.125.074536.

231. Donal E, Dreyfus J, Leurent G, et al. Transcatheter edge-to-edge repair for severe isolated tricuspid regurgitation: the Tri.Fr randomized clinical trial. JAMA. 2025;333:124–132. doi:10.1001/jama.2024.21189.

232. Hahn RT, Makkar R, Thourani VH, et al. Transcatheter valve replacement in severe tricuspid regurgitation. N Engl J Med. 2025;392:115–126. doi:10.1056/NEJMoa2401918.

233. Hausleiter J, Stocker TJ, Geisler T, et al. Tricuspid-valve intervention in heart failure. N Engl J Med. 2026;395:1363–1373. doi:10.1056/NEJMoa2606934.

234. Brugts JJ, Radhoe SP, Clephas PRD, et al. Remote haemodynamic monitoring of pulmonary artery pressures in patients with chronic heart failure (MONITOR-HF): a randomised clinical trial. Lancet. 2023;401:2113–2123. doi:10.1016/S0140-6736(23)00923-6.

235. Lindenfeld J, Zile MR, Desai AS, et al. Haemodynamic-guided management of heart failure (GUIDE-HF): a randomised controlled trial. Lancet. 2021;398:991–1001. doi:10.1016/S0140-6736(21)01754-2.

236. Abraham WT, Kuck KH, Goldsmith RL, et al. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation. JACC Heart Fail. 2018;6:874–883. doi:10.1016/j.jchf.2018.04.010.

237. Zile MR, Lindenfeld J, Weaver FA, et al. Baroreflex activation therapy in patients with heart failure and a reduced ejection fraction: long-term outcomes. Eur J Heart Fail. 2024;26:1051–1061. doi:10.1002/ejhf.3232.

238. Lee DS, Straus SE, Farkouh ME, et al. Trial of an intervention to improve acute heart failure outcomes. N Engl J Med. 2023;388:22–32. doi:10.1056/NEJMoa2211680.

239. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41:543–603. doi:10.1093/eurheartj/ehz405.

240. Gray A, Goodacre S, Newby DE, et al. Noninvasive ventilation in acute cardiogenic pulmonary edema. N Engl J Med. 2008;359:142–151. doi:10.1056/NEJMoa0707992.

241. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364:797–805. doi:10.1056/NEJMoa1005419.

242. ter Maaten JM, Beldhuis IE, van der Meer P, et al. Natriuresis-guided diuretic therapy in acute heart failure: a pragmatic randomized trial. Nat Med. 2023;29:2625–2632. doi:10.1038/s41591-023-02532-z.

243. Dauw J, Charaya K, Lelonek M, et al. Protocolized natriuresis-guided decongestion improves diuretic response: the multicenter ENACT-HF study. Circ Heart Fail. 2024;17:e011105. doi:10.1161/CIRCHEARTFAILURE.123.011105.

244. Trullàs JC, Morales-Rull JL, Casado J, et al. Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial. Eur Heart J. 2023;44:411–421. doi:10.1093/eurheartj/ehac689.

245. Emmens JE, ter Maaten JM, Matsue Y, et al. Worsening renal function in acute heart failure in the context of diuretic response. Eur J Heart Fail. 2022;24(2):365–374. doi:10.1002/ejhf.2384.

246. Ahmad T, Jackson K, Rao VS, et al. Worsening renal function in patients with acute heart failure undergoing aggressive diuresis is not associated with tubular injury. Circulation. 2018;137:2016–2028. doi:10.1161/CIRCULATIONAHA.117.030112.

247. Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med. 2012;367:2296–2304. doi:10.1056/NEJMoa1210357.

248. Kozhuharov N, Goudev A, Flores D, et al. 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. doi:10.1001/jama.2019.18598.

249. Chen HH, Anstrom KJ, Givertz MM, et al. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. JAMA. 2013;310:2533–2543. doi:10.1001/jama.2013.282190.

250. Naidu SS, Baran DA, Jentzer JC, et al. SCAI SHOCK Stage Classification Expert Consensus Update: A Review and Incorporation of Validation Studies. J Am Coll Cardiol. 2022;79(9):933–946. doi:10.1016/j.jacc.2022.01.018.

251. Sinha SS, Morrow DA, Kapur NK, Kataria R, Roswell RO. 2025 Concise Clinical Guidance: an ACC expert consensus statement on the evaluation and management of cardiogenic shock. J Am Coll Cardiol. 2025;85:1618–1641. doi:10.1016/j.jacc.2025.02.018.

252. Electronic Medicines Compendium. Noradrenaline (norepinephrine) 0.08 mg/mL, solution for infusion: summary of product characteristics. Product 8776. Sections 2, 4.1–4.4. Accessed 15 October 2026. Available from: https://www.medicines.org.uk/emc/product/8776/smpc

253. Electronic Medicines Compendium. Dobutamine 5 mg/mL solution for infusion: summary of product characteristics. Product 6462. Section 4.2 and safety information. Accessed 15 October 2026. Available from: https://www.medicines.org.uk/emc/product/6462/smpc

254. Electronic Medicines Compendium. Milrinone 1 mg/mL solution for injection/infusion: summary of product characteristics. Product 2625. Sections 4.2–4.4. Accessed 15 October 2026. Available from: https://www.medicines.org.uk/emc/product/2625/smpc

255. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010;362:779–789. doi:10.1056/NEJMoa0907118.

256. Levy B, Clere-Jehl R, Legras A, et al. Epinephrine versus norepinephrine for cardiogenic shock after acute myocardial infarction. J Am Coll Cardiol. 2018;72:173–182. doi:10.1016/j.jacc.2018.04.051.

257. Mathew R, Di Santo P, Jung RG, et al. Milrinone as compared with dobutamine in the treatment of cardiogenic shock. N Engl J Med. 2021;385:516–525. doi:10.1056/NEJMoa2026845.

258. Thiele H, Akin I, Sandri M, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. N Engl J Med. 2017;377:2419–2432. doi:10.1056/NEJMoa1710261.

259. Thiele H, Zeymer U, Neumann FJ, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med. 2012;367:1287–1296. doi:10.1056/NEJMoa1208410.

260. Thiele H, Zeymer U, Akin I, et al. Extracorporeal life support in infarct-related cardiogenic shock. N Engl J Med. 2023;389:1286–1297. doi:10.1056/NEJMoa2307227.

261. Møller JE, Engstrøm T, Jensen LO, et al. Microaxial flow pump or standard care in infarct-related cardiogenic shock. N Engl J Med. 2024;390:1382–1393. doi:10.1056/NEJMoa2312572.

262. Morici N, Sacco A, Frea S, et al. Early intra-aortic balloon support for heart failure-related cardiogenic shock: a randomized clinical trial. J Am Coll Cardiol. 2025;85:1587–1597. doi:10.1016/j.jacc.2025.03.003.

263. Cox ZL, Collins SP, Hernandez GA, et al. Efficacy and safety of dapagliflozin in patients with acute heart failure. J Am Coll Cardiol. 2024;83:1295–1306. doi:10.1016/j.jacc.2024.02.009.

264. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med. 2021;384:117–128. doi:10.1056/NEJMoa2030183.

265. Ponikowski P, Kirwan BA, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. Lancet. 2020;396:1895–1904. doi:10.1016/S0140-6736(20)32339-4.

266. Kitzman DW, Whellan DJ, Duncan P, et al. Physical rehabilitation for older patients hospitalized for heart failure. N Engl J Med. 2021;385:203–216. doi:10.1056/NEJMoa2026141.

267. Glargaard S, et al. A randomized controlled trial of thoracentesis in acute heart failure. Circulation. 2025;151:1150–1161. doi:10.1161/CIRCULATIONAHA.124.073521.

268. Dunlay SM, Roger VL, Killian JM, et al. Advanced Heart Failure Epidemiology and Outcomes: A Population-Based Study. JACC Heart Fail. 2021;9:722–732. doi:10.1016/j.jchf.2021.05.009.

269. Bernhardt AM, Copeland H, Deswal A, et al. The International Society for Heart and Lung Transplantation/Heart Failure Society of America Guideline on Acute Mechanical Circulatory Support. J Heart Lung Transplant. 2023;42(4):e1–e64. doi:10.1016/j.healun.2022.10.028.

270. Dew MA, DiMartini AF, Dobbels F, et al. The 2018 ISHLT/APM/AST/ICCAC/STSW recommendations for the psychosocial evaluation of adult cardiothoracic transplant candidates and candidates for long-term mechanical circulatory support. J Heart Lung Transplant. 2018;37(7):803–823. doi:10.1016/j.healun.2018.03.005.

271. Saeed D, Feldman D, El Banayosy A, et al. The 2023 International Society for Heart and Lung Transplantation Guidelines for Mechanical Circulatory Support: A 10-Year Update. J Heart Lung Transplant. 2023;42(7):e1–e222. doi:10.1016/j.healun.2022.12.004.

272. Velleca A, Shullo MA, Dhital K, et al. The International Society for Heart and Lung Transplantation guidelines for the care of heart transplant recipients. J Heart Lung Transplant. 2023;42(5):e1–e141. doi:10.1016/j.healun.2022.10.015.

273. Stevenson LW, Pagani FD, Young JB, et al. INTERMACS profiles of advanced heart failure: the current picture. J Heart Lung Transplant. 2009;28(6):535–541. doi:10.1016/j.healun.2009.02.015.

274. Mancini DM, Eisen H, Kussmaul W, et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation. 1991;83:778–786. doi:10.1161/01.CIR.83.3.778.

275. Morine KJ, Kiernan MS, Pham DT, et al. Pulmonary Artery Pulsatility Index Is Associated With Right Ventricular Failure After Left Ventricular Assist Device Surgery. J Card Fail. 2016;22(2):110–116. doi:10.1016/j.cardfail.2015.10.019.

276. Cooper LB, Mentz RJ, Stevens SR, et al. Hemodynamic predictors of heart failure morbidity and mortality: fluid or flow? J Card Fail. 2016;22:182–189. doi:10.1016/j.cardfail.2015.11.012.

277. Kittleson MM, Sharma K, Brennan DC, et al. Dual-Organ Transplantation: Indications, Evaluation, and Outcomes for Heart-Kidney and Heart-Liver Transplantation: A Scientific Statement From the American Heart Association. Circulation. 2023;148(7):622–636. doi:10.1161/CIR.0000000000001155.

278. Mann DL, Givertz MM, Vader JM, et al. Effect of Treatment With Sacubitril/Valsartan in Patients With Advanced Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. JAMA Cardiol. 2022;7:17–25. doi:10.1001/jamacardio.2021.4567.

279. Comín-Colet J, Manito N, Segovia-Cubero J, et al. 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(7):1128–1136. doi:10.1002/ejhf.1145.

280. Birks EJ, Drakos SG, Patel SR, et al. Prospective Multicenter Study of Myocardial Recovery Using Left Ventricular Assist Devices (RESTAGE-HF): Medium-Term and Primary End Point Results. Circulation. 2020;142(21):2016–2028. doi:10.1161/CIRCULATIONAHA.120.046415.

281. Allen LA, McIlvennan CK, Thompson JS, et al. Effectiveness of an Intervention Supporting Shared Decision Making for Destination Therapy Left Ventricular Assist Device: The DECIDE-LVAD Randomized Clinical Trial. JAMA Intern Med. 2018;178(4):520–529. doi:10.1001/jamainternmed.2017.8713.

282. Soliman OII, Akin S, Muslem R, et al. Derivation and Validation of a Novel Right-Sided Heart Failure Model After Implantation of Continuous Flow Left Ventricular Assist Devices: The EUROMACS Right-Sided Heart Failure Risk Score. Circulation. 2018;137(9):891–906. doi:10.1161/CIRCULATIONAHA.117.030543.

283. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-Term Use of a Left Ventricular Assist Device for End-Stage Heart Failure. N Engl J Med. 2001;345:1435–1443. doi:10.1056/NEJMoa012175.

284. Mehra MR, Uriel N, Naka Y, et al. A Fully Magnetically Levitated Left Ventricular Assist Device—Final Report. N Engl J Med. 2019;380:1618–1627. doi:10.1056/NEJMoa1900486.

285. Mehra MR, Goldstein DJ, Cleveland JC Jr, et al. Five-Year Outcomes in Patients With Fully Magnetically Levitated vs Axial-Flow Left Ventricular Assist Devices in the MOMENTUM 3 Randomized Trial. JAMA. 2022;328(12):1233–1242. doi:10.1001/jama.2022.16197.

286. Jorde UP, Saeed O, Koehl D, et al. The Society of Thoracic Surgeons Intermacs 2023 Annual Report: Focus on Magnetically Levitated Devices. Ann Thorac Surg. 2024;117:33–44. doi:10.1016/j.athoracsur.2023.11.004.

287. Mehra MR, Netuka I, Uriel N, et al. Aspirin and Hemocompatibility Events With a Left Ventricular Assist Device in Advanced Heart Failure: The ARIES-HM3 Randomized Clinical Trial. JAMA. 2023;330(22):2171–2181. doi:10.1001/jama.2023.23204.

288. Hollis IB, Jennings DL, Krim S, et al. An ISHLT consensus statement on strategies to prevent and manage hemocompatibility related adverse events in patients with a durable, continuous-flow ventricular assist device. J Heart Lung Transplant. 2024;43(8):1199–1234. doi:10.1016/j.healun.2024.04.065.

289. Feuerstein A, Schoenrath F, Belyavskiy E, et al. Supervised exercise training in patients with advanced heart failure and left ventricular assist device: a multicentre randomized controlled trial (Ex-VAD). Eur J Heart Fail. 2023;25(12):2252–2262. doi:10.1002/ejhf.3032.

290. Adamopoulos S, Corrà U, Laoutaris ID, et al. Exercise training in patients with ventricular assist devices: a review of the evidence and practical advice. A position paper from the Committee on Exercise Physiology and Training and the Committee of Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019;21(1):3–13. doi:10.1002/ejhf.1352.

291. Jha SR, Hannu MK, Chang S, et al. The Prevalence and Prognostic Significance of Frailty in Patients With Advanced Heart Failure Referred for Heart Transplantation. Transplantation. 2016;100(2):429–436. doi:10.1097/TP.0000000000000991.

292. Colvin MM, Smith JM, et al. OPTN/SRTR 2024 Annual Data Report: Heart. Am J Transplant. 2026;26(8 Suppl 1):S367–S473. doi:10.1016/j.ajt.2026.05.723.

293. Schroder JN, Patel CB, DeVore AD, et al. Transplantation Outcomes with Donor Hearts after Circulatory Death. N Engl J Med. 2023;388:2121–2131. doi:10.1056/NEJMoa2212438.

294. Woolley AE, Singh SK, Goldberg HJ, et al. Heart and Lung Transplants from HCV-Infected Donors to Uninfected Recipients. N Engl J Med. 2019;380:1606–1617. doi:10.1056/NEJMoa1812406.

295. Mehra MR, Mohiuddin MM, Reichart B, et al. The 2026 International Society for Heart and Lung Transplantation Consensus Statement on clinical cardiac xenotransplantation. J Heart Lung Transplant. 2026;45(4):e129–e147. doi:10.1016/j.healun.2025.12.012.

296. Kobashigawa JA, Katznelson S, Laks H, et al. Effect of Pravastatin on Outcomes after Cardiac Transplantation. N Engl J Med. 1995;333(10):621–627. doi:10.1056/NEJM199509073331003.

297. Pham MX, Teuteberg JJ, Kfoury AG, et al. Gene-Expression Profiling for Rejection Surveillance after Cardiac Transplantation. N Engl J Med. 2010;362:1890–1900. doi:10.1056/NEJMoa0912965.

298. Khush KK, Patel J, Pinney S, et al. Noninvasive detection of graft injury after heart transplant using donor-derived cell-free DNA: a prospective multicenter study. Am J Transplant. 2019;19(10):2889–2899. doi:10.1111/ajt.15339.

299. Dalal HM, et al. The effects and costs of home-based rehabilitation for heart failure with reduced ejection fraction: The REACH-HF multicentre randomized controlled trial. Eur J Prev Cardiol. 2019;26(3):262–272. doi:10.1177/2047487318806358.

300. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020;383(15):1436–1446. doi:10.1056/NEJMoa2024816.

301. EMPA-KIDNEY Collaborative Group. Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2023;388:117–127. doi:10.1056/NEJMoa2204233.

302. Medicines and Healthcare products Regulatory Agency. Ferric carboxymaltose: risk of symptomatic hypophosphataemia leading to osteomalacia and fractures. Drug Safety Update. 16 November 2020; post-publication note September 2026. Available from: https://www.gov.uk/drug-safety-update/ferric-carboxymaltose-ferinject-risk-of-symptomatic-hypophosphataemia-leading-to-osteomalacia-and-fractures

303. Perkovic V, Tuttle KR, Rossing P, et al. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. N Engl J Med. 2024;391(2):109–121. doi:10.1056/NEJMoa2403347.

304. Cruz-Jentoft AJ, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48:16–31. doi:10.1093/ageing/afy169.

305. Kalra PR, et al. Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial. Lancet. 2022;400:2199–2209. doi:10.1016/S0140-6736(22)02083-9.

306. Mentz RJ, et al. Ferric Carboxymaltose in Heart Failure with Iron Deficiency. N Engl J Med. 2023;389:975–986. doi:10.1056/NEJMoa2304968.

307. Lewis GD, Malhotra R, Hernandez AF, et al. 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(19):1958–1966. doi:10.1001/jama.2017.5427.

308. Swedberg K, et al. Treatment of Anemia with Darbepoetin Alfa in Systolic Heart Failure. N Engl J Med. 2013;368:1210–1219. doi:10.1056/NEJMoa1214865.

309. Dransfield MT, et al. Metoprolol for the Prevention of Acute Exacerbations of COPD. N Engl J Med. 2019;381:2304–2314. doi:10.1056/NEJMoa1908142.

310. Bueno H, et al. 2025 ESC Clinical Consensus Statement on mental health and cardiovascular disease. Eur Heart J. 2025;46:4156–4225. doi:10.1093/eurheartj/ehaf191.

311. Angermann CE, et al. 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. doi:10.1001/jama.2016.7635.

312. FitzGerald JD, et al. 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis Care Res (Hoboken). 2020;72:744–760. doi:10.1002/acr.24180.

313. US National Library of Medicine. COLCRYS (colchicine) prescribing information. DailyMed. Accessed 16 October 2026. Available from: https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=5ecaa34e-1bed-49a5-b97c-a8f8c0d885a7

314. Stott DJ, et al. Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism. N Engl J Med. 2017;376:2534–2544. doi:10.1056/NEJMoa1603825.

315. Molloy C, Long L, Mordi IR, et al. Exercise-based cardiac rehabilitation for adults with heart failure. Cochrane Database Syst Rev. 2024;2024(3):CD003331. doi:10.1002/14651858.CD003331.pub6.

316. Correction to: 2026 ESC Guidelines on cardiac rehabilitation: Developed by the task force on cardiac rehabilitation of the European Society of Cardiology (ESC). Eur Heart J. Published online 23 October 2026. doi:10.1093/eurheartj/ehag887.

317. O'Connor CM, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA. 2009;301:1439–1450. doi:10.1001/jama.2009.454.

318. Ellingsen Ø, Halle M, Conraads V, et al. High-Intensity Interval Training in Patients With Heart Failure With Reduced Ejection Fraction. Circulation. 2017;135(9):839–849. doi:10.1161/CIRCULATIONAHA.116.022924.

319. Piotrowicz E, Pencina MJ, Opolski G, et al. Effects of a 9-week hybrid comprehensive telerehabilitation program on long-term outcomes in patients with heart failure: the Telerehabilitation in Heart Failure Patients (TELEREH-HF) randomized clinical trial. JAMA Cardiol. 2020;5(3):300–308. doi:10.1001/jamacardio.2019.5006.

320. Taylor JL, Myers J, Bonikowske AR. Practical guidelines for exercise prescription in patients with chronic heart failure. Heart Fail Rev. 2023;28(6):1285–1296. doi:10.1007/s10741-023-10310-9.

321. Koehler F, et al. Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): a randomised, controlled, parallel-group, unmasked trial. Lancet. 2018;392(10152):1047–1057. doi:10.1016/S0140-6736(18)31880-4.

322. Ezekowitz JA, et al. Reduction of dietary sodium to less than 100 mmol in heart failure (SODIUM-HF): an international, open-label, randomised, controlled trial. Lancet. 2022;399:1391–1400. doi:10.1016/S0140-6736(22)00369-5.

323. Herrmann JJ, et al. Liberal fluid intake versus fluid restriction in chronic heart failure: a randomized clinical trial. Nat Med. 2025;31:2062–2068. doi:10.1038/s41591-025-03628-4.

324. Loeb M, et al. Influenza vaccine to reduce adverse vascular events in patients with heart failure: a multinational randomised, double-blind, placebo-controlled trial. Lancet Glob Health. 2022;10:e1835–e1844. doi:10.1016/S2214-109X(22)00432-6.