2020 Clinical Practice Guidelines on the Diagnosis and Management of Heart Failure

– A Comprehensive Updated Guideline from the Heart Failure Society (Singapore)

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Abstract

There have been major changes in the therapeutic landscape of heart failure, since the last Singapore Clinical Practice Guidelines on heart failure in 2004. The Writing Committee members of the 2004 heart failure guideline along with additional experts in the field convened, conducted a comprehensive review of the literature and developed this updated set of heart failure guidelines under the auspices of the Heart Failure Society (Singapore). These updated guidelines will provide a detailed overview of the – (1) diagnosis, including various laboratory assessments and imaging tests; (2) pharmacological and surgical treatment; (3) use of cardiac implantable electronic devices; (4) treatment of co-morbidities (non-cardiovascular, iron deficiency, atrial fibrillation and diabetes mellitus); and (5) multi-disciplinary treatment – for the optimized management of heart failure. Separate sections have also been included for guidance on the treatment of acute heart failure, palliative care for advanced heart failure and management of heart failure with preserved ejection fraction. The recommendations provided in this guideline are intended to provide guidance in the overall clinical decision making by healthcare providers for the optimal diagnosis and management of heart failure.

Keywords: Heart failure, Diagnosis, Treatment, Singapore

List of Commonly Used Abbreviations

ACEi: Angiotensin-converting enzyme inhibitor
AHF: Acute heart failure
AF: Atrial fibrillation
ARB: Angiotensin receptor blocker
ARNI: Angiotensin receptor neprilysin inhibitor
BiPAP: Bi-level positive airway pressure
BNP: B-type natriuretic peptide
CABG: Coronary artery bypass graft
CAD: Coronary artery disease
CMR: Cardiac magnetic resonance
COX: Cyclooxygenase
CPAP: Continuous positive airway pressure
CPET: Cardiopulmonary exercise testing
CrCl: Creatinine clearance
CRS: Cardiorenal syndrome
CRT: Cardiac resynchronisation therapy
cTnT: cardiac troponin T
DASH: Dietary approaches to stop hypertension
DHA: Docosahexaenoic acid
EF: Ejection fraction
eGFR: Estimated glomerular filtration rate
EPA: Eicosapentaenoic acid
ETT: Exercise treadmill test
FoCUS: Focused cardiac ultrasound
HFC: Heart failure clinic
HFpEF: Heart failure with preserved ejection fraction
HFrEF: Heart failure with reduced ejection fraction
H-ISDN: Hydralazine plus isosorbide dinitrate
HIV: Human immunodeficiency virus
HRR: Heart rate reserve
HsTnT: Highly sensitive troponin T
GPP: Good practice points
ICD: Implantable cardioverter defibrillator
IVC: Inferior vena cava
LBBB: Left bundle branch block
LVAD: Left ventricular assist device
LVH: Left ventricular hypertrophy
LVEDP: Left ventricular end-diastolic pressure
LVEF: Left ventricular ejection fraction

MCS: Mechanical circulatory support
MDCT: Multidetector computed tomography
METS: Metabolic equivalents
MPI: Myocardial perfusion imaging
MRA: Mineralocorticoid receptor antagonist
NSAID: Nonsteroidal anti-inflammatory drug
NT-proBNP: N-terminal prohormone B-type natriuretic peptide
NYHA: New York Heart Association
OMT: Optimal medical therapy
PAC: Pulmonary artery catheterisation
PASP: Pulmonary artery systolic pressure
PCWP: Pulmonary capillary wedge pressure
PET: Positron emission tomography
Peak VO_2: Peak oxygen consumption
RAAS: Renin-angiotensin–aldosterone system
RCT: Randomised controlled trials
RPE: Rating of perceived exertion
STEMI: ST-segment elevation myocardial infarction
SGLT-2: Sodium-glucose cotransporter 2
SNS: Sympathetic nervous system
SPECT: Single-photon emission computed tomography
STICH: Surgical treatment for ischaemic heart failure
TSAT: Transferrin saturation
VAD: Ventricular assist device
VE/VCO_2: Ventilation-to–carbon dioxide

1. Introduction

The Heart Failure Society (Singapore) developed this set of guidelines as an aid for doctors, nurses, and ancillary health professionals when managing patients with heart failure. These guideline recommendations reflect a consensus of expert opinion after review of the available, current scientific evidence. The recommendations are intended to help in overall clinical decision making by healthcare providers. However, final decisions on patient care should be based on individual patient circumstances and after caregiver consultation.

Most members of this writing group were initially appointed by Ministry of Health, Singapore to a review committee, formed specifically to update the MOH Clinical Practice Guidelines (CPG). The first CPG on Heart Failure was published in 2004, which has not been updated since. However, the review committee's work was terminated, as MOH discontinued the practice of publishing CPGs.

The members continued with this work, under the auspices of the Heart Failure Society (Singapore). With the emergence of new evidence, we enrolled additional members to update and complete this set of guidelines. This set of guideline recommendations was approved by the council of the Heart Failure Society (Singapore).

1.1. Methodology

The classification for level of evidence and grading of recommendations follow those adopted in previous CPGs of the Ministry of Health (Tables 1 and 2). This format should already be familiar to many local healthcare providers.

Table 1: Levels of Evidence

Level	Type of Evidence
1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias – Class I, level a
1^{+}	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias – Class IIa, level a (level b, if single RCT)
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias – Class IIb, level a (level b, if single RCT)

2^{++}	High-quality systematic reviews of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal – Class I, level b
2^{+}	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal – Class IIa, level b
2^{-}	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal – Class IIa, level b
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

RCT: Randomized controlled trials

Table 2: Grades of Recommendation

Grade	Recommendation
A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1^{++} and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results – Level a
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1^{++} or 1^{+} – Level b
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2^{++}– Level c
D	Evidence level 3 or 4; or Level c Extrapolated evidence from studies rated as 2^{+}
GPP	Recommended best practice based on the clinical experience of the guideline development group

RCT: Randomized controlled trials; GPP: Good practice points

2. Diagnostics

2.1. Clinical Diagnosis

Heart failure is a clinical syndrome characterised by symptoms and signs of volume overload, in which cardiac dysfunction is responsible for the failure of the heart to supply adequate peripheral oxygen delivery to meet the requirements of metabolising tissues, or to do so only with elevated cardiac filling pressure.[1] The diagnosis of heart failure is primarily a clinical diagnosis, based on typical symptoms and signs:

2.1.1. Symptoms

Typical symptoms of heart failure include breathlessness, fatigue, exercise intolerance, and fluid retention. The primary symptom of heart failure is breathlessness, which may be exertional or at rest. Orthopnoea and paroxysmal nocturnal dyspnoea are specific but insensitive symptoms. Other nonspecific symptoms of heart failure include ankle swelling, nocturnal cough, nocturia, anorexia, abdominal bloating, constipation, and cerebral symptoms of hypoperfusion such as confusion and dizziness.

2.1.2. Signs

Elevated jugular venous pressure has a high positive predictive value for the diagnosis of heart failure but is often poorly elicited. Other clinical signs include hepatojugular reflux, tachycardia, third heart sound, displaced apex beat, pulmonary crepitations, hepatomegaly, peripheral oedema, and ascites.

Patients with heart failure often present with one or more symptoms that are sensitive but not specific for heart failure. During a physical examination, the clinician may identify clinical signs that are either sensitive or specific for heart failure. When multiple signs and symptoms are present, a diagnosis can be made with greater confidence. The patient's medical history is also important–heart failure is unusual in a patient with no relevant medical history (e.g. a potential cause of cardiac damage), whereas a history of cardiovascular disease (e.g. myocardial infarction) greatly increases the likelihood of heart failure in a patient with appropriate symptoms and signs.

Symptoms and signs may be particularly difficult to identify and interpret in obese individuals, in the elderly, and in patients with chronic lung disease. Further investigations may be required in cases of uncertainty. For example, a

chest X-ray is useful to confirm the presence of pulmonary congestion, and electrocardiography or echocardiography provides objective evidence of the underlying structural or functional cardiac abnormality that is thought to account for the patient's symptoms and signs. Other tests (e.g. natriuretic peptide measurement) are discussed below. Importantly, investigations can aid but cannot replace a clinical diagnosis of heart failure.

The full evaluation of the patient with suspected heart failure involves more than making the diagnosis. The aims of clinical assessment include:

a) Consideration of differential diagnoses and confirmation of the diagnosis of heart failure
b) Assessment of the severity of the syndrome
c) Identification of the underlying cardiac abnormality, aetiology, and precipitating or exacerbating factors
d) Identification of comorbidities that may impact management
e) Estimation of prognosis

2.1.3. Differential Diagnoses

a) Myocardial ischaemia
b) Obesity and deconditioning
c) Chest disease – including lung, pulmonary embolic, diaphragm, or chest wall disease
d) Venous insufficiency in lower limbs
e) Drug-induced ankle swelling (e.g. dihydropyridine calcium-channel blockers) or fluid retention (e.g. NSAIDs)
f) Hypoalbuminaemia
g) Intrinsic renal or hepatic disease
h) Severe anaemia or thyroid disease
i) Depression and/or anxiety disorders

2.1.4. Severity of Symptoms

The degree of exertion required to elicit breathlessness is used to grade the severity of symptoms into four NYHA functional classes (Table 3).

Table 3: NYHA functional classes of heart failure

Grade	Functional limitation	Description
Class I	No limitations	Ordinary physical activity does not cause fatigue or breathlessness

Grade	Functional limitation	Description
Class II	Slight limitation of physical activity	Ordinary physical activity results in fatigue or breathlessness
Class III	Marked limitation of physical activity	Less than ordinary physical activity will lead to symptoms, although patients are comfortable at rest
Class IV	Symptoms of heart failure at rest	Inability to carry out any physical activity without discomfort

The severity of symptoms is not necessarily equated with the severity of the underlying heart problem – some patients with severely reduced LVEF may have only mild or no symptoms (asymptomatic left ventricular systolic dysfunction), and vice versa.

2.1.5. Stages of Heart Failure

Current international guidelines emphasise the progressive nature of heart failure,[2–5] and the importance of recognising patients with asymptomatic structural or functional heart disease. Such patients should receive interventions aimed at modifying risk factors for heart failure or treating asymptomatic left ventricular dysfunction, to delay or prevent the progression to symptomatic heart failure. The progressive stages of heart failure are shown in Table 4.

Table 4: Stages of heart failure

Stages	Definition
Stage A Cardiovascular disease	At risk for developing stages of heart failure, but no structural or functional abnormality detected and no symptoms or signs
Stage B Structural/functional heart disease	Structural or functional left ventricular disease present in a patient who has never developed symptoms or signs of stages of heart failure*
Stage C Overt heart failure	Symptomatic heart failure associated with underlying cardiac abnormalities†
Stage D Terminal heart failure	Advanced structural heart disease and severe symptoms despite maximal medical therapy

*A patient who has developed an episode of heart failure in the past has transitioned from Stage B to Stage C, even if symptoms have been controlled with treatment or lifestyle change.

[†]Note that symptoms may fluctuate in a patient with Stage C heart failure, i.e. a Stage C patient may have NYHA Functional Class I–IV, depending on fluid status.

2.1.6. Aetiology of Heart Failure

Once the diagnosis of heart failure is established, it is very important to identify and treat the underlying cause of cardiac dysfunction, as well as precipitating factors, for acute decompensation (Table 5).

Table 5: Causes of heart failure and precipitating factors for acute decompensation

Causes of heart failure	
Ischaemia	CAD
Pressure overload	Hypertension
Cardiomyopathies	Familial and nonfamilial (acquired)
Drugs	Cytotoxic agents
Toxins	Alcohol, cocaine
Endocrine	Diabetes mellitus, thyroid disorder, adrenal disorder, excess growth hormone, phaeochromocytoma
Nutritional	Deficiency of thiamine/selenium/carnitine, obesity, cachexia
Infiltrative	Sarcoidosis, amyloidosis, haemochromatosis, connective tissue disease
Others	HIV, peripartum, uraemia
Precipitating factors	
Cardiac	Cardiac arrhythmia, acute coronary syndrome, mechanical complications of myocardial infarction, cardiac tamponade, pericardial disease, infective endocarditis
Pulmonary	Acute pulmonary embolism, pneumonia, exacerbation of chronic obstructive lung disease/asthma
Vascular	Hypertensive crisis, aortic dissection
Noncompliance	Nonadherence to drugs or diet
Others	Anaemia, renal dysfunction, iatrogenic, thyroid dysfunction, toxins

2.2. Investigations

Investigations must fulfil at least one of the following roles:

a) Identify the presence of abnormal cardiac structure and function that supports the clinical diagnosis
b) Quantify abnormal cardiac structure and function
c) Provide prognostic information
d) Guide therapy
e) Exclude conditions mimicking the signs and symptoms of heart failure

2.2.1. Laboratory Tests

Full Blood Count

Anaemia may be an alternative cause of the patient's symptoms and signs or a consequence of chronic heart failure. It carries prognostic information and may itself be a therapeutic target.

Recommendation:

- A full blood count should be performed inpatients presenting with heart failure or symptoms suggestive of heart failure.[6,7] **(Grade C, Level 2^{+})**

Renal Panel

The associative and causative relationship between heart failure and renal failure is well-recognised and the nomenclature has been defined into Cardiorenal Syndrome (CRS) types 1 to 5. There is also a need to monitor electrolytes and renal function prior to and after initiation of pharmacotherapy.

Recommendation:

- A renal panel should be performed routinely for patients presenting with heart failure and during routine follow-up of the patient.[8–10] **(Grade C, Level 2^{+})**

Plasma Natriuretic Peptides

Plasma BNP or NT-BNP may be used as an initial investigation to diagnose or exclude heart failure as a cause of shortness of breath, and to monitor and manage therapy.

Recommendations:

- Plasma BNP or NT-BNP may be measured in patients presenting with heart failure or symptoms suggestive of heart failure, to guide diagnosis.[11,12] **(Grade B, Level 1^{+})**
- Plasma BNP or NT-BNP may be measured in patients during routine follow-up of patients with heart failure, to guide therapy.[13] **(Grade B, Level 1^{+})**

Glucose

Patients presenting with heart failure may have undiagnosed or pre-existing diabetes; patients with pre-existing or newly diagnosed diabetes have a worse prognosis. Even for patients without diabetes, there is an association between blood glucose and prognosis as well as functional capacity in chronic HFrEF. Plasma glucose is also an early prognostic indicator in AHF and may be a possible therapeutic target in the future.

Recommendation:

- Plasma blood glucose should be measured in patients presenting initially with heart failure and during routine follow-up.[14–17] **(Grade B, Level 1^{+})**

Cardiac Biomarkers

Cardiac biomarkers, which are elevated in acute coronary syndrome, may also be elevated in AHF. These include HsTnT and assays cTnT, which are elevated in both acute and chronic heart failure without acute coronary syndrome; they provide additional prognostic information, even when used alongside other biomarkers such as plasma BNP/NT-proBNP. Cardiac biomarkers also serve to diagnose or exclude acute coronary syndrome, which is a possible precipitant of AHF.[18]

Recommendation:

- Cardiac biomarkers should be measured in patients presenting with acute decompensated heart failure.[19–21] **(Grade C, Level 2$^+$)**

Arterial Blood Gas

There is a lack of evidence for the routine measurement of arterial blood gas. In a small observational study, partial pressure of oxygen, partial pressure of carbon dioxide, and pH values did not predict mortality.[22] There is no indication to routinely measure arterial blood gases in patients with acute decompensated heart failure, unless there is an increased respiratory rate of >22% or oxygen saturation <92%, despite high flow inspired oxygen (>8L/min) or when invasive or non-invasive ventilation is being considered. Venous blood gas is an acceptable alternative to reduce the risk of vascular injury.

Recommendations:

- Arterial blood gas should not be measured routinely in patients with haemodynamically stable acute decompensated heart failure.[22] **(Grade C, Level 2$^+$)**
- Arterial blood gas may be measured in select patients with acute decompensated heart failure if ventilator support is under consideration.[23] **(Grade B, Level 1$^+$)**
- Venous blood gas may be measured in select patients with acute decompensated heart failure as an alternative to arterial blood gas if there is risk of vascular injury.[24] **(Grade B, Level 1$^+$)**

Iron Status

Iron deficiency due to both absolute and functionally depleted iron stores can occur with or without anaemia in heart failure. Iron status predicts both exercise capacity and prognosis and may, in itself, be a therapeutic target. Measurement of both serum ferritin and TSAT is necessary.

Recommendation:

- An iron panel consisting of serum ferritin and TSAT should be measured in patients with HFrEF.[25–30] **(Grade B, Level 1$^+$)**

2.2.2. Imaging Tests

Electrocardiogram

Patients with chronic heart failure are unlikely to present with a normal electrocardiogram; however, 20% may have a normal electrocardiogram. Changes that may be seen include, but are not limited to: LVH, left axis deviation, LBBB, and pathological Q-waves. Presence of sinus tachycardia may suggest cardiac decompensation, and AF may be the cause or complication of heart failure with prognostic and therapeutic implications. Acute heart failure may also be a complication of ongoing STEMI.

Recommendation:

- An electrocardiogram should be performed in all patients presenting with acute decompensated heart failure.[31–34] **(Grade C, Level 2^{+})**

Chest X-Ray

Chest X-ray may show prominent pulmonary vasculature suggestive of raised pulmonary pressures in AHF. A vascular pedicle width of >85mm suggests increased intravascular volume.[35] It may also detect conditions causing shortness of breath and mimicking features of heart failure.

Recommendation:

- Chest X-ray should be performed as an initial investigation in all patients presenting with acute decompensated heart failure.[36] **(Grade B, Level 1^{+})**

Echocardiogram

Echocardiogram improves the sensitivity and specificity of the diagnosis of heart failure in the acute setting, even after careful clinical history-taking and examination, and should include assessment of:

a) Left ventricular systolic and diastolic function
b) Cardiac haemodynamics

c) Chamber structure and size, including septal defects, valvular morphology and function

A goal-directed FoCUS performed at the point of care may provide timely and critical information in aid of patient management. A FoCUS study should be considered as an extension of clinical examination.[37]

2.2.3. Systolic and Diastolic Function

Current pathophysiological classification, as well as management of heart failure, is predominantly based on the EF and classifies heart failure into HFrEF or HFpEF.[38] This nomenclature replaces the old terms systolic and diastolic heart failure, respectively. This nomenclature has since been incorporated into major heart failure guidelines.[39,40]

Ejection fraction is the most common method used for the assessment of systolic function. While this was initially assessed using radionuclide techniques,[41] echocardiographic methods have since become more readily accessible and affordable. Ejection fraction was shown to be a prognostic indicator in patients with or without symptoms of heart failure. In addition, initial clinical trials for heart failure were mainly conducted among patients with a demonstrable reduction in EF. Visual estimation of systolic function in acute situations is adequate.[42]

Diastolic dysfunction has been shown to be correlated with symptoms[43] and prognosis in patients with HFrEF.[44,45] Worsening diastolic function without heart failure has also been shown to have prognostic significance.[46]

Cardiac Haemodynamics

Pulmonary oedema and associated symptoms occur primarily due to raised LVEDP. It is not practical to monitor LVEDP safely in real-time. Therefore, surrogate measures of raised LVEDP are used to guide diagnosis and therapy. The most established invasive method is measurement of PCWP using a flow-directed balloon-tipped catheter.[47]

Recommendations:

- Pulmonary artery systolic pressure (PASP) may be estimated with Doppler interrogation of the tricuspid regurgitant jet (if present);[48] this is a surrogate marker of left atrial pressure, which in turn, is a marker of left ventricular diastolic filling pressure. (**Grade B, Level 2^{+})**
- Inferior vena cava (IVC) size may be used to estimate right atrial pressure, to guide therapy.[49] **(Grade B, Level 2^{+})**

Chamber Structure and Size, Including Valvular Morphology and Function

A significant structural pathology, such as ventricular septal rupture or ischaemic mitral valve papillary muscle rupture, as a cause of AHF should be excluded. A complete echocardiographic study should include qualitative and quantitative analysis of significant valvular stenosis or regurgitation and exclude significant congenital structural heart diseases.

Dyssynchrony

Cardiac dyssynchrony study should not be performed routinely to select patients for CRT in patients with HFrEF and normal QRS width.[50,51]

Stress and Viability Echocardiography

Stress echocardiography may be used as an initial test to exclude ischaemic heart disease as a cause of cardiomyopathy. For the diagnosis of ischaemia, it has better specificity at the expense of lower sensitivity, when compared to MPI with SPECT imaging.[52,53]

Among the various imaging modalities used for assessment of viability, the oldest and largest database exists for low-dose dobutamine stress echocardiography; patients with contractile reserve on stress echocardiography have a better prognosis than other imaging modalities.

Stress echocardiography may have additional diagnostic and prognostic value in HFpEF.

Recommendations:

- A FoCUS may be performed as an initial investigation in all patients presenting with AHF or symptoms mimicking heart failure.[54,55] **(Grade B, Level 1^{+})**
- A FoCUS should be performed in a patient with AHF post myocardial infarction or cardiac procedure to exclude for mechanical complications, e.g. ventricular septal rupture or ischaemic papillary muscle rupture.[56,57] (**Grade B, Level 2^{++})**
- A complete echocardiographic study, including measurement of systolic and diastolic parameters, haemodynamics, cardiac chamber size, and valvular function, should be performed in all patients presenting with heart failure.[44,58–61] **(Grade A, Level 1^{++})**
- A goal-directed strategy to titrate diuretics and vasodilator using FoCUS or other modalities may be performed in a patient with chronic stable heart failure and equivocal symptoms.[62,63] **(Grade C, Level 2^{+})**
- Assessment of viability and contractile reserve may be performed using dobutamine echocardiography.[64] **(Grade B, Level 1^{+})**
- Assessment of cardiac function with stress echocardiography may be performed in patients with possible HFpPEF for additional diagnostic and prognostic information.[65,66] **(Grade B, Level 1^{+})**

2.2.4. Cardiopulmonary Exercise Testing (CPET)

In HFrEF, objective assessment of functional testing with measured Peak VO_2 or minute VE/VCO_2 production relationship[67] on a cardiopulmonary stress test provides prognostic information. Cardiopulmonary exercise testing (CPET) also provides additional diagnostic and prognostic information in patients with HFpEF.[68,69]

However, functional assessment can be done using simple clinical history;[70] formal functional testing is not indicated unless there is a need to:

a) Distinguish between cardiovascular versus respiratory disease as a cause of limitation of exercise in a patient affected by both conditions
b) Consider cardiac transplantation
c) Exercise prescription for cardiac rehabilitation

Recommendations:

- A CPET may be performed in patients with stable heart failure to risk stratify patients for cardiac transplant.[71] **(Grade C, Level 2^{+})**
- A CPET may be performed in patients with concomitant comorbidities and symptoms of uncertain aetiology.[72] **(Grade D, Level 3)**
- A CPET may be performed in patients to guide exercise prescription.[73] **(Grade C, Level 2^{+})**

Multidetector Computed Tomography Coronary Angiography

Multidetector computed tomography (MDCT) may be used as an alternative to direct invasive coronary angiography, to exclude significant coronary artery stenosis, particularly in patients with a low pre-test probability of coronary atherosclerosis and in the absence of significant renal impairment. Multidetector computed tomography may be used to identify delayed contrast enhancement in lieu of other more established techniques such as CMR, if there is a contraindication to the latter or if other techniques are not available; this provides additional prognostic data and predicts improvement in cardiac function.

Recommendations:

- A MDCT study may be performed to exclude significant CAD as an alternative to invasive coronary angiography in select patients.[74] **(Grade B, Level 2^{++})**
- A MDCT study may be performed in lieu of other established techniques if there are contraindications or lack of access to more established methods to identify delayed contrast enchancement.[75,76] **(Grade C, Level 2^{+})**

Myocardial Perfusion Imaging

Myocardial perfusion imaging (MPI), using SPECT with thallium or technetium, may be used as an initial investigation to assess systolic function. It may be used to assess whether ischaemia could be a contributory factor to symptoms of dyspnoea or the cause of cardiomyopathy, as well as to guide therapy.[77] However, data do not support the assessment of ischaemia as a

guide to revascularisation, using either echocardiographic or MPI techniques in patients with both symptomatic or asymptomatic systolic dysfunction.

Myocardial perfusion imaging with PET using F-18-fluorodeoxyglucose for initial assessment of cardiomyopathy may be considered for patients who are diagnosis-naïve;[78] however, it is not as established as SPECT imaging.

Viability imaging with MPI can be carried out with either technetium- or thallium-based SPECT or F-18-fluorodeoxyglucose-based PET imaging. All techniques confer similar sensitivity to predict improvement in wall motion with PET, showing improved specificity.[79]

Recommendations:

- Myocardial perfusion imaging may be used as an initial test to assess for ischaemia as the cause of cardiomyopathy in patients with HFrEF.[80,81] **(Grade B, Level 2^{++})**
- Myocardial perfusion imaging should not be used to routinely to assess for ischaemia or viability in patients prior to revascularisation in HFrEF.[82] **(Grade B, Level 1^{+})**
- Myocardial perfusion imaging may be used to assess for ischaemia or viability only in select patients prior to revascularisation without HFrEF.[83] **(Grade C, Level 2^{+})**

Cardiac Magnetic Resonance (CMR) Imaging

Cardiac magnetic resonance is indicated in select patients with heart failure of uncertain aetiology; it is also indicated for assessment of viability as an alternative to MPI.

Recommendation:

- Cardiac magnetic resonance may be used to help elucidate the aetiology of heart failure in patients with HFrEF or HFpEF.[84,85] **(Grade B, Level 2^{++})**

2.2.5 Invasive Tests

Pulmonary Artery Catheterisation

Pulmonary artery catheterisation (PAC) may demonstrate normal cardiac output and filling pressures in adequately treated patients with heart failure;[86,87] however, it may be indicated in patients with concomitant systemic disease or to titrate vasodilator or inotropic therapy. Although this was not tested in a heart failure population, there may be no advantage of PAC over a simpler central venous catheter.

Recommendations:

- A pulmonary artery catheter should not be routinely placed in haemodynamically stable patients with acute heart failure.[88] **(Grade B, Level 1^{+})**
- A pulmonary artery catheter or central venous catheter can be placed in a patient with acute heart failure in shock requiring high-dose inotropes and/or co-concomitant illness to help guide therapy.[89,90] **(Grade D, Level 3)**

Coronary Angiography

Coronary angiography may be performed to exclude the presence of significant coronary artery stenosis as the cause of cardiomyopathy, as clinical history and electrocardiogram may be inadequate. Urgent coronary angiography with a view to percutaneous coronary intervention should be carried out if there is evidence or suspicion of acute coronary syndrome causing heart failure.

Recommendations:

- Coronary angiography may be performed in a patient with HFrEF as an initial investigation into the cause of cardiomyopathy.[91] **(Grade C, Level 2^{+})**
- Urgent coronary angiography with a view to revascularisation should be performed in patient with clinical or electrocardiogram evidence of acute coronary syndrome and heart failure.[92] **(Grade A, Level 1^{++})**

Electrophysiological Testing

Recommendation:

- Patients with HFrEF who have asymptomatic non-sustained ventricular tachycardia should not undergo routine electrophysiological testing prior to the decision to implant a cardioverter defibrillator device.[93] **(Grade C, Level 2^{+})**

2.2.6. Genetic Testing

Genetic testing may be indicated in cardiomyopathy associated with muscular dystrophies, metabolic derangements, or in those with a strong family history of the same. However, at present, data on Asian cohorts are lacking and care must be taken when extrapolating results from other population groups. Genetic testing should be performed with informed consent and facilities for adequate counselling.

Recommendation:

- Genetic testing in patients with HFrEF and HFpEF should only be performed with informed consent and facilities for counselling and follow-up.[94] (**Grade C, Level 2^{+})**

3. Pharmacological Management

The aims of pharmacological therapy in HFrEF are: (1) to reduce morbidity and mortality while improving the quality of life through symptom control; and (2) to delay or halt the progression of heart failure.

3.1. Angiotensin-Converting Enzyme Inhibitors

It has been shown that chronic hyperactivation of the neurohormonal axis (the SNS and the RAAS) is important for the progression of heart failure;[60] thus, its blockade has become one of the cornerstones of successful therapy for systolic ventricular dysfunction with or without heart failure.[61] Angiotensin-converting enzyme inhibitors work by inhibiting the RAAS system.

Angiotensin-converting enzyme inhibitors are prescribed to reduce mortality, heart failure readmissions, and to improve symptoms, exercise tolerance, quality of life, and exercise performance.

3.1.1. Indications

Recommendations:

- Angiotensin-converting enzyme inhibitors should be used in all patients with HFrEF, unless contraindicated.[60,61,95] **(Grade A, Level 1^{++})**
- The dosage of ACEis should be uptitrated to levels that have been shown to be of benefit in major trials.[96,97] If this is not possible, a lower dose of ACEi is preferable to none at all. **(Grade A, Level 1^{+})**
- Any ACEi may be used in HFrEF, as available data suggest that there are no differences among available ACEis in their beneficial effects on symptoms or survival.[98] **(Grade B, Level 1^{++})**

3.1.2. Contraindications or Precautions

Known contraindications to ACEi use are history of life-threatening adverse reactions during prior exposure (e.g. angioneurotic oedema, anuric renal

failure), known bilateral renal artery stenosis, and patients who are pregnant or are planning to get pregnant.

Caution should be exercised in prescribing ACEis in patients with significant hyperkalaemia, significant renal dysfunction (creatinine >221µmol/L or >2.5mg/dL or eGFR <30mL/min/1.73m^2), and symptomatic or severe asymptomatic hypotension (SBP <90mmHg).

Drug interactions to look out for include:

a) Potassium (K^+) supplements/K^+-sparing diuretics, e.g. amiloride and triamterene (including combination preparations with furosemide)
b) Nonsteroidal anti-inflammatory drugs[60]
c) "Low salt" substitutes with high K^+ content

3.1.3. Initiation and Dose Titration

Recommendations:

- If lower doses have been well-tolerated, the dosage should be titrated upwards at short intervals (e.g. after every 2 weeks) until the maximally tolerated or target dose (as used in large, randomised trials) is achieved. (**Grade A, Level 1^{++})**
- Check blood pressure, renal function, and serum K^+ soon after initiation of ACEi therapy or dose adjustment of ACEi (e.g. after 2 weeks).[99,100] **(GPP)**

Treatment with an ACEi should be initiated at low doses (Table 4).

Table 6 summarises the titration of ACEis. Upon achieving the target dose, further increments may be necessary in the presence of persistently elevated blood pressure.

Table 6: Dosing guide for ACEi

ACEi	Starting dose (mg)	Target dose (mg)	Maximum dose (mg)
Captopril	6.25 tds	50 tds	100 tds
Enalapril	2.5 bd	10 bd	20 bd
Lisinopril	2.5–5 once daily	20 once daily	40 daily

Ramipril	1.25–2.5 once daily or bd	10 daily (or 5 bd)	20 daily (or 10 bd)
Perindopril* as erbumine (as arginine)	2 once daily (2.5 once daily)	4 once daily (5 once daily)	8 once daily (10 once daily)
Trandolapril	0.5 once daily	4 once daily	4 once daily

*Data from a trial (PEP-CHF) showed improved morbidity but not mortality in patients ≥70 years old, with PEP-CHF.

During episodes of AHF, oral disease-modifying HF therapy, including ACEis, should be continued, except in the presence of haemodynamic instability or biochemical adverse reactions. In such cases, the daily dosage of oral therapy may be reduced or stopped temporarily until the patient is stabilised.[100]

Recommendation:

- Abrupt withdrawal of treatment with an ACEi can lead to clinical deterioration and should be avoided if not indicated. **(GPP)**

3.2. Angiotensin II Receptor Blockers (ARBs)

ARBs work by inhibiting RAAS.

3.2.1. Indications

Recommendations:

- ARBs should be used in patients with HFrEF who are ACEi-intolerant to reduce morbidity and mortality, unless contraindicated.[101–103] **(Grade A, Level 1$^+$)**
- ARBs can be used as alternatives to ACEis as first-line therapy for patients with HFrEF, especially for patients already taking an ARB for other indications.[104–107] **(Grade A, Level 1$^+$)**
- Routine combination of an ACEi, ARB, and MRA should not be used, as it is potentially harmful. This combination does not confer additional benefits and can contribute to a higher risk of adverse events such as hypotension, hyperkalaemia, and reduced renal function. **(GPP)**

3.2.2. Contraindications or Precautions

Although ARBs may be considered as an alternative therapy for patients who have developed angiooedema while taking an ACEi, there are some patients who may also develop angiooedema with ARBs. ARBs have been infrequently (0.1%) associated with angiooedema.[108–111] (The other contraindications and precautions are similar to ACEis.)

Recommendation:

- In patients who develop angiooedema while on ACEis, ARBs can still be used, but caution is advised. **(Grade D, Level 3)**

3.2.3. Initiation and Dose Titration

Treatment with ARBs should be initiated at low doses (Table 5).

Recommendations:

- If lower doses have been well-tolerated, the dosage should be titrated upwards at short intervals (e.g. after every 2 weeks), until the maximally tolerated or target dose (as used in large, randomised trials) is achieved. (**Grade A, Level 1^{++})**
- Check blood pressure, renal function, and serum K^+ soon after initiation or dose adjustment of ARB (e.g. after 2 weeks).[100] **(GPP)**

Table 7 summarises the titration of ARBs to their respective target doses. (Only the following 3 ARBs have been studied in randomised heart failure trials.)

Table 7. Dosing guide for evidence-based ARBs

ARB	Starting dose (mg)	Target dose (mg)	Maximum dose (mg)
Candesartan	4–8 once daily	32 once daily	32 once daily
Losartan*	25 once daily	150 once daily	150 once daily
Valsartan	40 bd	160 bd	160 bd

*Use is less well established in heart failure trials.[112–114]

During episodes of AHF, oral disease-modifying HF therapy, including ARBs, should be continued, except in the presence of haemodynamic instability or biochemical adverse reactions. In such cases, the daily dosage of oral therapy may be reduced or stopped temporarily until the patient is stabilised.[100]

Recommendation:

- Abrupt withdrawal of treatment with an ARB can lead to clinical deterioration and should be avoided if not indicated. **(GPP)**

3.3. Beta-adrenergic Blockers (Beta-blocker)

Beta-blockers work in heart failure by inhibiting the SNS. The aim of beta-blocker therapy and uptitration is to improve symptoms, reduce hospitalisation, improve survival, and improve quality of life.

Recommendations:

- An evidence-based beta-blocker should be used in all patients with HFrEF, unless contraindicated.[115–123] **(Grade A, Level 1^{++})**
- Only evidence-based beta-blockers such as bisoprolol, carvedilol, metoprolol succinate, or nebivolol are recommended for use in HFrEF.[117–125] **(Grade A, Level 1^{+})**

3.3.1. Indications

Evidence-based beneficial beta-blockers are listed in Table 3. The use of beta-blockers in HFrEF should not be considered as a class effect. Bucindolol has been shown to lack uniform effectiveness across different populations,[124] and short-acting metoprolol tartrate has been found to be less effective than carvedilol in heart failure clinical trials.[125]

RCTs suggest that major clinical outcomes are similar, regardless of whether a beta-blocker is started first followed by ACEi, or the opposite conventional order is followed.[126,127]

Recommendation:

- The order of commencing evidenced-based beta-blocker and ACEi (or ARB) is left to the individual physician, based on clinical circumstances.[126,127] **(Grade A, Level 1^{+})**

Patients need not take high doses of ACEis before initiation of beta-blocker therapy. In patients taking a low dose of an ACEi, the addition of a beta-blocker produces a greater improvement in symptoms and reduction in the risk of death than does an increase in the dose of the ACEi, even to the target doses used in clinical trials.[96,97]

Recommendation:

- For stable patients, it is reasonable to add therapy with beta-blocking agents before full target doses of either ACEis or ARBs are reached. **(Grade B, Level 1^{+})**

3.3.2. Contraindications or Precautions

Known contraindications to beta-blockers include active bronchial asthma, high-grade AV block without permanent pacemaker implant, patients on IV inotropic therapy.

Clinicians must be cautious in prescribing beta-blockers in patients with severe (NYHA Class IV) heart failure; heart rate <60 beats/min; persisting signs of hypervolaemia (raised jugular venous pressure, ascites, marked peripheral oedema) and hypotension/low blood pressure (systolic <90mmHg); and sick sinus syndrome.

Drug interactions to look out for include:

a) Use of verapamil/diltiazem should be discontinued when a beta-blocker is used.
b) Use of digoxin and/or amiodarone with a beta-blocker might result in severe bradycardia; thus indications should be reviewed and close monitoring is advised if concomitant use is indicated.

3.3.3. Initiation and Dose Titration

Recommendation:

- Beta-blocker therapy for heart failure should be introduced in a "start low, go slow" manner. It is recommended to increase the dose gradually at intervals of 2weeks with reassessment of symptoms, blood pressure, and heart rate.[115,118] **(Grade A, Level 1^{++})**

Increments in the dose of a beta-blocker should be delayed until any worsening heart failure symptoms observed with lower doses have disappeared.

When such a cautious approach was used, most patients (approximately 85%) enrolled in clinical trials and who received beta-blockers were able to tolerate short- and long-term treatment with these drugs and achieve the maximum planned trial dose.[115,118]

Table 8 summarises the titration of evidenced-based beta-blockers to their respective target doses.

Table 8: Recommended beta-adrenergic blockers dosing guide

Beta-blocker	Initial dose (mg)	Target dose (mg)
Bisoprolol	1.25 once daily	10 once daily
Carvedilol*	3.125 twice a day	25–50 twice daily
Metoprolol Succinate	12.5–25 once daily	200 once daily
Nebivolol†	1.25 once daily	10 once daily

*For patients weighing >85kg, up to 50mg twice a day can be used.

†The SENIORS trial showed a reduction in all-cause mortality or cardiovascular hospitalisation and cardiovascular mortality or cardiovascular hospitalisation in patients ≥70 years old.[123]

During episodes of AHF, oral disease-modifying HF therapy, including beta-blockers, should be continued, except in the presence of haemodynamic instability or biochemical adverse reactions. In such cases, the daily dosage of oral therapy may be reduced or stopped temporarily until the patient is stabilised.[100]

Recommendation:

- Beta-blockers should be and can be safely continued during AHF presentations, except in cardiogenic shock.[100] **(Grade A, Level 1^{+})**

Discontinuation of beta-blockers in patients hospitalised with AHF was associated with significantly increased in-hospital mortality, short-term

mortality, and the combined endpoint of short-term rehospitalisation or mortality.[128–130]

3.4. Mineralocorticoid Receptor Antagonist

Aldosterone receptors within the heart can mediate cardiac fibrosis, hypertrophy, and arrhythmogenesis.

Spironolactone and eplerenone (a selective aldosterone antagonist without antiandrogenic effects) are known as MRA, and they can attenuate these deleterious effects of aldosterone on the cardiovascular system.

The aim of MRA therapy is to improve symptoms, reduce hospitalisation, improve survival, and improve quality of life.

3.4.1. Indications

Recommendation:

- An MRA should be used for symptomatic patients (NYHA classes II–IV) with HFrEF (EF≤35%) already on an ACEi (or an ARB) and a beta-blocker, unless contraindicated.[131,132] **(Grade A, Level 1^{++})**

Mineralocorticoid receptor antagonists have been shown to reduce the risk of sudden cardiac death, total and cardiovascular mortality in patients with HFrEF (LVEF≤45%).[133]

Recommendation:

- An MRA is recommended in patients following a myocardial infarction who develop HFrEF (LVEF≤40%) or have a history of diabetes mellitus.[134] **(Grade A, Level 1^{+})**

3.4.2. Contraindications or Precautions

Known contraindications to MRA include patients with significant renal impairment (serum creatinine >221μmol/L[2.5mg/dL] or CrCl <30mL/min in elderly patients or patients with low muscle mass in whom serum creatinine does not accurately reflect GFR).

Caution should be exercised in prescribing MRA in patients with significant hyperkalaemia or history of hyperkalaemia.

Drug interactions to look out for include:
a) K^+ supplements/K^+-sparing diuretics, e.g. amiloride and triamterene (including combination preparations with furosemide)
b) Nonsteroidal anti-inflammatory drugs
c) "Low salt" substitutes with high K^+ content

3.4.3. Initiation and Dose Titration

Table 9: Dosing guide for MRAs

MRA	Initial dose (mg)	Target dose (mg)
Spironolactone	eGFR ≥50 mL/min/1.73m^2 12.5 to 25 once daily eGFR 30–49 mL/min/1.73m^2 12.5 once daily or alternate days	eGFR ≥50 mL/min/1.73m^2 25 once or twice daily eGFR 30–49 mL/min/1.73m^2 12.5 to 25 once daily
Eplerenone	eGFR ≥50 mL/min/1.73m^2 25 once daily eGFR 30–49 mL/min/1.73m^2 25 once daily or alternate days	eGFR ≥50 mL/min/1.73m^2 50 once daily eGFR 30–49 mL/min/1.73m^2 25 once daily

Spironolactone can cause breast discomfort and/or gynaecomastia in men that is usually reversible and dose-related.

Consider switching to eplerenone, a selective aldosterone antagonist without antiandrogenic effects.

Consider uptitration of dose after 4–8 weeks.

3.5. Angiotensin Receptor Neprilysin Inhibitor

Angiotensin receptor neprilysin inhibitor is a combination of ARB and neprilysin inhibitor. The only currently available ARNIs are valsartan and sacubitril.

Angiotensin receptor neprilysin inhibitor inhibits neprilysin, thus slowing the breakdown of natriuretic peptides, bradykinin, and other peptides. The resulting higher levels of these vasoactive peptides augment the generation of cyclic guanosine monophosphate, thereby enhancing diuresis, natriuresis, myocardial relaxation, and anti-remodelling actions. Angiotensin receptor neprilysin inhibitor also inhibits renin and aldosterone secretion. This reduces vasoconstriction, sodium and water retention, and myocardial hypertrophy.[135,136]

3.5.1 Indications

Recommendation:

- Angiotensin receptor neprilysin inhibitor is recommended as a replacement for ACEi or ARB to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACEi or ARB, a beta-blocker, and an MRA.[137] **(Grade B, Level 1^{+})**

3.5.2 Contraindications and Precautions

Known contraindications to ARNI include history of life-threatening adverse reactions during prior exposure (e.g. angioneurotic oedema, anuric renal failure) to ACEi or ARB, known bilateral renal artery stenosis, severe hepatic impairment (Child-Pugh C classification), and patients who are pregnant or are planning to get pregnant.

Caution should be exercised while prescribing ARNI in patients with significant hyperkalaemia, significant renal dysfunction (creatinine >221µmol/L or >2.5mg/dL or eGFR <30mL/min/1.73m^2), symptomatic or severe asymptomatic hypotension (SBP <90 mmHg).

Angiotensin receptor neprilysin inhibitor should not be administered concomitantly with ACEis or within 36 hours of the last dose of an ACEi.[138,139]

Combined treatment with an ACEi, ARB, or direct renin inhibitor and ARNI is contraindicated.

3.5.3 Initiation and Dose Titration

Stop existing ACEi for at least 36 hours before initiation of ARNI, to prevent chances of angiooedema, as concomitant inhibition of both ACE and neprilysin can increase bradykinin, which directly or indirectly can cause angiooedema.

Start with standard starting dose at 100 mg BD. Initiate a lower dose of 50 mg BD in the following patients: (1) those not taking an ACEi or other ARB, or previously taking a low dose of these agents when initiating treatment, and (2) those with severe renal impairment (eGFR <30mL/min/1.73m^2), or moderate hepatic impairment (Child-Pugh B classification).

If lower doses are well-tolerated, the dosage should be titrated upwards at short 2–4-week intervals, until the maximally tolerated or target dose of 200 mg BD is achieved.

Symptomatic hypotension is more common in patients aged ≥75 years. Thus, take greater precautions in patients belonging to this age group.[137]

Check blood pressure, renal function, and serum potassium soon after initiation or dose adjustment of medication (e.g. after 2 weeks).

During episodes of AHF, oral disease-modifying HF therapy should be continued, except in the presence of haemodynamic instability or biochemical adverse reactions. In such cases, the daily dosage of oral therapy may be reduced or stopped temporarily until the patient is stabilised.

Serum NT-ProBNP, but not serum BNP, is an accurate biomarker of cardiac wall stress (levels increase with increased cardiac wall stress) when ARNI is used, as, unlike BNP, NT-proBNP is not a substrate for neprilysin.[140]

3.6 Ivabradine

Ivabradine is a direct sinus node inhibitor. It inhibits the If channel in the sinus node. Its pharmacological effect is to slow the heart rate in patients in sinus rhythm.

The aim of ivabradine therapy by slowing the heart rate is to improve symptoms, reduce hospitalisation, and improve quality of life.

3.6.1. Indications

Recommendations:

- Ivabradine can be used in symptomatic (NYHA classes II–IV) HFrEF patients in sinus rhythm with an EF≤35%, a heart rate ≥70 beats/min, despite treatment with evidence-based beta-blocker, ACEi (or ARB), and an MRA.[141] **(Grade B, Level 1^{+})**
- Ivabradine may be considered in patients in sinus rhythm with an EF≤35%, a heart rate ≥70 beats/min who are unable to tolerate a beta-blocker. Patients should also receive an ACEi (or ARB) and an MRA. **(Grade B, Level 1^{+})**

3.6.2. Contraindications or Precautions

Known contraindications to ivabradine include pregnancy, lactation, cardiogenic shock, acute myocardial infarction, severe hypotension (<90/50 mmHg), moderate-to–severe hepatic insufficiency, severe renal dysfunction (no evidence on safety or pharmacokinetics for CrCl<15mL/min), sick sinus syndrome, sinoatrial block, or high-grade AV block.

Ivabradine is not recommended in patients with AF or other cardiac arrhythmias that interfere with sinus node rhythm; regular monitoring is needed for AF occurrence.

Drug interactions to look out for include:

a) The concurrent use of ivabradine with strong cytochrome P450 inhibitors (such as the azole antifungals, macrolides, HIV protease inhibitors, nefazodone), is contraindicated.
b) The concomitant use of ivabradine with medications that prolong the QT interval should be avoided, since QT prolongation may be exacerbated by heart rate reduction.
c) The concomitant use of ivabradine with heart rate-reducing calcium-channel blockers such as verapamil or diltiazem is not recommended.

3.6.3. Initiation and Dose Titration

Recommendations:

- Initiate with a dose of ivabradine 5mg twice daily and titrate to 7.5mg twice daily after 2–4 weeks if the resting heart rate is above 70 beats/min. Titrate downward to 2.5 mg twice daily if the patient develops bradycardia symptoms (e.g. dizziness, fatigue) or if the resting heart rate is persistently less below50 beats/min. Discontinue if heart rate is below 50 beats/min and symptoms persist.[142] **(GPP)**
- Consider a lower starting dose of ivabradine 2.5mg twice daily in patients ≥75 years of age. Titrate upwards, if necessary, to reach target heart rate safely.[142] **(GPP)**

Luminous phenomena (phosphenes), i.e. enhanced brightness in the visual field, have been reported in 14.5% of patients. These effects appear generally within the first two months of initiation, and the frequency increases with the dose of ivabradine. Visual disturbances usually resolve upon discontinuation of the drug.

3.7 Vasodilators (Hydralazine Plus Isosorbide Dinitrate)

Hydralazine plus isosorbide dinitrate (H-ISDN) combination is a vasodilator that helps in HFrEF by improving the haemodynamic profile of the patient.[139]

3.7.1. Indications

Recommendation:

- Hydralazine plus isosorbide dinitrate may be considered as an alternative to an ACEi or ARB if neither is tolerated in HFrEF patients:
  a) With an EF≤45% and dilated left ventricle
  b) With an EF≤35%

Patients should also receive a beta-blocker and an MRA.[39] **(Grade B, Level 1^{+})**

This is to reduce the risk of heart failure hospitalization and risk of premature death.[59,142]

3.7.2. Contraindications and Precautions

Recommendation:

- Hydralazine plus isosorbide dinitrate may be considered in addition to treatment with a beta-blocker, ACEi (or ARB), and an MRA in persistently symptomatic patients. **(Grade C, Level 2^{+})**

  This is to reduce the risk of heart failure hospitalization and risk of premature death in patients with persisting symptoms (NYHA classes II–IV). However, it has been demonstrated to be of benefit in African Americans with HFrEF, and in NYHA III–IV, but this is of limited applicability in Singapore context.[144]

Hydralazine hydrochloride can cause reflex tachycardia, potentially leading to myocardial ischaemia and angina attacks. Careful clinical and haemodynamic monitoring is recommended when H-ISDN is administered to patients with acute myocardial infarction, to avoid the hazards of hypotension and tachycardia.

Augmentation of the vasodilatory effects of isosorbide dinitrate by phosphodiesterase inhibitors such as sildenafil, vardenafil, or tadalafil could result in severe hypotension; hence, this combination is contraindicated.

3.7.3. Initiation and Dose Titration

Recommendations:

- Start with initial dose of hydralazine 10 mg TDS-QDS, stepping up to 25 mg TDS-QDS and thereafter at 25-mg increments per dose (e.g. 25 mg TDS-QDS to 50 mg TDS-QDS etc) up to maximum of 300 mg a day (see Table 10).[144] **(GPP)**
- Isosorbide dinitrate may be initiated at 5–10mg TDS-QDS and stepped up as tolerated, up to 120–240mg per day.[144] **(GPP)**
- Switching to isosorbide mononitrate may be considered if the patient is tolerating isosorbide dinitrate.[144] Compliance may be an issue due to the multiple tablets and side effects.[142]
- If systolic blood pressure is <80mmHg and/or patient has signs of orthostasis with vasodilator therapy, do not begin or increase dose.[144] **(GPP)**

Table 10: Dosing guide for H-ISDN

Drug	Initial dose (mg)	Target dose (mg)	Maximum dose (mg)
Hydralazine	10 tds–qds	75 tds	75 qds or 100 tds
Isosorbide dinitrate	5–10 tds–qds	30 qds or 40 tds	60 qds or 80 tds

tds: Three times daily; qds: Four times daily.

3.8. Digoxin

Digoxin is a cardiac glycoside. It acts as an oral inotrope by inhibiting myocardium sodium–potassium ATPase. Blockade of this enzyme has been associated with improved inotropic responsiveness in patients with ventricular dysfunction.

Digoxin may also sensitise cardiopulmonary baroreceptors, reduce central sympathetic outflow, increase vagal activity, and reduce renin secretion.

3.8.1 Indications

Recommendations:

- Digoxin may be considered in persistently symptomatic HFrEF patients in sinus rhythm, with an EF≤45% (NYHA classes II–IV) despite treatment with a beta-blocker, ACEi (or ARB), and an MRA.[145] **(Grade B, Level 1^{+})**
- This is to reduce the risk of heart failure hospitalisation.[145] Treatment with digoxin has been shown to improve symptoms, quality of life, and exercise tolerance in patients with mild-to–moderate heart failure.[146–150]
- In patients with symptomatic heart failure and atrial fibrillation, digoxin may be used to slow a rapid ventricular rate, although other treatments are preferred. See the section on arrhythmia.[151] **(Grade B, Level 1+)**

Digoxin is not indicated as primary therapy for the stabilisation of patients with an acute exacerbation of heart failure symptoms, including fluid retention or hypotension.

3.8.2. Contraindications and Precautions

Contraindications to the use of cardiac glycosides include bradycardia, second and third atrioventricular block, sick sinus syndrome, carotid sinus syndrome, Wolff-Parkinson-White Syndrome, hypertrophic obstructive cardiomyopathy, hypokalaemia, and hyperkalaemia.

Digoxin should be used cautiously in patients taking other drugs that can depress sinus or atrioventricular nodal function or affect digoxin levels (e.g. amiodarone), even though such patients usually tolerate digoxin without difficulty.

3.8.3. Initiation and Dose Titration

Recommendation:

- Initiate digoxin at a dose of 62.5–125 mcg daily. Low doses (62.5mcg daily or every other day) may be used initially, if the patient is >70 years old, has impaired renal function, or has a low lean body mass.[146] (**GPP)**

Higher doses (>250mcg daily) are rarely used or needed in the management of patients with heart failure in the absence of AF.

Loading doses of digoxin to initiate therapy in patients with heart failure are not recommended. In the majority of patients, there is no need to uptitrate the dosage of digoxin. Digoxin at a serum concentration between 0.5 and 0.9 ng/mL has been shown to reduce mortality and hospitalisation in all heart failure patients.[152]

However, routine monitoring of serum digoxin level is often not required. Consider obtaining digoxin level if:

a) Renal function worsens
b) Patient exhibits signs of toxicity (see below)
c) There is a high level of suspicion of patient noncompliance

The dose of digoxin may need to be reduced when drugs that increase serum digoxin concentration are added (e.g. amiodarone).

If a patient is currently on digoxin, but not an ACEi (or ARB) or beta-blocker, treatment with digoxin should not be withdrawn. Instead, appropriate therapy with ACEi and/or beta-blocker should be instituted.[153] Digoxin doses may

require reduction while optimising beta-blocker therapy, because of the risk of bradycardia.

3.8.4. Digoxin Toxicity

Digoxin toxicity manifests as confusion, nausea, visual disturbances (blurred vision, halos around bright objects, yellow discolouration), anorexia, arrhythmia.

Overt digitalis toxicity is commonly associated with serum digoxin levels >2ng/mL. However, toxicity may occur with lower digoxin levels, especially if hypokalaemia, hypomagnesaemia, or hypothyroidism coexists.[154,155]

3.9. Diuretics

Diuretics inhibit the reabsorption of sodium or chloride at specific sites in the renal tubules. Loop diuretics (e.g. bumetanide, furosemide) act at the loop of Henle; thus the term "loop diuretics". Thiazides (e.g. metolazone, hydrochlorothiazide) act in the distal portion of the tubule.[156,157]

Loop diuretics have emerged as the preferred diuretic agent for use in most patients with heart failure. Thiazide diuretics may be considered in hypertensive patients with heart failure and mild fluid retention because they confer more persistent antihypertensive effects.[158]

Diuretics have been shown to increase urine sodium excretion and decrease the physical signs of fluid retention, thereby rapidly improving symptom status. The effects of diuretics on morbidity and mortality are, however, not known.

3.9.1. Indications

Recommendation:

- Diuretics should be used in patients with HFrEF who have evidence of fluid retention, unless contraindicated, to improve symptoms.[159,160] **(Grade C, Level 2^{+})**

There are no RCTs assessing the effects of diuretics alone on symptoms or survival. When used, diuretics should always be used in addition to standard therapy.

3.9.2. Contraindications and Precautions

Diuretics are contraindicated in patients with anuria.

3.9.3. Initiation and Dose Titration

Diuretics are generally combined with moderate dietary sodium and fluid restriction to achieve and maintain euvolaemia.

Appropriate use of diuretics is a key element in the success of standard therapy used for the treatment of heart failure. The use of inappropriately low doses of diuretics will result in fluid retention, which can diminish response to ACEis and increase the risk of symptoms with beta-blockers**.**[161]

Conversely, the use of inappropriately high doses of diuretics will lead to volume contraction, which can increase the risk of hypotension and the risk of renal insufficiency, especially with ACEis or ARBs.[162,163]

Commonly used oral diuretics are listed in Table 11.

Table 11: Diuretics recommended for use in treatment of fluid retention in heart failure

Drug	Usual oral daily dose (mg)
Loop diuretics	
Bumetanide	0.5-6 daily (in 2 to 3 divided doses)
Frusemide	20-240 daily (in 2 to 3 divided doses)
Thiazide diuretics (for sequential blockade)	
Hydrochlorothiazide	12.5–25 once to twice daily
Metolazone	2.5–5 once daily or alternate day

In outpatients with heart failure symptoms, diuretic therapy is commonly initiated with low doses, and the dose is increased until urine output increases and weight decreases, generally by 0.5 to 1.0 kg daily. Increases in the dose or frequency (i.e. twice-daily dosing) of diuretic administration may be required

to maintain an active diuresis with the aim of achieving and then maintaining euvolaemia.[164]

Check volume status, blood pressure, renal function, and serum potassium soon after initiation or dose adjustment of medication (e.g. after 2 weeks).

Recommendation:

- Once euovlaemia is attained, the diuretic dose should be decreased, if possible, to a minimum dose needed to maintain clinical euvolaemia. The dose should be regularly reassessed, as it may need to be adjusted according to volume status. (**GPP)**

Patients are commonly prescribed a fixed dose of diuretic, but the diuretic dose may need adjustment.[164] In many cases, this adjustment can be accomplished by having patients record their weight each day and by adjusting the diuretic dosage if weight increases or decreases beyond a specified range.

Recommendation:

- At each consultation, it is advisable to record the patient's body weight, assess for symptoms of hypervolaemia, and examine for signs of hypervolaemia (e.g. estimates of jugular venous pressure and the presence of peripheral oedema or orthopnoea or third heart sound).[165–167] **(Grade B, Level 2^{+})**

3.9.4. Diuretic Resistance

If there is insufficient response to the diuretic by the patient, and more diuresis is needed, consider the following:

a) The patient is consuming large amounts of overt or covert dietary sodium;
b) The patient is taking agents that can diminish diuretic effects, e.g. NSAIDs,[168] COX-2 inhibitors;[169]
c) There is significant impairment of renal function or perfusion;[170]
d) Impaired or delayed absorption of oral diuretic.

The following strategies can be used to manage diuretic resistance:

a) Review patient's diet for dietary sodium indiscretion
b) Review patient's medications for agents that can diminish diuretic effects
c) Assess for and treat renal impairment, if present
d) Increasing dose and/or frequency of loop diuretics

e) Combination of different diuretic classes (e.g. metolazone or hydrochlorothiazide with a loop diuretic)[171,172] (Chronic combined use of multiple diuretics can cause electrolyte shifts and volume depletion; hence volume status and electrolytes must be monitored closely.)
f) Admit patient for IV diuretic, and if that is still inadequate, switch from IV bolus to IV continuous infusion of diuretic.[173]

3.9.5. Side Effects

The principal adverse effects of diuretics include electrolyte and fluid depletion, as well as hypotension and azotaemia.

Diuretics can cause the depletion of potassium and magnesium, which can predispose patients to serious cardiac arrhythmias, particularly in the presence of digoxin therapy.[174] The risk of electrolyte depletion is markedly enhanced when two diuretics are used in combination.[164]

When the patients are treated with diuretics, especially at high doses and in combination, it is recommended to carefully observe for the development of the following side effects:

a) Electrolyte abnormalities
b) Renal dysfunction
c) Symptomatic hypotension
d) Ototoxicity (with higher IV doses)
e) Gout flares

Hypokalaemia may be corrected with the use of potassium supplements. When MRA is concurrently used, long-term oral potassium supplementation may not be required.

Worsening renal function is common with excessive diuresis, especially when patients are receiving ACEi or ARB. Reduction in the diuretic dose and restoration of euvolaemia will likely return renal function to baseline in almost all cases, unless hypovolaemia has been prolonged. In the presence of renal impairment, consider discontinuing nephrotoxic drugs.

Hypotension may be a sign of volume depletion. Symptoms of hypotension may include fatigue and shortness of breath, rather than the more predictable symptom of dizziness.

Cases of tinnitus and reversible or irreversible hearing impairment and deafness have been reported with certain diuretics. Reports of frusemide ototoxicity may be due to rapid injection, severe renal impairment, the use of higher-than–recommended doses, hypoproteinaemia, or concomitant therapy with ototoxic drugs, e.g. aminoglycoside antibiotics.

To reduce the risk of gout flares, use the minimal dose of diuretics needed to obtain and maintain euvolaemia. Avoid NSAIDs and COX-2 inhibitors for analgesia.[100] Use colchicine with caution in patients with heart failure and concomitant renal impairment.

3.10. Sodium-Glucose Co-Transporter-2-Inhibitors

Sodium-Glucose Co-Transporter-2 Inhibitors (SGLT2i) have been shown to reduce the risk of heart failure-associated events in patients with type 2 diabetes mellitus and high cardiovascular risk.[175-177] There are ongoing trials to evaluate the efficacy of SGLT2i in heart failure patients without diabetes mellitus. In the DAPA-HF trial, dapagliflozin reduced the risk of worsening heart failure events and cardiovascular deaths, and improved symptoms when added to standard therapy in patients with HFrEF regardless of diabetes mellitus status.[178] The beneficial effect on heart failure-associated events seen with DAPA-HF was likely due to a SGLT2i class effect.

The mechanism of SGLT2i reducing heart failure-associated events could be related to direct effects on cardiac metabolism and function or effects on hemodynamic parameters such as reduced plasma volume, decrease in blood pressure and weight reduction.

3.10.1. Indications

Recommendations:

- In patients with heart failure and type 2 diabetes mellitus, combination therapy with any SGLT2i should be considered to reduce HF hospitalization and death in patients with HFrEF (LVEF of less than or equal to 40%) who remain symptomatic despite optimal medical treatment (ACEi or ARB or ARNI, beta-blocker, and MRA) in the absence of severe renal impairment. (**Grade B, Level 2^{+}**)
- In patients with heart failure without diabetes mellitus, dapagliflozin can reduce the risk of HF hospitalization and death in patients with HFrEF (LVEF of less than or equal to 40%) who remain symptomatic despite optimal medical treatment (ACEi or ARB or ARNI, beta-blocker, and MRA), and in the absence of severe renal impairment. (**Grade B, Level 2^{+}**)

3.10.2. Contraindications or Precautions

SGLT2i should not be used in patients with significant renal impairment (eGFR less than 30ml/min/1.73m^2). There is an increased risk of genital mycotic infections (balanitis in males, and vaginitis in females) associated with the use of SGLT2i. As SGLT2i have blood pressure lowering effects, patients should be monitored for symptomatic hypotension. SGLT2i should be suspended during diabetic ketoacidosis, and prior to events that may precipitate diabetic ketoacidosis. Rare cases of necrotising fasciitis of the perineum in patients on SGLT2i have been reported.

3.10.3. Initiation Dosing Guide for SGLT2i in Heart Failure

When used to treat heart failure, suggested dose is Dapagliflozin 10mg once daily. There is an ongoing clinical trial using Empagliflozin 10mg once daily.[179]

3.11. n-3 PUFA

Recommendation:

- An n-3 PUFA preparation may be considered in patients with NYHA II-IV HFrEF (EF ≤40%) to reduce the risk of all-cause mortality, cardiovascular mortality, and cardiovascular hospitalization in patients treated with an ACEi (or ARB), beta-blocker, and an MRA.[100,180] **(Grade B, Level 1$^+$)**

The recommended dose of n-3 PUFA preparation is 1 g daily (850 to 882 mg of EPA and DHA as ethyl esters in the ratio of 1:1.2).[181] Also, n-3 PUFA preparations differ in composition, and the dose may be important.

This therapy has been safe and very well-tolerated.[182] The main adverse effects of n-3 PUFAs reported in trials were nausea and other minor gastrointestinal disturbances.

3.12. Drugs of Unproven Benefit in Heart Failure

There are several drugs that have shown promise in the therapy of HFrEF. However, subsequent trials have not demonstrated any clear benefit in heart failure (Table 12).

Table 12: Drugs of unproven benefit in heart failure

Drug	Comments
3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (Statins)	Although there is strong evidence for the benefit of statins in patients with atherosclerotic disease, most trials excluded patients with heart failure (as it was uncertain whether they would benefit).[183] Two trials studied statin treatment specifically in patients with chronic HFrEF and did not demonstrate convincing evidence of benefit (although there was little evidence of harm).[184,185] Thus, statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of heart failure in the absence of other indications for their use.
Oral anticoagulants	Oral anticoagulants can be used in heart failure (HFrEF and HFpEF) patients with AF with additional risk factors for cardioembolic stroke.[186,187] There is, however, no evidence that an oral anticoagulant reduces morbidity and mortality to a greater extent compared with placebo or aspirin in patients with HFrEF in sinus rhythm, without prior thromboembolic event of a cardioembolic source.[188]
Direct renin inhibitor (aliskiren)	Aliskiren, in addition or as replacement of standard therapy, did not show benefits but increased the incidence of adverse events in two heart failure trials.[189–193] There are concerns about renal dysfunction, hyperkalaemia, and hypotension, as well as increased stroke incidence, with the use of direct renin inhibitors.[194] Aliskiren is not recommended as an alternative to an ACEi or ARB in heart failure.

3.13. Drugs to Avoid or to Use With Caution

There are drug therapies that may cause harm in patients with symptomatic (NYHA classes II–IV) HFrEF and, thus, should be avoided. If they are strongly indicated, they are to be used with caution, and with close monitoring (Table 13).

Table 13: Drugs to be avoided or used with caution

Drug	Comments
Metformin	The use of metformin appeared to be safe in a recent analysis of patients with heart failure, except in cases of concomitant renal impairment.[195]
Thiazolidinediones (glitazones)	These drugs should be avoided, and alternatives should be used. They worsen heart failure and increase the risk of heart failure hospitalisation.[196–198]
Nonsteroidal anti-inflammatory drugs and COX-2 inhibitors	They should be avoided, if possible, and alternatives should be used. These drugs may cause sodium and water retention, worsening of renal function, and worsening of heart failure.[199–201]
Non-dihydropyridine calcium-channel blockers (verapamil, diltiazem)	They should not be used, as they have a negative inotropic effect and can cause worsening of heart failure.[202]
Nutritional supplements (e. g. coenzyme Q10, carnitine, taurine, and antioxidants)	No clinical trials have demonstrated conclusively improved clinical outcomes and survival rates with the use of these nutritional supplements. Until more data are available, nutritional supplements are not recommended for the treatment of heart failure.[164,203–206]
Anti-arrhythmic agents (apart from beta-blockers and amiodarone)	Most antiarrhythmics have a few negative inotropic effects and some anti-arrhythmic drugs, particularly class I and class III drugs, have proarrhythmic effects. Hence, class I sodium channel antagonists and class III potassium-channel blockers such as d-sotalol and dronedarone should be avoided in patients with heart failure. Amiodarone and dofetilide are the only anti-arrhythmic agents noted to have neutral effects on mortality in clinical trials involving patients with heart failure and, thus, are preferred drugs for treating arrhythmias in this patient group.[164,207–210]

Trastuzumab	This drug has been associated with the development of reduced LVEF and heart failure. Hence, it is contraindicated in patients with symptomatic heart failure or reduced LVEF (<45%). Baseline and periodic evaluation of cardiac status, including assessment of LVEF, should be done in patients on trastuzumab.[211,212]
Tyrosine kinase inhibitors such as sunitinib	They have been associated with hypertension, reduced LVEF, and heart failure.[213] The risk–benefit profile must be considered with these agents in patients with a history of symptomatic heart failure or cardiac disease. Baseline and periodic evaluation of LVEF should be considered, especially in the presence of cardiac risk factors.[212]

4. Treatment Using Cardiac Implantable Electronic Devices

4.1. Cardiac Implantable Electronic Devices

Large randomised clinical trials have clarified the roles of implantable devices in patients with heart failure. Devices like Implantable Cardioverter-Defibrillator (ICD), and devices with Cardiac Resynchronisation Therapy (CRT), or their combination have been proven to be beneficial therapies for selected group of patients with HFrEF. This section provides recommendations for the use of ICDs and CRTs in patients with heart failure.

4.1.1. Implantable Cardioverter-Defibrillators Therapy

Optimal medical therapy (OMT) in patients with systolic heart failure significantly reduces the risk of sudden cardiac death. Despite OMT, these patients remain at increased risk for sudden cardiac death due to ventricular tachyarrhythmias. Patients with prior history of sustained ventricular tachycardia, ventricular fibrillation, resuscitated cardiac arrest, or unexplained syncope in the setting of severely depressed LVEF are at the highest risk for recurrence. Evidence from multiple RCTs supports the use of ICDs for the secondary prevention of sudden cardiac arrest, regardless of the aetiology of heart disease. In these patients, ICD is associated with a clinically and statistically significant reduction in sudden death and total mortality compared with anti-arrhythmic drug therapy in prospective RCTs.

The use of ICD in primary prevention of sudden cardiac death in patients with systolic heart failure without prior history of ventricular tachyarrhythmias or syncope has been evaluated in multiple RCTs. Implantable cardioverter defibrillator was demonstrated to reduce all-cause mortality. For patients with LVEF ≤30% after remote myocardial infarction, ICD therapy led to a 31% decrease in mortality over 20 months, for an absolute decrease of 5.6%.[214] For patients with mild-to–moderate symptoms of heart failure with LVEF ≤35% due either to ischaemic or nonischaemic aetiology, there was a 23% decrease in mortality over a five-year period, for an absolute decrease of 7.2%.[215]

Recommendations:

- Implantable cardioverter-defibrillator therapy should be offered to patients who are survivors of cardiac arrest due to ventricular fibrillation or haemodynamically unstable sustained ventricular tachycardia after evaluation to define the cause of the event and to exclude any completely reversible causes.[100,216] **(Grade A, Level 1++)**
- Implantable cardioverter-defibrillator therapy should be offered to patients with structural heart disease and spontaneous sustained ventricular tachycardia, whether haemodynamically stable or unstable.[216] **(Grade B, Level 1^{+})**
- Implantable cardioverter-defibrillator therapy should be offered to patients with syncope of undetermined origin with clinically relevant, haemodynamically significant sustained ventricular tachycardia, or ventricular fibrillation induced during electrophysiological study.[216] **(Grade B, Level 1^{+})**
- Implantable cardioverter-defibrillator therapy should be offered for the primary prevention of sudden cardiac death in patients with **ischaemic cardiomyopathy** (at least 40 days post-myocardial infarction) with **LVEF ≤35%,** NYHA **class II/III symptoms** on OMT, and who have reasonable expectation of survival for >1 year.[100,216] **(Grade A, Level 1^{++})**
- Implantable cardioverter-defibrillator therapy should be offered for the primary prevention of sudden cardiac death in patients with **ischaemic cardiomyopathy** (at least 40 days post-myocardial infarction), **LVEF ≤30%,** and NYHA **class I symptoms** while receiving OMT, who have reasonable expectation of survival for >1 year.[216] **(Grade A, Level 1^{++})**
- Implantable cardioverter-defibrillator therapy should be offered in patients with **nonischaemic cardiomyopathy** with **LVEF ≤35%** and NYHA **class II or III symptoms** while receiving OMT.[216] **(Grade B, Level 1^{++})**
- Implantable cardioverter-defibrillator therapy should be offered in patients with **non-sustained VT due to prior MI**, **LVEF ≤40%,** and **inducible ventricular fibrillation or sustained ventricular tachycardia at electrophysiological study.**[216] **(Grade B, Level 1^{++})**
- Implantable cardioverter-defibrillator therapy may be offered to patients with **unexplained syncope, significant left ventricular dysfunction, and non-ischaemic dilated cardiomyopathy.**[216] **(Grade D, Level 4)**

Recommendations:

- Implantable cardioverter-defibrillator therapy may be offered to **non-hospitalised patients awaiting transplantation.**[216] **(Grade D, Level 4)**
- Implantable cardioverter-defibrillator therapy may be offered in patients with **non-ischaemic heart disease** who have an **LVEF of ≤35%** and who are in NYHA functional **class I.**[216] **(Grade D, Level 4)**
- Implantable cardioverter-defibrillator therapy may be offered in patients with **syncope and advanced structural heart disease** in whom through invasive and noninvasive investigations have **failed to define a cause.**[216] **(Grade D, Level 4)**
- Implantable cardioverter-defibrillator therapy may be offered in patients with a **familial cardiomyopathy associated with sudden death.**[216] **(Grade D, Level 4)**
- Implantable cardioverter defibrillator therapy is **not indicated** for patients with **incessant ventricular tachycardia or ventricular fibrillation.**[216] **(Grade D, Level 4)**
- Implantable cardioverter-defibrillator therapy is **not indicated** in patients **with significant psychiatric illnesses** that may be aggravated by device implantation or that may **preclude systematic follow-up.**[216] **(Grade D, Level 4)**
- Implantable cardioverter-defibrillator therapy **is not indicated** for NYHA **Class IV** patients with **drug-refractory** congestive heart failure who are **not candidates for cardiac transplantation or CRT -defibrillator.**[100, 216] **(Grade C, Level 2^{+})**
- Patients should be carefully evaluated by an experienced cardiologist before generator replacement, because management goals and the patient's needs and clinical status may have changed.[100] **(Grade B, Level 2^{+})**
- **Wearable** ICD therapy may be considered in patients with heart failure who are at **risk of sudden cardiac death for a limited period** or as a **bridge to an implanted device**.[100] **(Grade C, Level 2^{-})**

The use of ICDs for primary prevention in patients with systolic heart failure should be considered in the setting of OMT and with a minimum of 3 to 6 months of appropriate medical therapy. Implantable cardioverter-defibrillators are indicated only in patients with a reasonable expectation of survival with good functional status beyond a year.

Recommendation:

- Implantable cardioverter-defibrillator or CRT devices are not recommended inpatients whose comorbidities and/or frailty limit their survival with good functional capacity to <1 year. **(GPP)**

4.1.2. Cardiac Resynchronisation Therapy (CRT)

In one in three patients with heart failure, progression of disease is accompanied by prolonged PR interval and widened QRS duration, most commonly LBBB. These changes result in regional mechanical delay within the left ventricle, worsen ventricular systolic function, alter myocardial metabolism, and increase functional mitral regurgitation.

Cardiac resynchronisation therapy involves the placement of two ventricular leads (right ventricle endocardium and left ventricle epicardium via the coronary sinus) to modify electromechanical delay due to LBBB. A meta-analysis of initial CRT trials in patients with NYHA III or IV heart failure symptoms confirmed an approximately 30% reduction in hospitalisation and a mortality benefit of 24%–36%. These results were replicated in recent trials with patients receiving contemporary OMT.

Recent evidence supports the role of CRT in patients with milder symptoms (NYHA I and II heart failure symptoms). These trials demonstrated reversal of left ventricular remodelling, with reduction in heart failure hospitalisation. In a meta-analysis of five trials of CRT in mild heart failure that included 4213 patients with class II symptoms, benefits were mainly seen in patients with QRS ≥150 ms and LBBB, with an adverse impact with shorter QRS duration or non-LBBB.[217]

Cardiac resynchronisation therapy has been shown to improve clinical outcomes in patients who have depressed EF who are pacing-dependent. Pacing-induced LBBB in these patients may lead to clinically significant ventricular dyssynchrony, thereby increasing the incidence of heart failure episodes.

Recommendations:

- Cardiac resynchronisation therapy should be offered to patients who have **LVEF ≤35%, sinus rhythm**, **LBBB** with a **QRS duration ≥150ms**, and NYHA **class III–IV** (except nonambulatory class IV) symptoms on ≥3 months' guideline-directed medical therapy (GDMT).[100,216] **(Grade A, Level 1^{++})**
- Cardiac resynchronisation therapy should be offered to patients who have **LVEF ≤35%, sinus rhythm**, **LBBB** with a **QRS duration ≥150ms**, and NYHA **class II symptoms** on ≥3 months' GDMT.[216] **(Grade B, Level 1^{++})**
- Cardiac resynchronisation therapy may be offered to patients who have **LVEF ≤35%, sinus rhythm**, a **non-LBBB pattern** with a **QRS duration of ≥150 ms**, and NYHA **class III/ambulatory class IV** symptoms on GDMT.[100,216] **(Grade A, Level 1^{+})**
- Cardiac resynchronisation therapy may be offered to patients who have **LVEF ≤35%, sinus rhythm, LBBB** with a **QRS duration** of **120 to 149 ms**, and NYHA **class II–IV** (except non-ambulatory class IV) symptoms on GDMT.[216] **(Grade B, Level 1^{+})**
- Cardiac resynchronisation therapy should be offered to symptomatic patients with heart failure in **sinus rhythm** with a **QRS duration130–149 ms** and **LBBB** QRS morphology and with **LVEF≤35%,** despite OMT in order to improve symptoms and reduce morbidity and mortality.[100] **(Grade B, Level 1^{++})**
- Cardiac resynchronisation therapy may be considered in patients who have LVEF **≤35%, sinus rhythm**, a **non-LBBB** pattern with QRS duration of **120 to 149 ms**, and NYHA **class III/IV** on GDMT.[216] **(Grade B, Level 2^{-})**
- Cardiac resynchronisation therapy may be considered in symptomatic patients with heart failure in **sinus rhythm** with a QRS duration **130–149 ms** and **non-LBBB** QRS morphology and with LVEF≤**35%,** despite OMT in order to improve symptoms and reduce morbidity and mortality.[100] **(Grade B, Level 2^{-})**
- Cardiac resynchronisation therapy may be considered in patients who have LVEF **≤35%, sinus rhythm**, a **non-LBBB** pattern with a QRS duration **≥150 ms**, and NYHA **class II** symptoms on GDMT.[216] **(Grade B, Level 2^{-})**
- Cardiac resynchronisation therapy rather than RV pacing should be offered to patients with heart failure with **reduced EF regardless of NYHA class** who have an **indication for ventricular pacing** (including patients in **AF**) and **high degree AV block** in order to reduce morbidity.[100] **(Grade A, Level 1++)**

Recommendations:

- Cardiac resynchronisation therapy may be offered in patients with **AF** and **LVEF ≤35%** on GDMT if a) the patient **requires ventricular pacing** or otherwise **meets CRT criteria** and b) **atrioventricular nodal ablation** or pharmacological rate control will **allow near-100% ventricular pacing** with CRT.[216] **(Grade B, Level 1+)**
- Cardiac resynchronisation therapy may be offered to patients with **Class III and Class IV** (except patients in end-stage HF deemed to be managed conservatively) with **LVEF≤35%** despite OMT in order to improve symptoms and reduce morbidity and mortality, if they are in **AF** and have a **QRS duration ≥130 ms,** provided a strategy to **ensure bi-ventricular capture** is in place or the patient is **expected to return to sinus rhythm**.[100] **(Grade B, Level 1+)**
- Cardiac resynchronisation therapy may be considered inpatients on OMT who have LVEF **≤35%** and are undergoing placement of a new or **replacement device implantation** with anticipated **requirement for significant (>40%) ventricular pacing**.[216] **(Grade C, Level 2+)**
- Patients with heart failure with **reduced EF** who have **received a conventional pacemaker** or **an ICD** and subsequently **develop worsening heart failure**, despite OMT, and who have a **high proportion of right ventricular pacing** may be considered for upgrade to CRT. This does not apply to patients with stable heart failure.[100] **(Grade B, Level 2-)**
- Cardiac resynchronisation therapy may be considered in patients with **ischaemic cardiomyopathy** who have LVEF **≤30%, sinus rhythm, LBBB with a QRS duration ≥150 ms,** and NYHA **class I** symptoms on GDMT.[216] **(Grade C, Level 2-)**
- Cardiac resynchronisation therapy is **not recommended** for patients with NYHA **class I or II** symptoms and **non-LBBB pattern** with QRS duration **<150 ms.**[216] **(Grade B, Level 2^{+})**
- Cardiac resynchronisation therapy is **contraindicated** in patients with a QRS duration **<130 ms**.[100] **(Grade A, Level 1^{++})**

5. Surgical Management of Heart Failure

Surgical management of heart failure is applicable if the causative or aggravating factor is amenable to surgery. The decision to operate should take into account response to medical therapy, associated comorbidities, prognosis, and operative risks.

These procedures should preferably be done at centres with demonstrable expertise, multidisciplinary medical and surgical teams experienced in the selection, care, perioperative, and long-term management of high-risk patients with severe heart failure.

5.1. Coronary Artery Bypass Surgery (CABG) in HFrEF Due to Ischaemia

This section deals only with heart failure associated with ischaemic heart disease.

Recommendation:

- Revascularisation is not recommended for routine management of patients with CAD and heart failure.[218] (**Grade B, Level 1+)**

The only RCT available on the role of CABG in heart failure is the Surgical Treatment for Ischemic Heart Failure (STICH) trial.[218] The trial addressed the role of CABG in patients with CAD and EF≤35%, who were suitable for surgery. Patients were randomised to CABG plus medical therapy or medical therapy alone. The primary outcome of all-cause mortality was not reduced by CABG. However, CABG did reduce the secondary outcomes of cardiovascular death (hazard ratio with CABG: 0.81) and death from any cause or cardiovascular hospitalisation (hazard ratio with CABG: 0.74).[218]

There is relatively little evidence for the role of a strategy involving the determination of reversibility of ischaemic myocardium by stress echocardiography, radio-isotope myocardial imaging, or CMR imaging, in selecting patients with heart failure for CABG and improving outcomes.

Recommendation:

- Imaging for myocardial viability (stress echocardiography, radio-isotope myocardial imaging, or CMR imaging) may be considered a strategy for selecting heart failure patients for CABG.[219–223] (**Grade C, Level 2+)**

5.2. Ventricular Reconstruction

The value of surgical ventricular reconstruction in ischaemic cardiomyopathy and CABG, during which scar tissue is excised from the left ventricular wall with the aim of restoring a more physiological left ventricular volume and shape, is uncertain and was not shown to be of benefit in the STICH trial.[224]

Recommendations:

- Surgical ventricular reconstruction in ischaemic cardiomyopathy is not recommended for routine use.[224] (**Grade B, Level 1+)**
- Surgical repair of left ventricular aneurysm is indicated in patients with heart failure. It is associated with improvement in symptoms and long-term survival.[225,226] (**Grade B, Level 2+)**

5.3. Valvular Surgery

Valvular heart disease may cause or aggravate heart failure. This section briefly addresses issues relevant to heart failure.

Recommendations:

- Mitral valve repair with preservation of the subvalvular apparatus may provide clinical and haemodynamic improvements in select patients who develop significant mitral regurgitation secondary to left ventricular dilatation.[227,228] (**Grade C, Level 2+)**
- Patients with associated right ventricular dysfunction and pulmonary hypertension are not suitable candidates for mitral valve repair.[227,228] (**Grade C, Level 2+)**

Substantial recovery of left ventricular function is only likely when the reduced EF is caused by excessive after load (aortic stenosis) or volume overload (aortic regurgitation) and is not due to myocardial scarring.

Recommendations:

- Aortic valve replacement may benefit patients with symptomatic significant aortic valve disease associated with low EF if their contractile reserve is reversible.[229–234] (**Grade B, Level 2++)**
- Transcatheter aortic valve replacement may be considered in patients who are medically not fit for surgery.[235] (**Grade B, Level 2++)**

5.4. Heart Transplantation

Advanced heart failure is present when the disease has progressed to the extent that, despite OMT or conventional surgical treatment, the end result will be death in the short term.

Heart transplantation is an accepted treatment for advanced heart failure, as it significantly increases survival, exercise capacity, and quality of life.

Donor availability is a universal limiting factor. Hence, indications and contraindications have been pragmatically defined, based on the consensus of experts, to maximise the utilisation of scarce donor hearts and to obtain the best results (Table 14).

Table 14: Indications and contraindications for heart transplant recipients

The criteria for a suitable heart transplant recipient are generally:
(a) Age <60 years (An older patient may be considered depending on the patient's general condition.) (b) Irreversible end-stage heart disease, with LVEF below 20% (c) New York Heart Association functional class III or worse, with a low likelihood of survival for >1 year (d) Normal function or reversible dysfunction of liver and/or kidneys (e) Acceptable psychological and social background
Potential heart transplant recipients are generally excluded if they have:
(a) Significant active infection (e.g. HIV, hepatitis, tuberculosis) (b) Recent pulmonary infarction

(c) Pulmonary vascular resistance over 8 Wood units and/or transpulmonary pressure gradient >15 mmHg
(d) Autoimmune antibodies
(e) Chronic gastrointestinal diseases, e.g. peptic ulcer, colitis
(f) Cancer
(g) Chronic bronchitis, emphysema
(h) Alcoholism, drug dependency, poor social support
(i) Irreversible dysfunction of liver and kidneys

Grade D, Level 4

Recommendation:

- Heart transplantation should be considered for advanced heart failure in suitable patients who have failed OMT.[236] (**Grade B, Level 2++)**

5.5. Mechanical Circulatory Support (MCS)

Mechanical circulatory support devices are devices designed as cardiac assist devices or as replacement devices for patients in advanced heart failure. There are different types of MCS devices using different technologies to support the failing heart. Some are designed to support the left heart; others are for right ventricular support or biventricular support. Some are designed for short-term use, while others called durable devices are used for long-term use, Total heart replacement has little role in surgical management. More than 90% of patients could be sustained with left ventricular support alone. Only those with advanced right ventricular pathology require right ventricular or biventricular support. Implantable durable continuous flow LVAD have revolutionised MCS therapy with superior outcomes. The contraindications for LVAD are listed in Table 15.

Recommendation:

- Patients awaiting heart transplantation who have become refractory to all means of medical therapy should be considered for a MCS device as a bridge to transplant.[237,238] (**Grade A, Level 1+)**

Table 15: Contraindications for LVAD

Contraindications
• High surgical risk for successful implantation • Recent or evolving stroke • Neurological deficits impairing the ability to manage device • Co-existing terminal condition (e.g. metastatic cancer, cirrhosis) • Biventricular failure • Active systemic infection or major chronic risk for infection • Portal hypertension • Severe pulmonary dysfunction (e.g. FEV_1<1 L) • Impending renal or hepatic failure • Multisystem organ failure • Inability to tolerate anticoagulation • Heparin-induced thrombocytopenia • Significant underlying psychiatric illness or lack of social support that may impair the ability to maintain and operate VAD

Recommendation:

- Left ventricular assist device should be considered as a permanent or destination therapy in highly select patients with refractory advanced heart failure, who are not candidates for heart transplantation.[239,240] (**Grade A, Level 1+)**

Patients on LVAD therapy should be referred before right ventricular or multi-organ failure develops; otherwise they will not be candidates for LVAD.

Indications for referral are NYHA III or IV plus one of the following:[241]

a) Inability to walk <1block without dyspnoea (shortness of breath)
b) Serum sodium <136 mmol/L
c) BUN >40mg/dL BUN (urea-N)
d) Intolerant or refractory to ACEi/ARB/beta-blocker
e) Diuretic dose >1.5mg/kg/day
f) One or more chronic heart failure-related hospital admissions within 6 months
g) Cardiac resynchronisation therapy nonresponder
h) Haematocrit <35%

Recommendation:

- Short-term temporary MCS may be used in select patients with AHF and cardiogenic shock who do not respond to conventional therapy, including inotropes and intra-aortic balloon counter pulsation.[242–245] (**Grade D, Level 2+)**

Extracorporeal membrane oxygenation cardiac support is gaining ground as a short-term MCS and as a bridge to decision for myocardial recovery or bridge to durable MCS or for termination of support if no neurological and end-organ recovery occurs from hypoxia.

6. Palliative Care in Advanced Heart Failure

An estimated 5% of patients with heart failure have advanced heart disease that is refractory to medical therapy.[246] Patients with advanced heart failure suffer from many physical symptoms besides dyspnoea and pain. Psychosocial and spiritual issues relating to the end of life are equally important and require a holistic approach. Good communication between healthcare providers and patients/families, with an emphasis on advance care planning, is crucial. It helps to establish the goals of care based on the patient's preferences and wishes.

The World Health Organization defines palliative care as an approach that improves the quality of life of patients and their families facing problems associated with life-threatening illnesses, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other physical, psychosocial, and spiritual problems.[247] Palliative and hospice care, which emphasise holistic care, should be made available to these patients.

6.1. Prognostication

Like many noncancer conditions, prognostication of advanced heart failure can be challenging. There are many available tools and models for prognostication of heart failure to help patients and healthcare providers determine when to refer patients to a hospice. There is, however, a paucity of data on how to recognise a patient in the terminal phase of advanced heart failure.

6.2. Supportive Care in Heart Failure

Disease management and supportive care should be offered concurrently during the course of the illness, with a patient-centred, family-focused approach. Clinicians caring for patients with advanced heart failure should consider referring these patients to palliative care services in the community. Care should address symptom control, psychosocial distress, end-of–life preferences, caregiver support, and reducing repeat hospitalisation. Emphasis on quality of life with an interdisciplinary approach involving counsellors/social workers, physical therapists, and pharmacists is important at this stage of the disease.

6.3 Symptom Management

The common symptoms associated with advanced heart failure include dyspnoea, pain, depression, fatigue, and oedema.[248] It is important to manage these symptoms well, as poor symptom control negatively impacts the quality of life.

6.3.1. Dyspnoea

Fluid and salt restriction is still important in patients at this stage, as it helps to reduce congestive symptoms. Hyponatraemia is relatively common at this stage, and fluid restriction may also help to maintain serum sodium concentrations.

Medical therapies, in particular those involving the use of diuretics and ACEis, have been shown to improve quality of life and symptoms in advanced heart failure.[60] However, the use of these drugs is usually limited by hypotension, which is common during this stage.

If the dyspnoea due to heart failure is refractory to both medical therapy and fluid and salt restriction, opioids, which have been shown to reduce dyspnoea, should be considered for symptom relief.

Recommendations:

- Fluid and salt restriction help to reduce congestive symptoms and should still be emphasised when counselling patients with advanced heart failure.[249] **(Grade C, Level 2+)**
- Opioids, such as morphine and fentanyl, should be prescribed for relief from dyspnoea if symptoms persist despite optimisation of diuretic therapy.[250,251] **(Grade B, Level 1+)**

6.3.2. Pain

Pain is a common, yet often undertreated, symptom in advanced heart failure. Pain can be the result of angina or other causes unrelated to the cardiac condition. Pharmacological agents that treat the underlying cause of pain should be initiated. Nitrates, which are effective in relieving angina, should be used as first-line agents for ischaemic chest pain. The choice of analgesics for pain other than those of cardiac origin is important. Nonsteroidal anti-

inflammatory agents have been shown to cause sodium and fluid retention and are therefore not advisable in this group of patients. Simple analgesics such as paracetamol may be effective in relieving mild pain. In situations where pain is moderate or severe in intensity, stronger analgesics such as opioids can be considered.

Recommendations:

- For nonanginal pain that is moderate or severe in intensity and not responding to weak analgesics, opioids should be considered.[252] **(Grade B, Level 1+)**
- Nonsteroidal anti-inflammatory agents should be avoided because of the risks of gastrointestinal bleeding, renal failure, and fluid retention.[253] **(Grade B, Level 1+)**

6.3.3. Depression

Psychosocial issues are not uncommon in patients with advanced heart failure. Failure to address these issues may adversely affect patients' quality of life. Depression has been reported in as high as one-third of patients with heart failure.[254,255] Unfortunately, the management of depression in heart failure is not well studied. Psychotherapy and cognitive behavioural therapy have demonstrated efficacy in the treatment of low mood.[256]There may be a role for a trial of antidepressant treatment if nonpharmacological therapy fails.[257]

(Refer to Section 10.11: Heart Failure Disease Management for the management of depression)

6.4. Advance Care Planning

Communication is an important component of end-of–life care. It is important to conduct discussions with patients and their families on issues related to treatment and care options. Unfortunately, studies have reported poor communication between physicians and bereaved families of heart failure patients. Many families are not aware of the consequences of the patient's medical condition.[258]

Unlike cancer patients, heart failure patients usually experience an unpredictable pattern of decline, punctuated by crises that result in hospitalisation. Up to one-third of patients may die suddenly or unexpectedly from cardiac arrest. This prognostic uncertainty makes it difficult for patients

to accept end of life care discussions.[259] A study comparing lung cancer and heart failure patients found that the latter group had a poorer understanding of their illness and prognosis. They also had fewer opportunities for making end-of–life plans.[260]

Recommendation:

Advance care planning is central to the palliative approach to advanced heart failure. Shared decision-making among patients, their families, and the medical team in establishing the goals of care should be initiated early in the disease trajectory – in view of the uncertainty of prognosis. **(GPP)**

6.5. Role of Inotropic Agents

Studies on the use of inotropic agents to treat refractory symptoms of heart failure have not shown survival benefits. However, continuous inotropic therapy may provide symptomatic relief from dyspnoea and oedema in a select group of patients affected by end-organ hypoperfusion and where the goal of care is mainly palliative.[259,261]

Recommendation:

- Patients with advanced heart failure and refractory symptoms may be considered for treatment with an ambulatory inotropic agent in an inpatient or home-based palliative setting.[259,261] (**Grade D, Level 2+)**

6.6. Implantable Cardiac Devices

It has been reported that over a quarter of patients received at least one shock in the last month of life and that as high as 30% receive a shock in the last minutes of life. Multiple shocks were reported in some cases, causing distress to the next of kin who witnessed them.[262]

In patients with implantable cardiac defibrillator (ICD), the option of deactivating the device when the condition is deteriorating, should be explored. However, patients on CRT have reported an improvement in their symptoms and quality of life.[263,264] As such, for this group of patients, continuing the pacing mode even when the decision is made to turn off the implantable cardiac devices, may be appropriate.

Recommendation:

- Discussions on deactivation of implantable cardiac devices when death is near may be appropriate in patients who are actively deteriorating. **(GPP)**

6.7. Conclusion

Given the physical, psychological, and economic burden of advanced heart failure, there is a need for palliative care to be integrated into the treatment plan along the disease trajectory. The integration of supportive care with heart failure management can improve the quality of life for heart failure patients and their families; as such, healthcare providers need to be educated on these options, so that timely palliative care interventions can be offered to patients.

7. Treatment of Acute Heart Failure

Acute heart failure is the term used to describe the rapid onset of, or change in, the symptoms and signs of heart failure. Acute heart failure may present *de novo* or as acute decompensation of chronic heart failure. In patients with pre-existing heart failure, there is often a clear trigger (Table 16)

Patients with AHF may be hospitalised. Diagnosis and treatment are usually carried out in parallel, and management must be initiated promptly. Close monitoring of the patient's vital functions (pulse, blood pressure, oxygen saturation, respiratory rate, and urine output) is essential during the initial evaluation and treatment. Ill patients should be managed with close monitoring in the high-dependency unit or intensive care unit. Immediate goals of treatment are to improve symptoms and stabilise the patient's haemodynamic condition. Long-term management is important to prevent recurrence and improve prognosis.

Table 16: Precipitants to decompensation in a patient with chronic heart failure

- Noncompliance to medications
- Dietary indiscretion (salt/fluid)
- Acute coronary syndrome
- Tachyarrhythmias, bradycardia
- Uncontrolled hypertension
- Anaemia
- Infection (e. g. upper respiratory tract)
- Medication (e.g. NSAIDS, corticosteroids)
- Alcohol abuse
- Hyperthyroidism/hypothyroidism
- Pulmonary embolism
- Exacerbation of chronic obstructive pulmonary disorder/asthma

7.1. Initial Assessment and Monitoring

Three parallel assessments must be made during the initial evaluation of the patient (Figure 1).[39]

1) Does the patient have AHF, or is there an alternative cause for their symptoms and signs?

2) If the patient does have AHF, is there a trigger and does it require immediate treatment?
3) Is the patient's condition immediately life-threatening because of hypotension or hypoxaemia leading to underperfusion of the vital organs?

7.2. Pharmacological Therapy (Figure 2)

7.2.1. Diuretics

Most patients with dyspnoea caused by pulmonary oedema obtain rapid symptomatic relief following administration of an intravenous loop diuretic. The dose should be individualised and titrated according to clinical response and renal function. The optimal route of administration is uncertain (bolus or continuous).[265]

Recommendation:

- Acute heart failure patients with dyspnoea caused by pulmonary oedema can be treated with diuretics. A combination of loop and thiazide diuretics may be needed to achieve adequate diuresis in patients with resistant peripheral oedema and/or ascites.[266,267] (**Grade D, Level 1+)**

7.2.2. Opiates

They are most useful in patients who are dyspnoeic and restless. They reduce pulmonary venous congestion, anxiety, and sympathetic drive.[268]

Recommendation:

- Acute heart failure patients who are dyspnoeic and restless can be treated with opiates, administering anti-emetics concomitantly. Care must be exercised in patients with chronic respiratory diseases.[268] (**Grade D, Level 3)**

7.2.3. Vasodilators

Vasodilators such as nitroglycerine are most useful in patients with hypertension and should be avoided in patients with systolic blood pressure <110mmHg.[269] Studies have shown that the combination of intravenous nitrate

and low-dose frusemide is more efficacious than high-dose frusemide treatment alone.[270]

Recommendation:

- Acute heart failure patients with hypertension, except patients with systolic blood pressure <110mmHg, can be treated with vasodilators. Vasodilators should be used with caution in patients with significant mitral or aortic stenosis.[269,270] (**Grade B, Level 1+)**

7.2.4. Inotropes

Recommendation:

- Use of an inotrope is usually reserved for patients with severely impaired cardiac output that compromises vital organ perfusion.[39] (**Grade B, Level 1+)**

Continuous electrocardiogram monitoring is required, as inotropes may induce myocardial ischaemia and arrhythmias. There is a concern regarding increased mortality with inotrope usage.[39]

Recommendation:

- To counteract the effects of beta-blockers, non-cathecholamine inotropes such as milrinone and levosimendan can be used.[271–275] (**Grade D, Level 1+)**

7.2.5. Vasopressors

Peripheral vasoconstrictors such as noradrenaline can be considered in patients with cardiogenic shock despite treatment with inotrope, to increase blood pressure and vital organ perfusion. Similar to inotropes, these agents can cause myocardial ischaemia and arrhythmias. Their use should be restricted to patients with persistent hypotension despite adequate left ventricular filling pressures.[39]

Recommendation:

- Acute heart failure patients with persistent hypotension despite adequate left ventricular filling pressures can be treated with vasopressors.[39] (**Grade D, Level 4)**

7.2.6. Anticoagulation

Hospitalised patients with heart failure are at increased risk of venous thromboembolism.[276] The increased risk is contributed by multiple factors including stasis of blood, reduced cardiac contractility, reduced mobility, and increased venous pressure.

Recommendations:

- Thromboembolism prophylaxis is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep-vein thrombosis and pulmonary embolism.[277–279] **(Grade A, Level 1+)**

7.3. Nonpharmacological Therapy

Recommendation:

- Oxygen may be given to treat hypoxaemia (SpO_2 <90%), maximize tissue oxygenation, and to prevent end-organ dysfunction.[280] (**Grade D, Level 4)**

It is common to restrict salt intake to <2g/day and fluid intake to <1.5L/day during an episode of AHF with volume overload.

Recommendations:

- Salt/fluid restriction can be used in AHF patients with volume overload.[39] **(Grade D, Level 4)**
- Noninvasive ventilation such as CPAP and BIPAP may be used as adjunctive therapy to relieve dyspnoea in patients with pulmonary oedema and severe respiratory distress or who fail to improve with pharmacological therapy. Contraindications include hypotension, vomiting, possible pneumothorax, and depressed consciousness.[281,282] (**Grade A, Level 1+)**
- Endotracheal intubation and mechanical ventilation can be used in AHF patients with respiratory failure leading to hypoxaemia, hypercapnia, and acidosis. Secondary indications for intubation and ventilation include diminished consciousness, respiratory muscle fatigue, and inability to maintain or protect the airway.[39] **(Grade D, Level 4)**
- Use venous ultrafiltration to remove fluid in patients with heart failure, especially in those resistant to diuretics.[283] **(Grade B, Level 1+)**
- Short-term MCS such as intra-aortic balloon pump[284,285] and extracorporeal membrane oxygenation should be considered ("bridge to recovery") in patients remaining severely hypoperfused despite inotropic therapy and with a potentially reversible cause (e.g. viral myocarditis) or a potentially surgically correctable cause (e.g. acute mitral regurgitation). It may also be considered ("bridge to decision") in patients deteriorating rapidly before a full diagnostic and clinical evaluation can be made.[284,285] **(Grade C, Level 2+)**
- Ventricular assist devices may be used as a bridge to myocardial recovery, bridge to heart transplant or long-term support (destination therapy).[239,241,286] **(Grade A, Level 1++)**

7.4. Invasive Monitoring

Recommendation:

- Insertion of an intra-arterial line should only be considered in patients with persistent heart failure and low systolic blood pressure despite treatment.[39] **(Grade D, Level 4)**

Pulmonary artery catheterisation (PAC) may help in the treatment of a minority of patients with acute (and chronic) heart failure.[287]

Recommendation:

- Pulmonary artery catheterisation should only be considered in patients: (i) who are resistant to pharmacological treatment; (ii) who are persistently hypotensive; (iii) in whom left ventricular filling pressure is uncertain; or (iv) who are being considered for cardiac surgery.[287] **(Grade B, Level 1+)**

7.5. Non-invasive Monitoring

Recommendations:

- Heart rate, rhythm, blood pressure, respiratory rate, and oxygen saturation should be monitored frequently for at least the first 24 hours following admission. Symptoms relevant to heart failure and related to the adverse effects of treatments used should be assessed at least daily.[39]

- Fluid intake, urine output, body weight, jugular venous pressure, and extent of pulmonary and peripheral oedema (and ascites if present) should be measured daily to evaluate the correction of volume overload.

- Blood urea, creatinine, and electrolytes should be monitored frequently during intravenous diuretic therapy and when RAAS antagonists are being initiated, or if the dose of any of these drugs is changed.[39]

(Grade D, Level 4)

7.6 Assessment after Stabilisation

Recommendation:

- Every patient should be assessed for possible aetiology of heart failure (*de novo*) and precipitants of worsening heart failure (chronic heart failure).[39] **(Grade D, Level 4)**

The focus is to identify and treat reversible causes.

Congestion should be absent, and a stable diuretic dose be established for at least 24 hours.[288–290] Disease-modifying medications for chronic heart failure should be initiated and up titrated before discharge. Enrolment in a heart failure management programme that includes patient education and initiation of appropriate lifestyle adjustments should be offered. For appropriate patients, assessment for device therapy should be considered.[39]

7.7 Special Patient Populations

GPP

7.7.1. Myocardial Ischaemia/Infarction

Reversible myocardial ischaemia causing AHF needs early recognition, rapid stabilisation, and referral for urgent coronary angiography. Treatment should be initiated according to current acute coronary syndrome guidelines.

7.7.2. Hypertension

Typically presents as "flash pulmonary oedema" with hypertensive crisis. Blood pressure must be reduced relatively quickly. It is generally suggested that systolic blood pressure be reduced by 25% over 3–12 hours. This is best achieved with parenteral drugs such as intravenous nitrates or nitroprusside. Look for secondary causes of hypertension such as renal artery stenosis.

7.7.3. Arrhythmias

Tachyarrhythmias, particularly atrial fibrillation/atrial flutter with fast ventricular rates, must be identified and treated accordingly. A rhythm control strategy with electrical or pharmacological cardioversion should be considered in patients with a first episode of AF of <48 hours' duration. Ventricular rate control of AF should be considered with the use of intravenous digoxin. Bradycardia may require temporary pacing.

7.7.4. Renal Failure

Acutely worsening heart failure, its treatment, or both may cause acute worsening of renal function (CRS) in up to one-third of patients and is associated with worse survival and prolonged hospitalisation.[291] Renal failure

influences the response to drug therapy. In patients with refractory fluid retention, continuous ultrafiltration may be helpful.

7.7.5. Valvular Heart Disease

Acute heart failure can be caused by valvular conditions such as acute mitral or aortic valve incompetence or stenosis, bacterial endocarditis, aortic dissection. Early access to echocardiography is crucial for diagnosis and management. Vasodilator therapy is beneficial in acute valvular regurgitation but is contraindicated in severe valvular stenosis. Treatment with percutaneous or surgical intervention is usually required.

Figure 1: Diagnosis and treatment of AHF.[39]

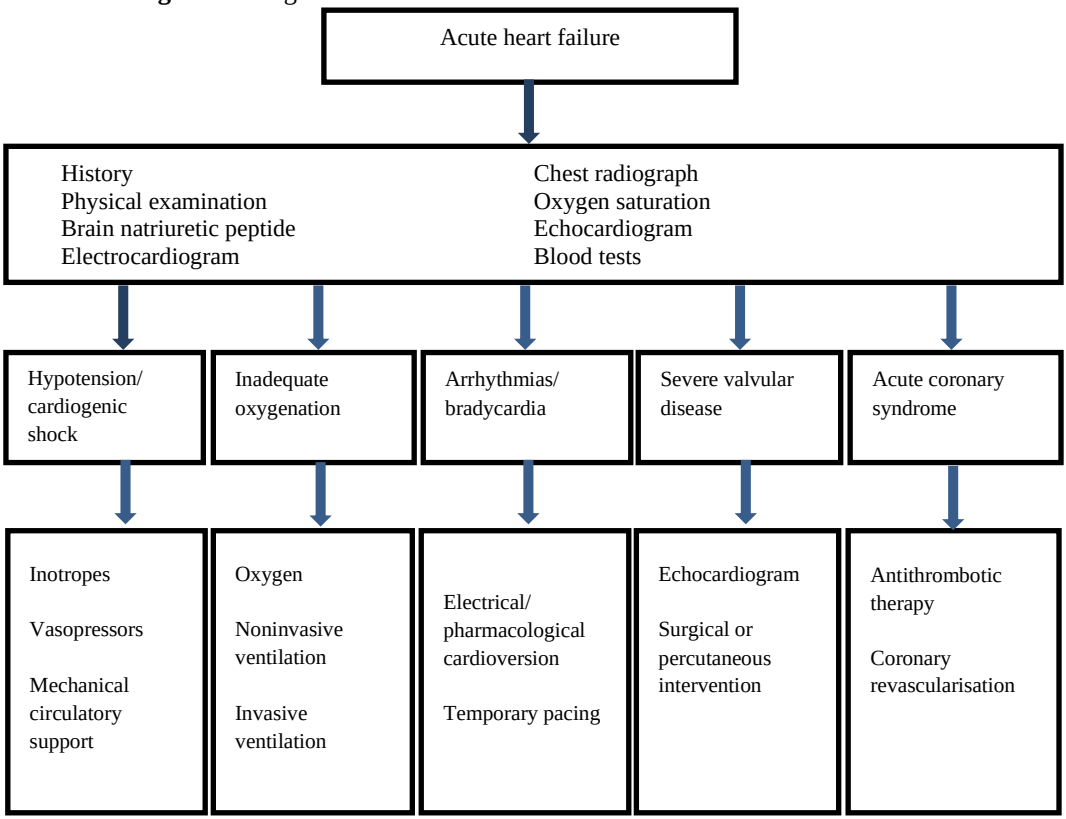
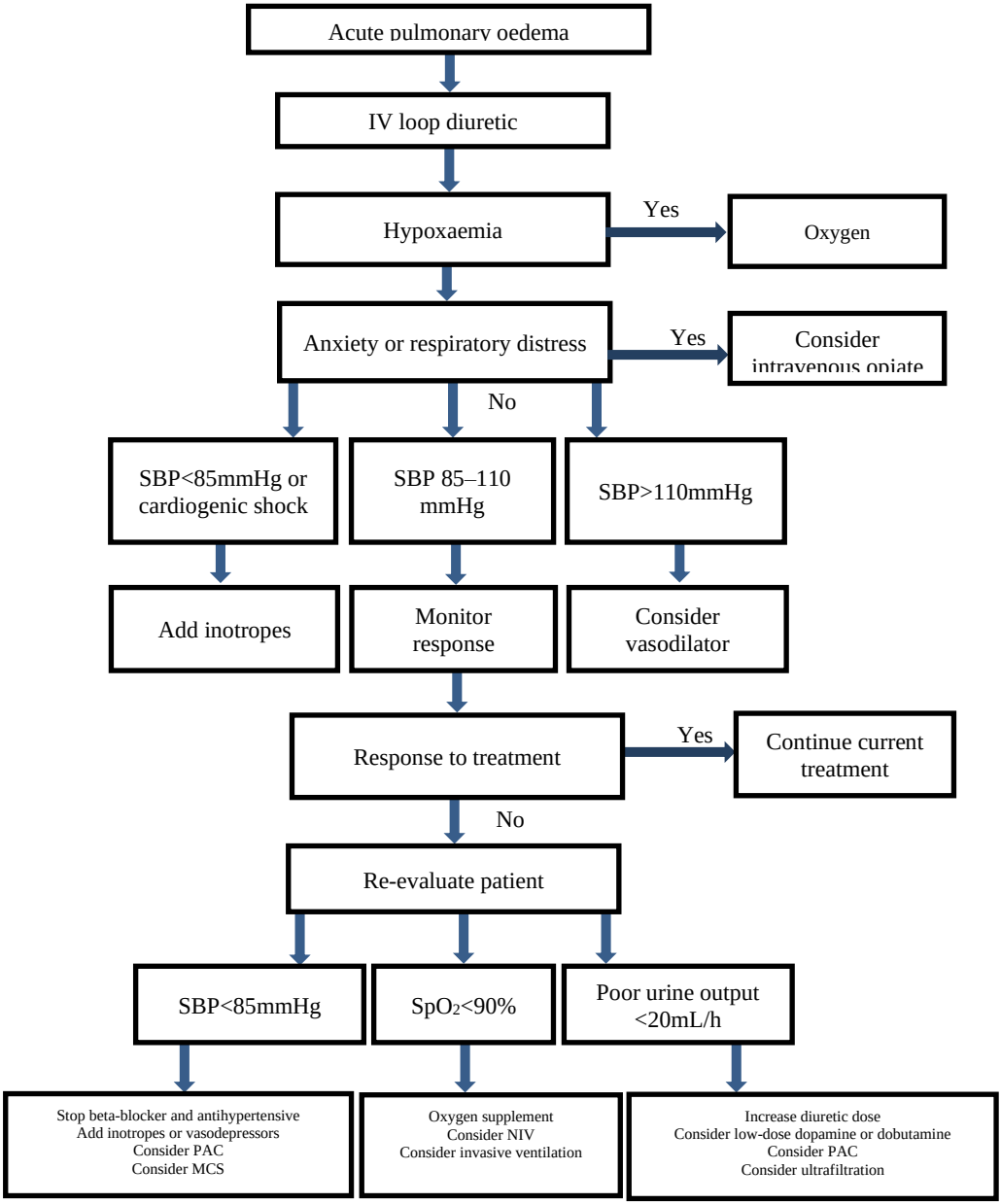


Figure 2: Treatment of acute pulmonary oedema.[39]



8. Management of Heart Failure With Preserved Ejection Fraction (HFpEF)

Heart failure can occur in the presence of normal pump function or preserved LVEF – the syndrome of HFpEF, also called diastolic heart failure. Western epidemiologic studies have shown that HFpEF is responsible for an average of 54% of all heart failure cases. In Singapore, the proportion of HFpEF cases is estimated at 22%–28%.[18,292] Outcomes are poor in these patients, with 17% mortality in twoyears.[292]

In sharp contrast to the wealth of proven therapies for HFrEF (also known as systolic heart failure), trials of conventional heart failure medications have been neutral in HFpEF and there is, to date, no therapy proven to reduce mortality in HFpEF.

8.1. Diagnosis of HFpEF

The diagnosis of HFpEF can be challenging. General principles for the diagnosis of HFpEF include:[2,3,293]

a) Clinical signs and/or symptoms consistent with heart failure
b) Normal or mildly abnormal left ventricular systolic function
c) Evidence of left ventricular diastolic dysfunction

In practice, the diagnosis of HFpEF is usually made by confirming the clinical diagnosis of heart failure (based on typical symptoms and signs or using validated criteria such as Framingham criteria) and finding a preserved EF (≥50%), usually by echocardiography, in the absence of significant valve or pericardial disease. Because the diagnosis of heart failure is a clinical one that relies on nonspecific symptoms (e.g. breathlessness and fatigue), pattern recognition of the typical patient profile, physical examination to confirm the presence of increased left ventricular filling pressure (e.g. raised jugular venous pressure), and careful exclusion of differential diagnoses are important.

Recommendation:

To diagnose HFpEF, first confirm the diagnosis of clinical heart failure based on the presence of typical symptoms (e.g. breathlessness, fatigue, orthopnoea) and signs (e.g. raised jugular venous pressure).[2,293](For further information, refer to Chapter 2(a): Clinical Diagnosis of Heart Failure) (**GPP)**

A recently proposed diagnostic approach to HFpEF uses a scoring system based on clinical and echocardiographic characteristics, to estimate the probability that HFpEF in a patient presenting with unexplained exertional dyspnoea.[294] However, this diagnostic scoring approach has not been validated in Asian patients.

8.2. Patient Characteristics

Heart failure with preserved ejection fraction predominantly affects elderly (>65 years) hypertensive women. Co-existing cardiovascular risk factors are common, and include obesity in 41%–46%, CAD in 20%–76%, diabetes mellitus in 13%–70%, AF in 15%–41%, and hyperlipidaemia in 16%–77% of cases.[295] In a contemporary, prospective, multicentre, observational study of patients with HFpEF in Singapore, the mean age was 68 years, 52% were women, 86% had hypertension, 59% had diabetes mellitus, and 33% had CAD.[292] The burden of concomitant noncardiovascular disease is high in patients with HFpEF, and includes renal impairment, chronic lung diseases, anaemia, cancer, and peptic ulcer disease.[296] Exertional dyspnoea and reduction in exercise tolerance are the most common presenting complaints.[296]

Heart failure with preserved ejection fraction is a common cause of unexplained pulmonary hypertension in the elderly.[297] Elderly patients with pulmonary hypertension and normal left ventricular chamber size and systolic function on transthoracic echocardiogram should be evaluated for HFpEF.

8.3. Investigations

Investigations are carried out to aid in the clinical diagnosis of heart failure syndrome, demonstrate normal LVEF and left ventricular diastolic dysfunction, assess cardiovascular risk factors, exclude differential diagnoses, look for comorbidities, and risk-stratify the patient (prognostication). These investigations include a combination of laboratory studies, invasive and noninvasive imaging studies, as already described in Section 2.2. While the following paragraphs consider issues pertinent to HFpEF, the general principles of investigation described in Section 2.2 still also apply to HFpEF.

8.3.1. Circulating B-Type Natriuretic Peptide (BNP) and N-Terminal proBNP (NT-proBNP)

Measurement of circulating natriuretic peptides may aid the diagnosis of HFpEF by ruling out heart failure (high negative predictive value) when levels

are below the following cut-offs: BNP<35 pg/mL or NT-proBNP<125 pg/mL in a nonacute setting; BNP <100 pg/mL or NT-proBNP <300 pg/mL in the acute setting.[2] Notable cases, where patients with HFpEF may display a falsely low BNP or NT-proBNP level, include obese patients and patients with "flash" pulmonary oedema. In general, levels of natriuretic peptides are higher in the HFrEF population compared to the HFpEF population.[292] Importantly, however, NT-proBNP is independently and similarly related to survival in heart failure, regardless of EF, and a given level of NT-pro BNP portends the same risk of death in HFpEF and HFrEF.[292]

8.3.2. Transthoracic Doppler Echocardiography

Transthoracic Doppler echocardiography is the main imaging modality used in HFpEF to establish the diagnosis by criteria, exclude valvular or pericardial disease, and assess for other potential differential diagnoses. No single echocardiographic parameter is sufficiently accurate and reproducible to be used in isolation to make a diagnosis of left ventricular diastolic dysfunction; therefore, a comprehensive echocardiographic examination incorporating all relevant two-dimensional and Doppler data is recommended, including both structural (LVH, left atrial dilation) and functional abnormalities (Doppler indices, AF). Echocardiographic criteria recommended by the European Society of Cardiology for the diagnosis of HFpEF (2016) include: Key structural alterations of a left atrial volume index >34 mL/m^2 or a left ventricular mass index ≥115 g/m^2 for males and ≥95 g/m^2 for females; and key functional alterations of an E/e′ (ratio of mitral early diastolic inflow velocity to mitral early annular lengthening velocity) ≥13 and a mean e' septal and lateral wall <9 cm/s.[2] The recently proposed diagnostic probability scoring system (the "H_2FPEF score") emphasises the importance of AF and Doppler echocardiographic-estimated PASP>35 mmHg and uses a different cut-off for E/e' (>9).[294]

Recommendation:

- Use transthoracic Doppler echocardiography to evaluate LVEF and establish the presence of left ventricular diastolic dysfunction (e.g. concentric LVH, left atrial dilatation, Doppler indices of raised left ventricular filling pressure); exclude valvular or pericardial disease; and assess for other potential differential diagnoses.[2,3] **(GPP)**

8.3.3. Cardiac Catheterisation

Cardiac catheterisation for the invasive assessment of haemodynamic parameters remains the gold standard for the diagnosis of HFpEF. Criteria for raised left ventricular filling pressure include LVEDP≥16mmHg or a mean PCWP≥15mmHg.[100,298] Cardiac catheterisation is particularly important in cases of diagnostic uncertainty (e.g. early HFpEF), or when there is a need to distinguish idiopathic pulmonary arterial hypertension from pulmonary venous hypertension secondary to HFpEF. Additional manoeuvers may be required during catheterisation to confirm the diagnosis, such as simple leg raise, exercise,[299] volume challenge, or nipride infusion.

Recommendation:

- Cardiac catheterisation should be considered for the diagnosis of HFpEF in cases of uncertainty.[2,3] **(GPP)**

8.3.4. Other Diagnostic Investigations

Other diagnostic investigations that may be considered include standard 12-lead electrocardiography (LVH, AF, ischaemia); chest X-ray (pulmonary venous congestion); stress testing (diastolic stress testing,[65,299–304]and myocardial ischaemia); coronary angiography (CAD); Holter monitoring (paroxysmal arrhythmias, rate control); or technetium scintigraphy (wild-type transthyretin amyloid).[305] Cardiac magnetic resonance is an emerging technology that is particularly useful for cardiac chamber size quantification and detection of myocardial fibrosis.[306–309]

8.4. Treatment of HFpEF

In contrast to heart failure with reduced EF, there is limited clinical trial evidence guiding the treatment of HFpEF. At present, no specific therapy has demonstrated a mortality benefit in patients with HFpEF. Yet despite the neutral trials, calcium-channel blockers, beta-blockers, ACEis, ARBs, MRAs (e.g. spironolactone), and digoxin are frequently used in patients with HFpEF because of concomitant cardiovascular diseases.[296]

In the absence of trial evidence, current management strategies should be based on an understanding of the underlying pathophysiological processes in HFpEF. The most well-recognised of these is left ventricular diastolic

dysfunction, which may be exacerbated by factors such as myocardial ischaemia, increased left ventricular after load, shortened left ventricular filling time due to tachycardia, or loss of atrial contribution to left ventricular filling (e.g. in AF). Moreover, since patients tend to be elderly with several comorbidities, management of these comorbidities is an important component of the overall management of HFpEF.[2,3,5]

The management of HFpEF should focus on symptom improvement, treatment of precipitating factors, and management of comorbidities.[2,3,5]

Recommendation:

- HFpEF should be managed by symptom control, treatment of precipitating factors, and management of comorbidities.[2,3,5] (**GPP)**

8.4.1. Symptom Improvement

Loop diuretics provide rapid symptomatic relief and are the preferred first-line therapy for most patients with heart failure syndrome, to lower left ventricular filling pressures and improve the clinical signs and symptoms of volume overload, i.e. pulmonary congestion and peripheral oedema.[2,3,5]

Recommendation:

- Use loop diuretics to provide rapid symptomatic relief in patients with HFpEF and fluid overload.[2,3,5] **(Grade D, Level 4)**

Optimal use of diuretics is vital. The main side effects of diuretics are electrolyte depletion, hypotension, and impairment of renal function. Patients with HFpEF are particularly susceptible to hypotension and azotaemia with over-diuresis due to the steep end-systolic pressure-volume relationship in HFpEF.[310]Regular monitoring of serum electrolytes and creatinine is recommended to avoid and treat electrolyte abnormalities and to aid the titration of diuretic doses. The aim is to achieve euvolaemia. Drugs that cause fluid retention or adversely affect renal function, such as NSAIDs, should be avoided if possible.

The 2017 updated American College of Cardiology/American Heart Association Heart Failure guidelines also suggest consideration of aldosterone receptor antagonists (e.g. spironolactone) in appropriately selected patients

with HFpEF (with EF 45%, elevated BNP levels or HF admission within 1 year, eGFR>30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L) to decrease hospitalisation, based on results of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial,[5,310–312] although confirmatory studies are required.

8.4.2. Treatment of Precipitating Factors

It is critically important to identify and treat specific precipitating factors. These include controlling blood pressure in patients with poorly controlled hypertension or hypertensive crisis and managing the ventricular rate in tachyarrhythmias (commonly AF), both according to standard guidelines.[2,3,5]

Patients with HFpEF commonly have underlying CAD. Myocardial ischaemia can adversely affect left ventricular systolic and diastolic function. Therefore, coronary revascularisation should be considered when myocardial ischaemia in patients with CAD is thought to contribute to symptoms.[3,5]

Recommendation:

- Identify and treat specific precipitating factors in patients with HFpEF. These include controlling blood pressure in patients with poorly controlled hypertension, managing fast ventricular rate in AF, and treating myocardial ischaemia that is contributing to symptoms.[3,5] (For further information, refer to Chapter 10: Treatment of Comorbidities [including AF].) **(Grade D, Level 4)**

8.4.3. Management of Comorbidities

Noncardiovascular comorbidities frequently seen in patients with HFpEF are renal impairment, chronic lung diseases, anaemia, cancer, and peptic ulcer disease.[296] These comorbidities play an important role in the increased morbidity and mortality in HFpEF; they should be managed according to recommended guidelines.[2]

Diet and Exercise

Patient education should address issues such as diet, activity level, medications, follow-up appointments, weight and symptom monitoring, and how to react if symptoms worsen. The sodium-restricted DASH diet was associated with favourable changes in left ventricular diastolic function and

ventricular-arterial coupling in a small clinical study.[313] Pilot trial data suggest that structured exercise training in patients with chronic HFpEF may improve symptoms and quality of life.[314]

Future treatment strategies in HFpEF include both novel devices and drugs. Haemodynamic mechanisms of left atrial hypertension, pulmonary hypertension, and volume overload are currently being targeted in clinical trials with devices (e.g. interatrial septal device) and pharmacotherapies (e.g. ARNI, SGLT-2 inhibitors). Therapies targeting cellular/molecular mechanisms of microvascular inflammation, cardiometabolic abnormalities, and cellular/extracellular structural changes are also being tested in ongoing clinical trials.[315]

9. Treatment of Comorbidities

9.1. Non-cardiovascular Comorbidities

Non-cardiovascular comorbidities are frequent and important in patients with HF, since they can contribute to increased morbidity and mortality in heart failure and can impact treatment options in patients with heart failure (e.g. RAAS blockade may not be possible in some patients with severe renal impairment). Furthermore, drugs used to treat comorbidities may worsen heart failure and vice versa (e.g. certain cancer chemotherapeutic drugs can worsen heart failure, whereas beta-blockade for heart failure can worsen some cases of asthma). The management of comorbidities is, therefore, an integral component of the management of patients with heart failure. In general, comorbidities should be managed according to guideline recommendations.

Recommendation:

- Heart failure patients should be screened for comorbidities, which should be managed according to current guidelines specific to those conditions. **(GPP)**

9.2. Iron Deficiency

Iron deficiency with or without anaemia is highly prevalent in patients with heart failure and associated with worse outcomes. Iron deficiency alone may contribute to symptoms and poor outcomes in heart failure, independent of anaemia. Iron deficiency and anaemia should be evaluated by standard methods and treatable causes (e.g. bleeding peptic ulcer) should be managed according to guidelines. Treatment of iron deficiency using intravenous iron has been studied in patients with heart failure and shown to improve self-reported patient global assessment, NYHA, functional capacity, and quality of life (QoL), and may be associated with a reduced risk of hospitalisation for worsening heart failure.[30,316] The utility of erythropoietin-stimulating agents as a treatment for anaemia of unknown aetiology is unproven.[317]

Recommendations:

- Iron deficiency should be screened for and treated in patients with heart failure.[30,316] **(Grade A, Level 1+)**
- Heart failure patients with anaemia should be investigated and treated according to standard good clinical practice. **(GPP)**

9.3. Atrial Fibrillation

Patients with heart failure are more likely than the general population to develop AF.[318] Patients with AF tend to have worse NYHA class. The presence of AF is also a strong independent risk factor for the subsequent development of heart failure.[319] The pathophysiology of heart failure and AF such as tachycardia-mediated cardiomyopathy,[320] fibrosis, and activation of neurohumoral vasoconstrictors may perpetuate heart failure and AF episodes.

The main goals of therapy in heart failure patients with AF are prevention of thromboembolism and symptom control. These patients should receive systemic anticoagulation, unless otherwise contraindicated. Warfarin and alternatives to warfarin such as apixaban, dabigatran, or rivaroxaban are suitable agents to reduce stroke risk in patients with heart failure.[321–323]

General principles of management include correction of reversible causes of AF and triggers of heart failure, in addition to optimisation of heart failure management. It is well known that AF with rapid ventricular response is a reversible cause of heart failure. In this regard, beta-blockers are preferred agents for achieving rate control, if they are not contraindicated. Digoxin may be given in addition to beta-blockers, although caution must be exercised in the presence of impaired renal function.[324] In patients with depressed LVEF, non-dihydropyridine calcium antagonists, such as diltiazem, should not be used because of their negative inotropic effect.

Recommendation:

- In patients whom rate control strategy is chosen, atrioventricular node ablation and CRT device implantation can be performed if rate control cannot be achieved adequately due to drug intolerance or inefficiency.[325] **(Grade C, Level 2++)**

The second approach is to restore sinus rhythm. In this regard, amiodarone is often used in combination with cardioversion. This may offer an AF free period to assess the effect of sinus rhythm on NYHA status, LVEF, and quality of life.[326–329]

Assessment of heart rate control during exercise and adjustment of pharmacological treatment to keep the rate in the physiological range is useful in symptomatic patients during activity.

Recommendations:

- Atrial fibrillation catheter ablation to restore sinus rhythm may be offered to eligible patients. This may lead to an improvement in left ventricular ejection fraction and quality of life in patients who remained in sinus rhythm after catheter ablation.[330] **(Grade B, Level 1+)**
- A beta-blocker or a non-dihydropyridine calcium channel antagonist can be used to control resting heart rate in compensated HFpEF patients with AF. **(GPP)**
- In the absence of pre-excitation, the following intravenous agents can be used acutely to reduce the ventricular response to AF in patients with heart failure (with caution needed in patients with overt congestion or hypotension).
  - Beta-blockers (or a non-dihydropyridine calcium channel antagonist)[331–335]
  - Digoxin[336]
  - Amiodarone[333,337]

  (Grade B, Level 1^{+})
- Digoxin can be used to control resting heart rate in patients with heart failure with reduced EF.[338] However, it is ineffective in controlling ventricular response during exercise. A few studies have raised concerns about its long-term use, due to its association with increasedmortality.[339,340] (**Grade C, Level 1+)**
- A combination of digoxin and a beta-blocker (or a non-dihydropyridine calcium-channel antagonist for patients with HFpEF) is reasonable to control resting and exercise heart rate in patients with AF.[324,338] **(Grade B, Level 2+)**
- It is reasonable to perform atrioventricular node ablation with ventricular pacing to control heart rate when pharmacological therapy is insufficient or not tolerated.[263,264,341,342] **(Grade B, Level 1++)**
- For patients with AF and rapid ventricular response causing or suspected of causing tachycardia-induced cardiomyopathy, it is reasonable to achieve rate control by either atrioventricular nodal blockade or a rhythm-control strategy.[343,344] **(Grade B, Level 2+)**

Recommendations:

- A rhythm-control strategy may be offered to patients with chronic heart failure who remain symptomatic from AF despite OMT. Suitable rhythm-control strategies include:
  - Amiodarone[327,328,345]
  - Sotalol
  - Catheter ablation[330,346,347]

  (Grade C, Level 2+)
- Atrioventricular node ablation should not be performed before a trial of pharmacological agents to achieve ventricular rate control. (**GPP)**

9.4 Diabetes Mellitus

Diabetes mellitus is more prevalent in patients with heart failure and confers worse outcomes and poorer functional status. Progression of diabetes mellitus in heart failure is influenced by genetics, physical activity, body weight and dietary habits. Patients with heart failure without diabetes mellitus are also at an increased risk of diabetes mellitus, which is influenced by the use of loop diuretics and severity of heart failure. The prevalence of diabetes mellitus increases with age in patients with heart failure.[348,349] Lifestyle modification and pharmacological therapies remain the mainstay of treatment.

In patients with heart failure and newly diagnosed type 2 diabetes mellitus, initiation of glucose lowering therapy with SGLT2i can be considered as first line therapy to reduce cardiovascular risk[350] in the absence of severe renal impairment (eGFR < 30 ml/min/1.73m^2). SGLT2i act in proximal tubules to increase urinary glucose and sodium excretion. In addition, SGLT2i reduce weight, blood pressure and glycated haemoglobin. There is an increased risk of genital mycotic infections (balanitis in males, and vaginitis in females) when prescribing SGLT2i.[175,176,350,351] The cardiovascular benefits of SGLT2i are mostly due to reduction in heart failure associated events. Metformin should be considered as add on therapy while on SGLT2i monotherapy if glycemic control remains suboptimal.[352,353]

In patients with heart failure and existing type 2 diabetes mellitus treated with metformin, combination therapy with SGLT2i can be considered in patients with suboptimal glycaemic control, in the absence of severe renal impairment.

9.4.1. Glucose-Lowering Agents in Patients with Heart Failure

Recommendations:

- SGLT2i can be initiated as first line therapy in patients with heart failure and newly diagnosed type 2 diabetes mellitus, or as an add on therapy to metformin in patients with type 2 diabetes mellitus to optimize glycemic control and to reduce heart failure hospitalization and cardiovascular deaths.[175,176,350,351] (**Grade B, Level 1+)**
- Metformin should be considered in combination with SGLT2i to improve glycemic control in patients with type 2 diabetes mellitus and heart failure in the absence of severe renal or hepatic impairment.[352,353] (**Grade C, Level 2+)**
- Thiazolidinediones should not be used in patients with heart failure and type 2 diabetes mellitus as it may cause fluid retention.[354,355] (**Grade A, Level 1+)**

10. Multidisciplinary Disease Management

10.1 Cardiac Rehabilitation and Exercise in Heart Failure Patients

A cardiac rehabilitation programme serves as an integral component in the comprehensive care and management of patients with heart failure. An effective cardiac rehabilitation programme should incorporate both supervised exercise training and disease-related self-care counselling.[356]

Recommendations:

- All patients with heart failure should be encouraged to enroll in a multidisciplinary care cardiac rehabilitation programme.[289,357,358] **(Grade A, Level 1++)**
- Regular aerobic exercise should be encouraged in patients with mild (NYHA class I) heart failure to improve functional capacity.[359,360] (**Grade A, Level 1++)**
- Heart failure patients with stable class II to class III heart failure, with no contraindications, are encouraged to undertake exercise. Exercise intensity and duration should be determined by a trained physician or physiotherapist.[158,361] (**Grade A, Level 1++)**

No serious adverse exercise training-related events have been reported among heart failure patients in large meta-analyses.[362–364]

Heart failure patients should initially participate in an institutional cardiac rehabilitation programme for safety and monitoring purposes before graduating to a community programme.[365]

Recommendation:

- Low-intensity strength training may be added as an adjunct treatment in stable patients.[366] **(Grade C, Level 2+)**

Combining aerobic and resistance components may provide similar benefits that could be associated with improved prognosis and an increased capacity to perform tasks of daily living.[367]

Recommendations:

- Cardiopulmonary testing can be used as an objective assessment of patient's aerobic fitness and prognosis.[368–374] **(Grade A, Level 1+)**
- Stress electrocardiogram with or without concomitant CPET may be used to guide exercise prescription in heart failure patients.[360,370] **(Grade B, Level 2+)**

10.1.1 Prognostic Value and Diagnostic Potential of Cardiopulmonary Exercise Testing and Six-Minute Walk Test in Patients with Chronic Heart Failure

Exercise testing allows objective evaluation of exercise capacity and exertional symptoms, such as dyspnoea and fatigue. It also helps the physician determine the therapeutic efficacy of ongoing treatments and necessity for any further interventions.[370]

Gas exchange analysis helps differentiate between cardiac and respiratory causes of dyspnoea, shows whether the anaerobic threshold has been reached, and provides prognostic information (Peak VO_2 is often measured as part of the assessment of candidates for heart transplantation). It gives an objective assessment of functional capacity.[370]

Recommendation:

- The six-minute walk test may be used instead of cardiopulmonary tests to evaluate exercise capacity and exertional symptoms in patients with NYHA Classes II–IV.[375–379] **(Grade B, Level 1+)**

10.1.2. Exercise Prescription

Ideally, the intensity of exercise can be set via the use of VO_2 max testing (CPET). It is recommended that the initial training intensity for patients beset at 40%–50% of the VO_2 peak or VO_2 reserve (i.e. the difference between the basal and VO_2 peak) and then progress to 70%–80% of VO_2 or VO_2R.[360]

When CPET is not available in the clinical setting, the HRR method can be used to prescribe the training intensity (the difference between the basal and peak heart rate). The peak heart rate can be obtained from either a

conventional stress test or a six-minute walking test. A training target set at 40%–70% of HRR is recommended. The RPE should be used to monitor patients in conjunction with the target heart rate. A rating of 10–14 on the 6–20 RPE scale is recommended.[375]

Monitoring During Exercise

Recommendations:

- Stable high-risk heart failure patients should be monitored during the initial phase of the exercise training programme.[380] (**Grade B, Level 1++)**
- It is recommended that patients with the following clinical presentations receive continuous electrocardiogram monitoring during exercise training, until safety is established:[282]
  1. NYHA Class III/IV
  2. History of significant life-threatening arrhythmias
  3. Exercise capacity ≤6 METS
  4. Known myocardial ischaemia at a workload <6 METS

(Grade D, Level 4)

10.2 Multidisciplinary Disease Management

Heart failure disease management programmes may reduce mortality, improve adherence to the treatment plan, reduce re-hospitalisation, as well as improve quality of life.

A multidisciplinary heart failure disease management programme may include, but is not limited to, cardiologists, primary care doctors, nurses, pharmacists, physiotherapists, dietitians, and medical social workers.

Heart failure disease management may include the following components:

a) Comprehensive education and counselling, individualised to patient needs
b) Optimisation of medical therapy
c) Promotion of self-care, including self-adjustment of diuretic therapy in appropriate patients (or with family member/caregiver assistance)
d) Emphasis on behavioural strategies to increase adherence to therapies
e) Increased access to healthcare providers
f) Early attention to signs and symptoms of fluid overload

g) Vigilant and early follow-up after hospital discharge or after periods of instability
h) Assistance with social and financial concerns

Recommendation:

- Patients with heart failure may be enrolled in a multidisciplinary heart failure disease management programme, where available.[381–387] **(Grade B Level 1+)**

10.3 Heart Failure Clinic (HFC)

A dedicated HFC has been shown to improve the quality of life, reduce hospital readmissions, and improve morbidity and mortality. Patients with heart failure who are discharged from hospital should return for an early follow-up visit to the clinic, to allow assessment of clinical response and prevent readmissions.

The HFC may include the following components:
a) Early and timely follow-up visits
b) Functional status assessment
c) Quality-of–life assessment
d) Medical therapy and drug evaluation
e) Device evaluation
f) Nutritional assessment
g) Advance care planning
h) Quality assessment of process and outcome measures

Recommendation:

- Patients may be referred to a dedicated clinic for heart failure patients, where available.[39,164,386,388–393] **(Grade C Level 2+)**

10.4 Patient Education and Counselling

Patient education and counselling are important components in empowering heart failure patients to achieve self-management, which has been shown to reduce hospital readmission. Patient education and counselling must be

individualised according to the individual patient's level of health literacy and readiness to learn, and any barriers to learning must be addressed.

Patient education and counselling may comprise the following components:

- Understanding how heart failure develops (i.e. pathophysiology)
- Recognising and understanding heart failure signs and symptoms
- Managing symptoms
- Diet recommendations
- Medication use
- Activity and exercise
- Compliance to the medical plan and attending follow-up visits
- Weight management
- Lifestyle modifications

Recommendation:

- Heart failure education and counselling should be made available to all heart failure patients and/or their caregivers upon diagnosis of heart failure.[394–400] **(Grade C, Level 2+)**

10.5 Diet Recommendations

Studies that examined the effects of a low-sodium diet in heart failure patients were inconclusive. Dietary Approaches to Stop Hypertension (DASH) is a dietary pattern that is rich in fruits, vegetables, whole grains, and low-fat dairy with a reduced content of sodium, saturated fat, and total fat. The DASH diet is good for both controlling metabolic risk factors and being healthy.[401]A sodium-restricted DASH-like diet has been shown to decrease mortality and hospital readmission in heart failure patients. While studies showed that a low sodium diet may improve clinical congestion in acute decompensated heart failure patients, a very low sodium intake of <2000 mg with concurrent reduced renal perfusion and low cardiac output is associated with greater neurohormonal activation and worsening heart failure symptoms.[402]

Recommendation:

- A DASH-like diet is recommended for patients with chronic heart failure.[401,403–408] **(Grade B, Level 2++)**

Recommendation:

- Individualise salt and fluid restriction in patients with chronic heart failure based on the patient's cultural, economic, and social habits.[388–390] One approach is to advise patients with chronic heart failure on how to reduce salt intake and fluid intake to <1.5 L/day.[403,405,409] **(Grade C, Level 2+)**

10.6 Weight Monitoring

Daily weight monitoring is an important component of self-management in patients with heart failure. Weight fluctuations in the short term (i.e. days) indicate fluid shifts. Sudden weight gain (e.g. >1 kg per day for >2 days) suggests fluid retention. Patients who detect weight changes can adjust their fluid intake and alert their healthcare provider.

Recommendation:

- Patients with chronic heart failure should be encouraged to monitor their weight daily.[39,410,411] **(GPP)**

10.7 Lifestyle Modifications: Smoking/Alcohol/Drug Abuse Cessation

10.7.1. Smoking and Alcohol

Smoking tobacco is an important modifiable risk factor for the development of cardiovascular disease. It is also associated with the development of pulmonary disease and cancer, which can worsen the symptoms and reduce physical performance.

Recommendation:

- Patients with heart failure must be advised to stop smoking tobacco.[17,412–417] (**Grade D, Level 4)**

Excessive alcohol consumption can cause cardiomyopathy. Alcohol intake in patients with chronic heart failure should be modest (not >2 units per day in men or 1 unit per day in women). One unit is 10mL of pure alcohol (e.g. 1

glass of wine, 1/2 pint of beer, 1 measure of spirit). However, patients with alcohol-induced cardiomyopathy should abstain from alcohol.

Recommendation:

- Heart failure patients with alcohol-induced cardiomyopathy should abstain from alcohol. Stable heart failure patients with other aetiologies may consume modest amounts of alcohol.[418,419] **(Grade D, Level 4)**

10.8 Sexual Activity

Clinicians should know the physiological requirements of sexual activity and the impact heart failure has on sexual performance. Fear of a cardiac event during intercourse can interfere with the patients' ability to perform and enjoy sex, and thus, it is important that the physician be able to counsel patients with heart failure about sexual activity.

Recommendations:

- Most patients with stable, treated heart failure can safely engage in sexual activity.[420–422] **(Grade D, Level 2+)**
- Heart failure patients with erectile dysfunction can be treated with PDE-5 inhibitor in the absence of significant myocardial ischaemia or with the concomitant use of nitrates.[420–423] **(Grade C, Level 2+)**

Absence of significant myocardial ischaemia could be assessed if the patient can achieve ≥5 to 6 METS on an ETT without demonstrating ischaemia.[424]

10.9 Travel

Most patients with stable heart failure who travel by commercial flights do not experience worsening of heart failure symptoms.[425] Patients can discuss planned travel activities with their physician.

Recommendations:

- Heart failure patients with new or worsening symptoms should consult a physician or a cardiologist for review of symptoms prior to travel.[426] **(Grade D, Level 4)**
- All heart failure patients should consider the following before planning to embark on travel:
  - Ensure adequate supply of all medications during the journey
  - Bring a record stating all the chronic medical conditions and regular medications
  - Have a good understanding of symptoms of exacerbation of heart failure
  - During long journeys, patients should exercise the calf and foot muscles regularly to reduce the risk of deep-vein thrombosis.

GPP

10.10 Vaccination Recommendations

Influenza is a common infectious respiratory disease that may manifest more complications in those with chronic diseases such as heart failure. Influenza is preventable with influenza vaccination. *S. pneumoniae* is the most common cause of community-acquired pneumonia, meningitis, and bacteraemia in children and adults, including in elderly individuals. Patients aged 65 years and above with underlying chronic diseases such as cardiovascular disease are at greater risk for pneumococcal pneumonia and mortality from pneumococcal pneumonia. Pneumococcal pneumonia can be prevented with pneumococcal vaccination.

Recommendations:

- Influenza and pneumococcal vaccinations are recommended in patients with chronic heart failure, unless contraindicated.[319,357,427–430] **(Grade D, Level 4)**

10.11 Depression

10.11.1. Prevalence

Clinicians should consider the possible presence of depression in patients with heart failure. Depression is common with an estimated prevalence rate 9%–60%, with an aggregate estimate of approximately 21.5%. The prognosis is worse in heart failure patients with depressive symptoms, which are more severe.

Recommendation:

- Clinicians should assess the presence and severity of depressive symptoms in patients with heart failure.[257] (**Grade D, Level 3)**

10.11.2. Management

There is no conclusive evidence that antidepressants provide additional benefit to supportive care in heart failure patients; clinicians may consider reserving the use of antidepressants only when patients do not respond to supportive care.

Clinicians may use antidepressants only when patients with depression do not respond to supportive care. Selective serotonin receptor uptake inhibitors are thought to be safe in heart failure patients. Tricyclic antidepressants are not safe because they may cause hypotension, worsening heart failure, and arrhythmias.

Recommendations:

- Clinicians should offer supportive care, including counselling patients on adaptive skills and providing more information about heart failure, to heart failure patients with depression. **(GPP)**
- When drug treatment is required for depression in heart failure patients, selective serotonin receptor uptake inhibitors are recommended, as they have a safer cardiovascular profile.[431,432] (**Grade B, Level 1+)**

10.12 Remote Monitoring

Randomised controlled trials on home telemonitoring, via scheduled structured telephone support or remote telemonitoring of physiological data (weight, heart rate, blood pressure) that are automatically transferred to a

service provider, have shown mixed results for all-cause mortality, heart failure readmissions, and quality of life. The selection of remote monitoring must be personalised to the patient.

10.12.1. Structured Telephonic Monitoring

Structured telephonic monitoring may be a complementary strategy to enhance adherence to heart failure therapy; it may allow for early identification of heart failure signs and symptoms, resulting in early intervention. Heart failure patients who are discharged from hospital and are amenable to structured telephonic monitoring may be contacted by telephone within 3–7 days for early assessment of clinical response and identification of potential barriers to adherence to the treatment plan. This has been shown to reduce heart failure readmission.

Recommendation:

- Heart failure patients who consent, may be enrolled in a structured telephonic monitoring programme.[433–437] (**Grade C, Level 2+)**

10.12.2. Transitional Care and Home Care

Effective discharge-planning and care-coordination prior to hospital discharge facilitates the delivery of evidence-based medical care, promotes adherence to the treatment plan, improves performance outcomes, and prevents readmission.

Recommendation:

- Heart failure patients at higher risk of re-hospitalisation may be referred for transitional care and home-care services.[438–441] **(Grade B, Level 2+)**

11. Clinical Quality Indicators

11.1 Performance Outcomes and Measurements

Measuring process and outcome indicators based on clinical guidelines improves the quality of care and mortality in HF patients.

Recommendations:

A heart failure disease management programme may adopt the following quality and process indicators:[164,442–445]

- Percentage of heart failure patients who have objective assessment of left ventricular systolic function using imaging (before admission, during hospitalization or planned on discharge)
- Percentage of heart failure patients with left ventricular systolic dysfunction and without contraindications who are prescribed an ACEi, ARB, or ARNI
- Percentage of heart failure patients with left ventricular systolic dysfunction and without contraindications who are prescribed a beta-blocker
- Percentage of heart failure patients with left ventricular systolic dysfunction and without contraindications who are prescribed an MRA
- Percentage of heart failure patients eligible for implantable defibrillators who are offered implantable defibrillators
- Percentage of heart failure patients who receive education material on heart failure or discharge instructions during hospitalization or at discharge

Grade C Level 2^{+}

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