2025 HFAI Guidelines for Diagnosis and Management of Heart Failure

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Preamble

Probably no other field in cardiology has witnessed as many advances emerging out of landmark clinical trials over the last decade as HF. New modalities of treatment have become available to supplement the existing therapies and other therapies have emerged for areas which had hardly anything to modify the course of the disease. It also appears that several other innovations are around the corner which gives a clinician wider choices to treat different phenotypes of HF.

This availability of several new therapies will be useful only if the clinicians have a clear understanding about appropriate application of the choices available to them to improve outcomes for their patients. The rapid expansion of the knowledge also means that for a large number of physicians it is impossible to keep abreast of the latest advances. Considering that a majority of patients of HF are treated by physicians and not by cardiologists, it is imperative that this information is available to them in a format which is easy to read and implement. This is even more important when one considers that a physician treats a much wider variety of ailments than a specialist. The existing guidelines are voluminous and a physician may find it difficult to go through them in detail. Hence this document, which is meant to distil the existing state of the art information in a concise and easy to read format to help our physician colleagues apply the available knowledge in their daily practice.

The handbook is divided into different sections which have been contributed by some of the luminaries from India in this field. It is our sincere hope that our colleagues will find it useful in their daily practice.

HEART FAILURE—INTRODUCTION, CLASSIFICATION, AND UNIVERSAL DEFINITION

Introduction

Heart failure (HF) is an end stage of most forms of heart disease. It is an important cause of morbidity and mortality especially in the elderly population. It is a progressive disease with an annual mortality rate of about 10%. The main causes of death are sudden cardiac death (>50%) or organ dysfunction due to hypoperfusion.

Definition

As per a universal definition proposed in 2021, "HF is a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion."[1]

HF is diagnosed based on clinical features and supported by an elevation of natriuretic peptides in the blood (more than 125 pg/mL of N-terminal pro-b-type natriuretic peptide in ambulatory patients and more than 300 pg/mL in decompensated or hospitalized patients). The symptoms and signs of HF as per the universal definition is given below. Some symptoms and signs are specific and some are relatively non-specific.

MAJOR CRITERIA	MINOR CRITERIA
•Paroxysmal nocturnal dyspnea or orthopnea	•Bilateral ankle edema
•Neck-vein distention	•Night cough
•Rales	•Dyspnea on exertion
•Cardiomegaly	•Hepatomegaly
•Acute pulmonary edema	•Pleural effusion
•S3 gallop	•Vital capacity ↓ 1/3 from maximum
•Increased venous pressure>16 cm of water	•Tachycardia (rate of ≥120 bpm)
•Hepatojugular reflux	**MAJOR OR MINOR CRITERION**
	•Weight loss ≥4.5 kg in 5 days

Stages of Heart Failure

The clinical syndrome of HF has four stages depending upon the level of progression. They are as follows:

Stage A: The patient is at risk for HF. Patients do not have current or prior symptoms or signs of HF and have no structural evidence or biomarkers of heart disease as in patients with risk factors for HF.

Stage B: It is a stage preceding manifest HF. Patients do not have current or prior symptoms or signs of HF but have evidence of structural heart disease, abnormal cardiac function, or elevated natriuretic peptide levels as in patients with valvular disease or a history of myocardial infarction.

Stage C: It is a stage of manifest HF. The patient has current or prior symptoms and/or signs of HF caused by a structural and/or functional cardiac abnormality.

Stage D: It is a stage of advanced HF. The patient has severe symptoms and/or signs of HF at rest, recurrent hospitalizations despite guideline-directed management and therapy (GDMT), refractory or intolerant to GDMT, requiring advanced therapies such as consideration for transplant, mechanical circulatory support, or palliative care.

This staging should not be confused with assessing the severity of symptoms using the New York Heart Association (NYHA) classification Classes 1–4.

Classification of HF

HF can occur due to impaired systolic contraction or impaired filling due to diastolic dysfunction. In many patients, both systolic and diastolic dysfunctions

co-exist. It is not easy to differentiate them purely based on clinical criteria or blood levels of natriuretic peptides. Left ventricular ejection fraction (LVEF), most often measured on echocardiography, is a useful criterion to differentiate. A new and revised classification of HF categorizes HF according to LVEF.

1. HF with reduced EF (HFrEF): LVEF ≤40%.
2. HF with mildly reduced EF (HFmrEF): LVEF in the range of 41%–49%.
3. HF with preserved EF (HFpEF): LVEF ≥50%.
4. HF with improved EF (HFimpEF): A baseline LVEF ≤40%, an improvement of ≥10%-point increase from baseline LVEF, and a second measurement of LVEF >40%.

This classification is often used in clinical trials and GDMT is based on LVEF.

EPIDEMIOLOGY OF HEART FAILURE: INDIAN SCENARIO

Heart failure (HF) is emerging as a major health problem in India. Hospital-based registries have provided us with data on the clinical profile and practice patterns. The first registry was the Trivandrum HF Registry[1] (THFR), which was conducted in 2013. Subsequently came the Kerala acute HF registry,[2] the National HF registry,[3] the Medanta registry,[4] and the ICC HF registry.[5]

The findings from these registries reveal that the patients were younger (mean age nearly 60 years) than the patients with acute heart failure from high-income countries (HIC) by a decade (mean age; Acute Decompensated Heart Failure National Registry[6] 74 years, European HFS registry[7] 70 years, and the Japanese decompensated heart failure syndromes registry[8] 73 years).

The younger age of onset of illness also points towards the socio-economic impact of the disease at an individual and community level. Another main difference is the predominance of male patients in India. In most of our registries, males contribute to 67%–70% of the population, whereas the distribution is nearly 50:50 in high-income countries. Patients under the age of 65 years comprised nearly three-fifth of the population in the Trivandrum Registry, whereas they accounted for less than a third of the heart failure patients in the west. This younger age at diagnosis has also important societal and health system implications.

Another feature of HF patients in India is a predominance of heart failure with reduced ejection fraction. HFrEF contributes to nearly 60%–65% of patients with HF. On the other hand, whereas heart failure with preserved ejection fraction contributes to nearly 50% of the burden of HF in western populations, its share in India is only 16%–18%. Ischemic heart disease contributed to nearly 75% of the burden of HF in India in all the registries. Dilated cardiomyopathy contributes 11%–18% and rheumatic heart disease contributes to 3%–8% of the patients with HF. Together, these three contribute to 95% of the burden of HF in India. So our strategies to mitigate the burden should focus on these three diseases [Table 1].

Prevalence of diabetes mellitus varied between 42% and 53% and hypertension was between 49% and 62%. The prevalence of diabetes in patients with HF is high, especially in the Southern Indian states. History of atrial fibrillation/ flutter varied between 9% and 14% and prevalence of chronic kidney disease varied between 8.5% and 15%. These low figures probably reflect the lower age of the Indian patients. Intake of guideline-directed therapy shows an improving trend. In THFR (2013) it was 19%, which improved to 25%–28% in Kerala and the Indian College of Cardiology registries (2018–2020).

Table 1: Data from major Indian registries

Registry	*N*	Enrollment period	Mean age	Female %	HFrEF	HFpEF	Etiology	In-hospital	Long-term mortality
THFR	1205	2013	61 (14)	31%	62	16	CAD—71% DCM—16% RHD—8%	8.4%	1 year 30.8% 3 years 45% 5 years 59%
KHFR	7512	2016–2018	64 (13)	36%	67	15	CAD—66 DCM—11 RHD—3.1	7%	3 months 10.3%
NHFR	10,851	2019–2020	60 (14)	31%	65	13	CAD—72 DCM—18 RHD—6	6.7%	3 months 14.2%
ICC – Registry	5269	2018–2020	62 (13)	67%	68		CAD—75 DCM—13 RHD—5	7%	1 year 22.1%

THFR: Trivandrum HF Registry, ICC: Indian College of Cardiology Registry, KHFR: Kerala Acute HF Registry, NHFR: National HF Registry, HFrEF: heart failure with reduced ejection fraction, HFpEF: heart failure with preserved ejection fraction, CAD: coronary artery disease, DCM: dilated cardiomyopathy, RHD: rheumatic heart disease

The guideline-directed therapy (GDT) prescription was 47% in the National HF registry (2019–2020). As per NHFR, patients with HFmrEF also benefited from GDT.[3] The short-term outcome data shows that our patients fare worse than those from HIC.

The in-hospital mortality varies from 6.7 to 8.4, which is much higher than that from the West, which varies from 3.8% to 5.5% from the US and Europe. One-year mortality data of 31% from the Trivandrum HF data is comparable with US data, but the 3 and 5-year mortality data from THFR of 45% and 59% is significantly higher.[9] The data from the National HF registry has reported an one year mortality of 22.1%.[10] Data for the mode of death showed that 47% of the patients in the THFR had sudden cardiac death and 46% died of pump failure. Device usage was very dismal <2% in all the Indian registries. This is much lower than registries from Europe where the usage is >30%.

DIAGNOSIS OF HEART FAILURE: ROLE OF CLINICAL EXAMINATION AND BIOMARKERS (INDIAN PROTOCOL)

Clinical Evaluation

- Clinical evaluation should start with a good history, which will give insights into the etiology, precipitating factors, and the severity of heart failure (HF).[1]
- Typical symptoms include dyspnea, with orthopnea and paroxysmal nocturnal dyspnea. Less typical symptoms are palpitations, tachypnea, nocturnal cough, fatigue, tiredness, reduced exercise tolerance, weight gain, dependent edema, and cachexia.
- Other points that are important in history are: (a) change in body weight indicates the need to increase diuretics; (b) recent or frequent prior hospitalizations are associated with adverse prognosis; (c) compliance to drug therapy, (d) causes of worsening like use of nonsteroidal anti-inflammatory drugs, ongoing myocardial ischemia, pulmonary emboli, systemic infection, or chronic right ventricular pacing (Alcohol abuse or binge drinking).
- In patients with cardiomyopathy, a three-generation family history should be obtained.
- Clinical evaluation should include an assessment of clinical congestion suggesting elevated cardiac filling pressures and features of low cardiac output (index).
- Clinical congestion can be assessed by jugular venous distention, orthopnea, bendopnea (dyspnea on bending forward at the waist like dyspnoea while tying shoelaces), a square wave response to the Valsalva maneuver [in healthy people blood pressure (BP) drops during strain phase of Valsalva. In patients of HF with elevated filling pressure BP rises and remains elevated throughout strain]. This is the square wave response in HF], and leg edema.
- Features of congestion are reliable and duplicable. However, features of low cardiac index (cold) are difficult to elicit. Clinical congestion is an important adverse risk factor in patients with HF.
- Some clinical features can help to identify patients who are likely to go into advanced HF. These include repeated hospitalizations, New York Heart Association class III/IV despite therapy, severely reduced exercise capacity, refractory clinical congestion, and frequent systolic blood pressure of ≤90 mmHg.
- Evaluation should include clues to conditions like amyloid heart disease, sarcoidosis, hemochromatosis, hypothyroidism, hyperthyroidism, connective tissue disease, tachycardia-induced cardiomyopathy, or high output HF.
- Specific signs of HF include elevated jugular venous pressure, hepatojugular reflux, third heart sound (gallop rhythm), and laterally displaced apical impulse. Less specific signs are peripheral edema, basal crepitations, tender hepatomegaly, and cold extremities since these can be seen in other conditions as well.

Biomarkers

- Measurement of natriuretic peptides (NPs) supplements clinical judgment when the cause of dyspnea is unclear. B-type natriuretic peptide (BNP) and its biologically inert, amino-terminal pro-peptide counterpart N-terminal prohormone of B-type NP (NT-proBNP) have become essential components in the diagnosis and prognosis of HF.
- For patients presenting in outpatients with dyspnea measurement of NT-proBNP is useful to support a diagnosis or exclusion of HF and for risk stratification [class 1A—American College of Cardiology (ACC)/American Heart Association (AHA) guidelines].[3] A BNP value of <35 pg/mL and a NT-proBNP of <125 pg/mL, make a diagnosis of HF unlikely Table 1.
- For patients presenting with acute decompensated HF (ADHF): The exclusion cutoff point is 100 pg/mL for BNP and 300 pg/mL for NT-proBNP. In these patients, besides the diagnosis, it helps in the prognosis as well. (class 1A—ACC/AHA guidelines). The higher the value, more is the certainty of diagnosis Table 2.
- NT-proBNP levels are age-dependent, whereas BNP levels have a single value for "rule in" and "rule out" of ADHF, as shown in Table 3.
- In the emergency setting, NT-proBNP levels have higher sensitivity than specificity and may be more useful for ruling out HF than ruling in HF.
- Predischarge NT-proBNP levels are strong predictors of risk of death or hospital readmission for HF.

Table 1: Features of dyspnea to be elicited in history

Duration: Days/months/years
Onset: Sudden/gradual
Progression: Worsening/improvement
New York Heart Association class: I–IV classes
Orthopnea/paroxysmal nocturnal dyspnea
Seasonal variation
Cough: Nonproductive

Table 2: NYHA classification for dyspnea, palpitation, fatigue and angina

Class I	No symptoms with ordinary physical activity
Class II	Symptoms with ordinary activity, slight limitation of physical activity.
Class III	Symptoms with less than ordinary activity. Marked limitation of activity.
Class IV	Symptoms with any physical activity or even at rest

Table 3: Rule in, rule out, and gray zone for BNP and NT-proBNP in ADHF

Diagnosis	BNP (pg/mL)	NT-proBNP (pg/mL)		
	Any age (years)	<50	50–74	≥75
Rule out	<100	<300	<300	<300
Gray Zone	100–500	300–450	300–900	300–1800
Rule in	>500	>450	>900	>1800

- There are many other causes of increased NPs besides HF. This includes cardiac causes like acute coronary syndrome, atrial fibrillation, pulmonary embolism, left ventricular hypertrophy, and hypertrophic cardiomyopathy. The noncardiac conditions with raised NPs are increasing age, renal dysfunction, ischemic stroke, and severe infection.
- Conversely, NP levels may be disproportionately low in obese patients. Other conditions in which NP levels may be lower than expected are given in Table 4.
- The use of angiotensin receptor-neprilysin inhibitors (ARNIs) leads to a pharmacologic rise in BNP values. These drugs do not affect NT-proBNP levels. In patients with ARNIs, we should keep this in mind.[4]
- More recently it is recognized that BNP, NT-proBNP, and even high sensitivity cardiac troponins are elevated in Stage B/PreHF patients also. In these patients, these biomarkers can be used as risk factors for progression to symptomatic disease.
- Higher levels of circulating cardiac troponins may be found in patients with HF, without any evidence of coronary artery disease (CAD). This suggests the presence of ongoing myocyte injury or necrosis in some patients with HF.
- Since CAD contributes to most of the HF burden in India, the measurement of troponin I or T should be routine in patients presenting with ADHF syndromes.[5]

Table 4: Conditions that have lower natriuretic peptides than expected

- Flash pulmonary edema
- Mitral stenosis
- Pericardial constriction
- "Burned-out" cardiomyopathy
- Acute mitral regurgitation
- Cardiac tamponade
- Genetic polymorphisms
- Heart failure with preserved ejection fraction
- Obesity

ELECTROCARDIOGRAPHY AND ECHOCARDIOGRAPHY IN HEART FAILURE

Protocol for Interpreting Electrocardiogram in Cases of Heart Failure

Introduction

This protocol provides a structured approach to interpreting electrocardiogram (ECG) findings in individuals with suspected or known heart failure (HF).

The heart rate in beats per minute (bpm), is a crucial factor in ECG interpretation. Normal resting heart rate typically ranges between 60 and 100 bpm. Tachycardia or bradycardia can be seen in heart failure [Figure 1]. In acute decompensated heart failure (ADHF), generally, the heart rate is >100 bpm. The target heart rate for optimal treatment in HF should be <70 bpm.

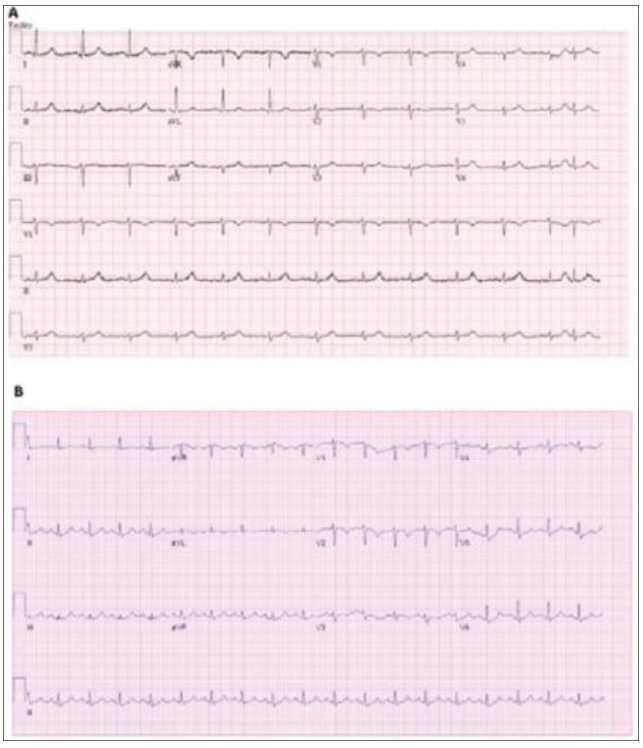


Figure 1: ECG before and after new onset ADHF

1. Rhythm:

Irregularities associated with HF are tachycardias of the likes of atrial fibrillation (AF) [Figure 2], ventricular tachycardia (VT), and supra-ventricular tachycardia (SVT) with aberrancy [Figure 3]. The presence of AF on ECG points to the enlarged left atrial volume and should prompt the measurement of indexed left atrial volume on echocardiography.

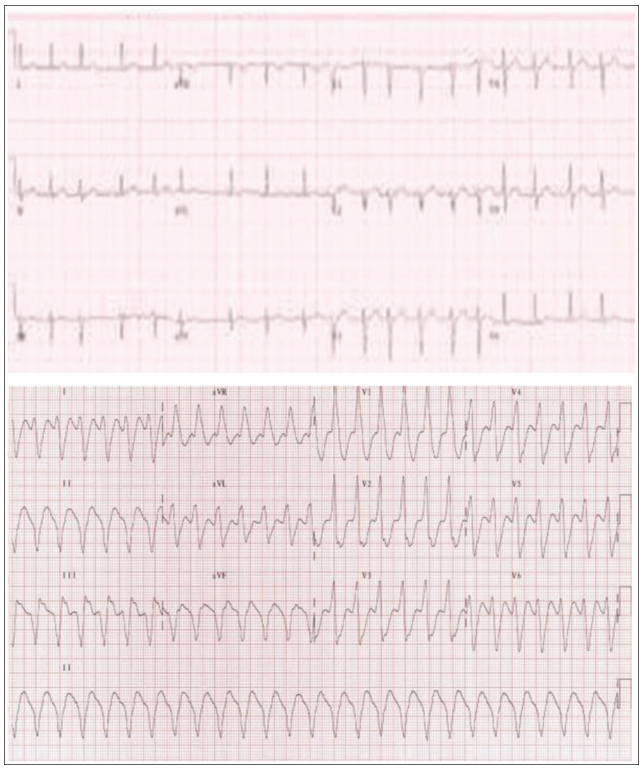


Figure 2: Atrial fibrillation was seen in a patient with heart failure with preserved ejection fraction, 12 lead ECG showing VT

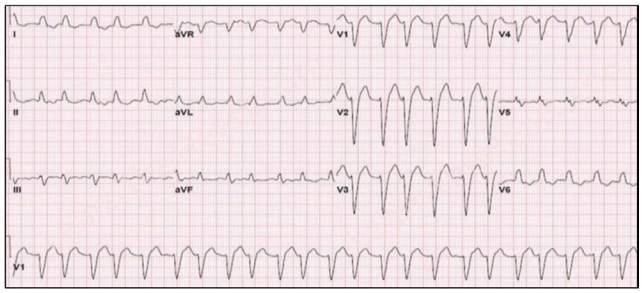


Figure 3: ECG showing SVT with aberrancy

2. **P waves:**

a.P pulmonale is an ECG finding indicative of right atrial enlargement. Characterized by tall and peaked P waves in leads II, III, and aVF, P pulmonale [Figure 4] often suggests increased right atrial pressure resulting from chronic lung disease or pulmonary embolism. Recognition of P pulmonale on the ECG is crucial in identifying and managing the underlying pulmonary conditions contributing to right heart strain.

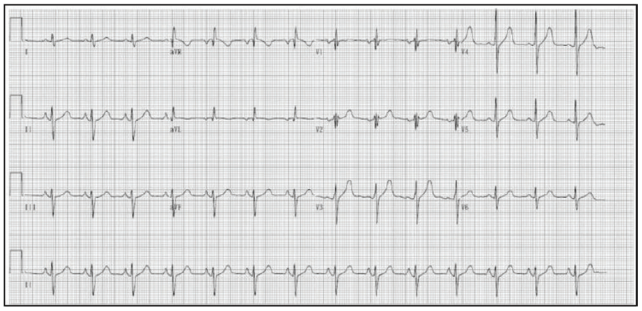


Figure 4: Twelve lead ECG showing P pulmonale in inferior leads

b.P mitrale, or left atrial enlargement, is reflected in the ECG by broadened and notched P waves in the inferior leads (II, III, and aVF). This finding suggests increased left atrial pressure, often related to mitral valve stenosis or regurgitation. Recognizing P mitrale [Figure 5] is essential in evaluating the impact of valvular heart disease on atrial function, or increased LV filling pressure aiding in appropriate treatment strategies for the underlying cardiac condition.

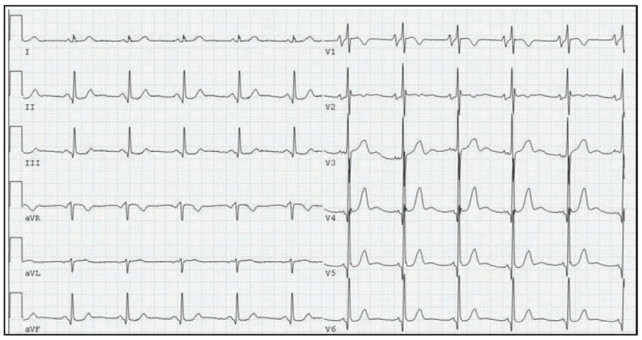


Figure 5: Twelve lead ECG showing P mitrale in V1 lead

3. **PR interval:**

Normal PR interval ranges from 0.12 to 0.21 s. Prolonged PR intervals may suggest atrioventricular (AV) conduction abnormalities, which can contribute to heart failure. Few cases that need to be kept in mind are:

a.Prolonged PR interval seen in the case of cardiac amyloidosis [Figure 6]

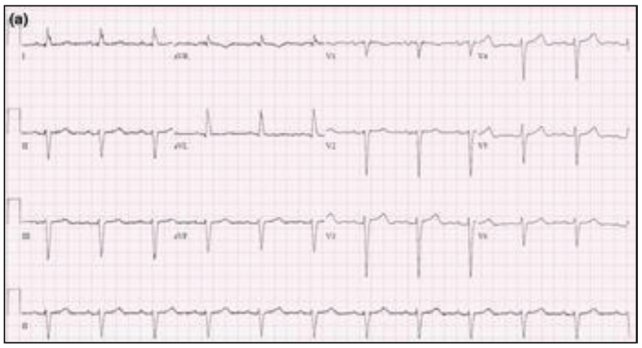


Figure 6: A 68-year-old male presenting with symptoms of heart failure and a family history of cardiac amyloidosis showing sinus rhythm on ECG along with incomplete left bundle branch block (LBBB), and prolonged PR interval.

b. Short PR interval in case of Hypertrophic cardiomyopathy (HCM).

c. Short PR wave along with delta wave (a sign of Wolff-Parkinson-White syndrome) can be seen in patients with HCM.

4. **QRS complex:**

The QRS complex reflects ventricular depolarization. The normal duration is <0.12s. Abnormalities, such as widened QRS complex, may indicate conduction system issues or ventricular hypertrophy, both common in heart failure. Few notable cases are:

a.Low voltage QRS complexes seen in cardiac amyloidosis [Figure 7]

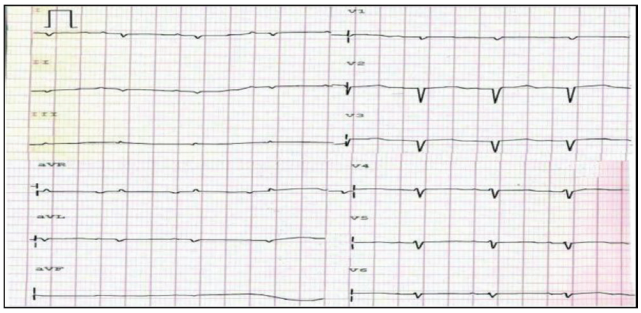


Figure 7: ECG of a 46-year-old male with primary cardiac amyloidosis showing low voltage on limb leads and pseudo-infarct pattern (pathological Q waves on leads V1–V3)

b.Prolonged QRS duration in LBBB warrants an assessment of ejection fraction by echocardiography

c.Epsilon wave presenting after the QRS in lead V1 in Arrhythmogenic right ventricular dysplasia (ARVD). The epsilon wave is frequently described as having a "grassy knoll" appearance and represents early afterdepolarizations or late potentials [Figure 8].

Brugada type 1 syndrome is often associated with the Brugada sign on ECG—which is the only ECG abnormality that is, potentially diagnostic. It is seen as coved ST segment elevation >2 mm in more than one of V1–V3 followed by a negative T wave [Figure 9].

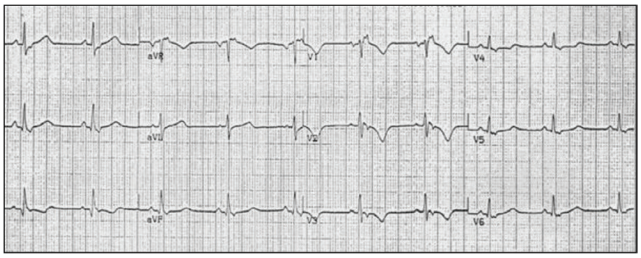


Figure 8: ARVD in a 23-year-old male presenting with syncope after sporting activity

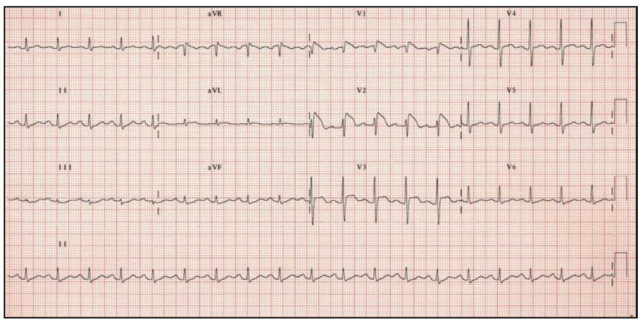


Figure 9: Twelve lead ECG of a 28-year-old man with a history of recurrent light headedness and syncope

d.Pattern of fragmentation in QRS (fQRS) [Figure 10] is often seen as a feature of poor LV function, due to abnormal ventricular repolarization because of myocardial scarring, fibrosis, or ischemia.

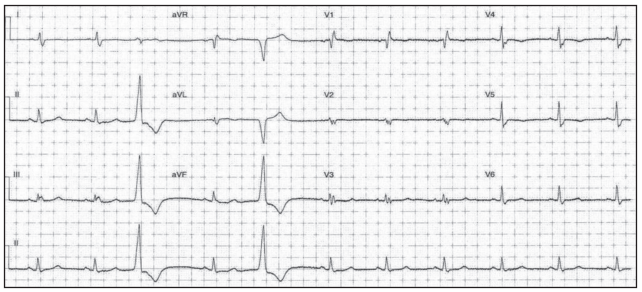


Figure 10: fQRS best seen in leads V2 (rsr′s′r″s″ pattern) and V3 (rsr′s′ pattern)

5. **ST segment:**

Changes in the ST segment may suggest myocardial ischemia or infarction, contributing to heart failure. Elevation or depression of the ST segment requires careful consideration.

ST elevation is seen in cases of

-Acute MI [Figure 11]

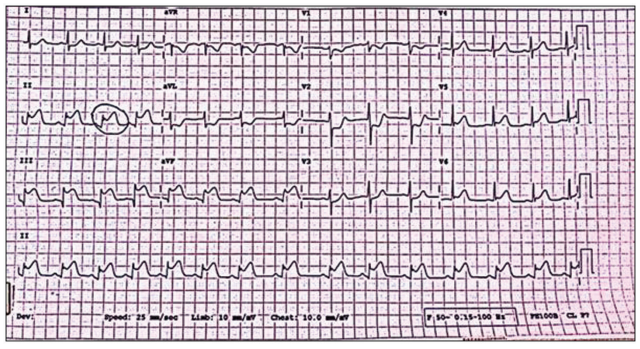


Figure 11: Twelve lead ECG showing inferior wall MI due to distal right coronary artery occlusion

-Pericarditis

-Prinzmetal angina

-Early repolarization

-Ischemia [Figure 12]

-Takotsubo Syndrome,

-ST depression is seen in

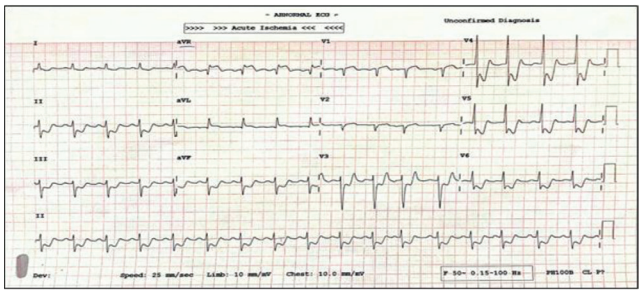


Figure 12: Twelve lead ECG showing acute myocardial ischemia due to left main disease showing ST elevation in aVR and V1 and ST depression in all other leads

-Non q wave MI

-Secondary to hypertrophy of ventricle (discussed later) [Figure 13]

-Secondary to bundle branch blocks

-Electrolyte imbalances

6. **T wave:**

The T wave represents ventricular repolarization. Flattened or inverted T waves may be indicative of myocardial ischemia, infarction, HCM, or electrolyte imbalances, all potential contributors to heart failure. T wave changes are also observed in hyperventilation, secondary to bundle branch block, post-cardioversion, and post-termination of VT/VF.

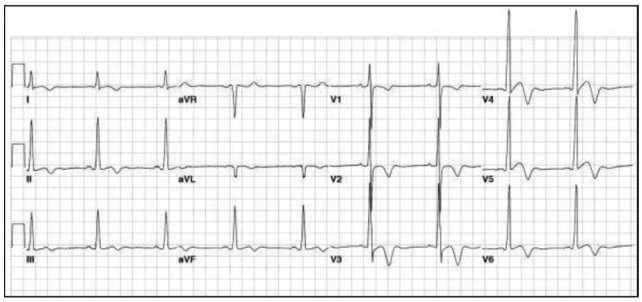


Figure 13: Twelve lead ECG of HCM associated with deep T wave inversions in all precordial leads

7. **QT interval:**

The QT interval measures ventricular depolarization and repolarization. The normal QT interval is 0.34–0.43s. Prolongation of the QT interval is seen in hypocalcemia, hypomagnesemia, and hypokalemia [Figure 14].

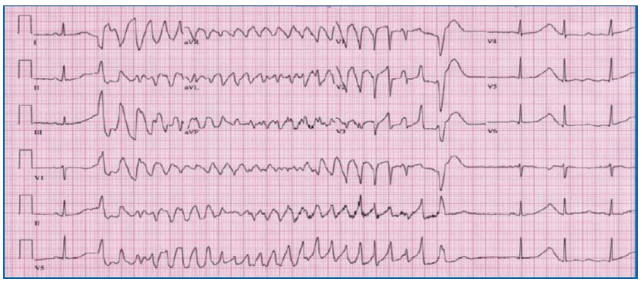


Figure 14: A 70-year-old male presenting with episodic dizziness and palpitation

8. **Cardiac chamber hypertrophy**

ECG can reveal signs of ventricular or atrial hypertrophy, common in heart failure. Patterns such as increased QRS voltage or prolonged P waves may suggest hypertrophic changes. Many of these patterns have been discussed in previous sections. A notable case is that of left ventricular hypertrophy with strain pattern (ST segment depression and T wave inversion in left-sided leads) [Figure 15].

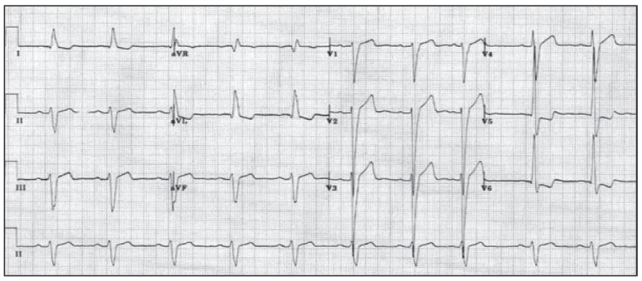


Figure 15: Left ventricular hypertrophy with strain pattern

Conclusion

This protocol serves as a guide for systematically interpreting ECG findings in the context of heart failure. Accurate analysis of ECG parameters enables clinicians to identify abnormalities early, facilitating timely intervention and optimal management of patients with heart failure.

Echocardiography in Heart Failure[1]

- Echo is a vital diagnostic tool that provides non-invasive insights into heart structure and function and ejection fraction (EF) measurement is a key indicator of the heart's pumping efficiency
- EF Typically ranges from 50% to 70%, frequencies between 1 and 5 MHz are used in measurement in adults.
- Echo aids in diagnosis, classification, and ongoing monitoring of heart failure

Ejection Fraction

- Healthy heart EF: 50%–70%. EF represents the percentage of blood pumped out from the left ventricle with each heartbeat [Table 1].

Table 1: Ejection fraction percentage[2]

Sex	Normal	Mildly abnormal	Moderately abnormal	Severely abnormal
Male	52%–72%	41%–51%	30%–40%	Below 30%
Female	54%–74%	41%–53%	30%–40%	Below 30%

- ***Ventricular Function Assessment:*** Real-time images of heart chambers, enable assessment of ventricular function.
- ***Valvular Abnormalities Detection:*** Identifies diseases like mitral regurgitation or aortic stenosis & is valuable in understanding their contribution to HF.
- ***Diastolic Function Assessment:*** Crucial in HFpEF cases, helps evaluate diastolic dysfunction and also assists in HFpEF diagnosis and management.
- ***Doppler Imaging:*** Measures blood flow across heart valves and chambers, and aids in assessing hemodynamics. Identifies abnormalities like elevated filling pressures common in HF.
- ***Structural Anomalies Identification:*** Detects cardiomyopathies or congenital heart defects and contributes to understanding factors causing HF.
- ***Role in Multidisciplinary HF Management:*** A safe and widely available imaging modality plays a pivotal role in the comprehensive approach to HF management.

Types of Heart Failure Based On EF (3)

	HF with reduced EF (HFrEF)	HF with Midly reduced EF EF (HFmEF)	HF with preserved EF (HFpEF)
EF range	<40%	40%–49%	>50%
Characteristics	Diminished contractility is often linked to conditions like myocardial infarction, where damage to the heart muscle compromises its pumping function	Moderately reduced contractile function	Preserved ability to contract, but challenges in relaxation and filling during the diastolic phase

Etiology of HF[4]

Multifaceted, involving various contributing factors:

- ***Ischemic heart disease:*** Driven by coronary artery disease (CAD), atherosclerotic plaques reduce blood flow, causing ischemia and myocardial infarction. Myocardial damage contributes significantly to heart failure.
- ***Chronic hypertension:*** Leads to left ventricular hypertrophy (LVH) and structural changes and compromises the heart's pumping function
- ***Valvular heart diseases and structural abnormalities:*** Contribute by impeding normal blood flow and altering the heart's architecture.
- ***Inflammatory processes:*** Myocarditis weakens heart muscle.
- ***Infiltrative disorders:*** Amyloidosis contributes to stiffness and impaired function.
- ***Metabolic factors:*** Diabetes mellitus promotes fibrosis, and impairs cardiac function, emphasizing the systemic nature of heart failure.

Heart Failure with Preserved Ejection Fraction (HFpEF)[5]

Left ventricular hypertrophy

- Chronic hypertension induces LVH with the thickening of the heart muscle.
- LVH alters the heart's architecture, impairs proper relaxation, and contributes to HFpEF.

Amyloidosis

- Infiltrative disorder where abnormal proteins accumulate in heart tissue.
- Causes stiffness and impaired function, hindering diastolic relaxation and contributing to HFpEF.

Heart Failure with Reduced Ejection Fraction (HFrEF)[6]

Coronary artery disease

- The major cause is caused by atherosclerotic plaques, reducing blood flow and leading to myocardial infarction.
- Irreversible damage impairs effective contraction, contributing to reduced ejection fraction and HFrEF.

Non-compaction of the left ventricle

- Structural abnormality with excessively trabeculated left ventricle.
- Hinders efficient contraction, contributing to reduced ejection fraction and HFrEF.

Takotsubo syndrome

- Sudden and reversible weakening of heart muscle is often triggered by severe emotional or physical stress.
- Temporary impairment of contractile function leads to reduced ejection fraction and HFrEF.
- Clinically mimics myocardial infarction.

MRI, CT AND CORONARY ANGIOGRAPHY IN HEART FAILURE

Other Diagnostic Tests

1. **Cardiac MRI (CMRI):** Cardiovascular magnetic resonance imaging (CMRI) plays a significant role in the evaluation of phenotype, cardiac morphology, myocardial texture, and function in heart failure (HF). It is particularly useful in assessing the etiology of the suspected HF, informing prognosis, and guiding therapy, especially where the echocardiographic examination is suboptimal or findings are inconclusive.[1,2]

   Its greatest strength lies in tissue characterization using T1, T2, and T2* parametric mapping. T1 imaging provides information about extra-cellular volume and its content, T2 about myocardial edema, and T2* imaging about iron overload and myocardial hemorrhage. CMRI aids in the detection of ischemia and fibrosis, assessment of viability, confirmation of suspected myocarditis, and a variety of genetic and infiltrative cardiomyopathies like noncompaction, cardiac amyloidosis, and Anderson–Fabry disease. Subendocardial or transmural late gadolinium enhancement (LGE) pattern and extent is sensitive and specific for the presence of underlying coronary artery disease as the putative cause of HF and its differentiation from other causes of HF like myocarditis and cardiomyopathies wherein mid-wall LGE is characteristic.[3] LGE trans-murality is often used as a surrogate for nonviability.

   CMRI is the gold standard modality for the assessment of left ventricular volumes and ejection fraction, thrombus, left atrium volumes, and right ventricular function.[2] Tissue characterization sequences are acquired selectively to answer disease-specific questions. Mid-wall LGE distribution observed in dilated cardiomyopathy in 10%–-28% confers a higher risk of cardiac death, heart failure, and inducible ventricular tachycardia besides less likelihood of reverse remodeling.[4] Myocardial edema detected on T2-weighted CMR in the setting of new-onset acute heart failure following stabilization provides clues to underlying pathology like Takotsubo syndrome, recent myocardial infarction with non-obstructive coronary arteries, myocarditis, and inflammatory cardiomyopathy like sarcoidosis.[5] However, CMRI is usually not recommended in acute heart failure on presentation because of logistic reasons. Recent American College of Cardiology/American Heart Association 2022 guidelines consider CMRI an appropriate investigation in HF for assessment of ejection fraction is those with inadequate echocardiographic imaging with a strong recommendation and for routine assessment with moderate strength of evidence.[6]

2. **Cardiac Computed Tomography (Cardiac CT):** Cardiac CT including coronary angiography in newly diagnosed HF enables non-invasive assessment of coronary artery disease, severity, and etiology of myocardial dysfunction and defines suitability for revascularization.[7] CT coronary angiography and dynamic CT myocardial perfusion imaging are central to diagnosing the ischemic etiology of HF. The major limitation in using CT angiography in HF is that a significant number of these patients are elderly and have renal impairment wherein the risk of iodinated contrast is high.[2] CT images provide high-quality information about cardiac structure and pericardium although exposure to radiation remains a big handicap. Cardiac anatomical information, such as the location, size, and tributaries of coronary sinuses, can assist in lead placement in cardiac resynchronization therapy. Cardiac CT with delayed contrast enhancement has an emerging role in myocardial tissue characterization, which can contribute to risk stratification and etiopathogenesis in cardiomyopathy patients.[7] Cardiac CT is unlikely to surpass echocardiography and CMR in morphological and functional assessment in patients with HF unless there is an attempt to seek extra-cardiac information, which can aid in the diagnosis of conditions like sarcoidosis etc.

Invasive Coronary Angiography

Coronary artery disease represents the most common underlying cause of HF through the myonecrosis and fibrosis of the infarcted area, the remodeling of the noninfarct area, and hibernation of the myocardium under chronic ischemia. A coronary angiogram is the first step to establish etiology especially in patients with risk factors for coronary artery disease like diabetes mellitus.

Nuclear Imaging in HF

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) are uncommonly used techniques in HF patients. ECG-gated SPECT can provide accurate and reproducible values for ejection fraction, regional wall motion, viability, wall thickening, and dyssynchrony and is an option in patients with suboptimal echocardiographic examination.[2] Nuclear techniques may help in assessing response to cardio-active HF drugs by innervation imaging. However, it has limited practical utility. Nuclear imaging can provide functional and molecular information about pathophysiological processes underlying heart failure as cardiac sarcoidosis and transthyretin amyloidosis, etc. that complements the assessment of cardiac structure and function by other imaging modalities.[8] Molecule-targeted radiopharmaceuticals enable studying several biological processes involved in heart failure beyond perfusion, including myocardial metabolism, innervation, inflammation, amyloidosis, and fibrosis, and may be indicated in specific diseases [Table 1].[3,6]

Table 1: Recommendations for evaluation of HF with cardiac imaging[1,2]

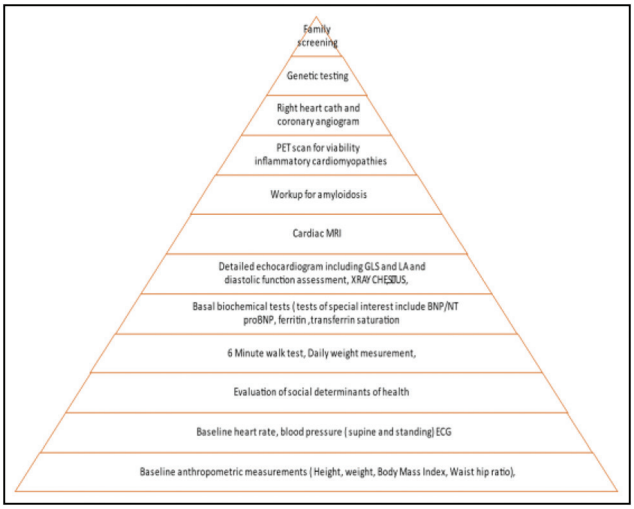
Imaging modality	Class	Level
1.Echocardiography is useful in diagnosing heart failure or for assessment of prognosis.	I	C
2.Cardiac MRI:	I	C
(i)for assessment of myocardial tissue characteristics	II a	C
(ii)LGE in differentiating the ischemic versus non-ischemic DCM		
3.Non-invasive stress imaging (CMR, SPECT, and PET) may be considered for the assessment of ischemia and viability in patients with CAD presenting with HF	II b	B
4.CT coronary angiogram in HFrEF:	II a	C
(i)Low–intermediate pretest probability of CAD	II a	C
(ii)Equivocal noninvasive stress tests		
5.Invasive coronary angiography:	II b	B
(i)HFrEF with intermediate to high pretest probability of CAD	II b	B
(ii)HFrEF with the presence of ischemia in non-invasive stress tests		

HEART FAILURE MANAGEMENT

General Measures

Pyramidal approach

- Baseline anthropometric measurements (height, weight, body mass index, waist–hip ratio, and waist circumference). Baseline heart rate, blood pressure (supine and standing), pedal edema, and jugular venous pressure.
- ECG—Left atrial enlargement, chamber hypertrophy, atrial fibrillation, pulmonary hypertension, and evidence of previous myocardial infarction.
- Daily weight measurement
- 6-Min walk distance and frailty assessment.
- Evaluation of social determinants of health.
- Basic lab workup: Complete blood count, liver and renal function tests, estimated glomerular filtration rate, fasting blood sugar, postprandial blood sugar, glycated hemoglobin, Free T3, Free T4, thyroid stimulating hormone, lipid profile, apo B, lipoprotein(a), and high sensitivity C-reactive protein.
- Advanced lab workup: hsTrop I/T, N-terminal pro-b-type natriuretic peptide, ferritin, transferrin saturation.
- Xray chest: Cardiomegaly, pulmonary venous congestion, and PA dilatation,
- Echocardiography: EF, Chamber dimensions and volumes, GLS, LA strain, diastolic function, PAH, RWMA, IVC assessment, Valves, congenital defects, pericardium
- Lung ultrasound, remote dielectric sensing (ReDS) for assessment of lung fluid in heart failure
- Cardiac MRI: T1 and T2 mapping, scar, viability assessment, and volumes.
- Workup for amyloidosis: Pyrophosphate SPECT, kappa-lambda ratio, urine, and serum immunofixation assays. Biopsies—Fat pad, endomyocardial.
- PET scan for viability and inflammatory cardiomyopathies
- Right heart catheterization, coronary angiogram, and endomyocardial biopsy
- Genetic testing and family screening



Non-pharmacological Measures

Sodium restriction

Increased salt intake is one of the common causes of clinical worsening of HFrEF. Conventionally salt restriction is advised for HFrEF. However, randomized controlled trial data is conflicting.

The SODIUM-HF trial showed that in ambulatory HFrEF patients, a low-sodium diet did not reduce events.[1] A meta-analysis of RCTs sodium restriction, even though reduced symptoms and improved quality of life, was not associated with reduced mortality or heart failure hospitalization.[2] American College of Cardiology/American Heart Association/Heart Failure Society of America in 2022 gave level C evidence for avoiding excessive sodium intake in stage C HF to reduce congestive symptoms. In India, it is reasonable to limit daily sodium intake to 2–3 g. In severe cases of heart failure sodium intake may be restricted to 500 mg/day.[3]

Fluid Restriction

Recommended in congested outpatients and those with symptomatic hyponatremia. Thirst and weight gain can be used to guide fluid restriction. There is no role for fluid

or salt restriction in patients who are clinically stable and have no evidence of congestion.

Nutrition

Cardiac cachexia should be managed with the help of a dietitian. Vitamin deficiencies should be corrected.

Obesity

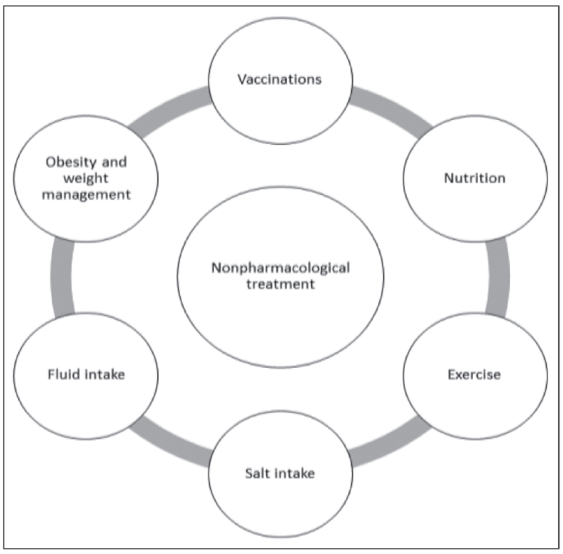
Weight reduction strategies should be advised. Obesity paradox: obese patients with heart failure have better survival. Semaglutide which reduced obesity in the SELECT trial reduced heart failure hospitalization also.[4]

Exercise Training

Cochrane review on exercise training which included 33 trials with 4740 patients with HF (majority HFrEF), reported that there was a trend of reduction in mortality. Regular aerobic exercise and inspiratory muscle training programs are recommended.[5]

Vaccination

Polysaccharide and conjugated pneumococcal vaccine PPSV23 and influenza vaccination every year are recommended in all HF patients who do not have any known contradictions.[6]



Pharmacological Measures

Diuretics

In hospitalized patients, decongestion is a key factor. Even though the majority receive intravenous diuretics, the majority are discharged without adequate decongestion. European Society of Cardiology 2023 guidelines have given class I C recommendation for IV loop diuretics for relief of signs and symptoms of hypervolemia and class IIa B recommendation for the addition of thiazide-like diuretics in case of resistant edema even after an increase of loop diuretic dose.[7] The TRANSFORM study[8] showed similar efficacy with torsemide and furosemide. Bolus or continuous infusions are both efficacious as shown in the DOSE trial.[9] A dose between 400 and 600 mg of intravenous furosemide is generally considered the maximal total daily dose.[10] The diuretic ceiling effect is reached at this level. Diuretic resistance is failure to increase urinary sodium >90 meq/L despite a high dose (more than 160 mg daily of furosemide) for 3 days. Options for diuretic resistance include changing diuretics, continuous infusion, loop diuretics with thiazides, loop diuretics with sodium-glucose cotransporter 2 inhibitors (SGLT2i).

Sequential nephron blockade is associated with decongestion but not with improved clinical outcomes. Adding intravenous acetazolamide was shown to improve decongestion in the Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial.

CLOROTIC trial[12] where hydrochlorothiazide was added to loop diuretics showed a significant weight reduction, but no effect on mortality. The role of tolvaptan and ultrafiltration is limited to non-responders as rescue therapy.

SGLT2i in the most vulnerable early phase in the DICTATE AHF trial showed greater natriuresis and lesser use of IV diuretics. There was a faster transition to oral diuretics and faster discharge. Spironolactone at discharge in the COACH trial[14] showed a significant reduction in 30-day death/hypertensive heart failure (HHF; $P = 0.039$)

DIURETICS IN HEART FAILURE

	DECONGESTION	GDMT OPTIMISATION	POST DISCHARGE OUTCOMES
LOOP DIURETICS + ACETAZOLAMIDE	++	NO	NO IMPROVEMENT
LOOP DIURETICS + THIAZIDES	++	NO	NO IMPROVEMENT
LOOP DIURETICS + SGLT2 INHIBITORS	++	++	IMPROVED OUTCOMES
TOLVAPTAN	+	NO	NO IMPROVEMENT
LOOP DIURETICS	+	NO	NO IMPROVEMENT
SPIRONOLACTONE	+	YES	IMPROVED OUTCOMES

THE FOUR PILLARS OF HF PHARMACOTHERPY

The pharmacotherapy for HF has evolved over these years with the discovery of new drugs which is found to be very effective in heart failure. We know that diuretics provide only symptomatic benefit and has no mortality benefit. Four pharmacological agents have been found to be reducing the outcome, especially mortality and HF hospitalisations in patients with HFrEF. These drugs are called as the "Four Pillars" of HFrEF therapy. They are ARNI, Betablockers, Aldosterone receptor blockers and SGLT2 inhibitors. It is found that it will add 5.5 years more life to a 55 year old man with HFrEF if initiated and titrated as recommended.

There are three aspects in initiating therapy with the four pillars.

We should try to initiate all the four drugs at what ever doses possible. Even small doses of these drugs have shown to benefit.

We should titrate the drugs to the target doses (as given in the trials) or to the maximum tolerated doses possible.

The titration should be completed within 6 weeks to 3 months to reach the target / maximum tolerated doses, as we can derive the maximum benefit and improve the patient outcomes. Considering that the rehospitalization and mortality after a HF related event is the maximum in the first 6 weeks, STRONG-HF trial proved that if all 4 therapies are started as soon as possible, preferably while the patient is still in the hospital, and up titrated over the next 4 -6 weeks, the rate of rehospitalization and mortality is significantly decreased.

The other factors we need to consider are

The up-titration can be done every two weeks. Creatinine, Serum electrolytes, Blood pressure including postural BP and heart rate should be assessed during each follow-up visits. If the patient cannot tolerate the drugs, the doses need to be reduced.

Once the patient is stable with the maximum tolerated or the target doses, we need to continue the therapy probably for years. There is data to show that if you stop and withdraw the therapy in patients whose EF has improved, 45% had recurrence. Probably fully recovery do not occur, and it is only a remission.

RAS BLOCKERS, MRA AND ARNI IN HF

Activation of renin–angiotensin system (RAS), aldosterone as well as natriuretic peptides forms a complex cadence of neurohormones that precisely regulate cardiovascular hemodynamics in heart failure (HF). While angiotensin II causes vasoconstriction and salt retention, aldosterone secretion results in salt retention in the short term and tissue fibrosis over the long term, whereas natriuretic peptides counteract these deleterious effects by producing vasodilation and natriuresis [Figure 1.1]. While angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) inhibit the RAS, mineralocorticoid receptor antagonists (MRA) block aldosterone, whereas neprilysin inhibitors [combined with ARB—angiotensin receptor neprilysin inhibitors (ARNI] increase circulating natriuretic peptides to promote vasodilation and natriuresis.[1,2]

Challenges

Hypotension, a fall in glomerulus filtration rate (increase in serum creatinine), and hyperkalemia are the three major challenges in initiation of ACEI, ARB, ARNI, and MRA in HF. Low-dose initiation, careful titration, and withdrawal of nonessential drugs that can cause hypotension (diuretics, antihypertensives, and nonsteroidal anti-inflammatory drugs)couldensurethatmorepeopletoleratethisfoundational therapy.[2]

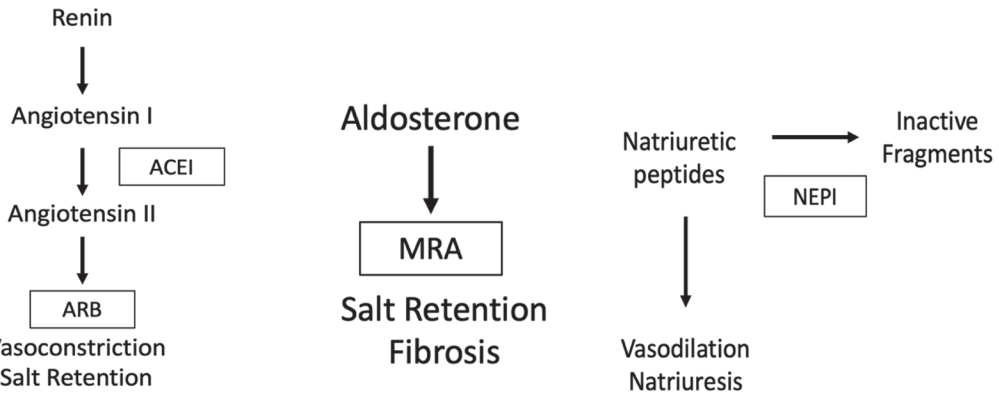


Figure 1.1: Renin-Angiotensin-Aldosterone pathway

Worsening renal function

A slight increase in serum creatinine up to 20% of baseline (with a consequent fall in GFR) is not an indication to stop ACEI, ARB, or ARNI. However, a progressive increase (2–2.5 mg creatinine) is a need for caution. A rise of serum creatinine of >2.5 mg% is an indication to temporarily stop or reduce the dose of ACEI, ARB, or ARNI. Similarly, a rise of serum potassium above 5mEq/L calls for caution especially with MRA, whereas >5.5 we need to stop therapy.[2,5]

The dose chart and titration of the renin–angiotensin–aldosterone system inhibitors, ARNI, and MRA in HF are shown in Table 1.

Commonly used drugs in HF with starting and target doses.[1,2]

Table 1: RAAS Blockers in Heart Failure

Drugs	Starting dose	Target dose
ACEI		
Captopril	6.25 mg three times a day (TID)	50 mg TID
Enalapril	2.5 mg two times a day (BID)	10 mg BID
Lisinopril	2.5 mg once daily (OD)	20 mg OD
Ramipril	1.25 mg OD	10 mg OD
ARB		
Candesartan	4 mg OD	32 mg OD
Losartan	25 mg OD	50 mg BD
Valsartan	40 mg BID	160 mg BID
MRA		
Spironolactone	25 mg OD	25 mg OD
Eplerenone	25 mg OD	50 mg OD

RAAS = renin-angiotensin-aldosterone system, ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blockers, MRA = mineralocorticoid receptor antagonist

Conclusion

ARNI, ACEI, ARB, and MRA form some of the major foundational pillars of HF treatment. Low-dose initiation, careful uptitration, and monitoring would ensure that the majority of patients received and benefitted from this treatment.

ROLE OF BETA-BLOCKERS IN HEART FAILURE

Beta-blockers reduce mortality and morbidity in patients with HFrEF and should be given in stable, euvolemic, patients at a low dose and gradually uptitrated. In patients admitted with HF, beta-blockers should be cautiously initiated in the hospital, once the patient is hemodynamically stabilized, off intravenous inotropes, mobile, and about to stop intravenous diuretics [Table 1].[1,2]

Table 1: Use of beta blockers in HF

Indication	Stable heart failure
Contraindication	• Second- or third-degree atrioventricular block • Critical limb ischemia. • Asthma (relative contraindication) • Known allergic reaction • New York Heart Association class IV HF. • Heart rate <50 bpm. • Persisting signs of congestion or hypotension
Dose	• Bisoprolol: starting dose 1.25 mg once daily (o.d.), target dose 10 mg o.d. • Carvedilol: starting dose 3.125 mg two times a day (b.i.d.), target dose 25 mg b.i.d. • Metoprolol succinate (CR/XL): starting dose 12.5/25 mg o.d., target dose 200 mg o.d. • Nebivolol: starting dose 1.25 mg o.d., target dose 10 mg o.d

Role of Sodium-Glucose Co-Transporter 2 Inhibitors (SGLT2) Inhibitors

SGLT2 inhibitors work in heart failure by blocking the SGLT2 protein in the proximal tubule of the nephron, reducing the reabsorbed glucose and sodium in the blood. This leads to glycosuria and also natriuresis. Along with this, there is a reduction in preload and afterload, improvements in myocardial metabolism, and a reduction in cardiac fibrosis.

The DAPA-HF trial investigated the long-term effects of dapagliflozin (SGLT2 inhibitor) in heart failure patients who were in New York Heart Association classes II–IV and had an LVEF ≤40%.[1] There was a 26% reduction in the primary endpoint: a composite of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or cardiovascular (CV) death. The EMPEROR-Reduced trial showed that empagliflozin reduced the combined primary endpoint of CV death or HF hospitalization by 25%.[2] The combined sodium-glucose co-transporter(SGLT)-1 and 2 inhibitor, sotagliflozin also showed that in diabetes who were hospitalized with HF there was a reduction in CV death and hospitalization [Table 2].

Table 2: SGLT2 in Heart Failure

	Sodium-glucose co-transporter 2 inhibitors (SGLT2) inhibitors
Indications	Patients with heart failure: reduced EF, mid-range EF, and HFPEF independent of diabetes, acute heart failure
Contraindications	• Known allergic reaction • Pregnancy and breastfeeding period. • Estimated glomerular filtration rate <20 mL/min/1.73 m2. • Hypotension • Glycosuria may predispose to fungal genito-urinary infections. • Patients should be made aware of the risk of dehydration, hypotension, hypoglycemia, ketoacidosis, and fungal genito-urinary infections, • Drug holiday in the peri-procedure period among patients undergoing surgical procedures in advisable to mitigate the risk of euglycemic diabetic keto acidosis
Dose	Dapagliflozin: starting (and target) dose 10 mg once daily (o.d.) Empagliflozin: starting (and target) dose 10 mg o.d

EF = ejection fraction; HFPEF = heart failure with preserved ejection Fraction

Vericiguat

In HFrEF, the nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) pathway is impaired: oxidative stress, endothelial dysfunction, and inflammation lead to decreased NO levels, which have negative effects on vascular tone., myocardial stiffness and fibrosis. Vericiguat acts as a direct sGC stimulator. It enhances cGMP independent of NO levels with antihypertrophic, antifibrotic, and vasodilatory effects [Table 3].

The Victoria trial with vericiguat was a Phase 3, randomized, double-blind, placebo-controlled trial that included patients with symptomatic chronic HF, a left ventricular ejection fraction <45%, elevated natriuretic peptide levels, and evidence of worsening heart failure, defined as HF hospitalization within the 6 months before randomization or receiving intravenous diuretic therapy, without hospitalization, within the previous 3 months.[1,2]

Table 3: Vericiguat

Indication	Vericiguat is indicated to reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for heart failure or need for outpatient IV diuretics, in adults with symptomatic chronic HF and ejection fraction less than 45%.
Contra indications	Vericiguat is contraindicated in patients with Concomitant use of Vericiguat and PDE-5 inhibitors, such as sildenafil. Concomitant use of other soluble guanylate cyclase (sGC) stimulators, such as riociguat
Dose	Vericiguat should be initiated at 2.5 mg once daily and increased in approximately 2-week intervals to 5 mg once daily and then reach the targeted dose of 10 mg once daily, as tolerated.

Approach to Worsening Heart Failure

Definition of worsening heart failure

Heart failure (HF) hospitalization

Over time, the meaning of worsening heart failure (WHF) has changed. WHF has long been associated with worsening heart failure symptoms that necessitate hospitalization.[1]

Worsening HF without hospitalization

It is known that many patients with WHF may receive treatment in an outpatient setting rather than being hospitalized for HF decompensation.

Beyond the four pillars

Vericiguat is the first drug approved by the European Medicines Agency, which has already been tested in patients with WHF during guideline-directed medical therapy treatment and is effective in reducing clinical events.[2]

In HFrEF, the nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) pathway is impaired: oxidative stress, endothelial dysfunction, and inflammation lead to decreased NO levels, which have negative effects on vascular tone., myocardial stiffness and fibrosis. Vericiguat acts as a direct sGC stimulator. It enhances cGMP independent of NO levels with antihypertrophic, antifibrotic, and vasodilatory effects.[4]

In the VICTORIA study, patients were randomised to Vericiguat 10 mg versus placebo. Vericiguat reduced the primary outcomes of cardiovascular death and heart failure hospitalizations by 10%. The absolute risk reduction for the primary outcome was 4.2 events per 100 patients per year and the number needed to treat was 24 to prevent one composite event per year.

Over the course of the VICTORIA study, the mean reduction in systolic blood pressure was approximately 2 mmHg greater in patients who received vericiguat compared with placebo.[3]

In patients with renal Impairment, no dose adjustment of Vericiguat is required in patients with estimated glomerular filtration rate (eGFR) ≥15 mL/min/1.73m^2 (without dialysis).Beneficial effects of vericiguat on the primary outcome were consistent across the full range of eGFR, irrespective of Worsening Renal Function(WRF).

IV diuretic treatment as an outpatient

A secondary analysis of the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy Post Approval Registry) trial of patients with heart failure and reduced ejection fraction was one of the first large studies to demonstrate that patients with WHF treated with intravenous diuretic therapy during urgent outpatient clinic visits had mortality comparable with those hospitalized, even though hospitalization easily identifies patients at high risk for clinical events.

Escalation of oral diuretic therapy in out-patient settings

In the past, there has been inadequate documentation regarding the escalation of outpatient oral diuretic therapy. While increasing the dosage of an oral diuretic during a hospital stay is recognized as an HF hospitalization event, increasing the dosage of an oral diuretic in an outpatient setting is not commonly regarded as a WHF event in clinical studies. Growing evidence indicates that increasing oral diuretic medication in the outpatient context is not benign and carries a significant risk of morbidity and death. In a recent meeting of cardiologists from India, it was strongly recommended that oral escalation to very high doses of diuretics in the absence of any other precipitating causes may be considered as WHF.[4]

In conclusion, maximal and rapid treatment of patients with WHF is a major challenge, since the natural progression of WHF leads to frequent rehospitalizations and worsening of symptoms to an advanced stage when treatment available is no longer effective or sufficient. No positive studies have been performed in this high-risk population with advanced heart failure, and pharmacological options are poor. Time plays an important role in the prognosis of WHF, and the introduction of new effective drugs should not be delayed. Currently, using all four pillars of heart failure management and newer drugs such as Vericiguat appears to be the way forward.

IVABRADINE, DIGOXIN, ISDN/ HYDRALAZINE, IRON, OAC, AND STATINS

Ivabradine

- Ivabradine is a specific inhibitor of the I_f current in the sinoatrial node causing dose-dependent reduction in heart rate without reduction in myocardial contractility or blood pressure.
- Recommended (class IIa, level of evidence B) to be used in patients with heart failure and reduced ejection fraction (HFrEF) [left ventricular ejection fraction (LVEF) <35%] in sinus rhythm, who have a heart rate >70 beats per minute (bpm) despite being treated with a maximally tolerated dose of a beta-blocker, additionally as an adjunct for uptitration of beta-blocker.[15]
- It plays an important role in the management of heart failure patients with severely reduced LVEF having low blood pressure (BP) and high resting heart rate as it does not reduce BP.
- The main side effects are visual symptoms (due to phosphenes), which occur in ~3% of patients, and increased QT interval rarely
- Contraindicated in pregnancy and co-therapy with CYP3A4 inhibitors such as ketoconazole or macrolide antibiotics

Digoxin

- Digoxin inhibits membrane-bound alpha subunits of sodium-potassium ATPase of the myocardium, promoting sodium-calcium exchange increasing intracellular calcium concentration available to contractile proteins thereby increasing the force of myocardial concentration[5,6]
- May be considered(class IIb, level of evidence B) in symptomatic patients in sinus rhythm to reduce the risk of hospitalizations despite guideline-directed medical therapy (GDMT) or who are unable to tolerate GDMT.[1] In patients with co-morbid atrial fibrillation (AF), digoxin can be used to reduce ventricular rate when other options can not be used (class I, level of evidence B).
- In contrast to other inotropic agents such as dobutamine, beta-agonists, milrinone, and enoximone which have shown excess mortality, digoxin does not have such an effect on mortality.
- In large randomized controlled trials (RCT) involving 6800 patients of heart failure(LVEF<45%) in sinus rhythm, digoxin reduced hospitalization rates with no effect on mortality, similar findings were observed in smaller RCTs[5,6]
- DIGIT HF and DECISION are ongoing trials evaluating the effects of digitoxin and digoxin, respectively, in heart failure (HF).
- Use of digoxin has gradually diminished (currently 20%–25% in European and ≈10% in the United States of HF prescriptions) as it has a narrow therapeutic window of 0.5–0.9 ng/mL. Should be used with caution in the elderly and patients with chronic kidney disease.

Combination of Hydralazine and Isosorbide Dinitrate

- There is a lack of evidence for the use of a fixed-dose combination of hydralazine and isosorbide dinitrate in all patients with heart failure.
- A small RCT has shown a reduction in mortality and heart failure hospitalization by these vasodilator drugs in African-Americans only and has Class I recommendation for them[15]
- For populations other than the group mentioned above can be used in symptomatic patients who cannot tolerate/have a contraindication for an ACE inhibitor/ ARB/ARNI, however, this recommendation is based on a small Veterans Administration Cooperative Study, which included only male patients with symptomatic HFrEF who were treated with digoxin and diuretics.
- Does not adversely affect electrolytes, may cause hypotension, and is contraindicated with PDE5i like sildenafil.

Usual dose: Fixed dose combination 20 mg isosorbide dinitrate and 37.5 mg hydralazine 3 times daily up to 40 mg isosorbide dinitrate and 75 mg hydralazine three times dailyIsosorbide dinitrate and hydralazine—20–30 mg isosorbide dinitrate and 25–50 mg hydralazine three to four times daily upto120 mg isosorbide dinitrate total daily in divided doses and 300 mg hydralazine total daily in divided doses.

Statins

- Two large RCTs as well as meta-analysis including 24 RCTs have not shown benefit in cardiovascular mortality and stroke in HF, however, a reduction in HF hospitalization and MI was found in meta-analysis of the CORONA and GISSI-HF trials.
- Should continue to be used in patients with clinically proven coronary artery disease disease to reduce future coronary events.

Iron

- Iron deficiency (serum ferritin level <100 or 100-300 µg/L with transferrin saturation <20%) is present in more than 50% of CHF patients and ~80% of AHF patients in HF patients with and without anemia[15]
- Intravenous repletion of ferric carboxymaltose (class IIa indication) improves exercise capacity and QOL and reduces hospitalization for worsening heart failure irrespective of the presence of anemia (FAIR HF, CONFIRM HF)
- Oral iron is not advised as it may not get absorbed and not found to improve exercise capacity (IRONOUT-HF).
- The recommended dose of IV ferric carboxymaltose is 500–1000 mg in 50 mL saline given over 10–15 min. Large outcome trials with other iron formulations are ongoing in HFrEF, HFpEF, and AHF
- It is recommended to test plasma iron level after 2–3 months. If the level is still low, then the dose may be repeated.

Antiplatelets–Anticoagulants

- There is no evidence of benefit for anticoagulation in HF patients without a specific indication[15]
- Patients with chronic HF with permanent/persistent/paroxysmal AF, intracardiac thrombus, and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke, or transient ischemic attack, or 75 years of age) should receive chronic anticoagulant therapy.
- Non-vitamin K antagonist oral anticoagulants (NOACs) are preferable if there is no metallic prosthetic heart valve and if the cost of therapy is not a major issue[5,7]
- Therapeutic anticoagulation with low-molecular-weight heparin (LMWH), in the first and last trimesters, and VKAs or LMWH for the second trimester, is recommended for patients with HF pregnancy if there is an indication for anticoagulation. DOACs should be avoided in pregnancy.
- Chronic anticoagulation is also reasonable for patients with chronic HF who have AF but do not have an additional risk factor for cardioembolic stroke.
- Antiplatelets should be used in patients with CAD.

Sequencing of HF therapies

For HFpEF, the choices are limited at present to Diuretics, SGLT2-I , ARNI for patients with LVEF<57% and probably Finerenone which is awaiting approval after the FINE-ARTS HF trial.

Sequencing of Heart failure therapies is more important in HFreF and HFmrEF, which largely behaves like the former. For them at present we have 4 approved therapies, namely BB, SGLT2-I, MRAs and ACE/ARB/ARNI, all of which have to be utilized for optimal results. The question arises, what should be the order in which they are to be used.

In a patient hospitalized with acute HF, diuretics are the first line of treatment to relieve congestion and improve symptoms. The choice of initial treatment of the "four pillars" will depend upon the hemodynamic profile, renal function and heart rate. SGLT2-I have no adverse hemodynamic consequences and do not cause electrolyte disturbances. ACE/ARBs/ARNI are all vasodilators and capable of increasing creatinine and K and can also reduce blood pressure. MRAs have a powerful effect on increasing K but do not cause much hypotension. BB reduce HR and can worsen dyspnea if a person is already fluid overloaded.

Considering that the rehospitalization and mortality after a HF related event is the maximum in the first 6 weeks, as shown in STRONG-HF trial we have to initiate all 4 therapies at the earliest possible, preferably in-hospital, and up titrated over the next 4 -6 weeks, then the rate of rehospitalization and mortality is significantly decreased. So that should be our aim [Figure 2.1].

Except SGLT2-I which requires no dose adjustment (except a mild reduction in diuretic dose),which can be started any time after admission, other drugs can be started at a lower dose during hospital admission and up titrated at each visit. Some times it may not have been possible to start all 4 drugs in hospital for some reason or the other. In that case they should be started at each visit, which after discharge should occur at 1-2 weeks interval.

How then should one proceed? It is important to individualize the sequencing for each patient. SGLT2-I can come in very early as also MRAs if K levels are okay. If a patient is euvolemic and has a reasonable HR, BB can be introduced early. If renal functions are normal and the BP allows, ACE/ARBs/ARNI, with a preference of ARNI can come in earlier. Of course, if all 4 drugs, at least in some dose can be started during hospitalization, the long-term results are better. It also reminds the physician to step up the doses at subsequent visits. Regardless of the order of sequencing, it is important that all 4 drugs are given according to Guideline directed doses or the maximally tolerated doses in the first 4-6 weeks [Figure 2.2].

The data from clinical trials strongly suggests that the initiation of treatment with a low dose of a new drug class is likely to be more beneficial for CV outcomes than up

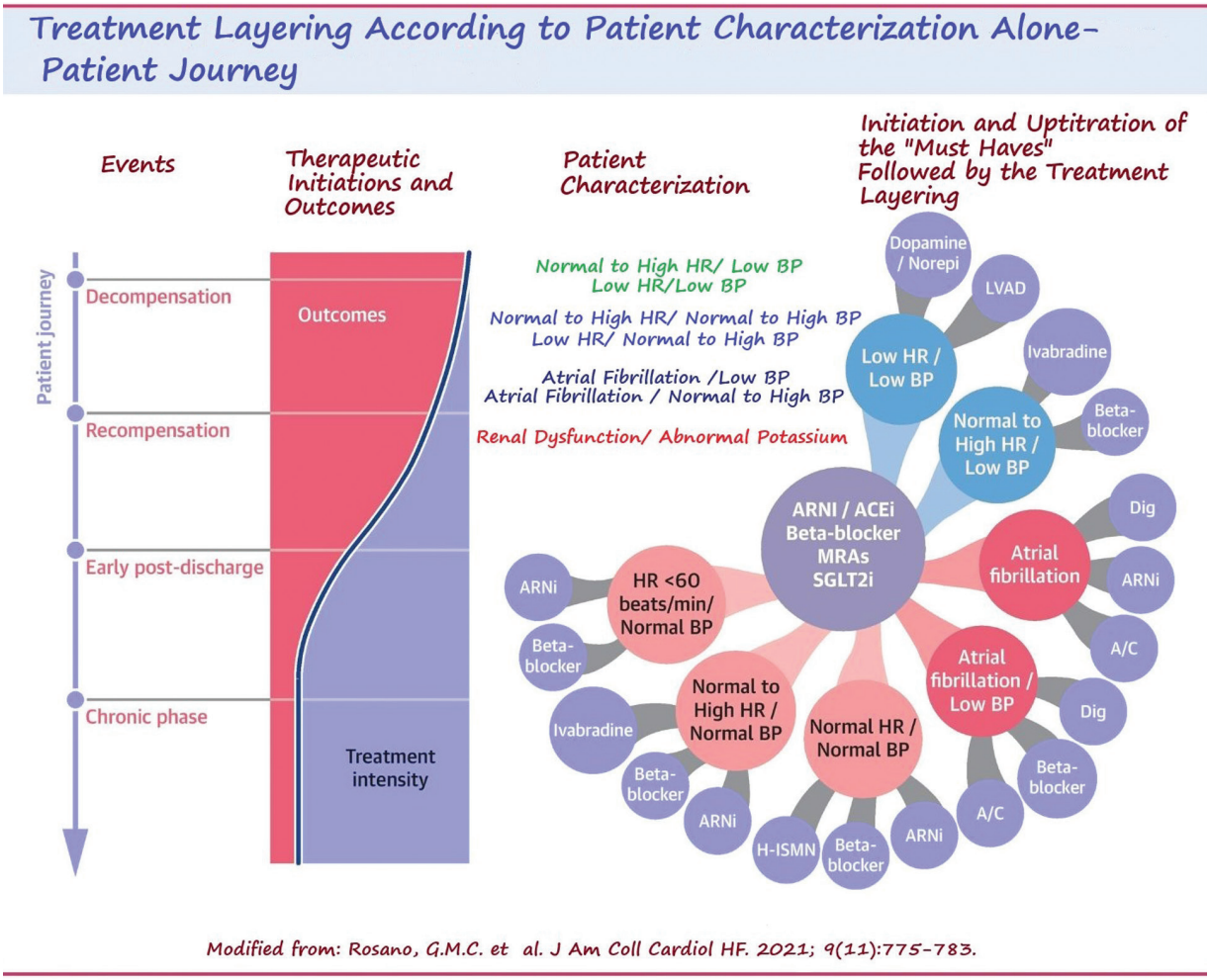
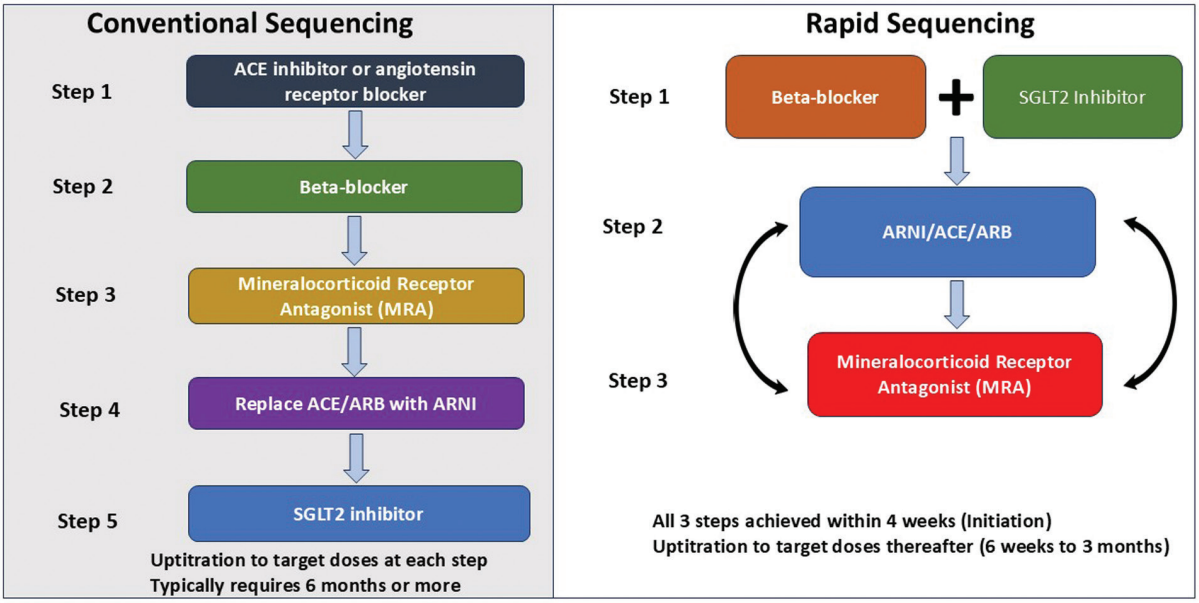


Figure 2.1: Treatment layering according to patient characterization alone



Modified from: Packer M, McMurray JJV. Rapid evidence-based sequencing of foundational drugs for heart failure and a reduced ejection fraction. Eur J Heat Fail. 2021 Jun;23(6):882-894.

Figure 2.2: Sequencing of drugs in conventional vs rapid method

titrating the dose of an existing drug. This has been observed in all the HF trials where addition of a new drug was done on top of the existing therapy, regardless of their doses.

1- Diuretics to relieve congestion.
2- SGLT-2 inhibitors and MRAs can be started early as they do not lead to any significant hemodynamic disturbances and SGLT-2-I do not require dose titration
3- Pre discharge BB if there is no bradycardia
4- ACEI/ARB/ARNI pre discharge if BP allows and no hyperkalemia

HEART FAILURE WITH PRESERVED EJECTION FRACTION

Heart failure with preserved ejection fraction (HFpEF) is a clinical condition having symptoms and signs of heart failure with left ventricular (LV) ejection fraction >50%, abnormal diastolic function (i.e., alteration in E and A ratio), evidence of raised LV filling pressure and increased level of circulating brain natriuretic peptides.[1]

Epidemiology and Aetiology

- HFpEF accounts for 40%–70% of HF diagnoses with a prevalence of 1.1%–5.5% of the overall population based on data from high-income countries. The data from Indian registries show only a prevalence of less than 20%.[2-4] The rates of hospitalization, duration of admission, and quality of life are similar between HFpEF and HFrEF.[4]
- Risk factors are systemic hypertension, type II diabetes mellitus, obesity, coronary artery disease, atrial fibrillation, and metabolic syndrome.[1]
- Recent studies show that mortality of HFpEF ranges from 30% to 60% at 5 years.[5,6]
- In-hospital mortality is about 3%–6.5% in patients admitted with an acute episode of heart failure in HFpEF patients.[7]
- The reported short-term (30–90 days) mortality for HFpEF ranges between 5% and 9.5%, whereas the annual mortality rate ranges from 4% to 15%.[5]

Pathophysiology

- Diastolic dysfunction happens due to problems in the heart's mechanical function leading to the inability of the left ventricle (LV) to relax properly.
- Any alterations in normal diastolic function are dependent on the rate and degree of ventricular pressure decline and filling.
- The guidelines grade diastolic dysfunction into four stages grade 1 diastolic dysfunction, where there is abnormal relaxation of LV, grade 2, characterized by pseudo-normalization, grade 3, characterized by a reversible restrictive pattern and grade 4 is characterized by a restrictive pattern, irreversible despite change in loading conditions.[8]
- In HFpEF, the myocardium undergoes structural and cellular changes expressed as myocyte hypertrophy, intercellular and interstitial fibrosis, abnormal myocyte relaxation, and inflammation.[9]
- Concentric LV remodeling is seen in around 53% of cases of HFpEF patients.
- Progressive LV concentric remodeling is associated with reduced subendocardial longitudinal deformation assessed by 2D strain imaging despite preserved LVEF.

Diagnosis

- Diagnosis of HFpEF needs hemodynamic evaluation at rest and after stress which helps in elevating filling pressure and cardiac output [Figure 3.1].
- Echo demonstration of LV hypertrophy, assessment of LV and right ventricular function, left atrium dilatation, elevation in LV filling pressure (E/E'), and presence of tricuspid regurgitation.
- Associated assessment of renal dysfunction, weight, anemia, and biomarkers like NT-proBNP. Several diagnostic algorithms and scores are available for HFpEF diagnosis.
- Usage of score-based algorithms like H2FPEF and HFA-PEFF) now represents the standard for diagnosis.[10]

Management

- SGLT2 inhibitors irrespective of diabetic status, fluid management to reduce congestion by diuretics—both loop diuretics and potassium-sparing diuretics, management of atrial fibrillation, control of heart rate and hypertension, strict glycemic, weight reduction and lifestyle modification, and regular walking. Tirzepatide (SUMMIT trial) and Semaglutide (STEP-HFpEF trial) has shown promising results recently in improving outcomes in HFpEF.

Heart Failure with Mildly Reduced Ejection Fraction

- Heart failure (HF) with mildly reduced ejection fraction (EF; HFmrEF) has been a condition when EF is between 40% and 49%.[1] It accounts for up to 25% of patients with HF.[11] HFmrEF is an intermediate HF type between HF with preserved EF (HFpEF) and HF with reduced EF (HFrEF) for some characteristics but is more similar to HFrEF for others, especially for the high prevalence of ischaemic heart disease. Patients with stable HFmrEF generally have lower heart failure hospitalization (HFH) rates as compared to stable HFrEF and higher HFH rates compared with stable HFpEF. In patients with

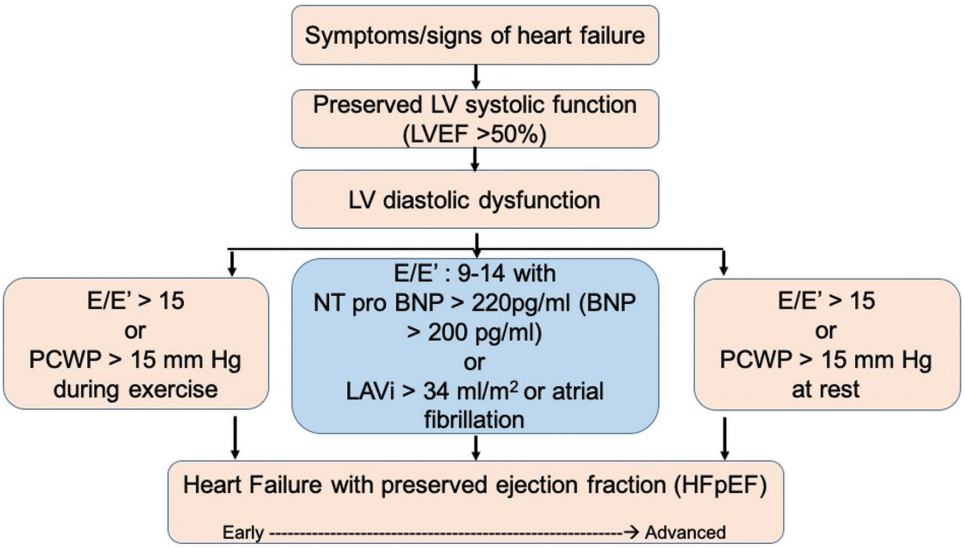


Figure 3.1: Diagnostic pathway for heart failure with preserved ejection fraction

stable HFmrEF, chronic kidney disease, NYHA class, use of beta-blockers, and loop diuretics are predictors of clinical outcomes.[12] Ongoing clinical trials in patients with HFmrEF or HFpEF, in particular of MRAs and SGLT2 inhibitors, will inform the future treatment landscape in HFmrEF. Currently the drugs which is found to be beneficial in the management of HFrEF is recommended for the management of HFmrEF also. Diuretics and SGLT2 have a Class I indication and ARNI/ACEI/ARB, betablockers and MRAs have Class IIb indication in HFmrEF.

CARDIOMYOPATHIES, INVESTIGATIONS, AND MANAGEMENT

Cardiomyopathies, Investigations, and Management

- The term ***Cardiomyopathy*** was first used by Dr. Bridgen in London in the year 1957 as the noncoronary cause of myocardial disease and later on, used by the World Health Organization in 1968[1]

Current Definitions

AHA[1]	Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electric dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders
ESC[2]	A disorder of the myocardium that is structurally and functionally abnormal in the absence of valvular heart diseases, coronary artery diseases, and congenital heart diseases sufficient to cause the observed myocardial abnormality

Classification of Cardiomyopathies

WHO	Dilated, Hypertrophic, Restrictive
AHA 2006	Primary, Secondary
ESC 2008	Dilated, Hypertrophic, Restrictive, ARVD, Unspecified
MOGE's	M = morphology, O = organ system, G = genetic/familial inheritance pattern, E = etiology, F = functional class ACC/AHA (A–D) and NYHA (I–IV)
ESC 2023	"Phenotypic based integrated etiological diagnosis" classification scheme with the addition of special traits, for example, LVNC is not cardiomyopathy but hypertrabeculation as a phenotypic trait in addition to hypertrophy, dilatation and/or systolic dysfunction

Investigations

- It is recommended that all patients undergo a systematic evaluation with a multiparametric approach with the aid of clinical history, physical examination, ECG, Holter, and Multimodality imaging with a "cardiomyopathy mindset"—Class 1 Level C
- At least a three generation family history should be elicited for pedigree analysis—Class 1 Level C

Common ECG Abnormalities in Cardiomyopathies

Atrial arrhythmias like AF	HCM, NMD's, DCM, Amyloidosis, Storage disorders
Repolarisation abnormalities	ACM, DCM, HCM, NMDs
Depolarization abnormalities	DCM, HCM, NMDs
AV blocks	Laminopathies, Familial AVBs, Anderson Fabry's disease, Sarcoidosis
Ventricular tachycardias	Sarcoidosis, DCM, ALVC, NMD

ECHO: Global and regional LV and RV anatomical abnormalities, myocardial deformation imaging is more accurate in detecting subtle abnormalities in AHA stage A to B, TEE for thrombi, mechanism of mitral regurgitation and planning for interventions, three-dimensional volume rendered images are accurate in diagnosing aneurysms, athlete's heart versus HCM, hypertrabeculation. For pediatric cases, wherever applicable *z*-scores are to be incorporated as there is a lack of normative data (Class I) 2.

Laboratory Investigations

- Level 1: Renal function, LFT, Proteinuria, Complete blood count, troponin, NT-Pro BNP, Ferritin, Iron, Calcium, Phosphate, Thyroid hormone levels, serum free light chain assay, and urine/serum protein immunofixation (only in case of suspected RCM)—Class IC[2]
- Level 2: Viral serology, organ-specific and non-organ-specific investigations, lactic acid, myoglobin, carnitine profile, alpha-galactosidase, thiamine, serum ACE, PTH, free fatty acids—Class II[2]

Holter: Ventricular tachycardias, nonsustained VTs, heart blocks, atrial arrhythmias

MRI: Class I[3]—contrast CMR during the initial evaluation,

ClassIIa[3]—during monitoring for disease progression or risk stratification for SCD, to assess for therapeutic response in cardiac amyloidosis, hemochromatosis, Anderson Fabry disease, sarcoid, and other inflammatory cardiomyopathies, in family screening genotype positive-phenotype negative to aid early detection and diagnosis.

Class IIb—nongenetically mediated cardiomyopathies in phenotype negative family members to aid early detection.

Endomyocardial Biopsy

1. Granulomatous cardiomyopathy showing areas of confluent granulomas in a patient of sarcoidosis who presented with recurrent VT episodes, controlled with AICD, high-dose steroids, and cyclophosphamide.
2. Amyloidosis- features of RCM with acellular subendocardial deposits showing apple-green birefringence under polarized light, Congo red staining positive.
3. Endomyocardial fibroelastosis—history of DCM—fibrotic areas with wavy elastic fibers on WG stain, no myocardial fibers in tissue bit, negative stains for amyloid, granulomas, and malignancy.

Genetic Testing and Counseling

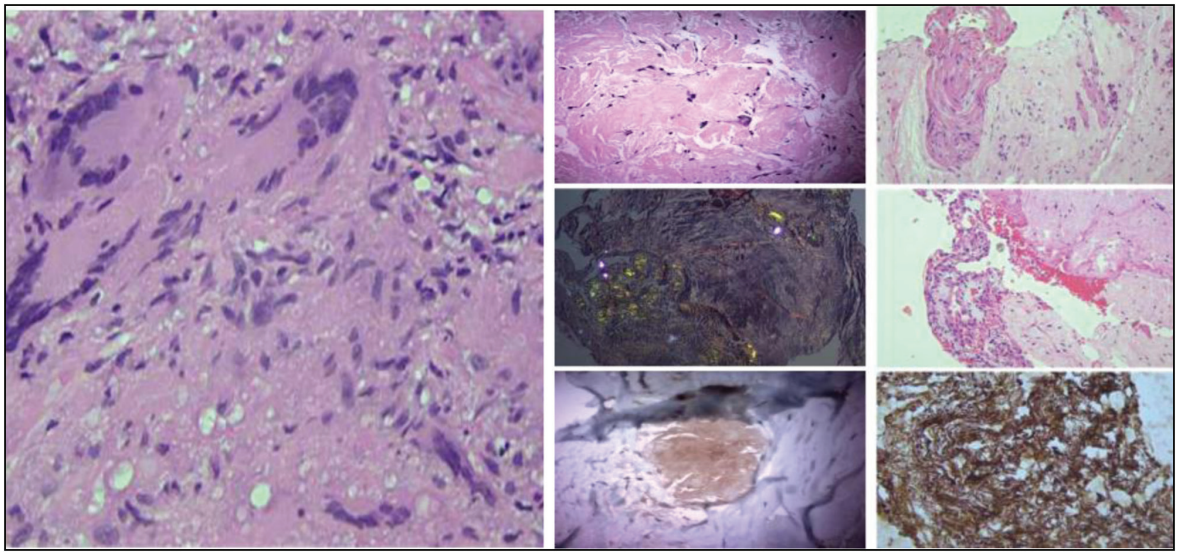
Class I recommendation:[2] Index patients as well as at-risk family members for genetically mediated cardiomyopathy

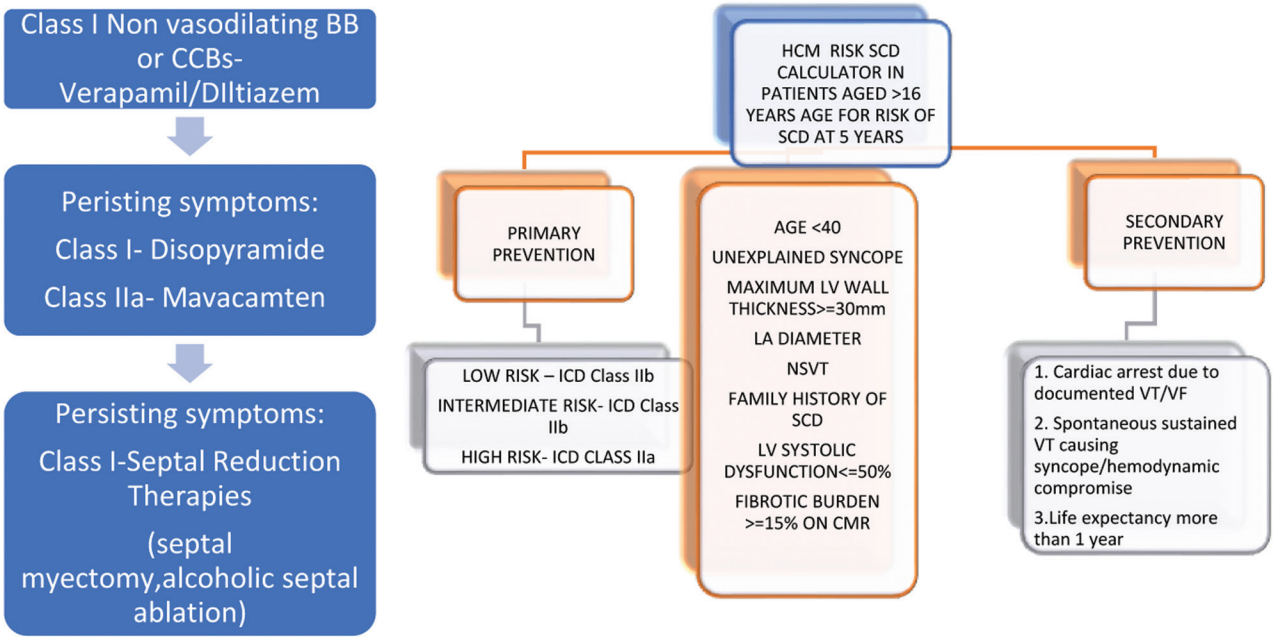
Specific Subtypes

Hypertrophic cardiomyopathy (HCM):-

Diagnostic criteria

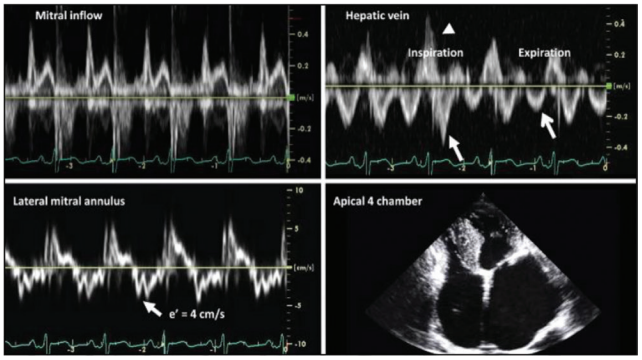
- Adults ≥15mm LV wall thickness in end-diastole, in children 2SD LV wall thickness
- Key elements: maximum provocable LVOT gradient ≥50 mm Hg, systolic anterior motion of the mitral valve, Mitral Regurgitation with a central or anterior jet with LA dilatation, CMR usually shows LV apical and anterolateral hypertrophy, myocardial crypts and papillary muscle abnormalities, LGE is noted in close to 65% patients—patchy mid-wall pattern, degree of myocardial fibrosis points towards adverse LV remodeling





Dilated Cardiomyopathy (DCM)

- LVEDd ≥58 mm in males and ≥52 mm in females, LVEDVi ≥75 mL/m^2 in males and ≥62 mL/m^2 in females/ LV global systolic dysfunction <50%
- Familial DCM by definition is diagnosed if
- (a) Family history of DCM in first or second-degree relative
- (b) History of unexplained sudden cardiac death in a first-degree relative, with an established diagnosis of DCM, regardless of age



The gold standard for diagnosis is the echocardiogram, which reveals features of diastolic dysfunction, normal LV and RV chamber size, increased atrial dimensions, IVC plethora, and early mitral inflow velocity greater than late velocity with a shortened deceleration time.

ICD Recommendations in Patients with DCM/ NDLVC

Cardiac arrest or VT with hemodynamic compromise	LVEF ≤35%	High risk gene	Additional risk factors: (a) Presence of Syncope (b) LGE on cardiac MRI
CLASS I	Class IIa		Class IIb

Restrictive cardiomyopathies (RCM)

- Primary RCM is due to intrinsic myocyte dysfunction (e.g., sarcomeric, cytoskeletal, filamin, and titin gene mutations); Secondary RCM is due to storage diseases (metabolic RCM), endomyocardial disorders like EFE, hypereosinophilia, carcinoid, chloroquine related; infiltrative disorders like amyloid, sarcoid, hyperoxaluria, fibrosis, radiation, and granulomas

Hemodynamic hallmarks

1. A prominent and rapid "y" descent and a "square root sign" maybe present and unlike CP; there will be poor atrial relaxation giving a blunted "x" descent

2. Absence of ventricular respirophasic changes

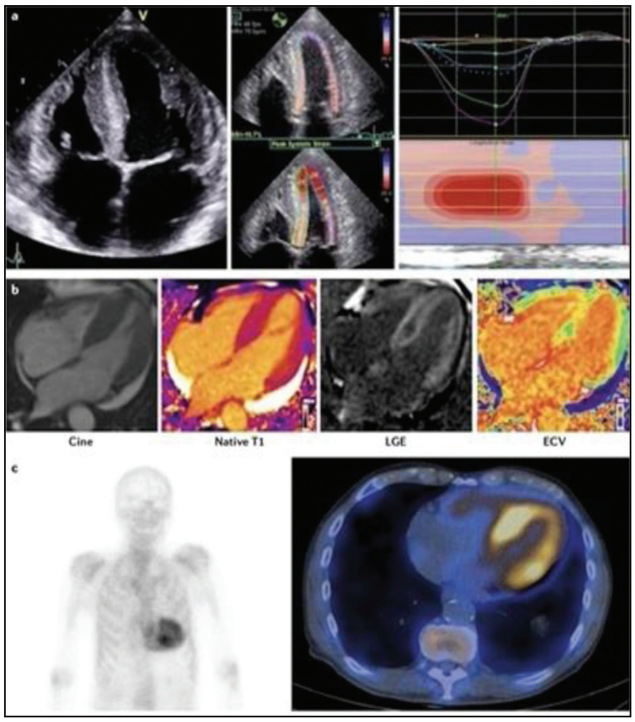
Recommendations for the management of RCM by the ESC include:

- Multimodality imaging: Class IC
- Cardiac catheterization at diagnosis and 6–12 months intervals: Class IB

- Endomyocardial biopsy (to diagnose the type of RCM to aid in management): Class IIA
- ICD implantation is recommended in survivors of cardiac arrest or a history of ventricular arrhythmias with hemodynamic instability: Class IC

Cardiac Amyloidosis

Features specific to amyloidosis are clinical red flag signs, severe biatrial enlargement with a thickened ventricular myocardium, IVC plethora and severely decreased septal and lateral velocities (5-5-5 sign), altered myocardial texture with a granular appearance, a cherry red spot on strain imaging characteristic of apical sparing



- Serum and urine monoclonal assay, serum and urine immunofixation electrophoresis, and serum-free light chains—Class I
- Bone scintigraphy for ATTR in the absence of light chain or monoclonal protein levels—Class I
- Once ATTR is diagnosed to distinguish between hereditary and wild-type variants, gene testing is recommended—Class I
- In select patients with Classes I–III symptoms and ATTRwt, ATTRv; Tafamidis (transthyretin tetramer stabilizer) should be considered—Class I
- In patients with amyloidosis and AF, anticoagulation to reduce stroke events is reasonable irrespective of CHADS2VAS2C score—Class IIa

Peripartum Cardiomyopathy (PPCM)

An idiopathic cardiomyopathy presenting with HF secondary to LV systolic dysfunction ≤45% toward the end of pregnancy or in the months following delivery,[3] where no other cause of heart failure is found. Outcomes vary from complete recovery, or persistent residual LV dysfunction to rapid deterioration in the form of acute decompensation requiring advanced heart failure therapies including MCS and/or transplantation

Arrhythmogenic Cardiomyopathy

- A thinned-out and scarred RV and or LV myocardium having fibrofatty replacement of the cardiac myocytes with a propensity to develop repolarization abnormalities on ECG and episodes of ventricular tachycardia and often profound decompensated HF[4,5]
- Genetic insults usually result from the following mutations: desmoplakin, plakophilin, desmoglein, and desmocollin-2 genes, which are pathogenic in almost 60% of cases
- It can be associated with woolly hair and palmoplantar keratoderma in the characteristic phenotypes, Prognosis is usually poor and may require heart transplantation as definitive therapy
- Beta-blockers in ACM with VE/NSVT/VT Class I indication. Amiodarone and Flecainide—Class IIa (when the above therapy fails to control arrhythmias). In incessant VT, Cath ablation maybe considered (with epicardial pacing facility)—Class IIa

Takotsubo Cardiomyopathy

- Not recognized anymore as a subtype of cardiomyopathy, but rather a phenotypic evidence of transient LV dilatation and systolic dysfunction in menopausal females during periods of stress with LV apical ballooning may involve the mid cavity, and it usually has a characteristic absence of demonstrable obstructive coronary artery disease. It presents with anginal pain and dyspnea with T wave inversions on ECG and enzyme elevations. It usually subsides within few days to weeks.[6,7]

ARRHYTHMIA AND HEART FAILURE

Patients with heart failure are prone to develop both atrial and ventricular arrhythmias. It worsens ventricular function leading to heart failure-related hospitalizations, and increases the risk of sudden cardiac death. Management depends on the type of arrhythmia, the underlying disease functional class, and amenability to catheter ablation. Heart failure may be solely caused by tachyarrhythmias, or more commonly pre-existing ventricular dysfunction is aggravated by arrhythmias.

Arrhythmia Induced Cardiomyopathy

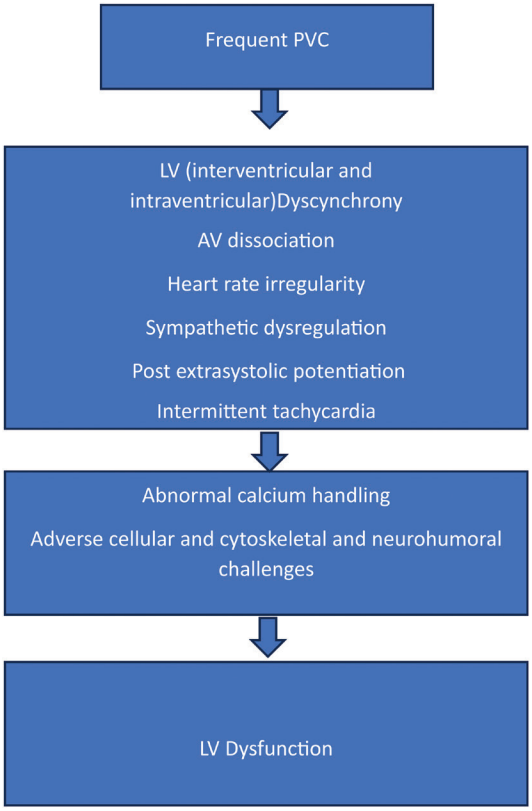
Arrhythmia-induced cardiomyopathy (AiCM) is a form of reversible left ventricular (LV) dysfunction caused by persistent atrial or ventricular arrhythmia. Detection of the significant burden of arrhythmia and reversal of LV dysfunction following elimination of the arrhythmia confirms the arrhythmia as the causative factor for cardiomyopathy.[1]

Common Arrhythmias Causing AiCM

- Atrial Fibrillation with rapid ventricular rate
- Atrial flutter with rapid ventricular rate
- Atrial tachycardia
- Permanent junctional reciprocating tachycardia
- Atrioventricular nodal re-entrant tachycardia (incessant)
- Premature ventricular complexes (PVC)
- Idiopathic ventricular tachycardia

Risk Factors for PVC-Induced Cardiomyopathy

- High burden PVC (cut off −24%)
- Wide QRS (>150 ms)
- Epicardial origin
- Interpolated PVC
- Coupling interval <450 ms
- Absence of symptoms
- Male sex



Treatment

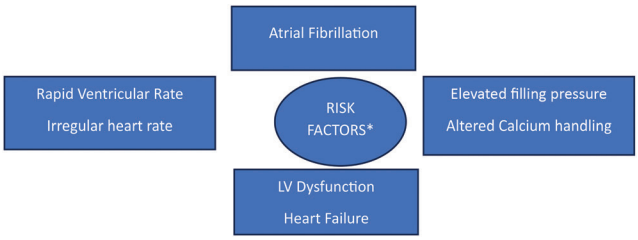
- Routine heart failure medications which include beta blockers
- Aim of the treatment—Reduction in PVC burden by at least 80%[1]
- Antiarrhythmics drugs

Antiarrhythmics drugs have limited efficacy.

- Many of the antiarrhythmics that are effective in reducing the PVC burden like calcium channel blockers cannot be used due to the presence of cardiomyopathy and LV dysfunction.
- Amiodarone is effective in reducing PVC burden and improving LV function.
- Catheter ablation has emerged as a safe alternative to antiarrhythmic drug therapy.
- Successful ablation of PVCs has been shown to frequently restore LV function.
- Radiofrequency catheter ablation is superior to pharmacotherapy in patients with right ventricular outflow tract PVCs.
- Large multicentre outcomes for catheter ablation of idiopathic premature ventricular complexes showed an acute success rate of 84%.[2]
- Normalization of LVEF occurs in more than 80% of the patients with PVC-induced cardiomyopathy following ablation.

Atrial Fibrillation

Atrial fibrillation and heart failure often co-exist and can adversely affect the prognosis of each other. AF can be the cause or consequence of HF and vice versa. AF is seen in 20%–40% of patients with heart failure.[3] The prevalence of AF increases with the severity of heart failure. The presence of atrial fibrillation with a fast ventricular rate can lead to tachycardiomyopathy. On the other hand, AF can occur in the background of heart failure due to several factors which can lead to worsening of heart failure symptoms. It can also lead to suboptimal CRT response due to the due to decrease in the BiV pacing percentage.



Treatment of AF in Heart Failure

The major treatment goal of atrial fibrillation is either rate control or rhythm control and oral anticoagulation.

Earlier studies comparing rate control and rhythm control with antiarrhythmic drugs showed rate control alone would be sufficient to manage AF. However, recent studies have shown the clear advantage of early rhythm control with the ablation strategy.

Recommendations for Management of AF in Heart Failure

- Early and aggressive rhythm control strategy should be pursued in patients with atrial fibrillation and heart failure, especially when AF-induced tachycardiomyopathy is suspected. In suitable patients with atrial fibrillation and HFrEF, catheter ablation might be considered first-line therapy to improve symptoms, quality of life (QOL), ejection fraction, and cardiovascular outcomes. In appropriate patients with symptomatic AF and HFpEF, catheter ablation improves exercise capacity and improve QOL.[4]
- Rhythm control is commonly achieved through pulmonary vein isolation. This can be achieved by radiofrequency ablation, cryoablation or by pulsed field energy.
- In patients with AF with HFrEF (LVEF <50%), atrioventricular nodal ablation with cardiac resynchronization therapy, or conduction system pacing is beneficial in patients in whom the rhythm control strategy has failed or not pursued
- In patients with AF, HF, and cardiac resynchronization therapy in whom maximum BiV pacing could not be achieved with drugs, AV nodal ablation is beneficial
  1. In patients with suspected AF-induced cardiomyopathy or refractory HF symptoms undergoing pharmacological rate-control therapy for AF, a stricter rate-control strategy (target heart rate <80 bpm at rest and <110 bpm during moderate exercise) may be reasonable.[4]
  2. In patients with AF and HFrEF who undergo AVNA, conduction system pacing of the His bundle or left bundle branch area may be reasonable as an alternative to biventricular pacing to improve symptoms, QOL, and LV function.

Ventricular Tachycardia and Heart Failure

- The presence and severity of VT are usually proportionate to the heart failure severity.
- Larger infarcts with reduced LVEF are more likely to be associated with VT.
- VT in heart failure patients may present either with sudden cardiac arrest or with palpitations, syncope, chest pain, or ICD shocks. Slow VT often leads to under-detection and may present with worsening heart failure symptoms
- Both non-sustained VT (<30 s) and sustained VT (>30 s) in patients with HF lead to significant morbidity and mortality.
- VT storm (three or more distinct episodes of VT or VF requiring intervention, in patients with ICD, three or more appropriate interventions such as ICD shock or ATP within 24 h) can occur in HF patients. Recurrent ICD (anti-tachycardia pacing) shocks are an independent predictor of mortality.[5]

Management of VT in Heart Failure

- Hemodynamically Stable VT is usually managed by antiarrhythmic drugs. Intravenous amiodarone is the most effective drug in this setting.
- In hemodynamically unstable VT, immediate DC cardioversion should be carried out.
- Slow VT (<150 bpm) may go undetected and cause hemodynamic instability and close monitoring of slow VT is necessary.
- Any patient who presents with VT should be evaluated for correctable causes (e.g., dyselectrolytemia and ischemia).
- Serum Potassium and magnesium should be kept above 4 and 2 mEq/L, respectively.
- Guideline-directed medical therapy including optimal device therapy ICD or CRT-D is recommended for secondary prevention.[6]
- Radiofrequency ablation is the therapeutic option for patients who have recurrence despite adequate antiarrhythmic drugs
- Autonomic modulation like surgical cardiac sympathetic denervation and renal denervation can be utilized to reduce VT reoccurrences.[7,8]

CARDIAC RHYTHM MANAGEMENT DEVICES IN HEART PRACTICE GUIDELINES

Severe LV dysfunction can lead to heart failure symptoms and also sudden death. It has been seen that the mechanism of sudden death is generally malignant ventricular arrhythmias. Devices have been used to improve left ventricular function, and also prevent sudden death for the last three decades and a lot of work has been done in this field leading to guidelines on the appropriate use of these devices which are mainly—CRT which is cardiac resynchronization device or implantable cardioverter-defibrillator (ICD), which is implantable cardioverter defibrillator.

Let's look at clinical scenarios and the use of these patients.

Case 1: A 65 years old diabetic presented with symptoms of breathlessness on minimal exertion for 6 months and her LVEF was 30%, with NT-pro-BNP levels of 2080, the patient had received GDMT using BBARNI, SGLT2 inhibitors, and MRA inhibitors but was still symptomatic. The ECG of this patient is depicted in Figure 4.1.

The ECG shows sinus rhythm and broad QRS with a QRS duration of 160 ms and LBBB. The criteria used for diagnosis of LBBB is Strauss's criteria which is

Evidence of LV conduction delay; QS or rS (in V1 and V2) and QRS duration ≥140 ms (males) or ≥130 ms (females), and specific evidence of LBBB with mid-QRS notch or slur in two or more of the following leads: V1, V2, V5, V6, I, and aVL. This provides the best evidence for a good response to CRT therapy.

This patient underwent CRT with leads placed in lateral LV through the coronary sinus, an RV lead, and a lead in RA this resulted in QRS narrowing and led to improvement in symptoms and improvement in LVEF Figure 4.2.

This is biventricular pacing which leads to QRS normalization and LBBB correction. The mortality reduction and improvement in Quality of life are well documented.

The ESC guidelines 2023 suggest CRT should be considered for symptomatic patients with HF in sinus rhythm with LVEF ≤35%, QRS duration 130 and above, and LBBB QRS morphology. CRT should be considered for patients with HF in sinus rhythm with LVEF ≤35%, QRS duration ≥150 ms, and non-LBBB QRS morphology.

Case 2: A 58-year-old man with a history of past anterior MI and stent to LAD 5 years back has LVEF of 30% and breathlessness on exertion class 2. He has received the best medical treatment and EF is still 30%. These are patients who are at risk of sudden cardiac death and ICD device implantation has shown to reduce mortality. The views from recent ESC guidelines are: ICD implantation is recommended in patients with documented VF or hemodynamically not-tolerated VT in the absence of reversible causes. This is called secondary prevention.

Current guidelines recommend an ICD for prevention of sudden death in patients with HF and reduced ejection fraction (HFrEF) specifically those with a left ventricular ejection fraction ≤35% after at least 3 months of optimized HF treatment. This recommendation is more than non-ischemic LV dysfunction.

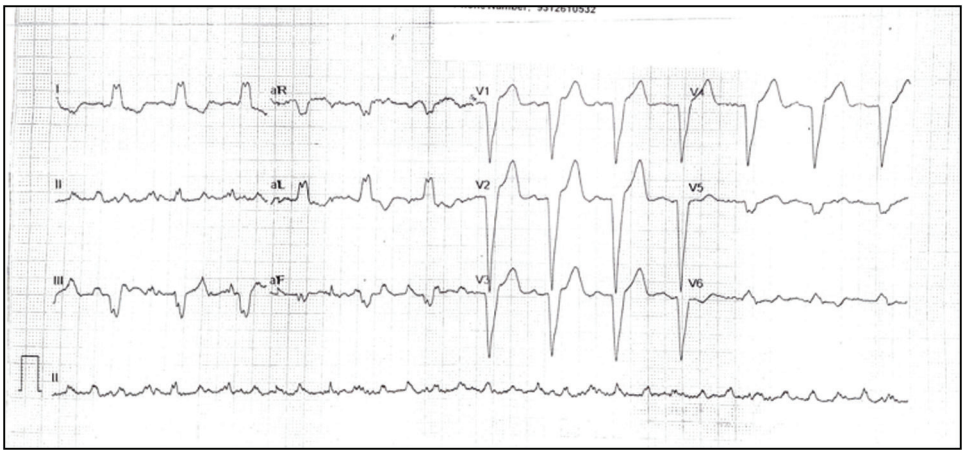


Figure 4.1: ECG of a patient aged 65 years

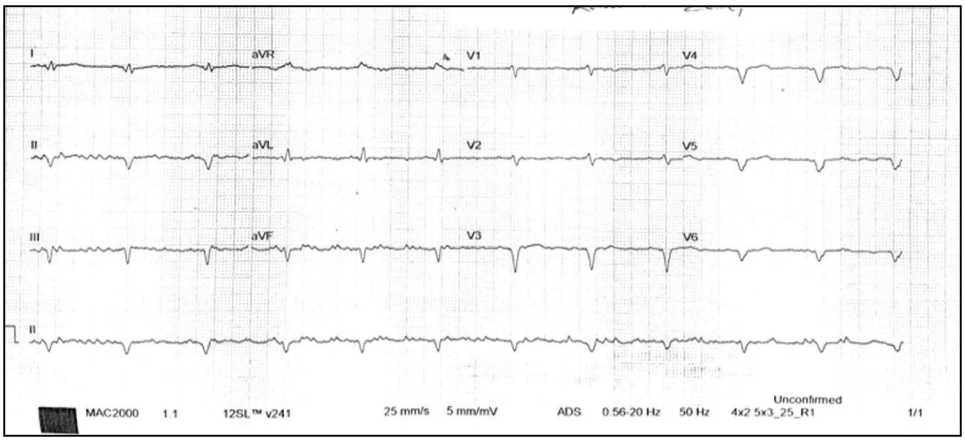


Figure 4.2: ECG of the patient who underwent CRT

GUIDELINES FOR ACUTE HEART FAILURE AND CARDIOGENIC SHOCK

Acute heart failure (AHF) refers to the rapid onset/worsening of heart failure symptoms and signs forcing the patient to seek urgent medical care. It can occur de novo, as initial presentation, or as acute decompensated heart failure in a previously diagnosed heart failure patient.[1]

Management of AHF

The central issue for most AHF patients is lung congestion, which may occur gradually due to salt and water retention, or more acutely due to redistribution of fluid to lungs. Loop diuretics remain the cornerstone of treatment. In general, most patients will require twice their regular oral daily dose [Figure 5.1].[3]

Apart from congestion, elevations of left and right-sided filling pressures must also be managed. In the absence of hypoperfusion and hypotension, vasodilators may be used with strict blood pressure monitoring.[4] Most patients have elevated blood pressure at presentation due to anxiety and sympathetic overactivity and may become hypotensive after initial management.

Starting/continuation and optimization of guideline-directed medical treatment (GDMT)—GDMT continuation during AHF hospitalization lowers the risk of death after discharge and re-hospitalization.[5] If due to hypotension or severe lung congestion, GDMT must be stopped, it should be started and optimized as soon as clinically feasible. In newly diagnosed AHF patients, GDMT should be started in-hospital soon after stabilization. Which drug to be introduced first depends on the patient's clinical profile (blood pressure, heart rate, lung congestion status, renal function, and potassium).

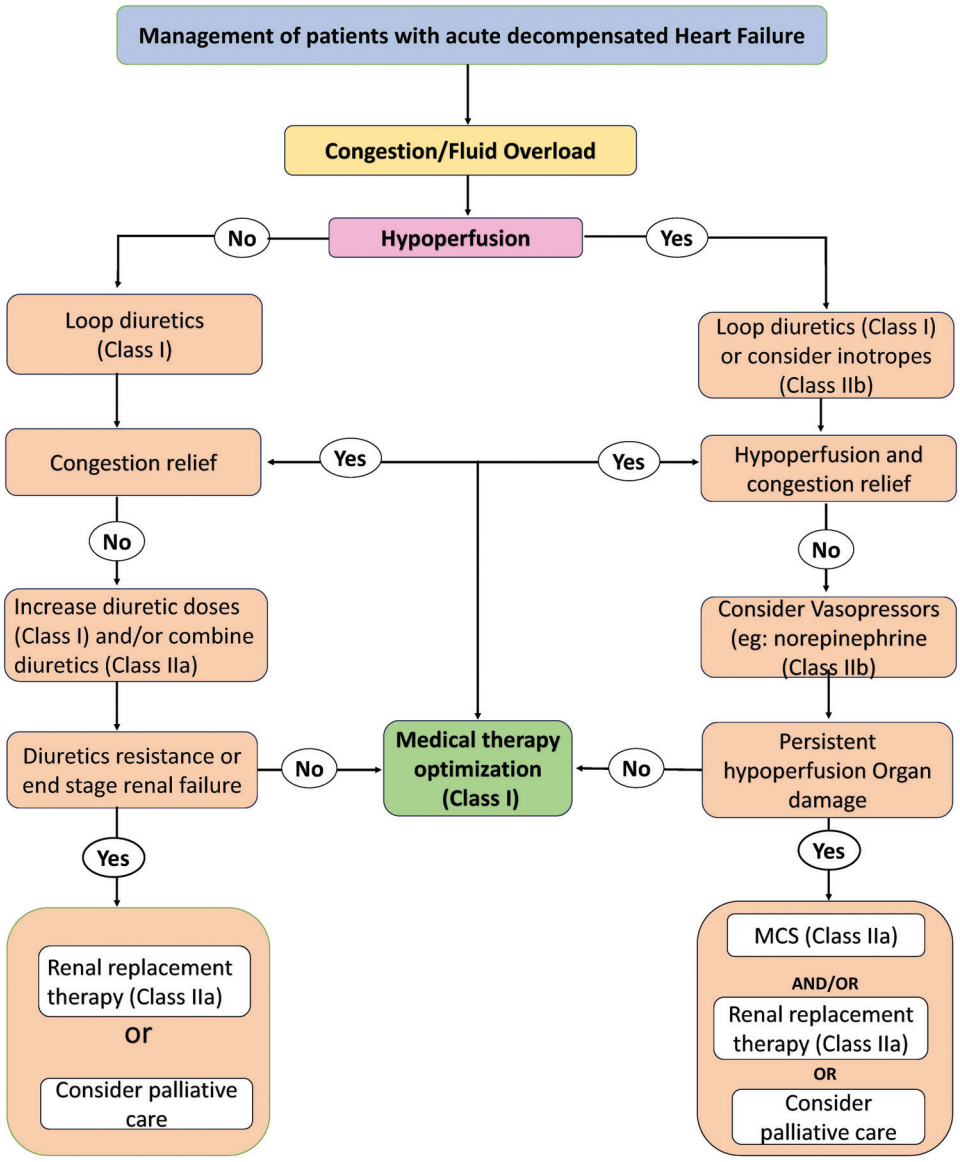


Figure 5.1: Management of patients with acute decompensated heart failure

Table 1: Commonly used inotropes and vasopressors in AHF[6]

Inotropic Agent	Dose (mcg/kg)		Effects				Special Considerations
	Infusion (/min)	Drug Kinetics and metabolism	CO	HR	SVR	PVR	
Adrenergic agonists							
Dopamine	5–10	$t_{1/2}$: 2–20 min	↑	↑	↔	↔	Caution: MAO-I
	10–15		↑	↑	↑	↔	
Dobutamine	2.5–20	$t_{1/2}$: 2–3 min	↑	↑	↔	↔	Caution: MAO-I; CI sulfite allergy
PDE 3 Inhibitor							
Milrinone	0.125–0.75	$t_{1/2}$: 2.5 h	↑	↑	↓	↓	Accumulation may occur in setting of renal failure; monitor kidney function and LFTs
Vasopressors							
Epinephrine	5–15 mcg/min	$t_{1/2}$: 2–3 min	↑	↑	↑	↔	Caution: MAO-I
	15–20 mcg/min	$t_{1/2}$: 2–3 min	↑	↑↑	↑↑	↔	Caution: MAO-I
Norepinephrine	0.5–30 mcg/min	$t_{1/2}$: 2.5 min	↔	↑	↑↑	↔	Caution: MAO-I

CO = cardiac output, HR = heart rate, SVR = systemic vascular resistance, PVR = pulmonary vascular resistance, MAO-I = monoamine oxidase inhibitor, LFT = liver function test

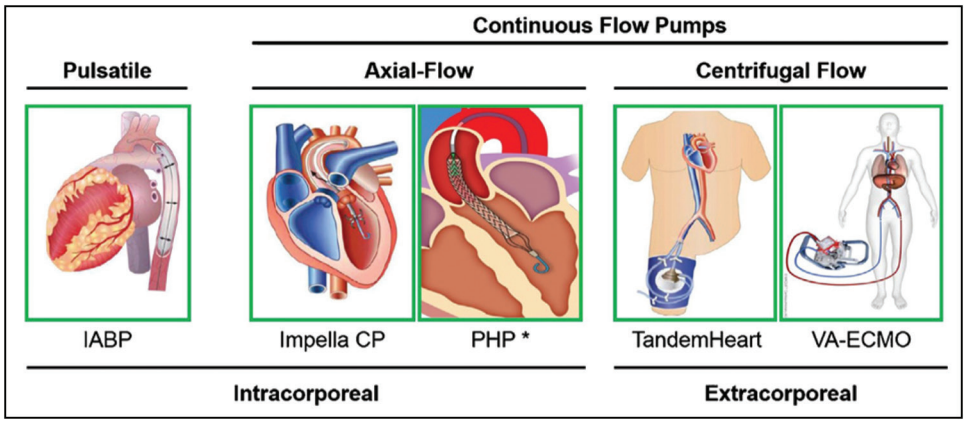


Figure 5.2: Short-term mechanical circulatory support for left ventricular support[8]

However, the aim should be to bring all four pillars (ARNI/ACE/ARB, B blocker, MRA, and SGLT-2i) on board quickly unless contraindicated.

Factors precipitating ADHF episode

Cardiac	Acute coronary syndrome
	Cardiac arrhythmias such as atrial fibrillation, ventricular tachycardia
	Hypertensive emergency
	Additional cardiac diseases like endocarditis
Non Cardiac	Acute infections like pneumonia, urinary tract infections
	Anemia
	Hyper or hypothyroidism
Drug-related	Medications increasing sodium and fluid retention like nonsteroidal anti-inflammatory drugs, steroids
	Medications with a negative inotropic effect like verapamil
	Non-compliance with medication regimen

Management of Cardiogenic Shock (CS)

CS is a life-threatening condition resulting from severe reduction of cardiac output leading to critical tissue hypoperfusion and end-organ dysfunction. It is typically characterized by hypotension (systolic blood pressure <90 mm Hg, or requiring vasopressors to maintain blood pressure) and evidence of hypoperfusion such as decreased mentation, cold clammy extremities, urine output <30 mL/h and lactate >2 mmol/L.

The most common cause of CS is ischemia. Mechanical complications of myocardial infarction, advanced heart failure, valvular heart disease, myocarditis, cardiomyopathies, and pericardial diseases are other important causes [Table 1].

Though inotropes (Table 1) may be are necessary to maintain BP, they increase myocardial oxygen demand and are arrhythmogenic leading to poor cardiac recovery and even higher mortality. Long term inotrope therapy is not recommended. Short-term mechanical circulatory support (MCS) devices have been shown to improve outcomes in some studies.[7] Continuous hemodynamic monitoring with a pulmonary artery catheter helps choose a device and guide the management of these patients [Figures 5.2 and 5.3].

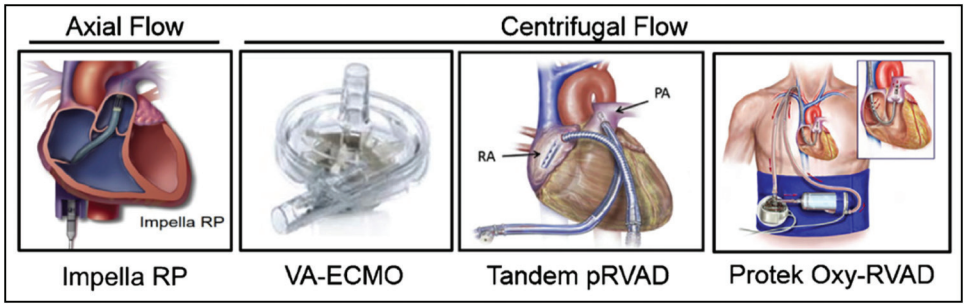


Figure 5.3: Short-term MCS for right ventricular support[8]

ADVANCED HF: INCLUDING MECHANICAL CIRCULATORY SUPPORT AND CARDIAC TRANSPLANTATION

Indications and contra-indications for Durable Mechanical Circulatory Support Devices (DMCS) have the following recommendations [Table 1]

Table 1: Recommendations of Indications and contra-indications for Durable Mechanical Circulatory Support Devices (DMCS)

Types of bridging therapy with DMCS	Recommendation	Evidence
Durable Mechanical Circulatory Support used as •Bridge to transplant *or* •Bridge to candidacy *or* •Destination therapy (*if ineligible for transplant*) should be considered in Patients with: •advanced HF symptoms (NYHA class IIIB-IV) •refractory to maximal medical management, •inotrope dependent or •on temporary circulatory support,	Class I	A
Durable Mechanical Circulatory Support used as •Bridge to recovery To be considered in patients with: •recent-onset dilated cardiomyopathy, •nonischemic etiology, and •refractory to maximal medical therapy *Pharmacological treatment should be with maximally tolerated neurohormonal modulation and surveillance for recovery of left ventricular function should be undertaken.*	Class IIA	B
To consider DMCS in patients with irreversible multi-organ failure is NOT recommended.	Class III	C

Source

Saeed D, Feldman D, Banayosy AE, Birks E, Blume E, Cowger J, *et al*. The 2023 International Society for Heart and Lung Transplantation Guidelines for Mechanical Circulatory Support: A 10-Year Update. The Journal of Heart and Lung Transplantation. 2023 Jul;42(7):e1–222.

Indications and Contraindications for Heart Transplantation

Absolute Indications in Appropriate Patients:

- For hemodynamic compromise due to HF

Refractory cardiogenic shock.

Documented dependence on intravenous inotropic support to maintain adequate organ perfusion.

Peak VO2 less than 10 mL/kg/min with achievement of anaerobic metabolism.

- Severe ischaemic symptoms that limit activity & are not amenable to CABG or PCI
- Recurrent symptomatic ventricular arrhythmias refractory to all therapeutic modalities

Relative indications

- Peak VO2 11–14 mL/kg/min (or 55% predicted) and major limitation of the patient's daily activities.
- Recurrent unstable ischemia not amenable to other interventions
- Recurrent instability of fluid balance/renal function not due to patient noncompliance with medical regimen

Insufficient indications

- Low left ventricular ejection fraction
- History of functional class III or IV symptoms of HF
- Peak VO2 greater than 15 mL/kg/min (and greater than 55% predicted) without other indications.

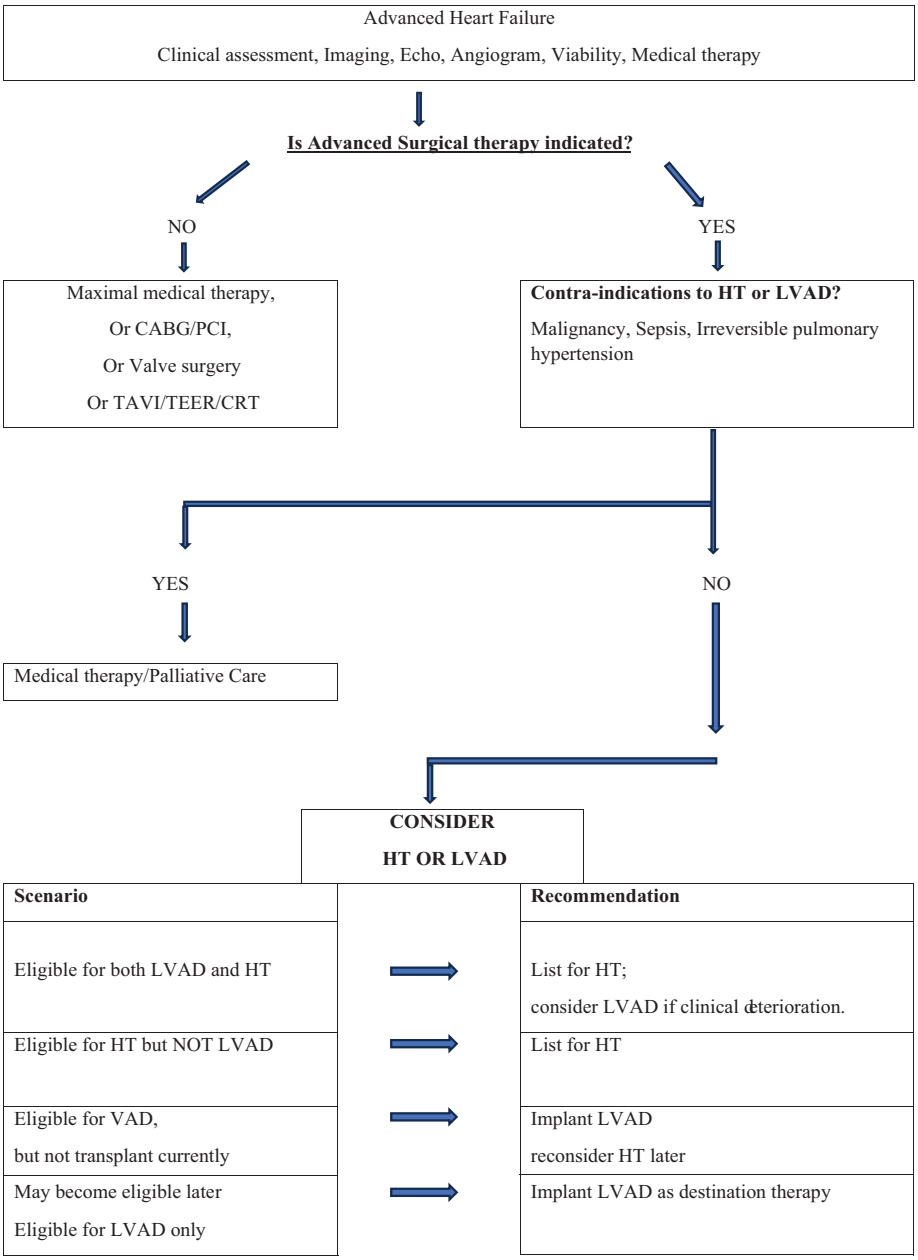
Contra-indications for Heart Transplantation

- Active current malignancy
- Active sepsis
- Irreversible pulmonary hypertension, renal, or liver failure (unless multi-organ transplantation is possible)

Source

Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, *et al*. 2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults. Journal of the American College of Cardiology. 2009 Apr;53(15):e1–90.

Decision-Making Process for Advanced Surgical Therapy for Heart Failure



Source

Guglin M, Zucker MJ, Borlaug BA, Breen E, Cleveland J, Johnson MR, *et al*. Evaluation for Heart Transplantation and LVAD Implantation. Journal of the American College of Cardiolo. gy. 2020 Mar;75(12):1471–87.

ELECTROLYTE DISTURBANCES AND MANAGEMENT IN HEART FAILURE

The common electrolyte disturbances in HF include hyponatremia, hypokalaemia, hyperkalemia and hypomagnesemia. Neurohormonal activation, renal dysfunction, and drug therapy are the important causes of electrolyte imbalance in heart failure (HF) patients.

Hyponatremia

HF patients have elevated antidiuretic hormone (ADH) levels. ADH increases water reabsorption from the collecting tubules. In addition, raised angiotensin II levels increase thirst resulting in increased water intake and neurohormonal activation decreases the glomerular filtration rate reducing water excretion. Thus, HF is associated with dilutional hyponatremia.

Hyponatremia occurs in HFrEF as well as HFpEF and correlates with the severity of HF.[1]

Clinical Manifestations

These are typically neurological and include tiredness, nausea, vomiting, giddiness, confusion, forgetfulness, and gait disturbances. Hyponatremia increases the risk of falls and hence fractures especially in the elderly. Seizures may occur in severe hyponatremia.

Hyponatremia is defined as serum sodium ≤135 mEq/L. In chronic hyponatremia, symptoms typically occur with serum sodium levels <120 mEq/L. Patients with sodium levels of 120-130 mEq/L may be asymptomatic or have more subtle manifestations.

Hyponatremia has prognostic implications and is associated with higher mortality in ambulatory as well as hospitalized HF patients. Even mild hyponatremia is associated with increased mortality.

Management

Symptomatic patients or those with serum sodium below <120 mEq/L should be treated.[2] Treatment of hyponatremia does not improve clinical outcomes in HF patients [Figure 6.1].

Hypokalemia

Hypokalemia is associated with a risk of life-threatening ventricular arrhythmias and increased cardiovascular mortality. Common causes of hypokalemia in HF patients are loop diuretic or thiazide use, reduced K^+ intake, vomiting or diarrhea, laxative abuse, and hypomagnesemia.[1] Thiazide diuretics produce more hypokalemia as compared to loop diuretics.

Clinical Manifestations

Most patients are asymptomatic. Symptoms appear once serum potassium levels fall below 3.0 mEq/L. These are usually non-specific including tiredness, muscle weakness, bloating, anorexia, nausea, and vomiting. Severe hypokalemia can result in respiratory muscle weakness and cardiac arrhythmias. Patients with myocardial infarction, long QT syndrome, and those on digoxin therapy have a higher risk of arrhythmias in the setting of hypokalemia.

ECG Changes

ST segment depression, reduced T wave amplitude, increased U wave amplitude and prolonged QT interval may be seen.

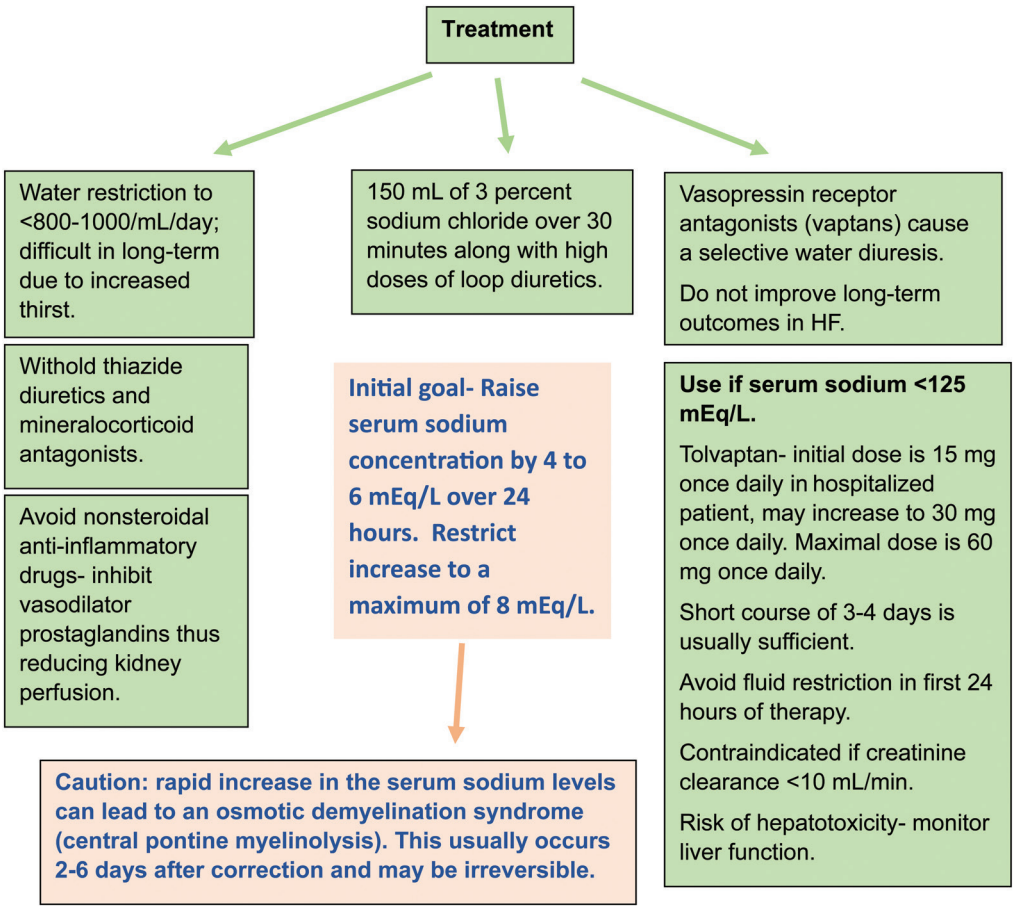


Figure 6.1: Treatment of hyponatremia.

Arrhythmias in patients with hypokalemia include premature atrial beats, ventricular ectopics, and sinus bradycardia. Atrioventricular blocks and ventricular tachycardia or fibrillation may be seen in patients with severe hypokalemia.

Hypomagnesemia in HF patients is commonly due to diuretic use, chronic diarrhea, proton pump inhibitor therapy, and alcoholism. Hypomagnesemia also predisposes to ventricular arrhythmias. Hypomagnesemia may result in refractory hypokalemia and Mg^{2+} levels should be measured in patients with hypokalemia.[2] Normal serum Mg^{2+} levels are 1.7–2.3 mg/dL. Oral repletion is preferable in a dose of 240–1000 mg of elemental magnesium per day. Intravenous magnesium may be used in patients with arrhythmias or those unable to tolerate oral therapy. Intravenous dose typically is 1–2 g of magnesium sulfate (8–6 mEq) given slowly over 2 to 15 min [Figure 6.2].

Hyperkalemia

Hyperkalemia is often multifactorial in HF patients. The most important causes are drug therapy and renal dysfunction.[1] Aldosterone receptor blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and neprilysin inhibitors are the most commonly implicated drugs.

Hyperkalemia is defined as serum K^+ >5 mEq/L.

Clinical Manifestations

Patients with hyperkalemia are usually asymptomatic. Severe hyperkalemia may cause muscle weakness, cardiac conduction defects, and arrhythmias. Severe hyperkalemia may result in sudden death.

ECG

The initial finding is usually T-wave tenting. The T waves are tall, narrow, and pinched. In addition, QT interval shortening, ST-segment elevation, atrioventricular and intraventricular conduction defects, and P wave disappearance. Arrhythmias include sinus bradycardia, idioventricular rhythm, asystole, ventricular tachycardia, and ventricular fibrillation. Appearance of sine waves is an emergency and indicates an impending risk of sudden death by ventricular standstill or fibrillation.

Management

Avoid starting renin-angiotensin-aldosterone system blockers when serum K^+ is more than 5 mEq/L.[2] Since hyperkalemia is more common in patients with renal dysfunction, drugs that increase serum K^+ levels should be avoided in individuals with serum creatinine >2.5 mg/dL [Figure 6.3].[3]

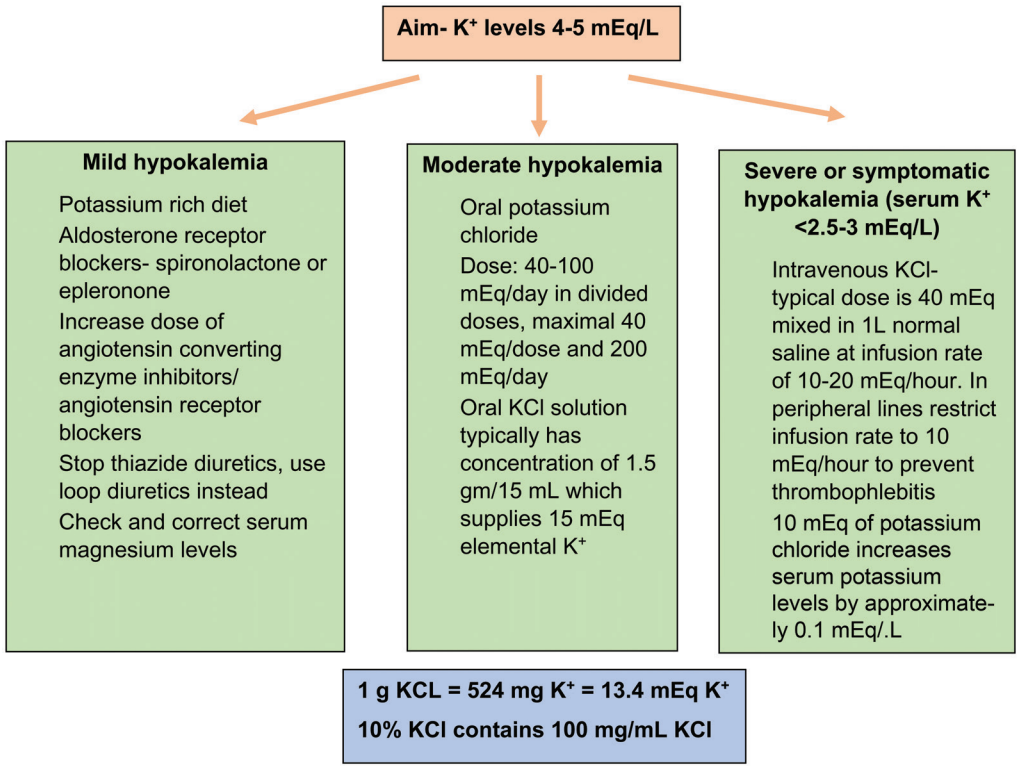


Figure 6.2: Treatment of hypokalemia

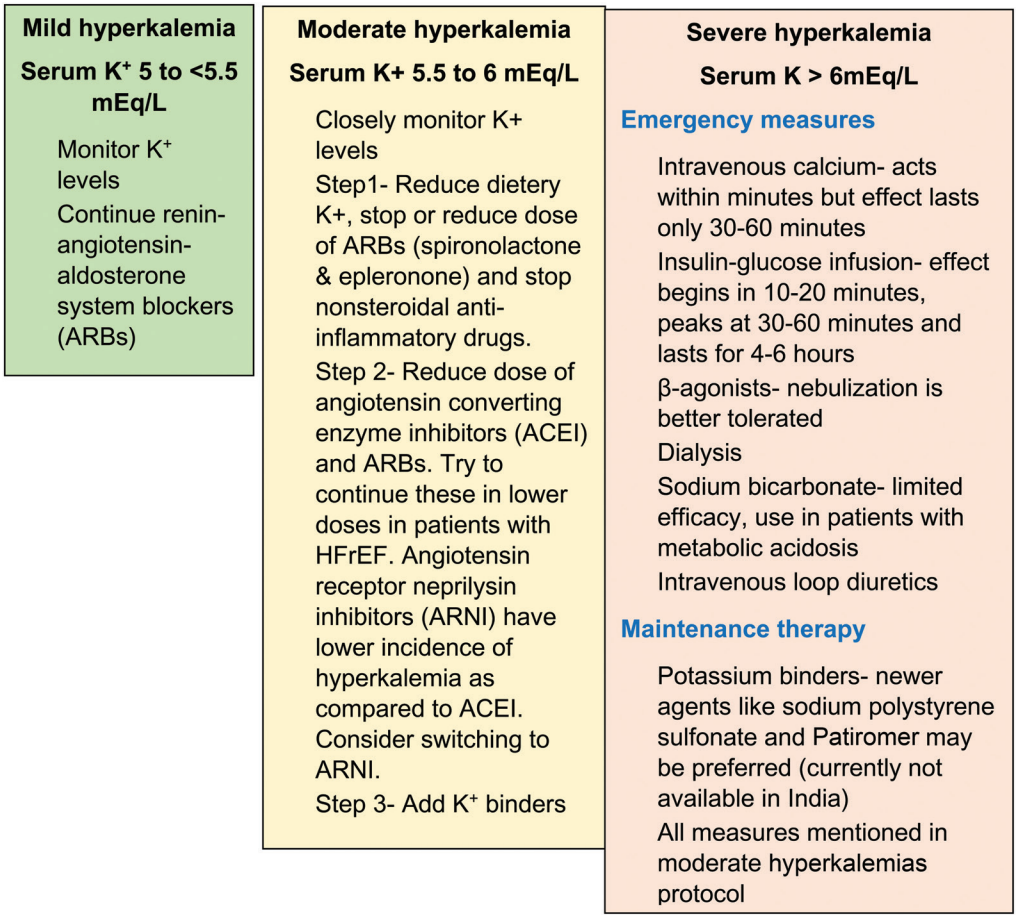


Figure 6.3: Treatment of hyperkalemia

HEART FAILURE AND CHRONIC KIDNEY DISEASE

Introduction

- Chronic kidney disease (CKD) and heart failure (HF) often coexist, sharing common risk factors.
- Almost 50% of individuals with HF experience some level of renal impairment, which independently predicts mortality in this patient population.[1]
- HF is prevalent in 17%–50% of CKD patients, emerging as a primary cause of hospitalization, morbidity, and mortality among them.[2]

The Pathophysiological Complexity

- The reciprocal mechanisms governing organ injury and dysfunction in individuals with both CKD and HF exhibit substantial bidirectionality and overlap.
- Within CKD patients, the initiation of HF is facilitated through hemodynamic pathways, including prolonged hypertension, arterial stiffness resulting in excessive afterload, and salt-water retention causing elevated preload.
- CKD-specific non-hemodynamic factors, such as neurohormonal activation, an abundance of reactive oxygen species, pro-inflammatory cytokines, profibrotic elements, impaired iron utilization, anemia, vitamin D deficiency, and retained uremic toxins, further contribute to the progression of HF.
- HF worsens the progression of CKD through neurohormonal and inflammatory activation, renal hypoperfusion due to low cardiac output, and renal congestion resulting from heightened cardiac pressures and preload.
- Recent findings also suggest that the failing heart releases increased levels of cardiokines, including cardiotrophin 1 (CT-1), directly inducing renal fibrosis and dysfunction.

Issues

Diagnosing HF-related congestion in CKD patients

- Various markers are utilized to detect HF in CKD patients, yet the diagnostic precision of plasma B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) decreases when the eGFR falls below 60 mL/min. Notably, the use of NT-proBNP for HF testing is discouraged, especially in individuals undergoing dialysis. Regarding BNP, its metabolism is not reliant on the kidneys, and some authors employ a cutoff of 200

to rule out HF in CKD cases, as its diagnostic accuracy is less influenced by renal dysfunction.[3,4]

- The Chronic Renal Insufficiency Cohort (CRIC) Study illustrated that in CKD patients, elevated levels of NT-proBNP, high-sensitivity troponin T (hsTnT), growth differentiation factor-15 (GDF-15), and soluble suppression of tumorigenicity-2 (sST2) were associated with incident HF. The correlation was more pronounced for NT-proBNP and hsTnT in heart failure with HFrEF and for GDF-15 and sST2 in heart failure with HFpEF.[5]

Management Challenges of HF in CKD

- Patients with varying renal function often experience multiple hospital visits and discontinue guideline-directed medical therapy due to the need for referrals between nephrologists and cardiologists.
- The establishment of multidisciplinary cardiology and renal clinics is needed.[5]
- CKD patients may receive inadequate treatment, given their increased vulnerability to the renal and metabolic impacts of various HF therapies.
- In the last two decades, a considerable portion of cardiovascular trials excluded patients with renal dysfunction, particularly those in CKD stages 4 and 5. Recent trials adopted lower cut-off values for inclusion, such as 25 mL/min/1.73 m^2 in DAPA-CKD, 20 mL/min/1.73 m^2 in EMPEROR-Reduced and GALACTIC-HF, and 15 mL/min/1.73 m^2 in VICTORIA. Despite baseline differences, subgroup analyses of these trials indicated no association between renal function and drug effects [Figure 7.1].[6-8]

Management of HF in CKD

Table 1 provides an overview of the HF management in CKD.

Managing Congestion in HF and CKD

- While diuretics are commonly prescribed, an excessive dose can lead to intravascular volume depletion, potentially exacerbating pre-renal insults in CKD.
- Diuretic resistance, characterized by the inability to alleviate congestion despite intensive diuretic use, nephron blockade, and sodium restriction, is more prevalent in advanced CKD patients than those with normal kidney function.
- Two alternative approaches in such cases are: ultrafiltration and peritoneal dialysis can be tried.

Renal Replacement Therapy in Heart Failure Patients

Patients with ESRD and HF are preferably treated with PD over extracorporeal hemodialysis (HD) due to several advantages:

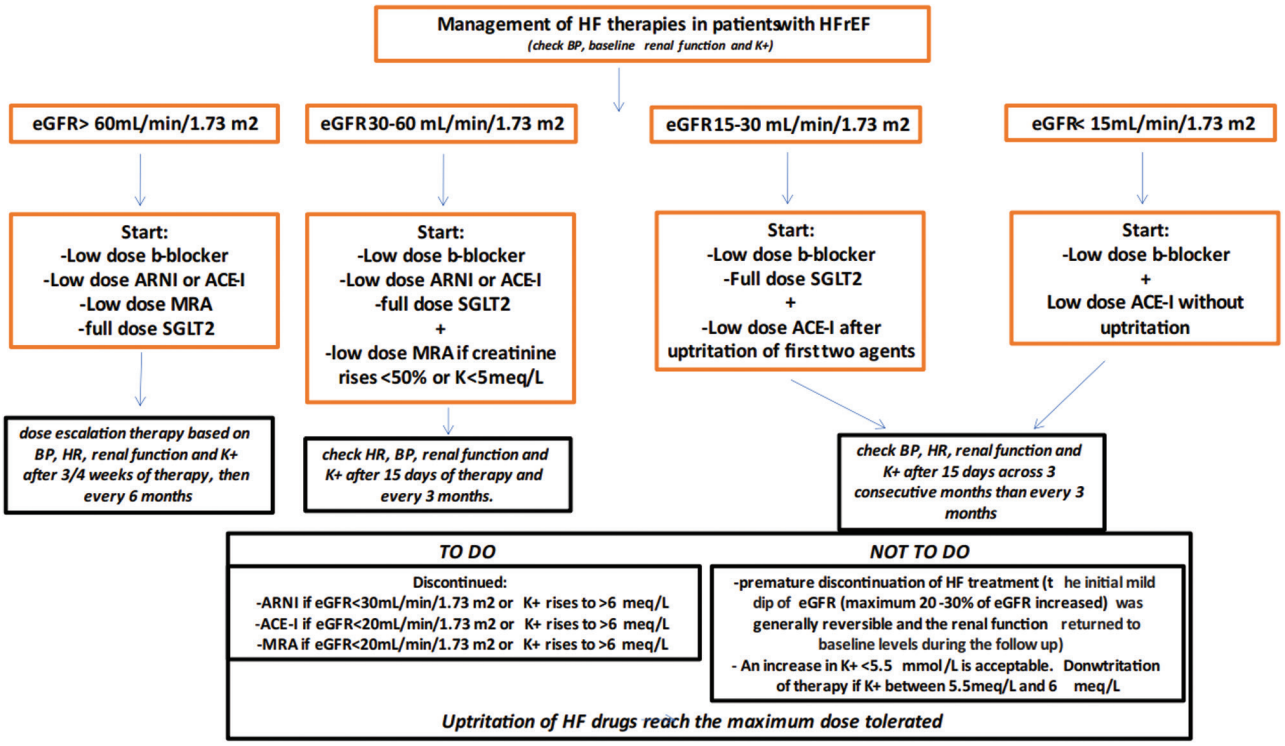


Figure 7.1: Heart Failure therapy according to renal dysfunction severity[9]

Table 1: Comprehensive overview of evidence-based HF management in CKD

Drug	Recommendation and Evidence
Diuretics	Evidence indicates that diuretics offer symptomatic relief across all EF ranges, but CKD patients may require higher doses, leading to transient worsening renal function, electrolyte imbalances, and diuretic resistance.
Beta-blockers	Subgroup analysis from trials like MERIT-HF and CIBIS-II supports beta-blocker use in HFrEF patients with CKD Stages 1–3. However, there is limited evidence for advanced CKD, with recent meta-analyses lacking sufficient data.
ACEis/ARBs	Large RCTs like SAVE, CONSENSUS, SOLVD (ACEi), and CHARM, VALHEFT (ARB) establish the benefits of RAAS inhibitors in HFrEF patients with CKD Stages 1–3, but advanced CKD patients were excluded from these trials.
ARNI	The PARADIGM-HF study demonstrates ARNI (Sacubitril/valsartan) superiority over enalapril in HFrEF, excluding patients with eGFR <30 mL/min/1.73 m^2. ARNIs show slower eGFR decline and reduced hyperkalemia compared with ACEi or ARBs.
Mineralocorticoid Receptor Antagonists	The Finearts trial (Solomon *et al*. DOI: 10.1056/NEJMoa2407107) has shown that above an eGFR of > 25mL/min/1.73m2, in patients with heart failure with mildly reduced or preserved ejection fraction, finerenone significantly reduced worsening heart failure events and death from cardiovascular causes compared to placebo. So Finerenone can be considered in such situations.
SGLT2 inhibitors	DAPA-HF and EMPEROR-Reduced trials show the efficacy and renal safety of dapagliflozin and empagliflozin in HFrEF patients with varying CKD stages (excluded patients with eGFR <30 mL/min/1.73 m^2 or rapidly declining renal function in DAPA-HF trial and included patients with an eGFR as low as 20 mL/min/1.73 m^2 in EMPEROR trial), with significant reductions in HF events and improved renal outcomes.
IV Iron	Recommended for symptomatic HF patients with EF <50% and iron deficiency, as well as CKD patients with anemia not on erythropoiesis-stimulating agents (ESAs) therapy and transferrin saturation <30% and ferritin <500 µg/L (as per the KDIGO 2012 guidelines).
Vericiguat	Studies on vericiguat, which included CKD patients across the full range of eGFR ≥15 mL/min/1.73 m^2 (without dialysis), show similar renal function trajectories and consistent efficacy between vericiguat- and placebo-treated patients.[13]
Hydralazine and Isosorbide dinitrate	This combination offers mortality and morbidity benefits, especially in African–American patients with HFrEF unable to use RAAS inhibitors.
Potassium binders	Ongoing investigations, like the LIFT study, explore the utility of potassium binders to manage hyperkalemia associated with RAAS inhibition.
Ivabradine	The SHIFT-HF study supports ivabradine's efficacy in stable HFrEF, but evidence is lacking for its safety and efficacy in CKD stages four to five patients.

- PD induces lower intra-dialytic hemodynamic shifts. It exerts less pressure on the myocardium, resulting in reduced periods of myocardial ischemia. PD patients demonstrate a superior response to diuretic therapy and experience a slower decline in kidney function. HD patients may face HF risks due to vascular access, with high arteriovenous fistula flow linked to left ventricular hypertrophy, dilation, reduced ejection fraction, pulmonary hypertension, and right ventricular dysfunction. Arteriovenous fistulas in HD act as left-to-right extracardiac shunts, substantially increasing cardiac workload and leading to a high-output state and HF over time.

Device Therapy

Wireless devices present a promising approach to address challenges related to vascular access in chronic kidney disease (CKD) patients:[10-12]

- Subcutaneous ICDs (S-ICD), exemplified by the EMBLEM from Boston Scientific, offer a viable alternative to transvenous ICDs. Leadless pacemakers, including the Micra device by Medtronic, provide an innovative solution for patients with CKD, eliminating the need for traditional transvenous leads. In the realm of cardiac resynchronization therapy, the WiSE (Wireless Stimulation Endocardially) CRT emerges as a cutting-edge technology, delivering wireless left ventricular endocardial pacing as a substitute for conventional epicardial left ventricular pacing.

DIABETES MELLITUS AND HEART FAILURE

Introduction

Diabetes and heart failure (HF) frequently coexist, with each condition independently elevating the risk of the other. Individuals with diabetes face an increased likelihood of developing heart failure, whereas those with heart failure are at a greater risk of developing diabetes.

Risk Factors

Diabetes mellitus is associated with a nearly twofold increase in the risk of incident HF in men and a fourfold increase in women, even after adjustment for other cardiovascular risk factors. In patients with stable coronary artery disease who are free from heart failure at baseline, diabetes, and glycemic control

are independent risk factors for new-onset heart failure.

Mechanism

"Diabetic cardiomyopathy" refers to ventricular dysfunction in individuals with diabetes, occurring in the absence of coronary artery disease and hypertension. Various factors described in the pathogenesis of diabetic cardiomyopathy include activation of the renin-angiotensin-aldosterone system, mitochondrial dysfunction, oxidative stress, inflammation, disruptions in intracellular calcium homeostasis, heightened formation of advanced glycation end products, and alterations in myocardial energy substrate usage. These alterations include increased utilization of free fatty acids, decreased use of glucose, and heightened oxygen consumption, collectively leading to decreased cardiac efficiency and the eventual development of HF.[1]

Outcome

Patients with heart failure who have diabetes have worse outcomes in terms of rehospitalization, morbidity, 5-year survival, and mortality. Diabetes mellitus was found to be an independent predictor of cardiovascular morbidity and mortality in patients with heart failure, regardless of ejection fraction.

Treatment of Heart Failure in Patients with Diabetes Mellitus

Beta-blockers sacubitril/valsartan and angiotensin-converting enzyme inhibitors provide benefits for individuals with diabetes mellitus, reducing mortality and hospitalizations. Similarly, angiotensin II receptor blockers are effective in managing heart failure in those where it is indicated.

Mineralocorticoid receptor antagonists demonstrate equal efficacy in patients with heart failure, irrespective of the presence of diabetes mellitus. However, since diabetic nephropathy commonly coexists, close monitoring of electrolytes and renal function is necessary to prevent hyperkalemia. Ivabradine is also equally effective in patients with and without diabetes.[2]

Antidiabetic Treatment in Patients with Diabetes and Heart Failure

Thiazolidinediones

Rosiglitazone, a thiazolidinedione was withdrawn from the market due to evidence indicating an elevated risk of cardiovascular events, including heart failure. Pioglitazone, the thiazolidinedione available for clinical use is, contraindicated in heart failure due to its properties of promoting fluid retention and aggravating heart failure.

Metformin

Metformin is commonly used as the initial therapy for patients with type 2 diabetes mellitus (T2DM). Metformin can be used in individuals with heart failure, if the estimated glomerular filtration rate is stable and ≥30 mL/min/1.73 m^2[3] and should be discontinued in unstable or hospitalized patients with HF.

SGLT-2 Inhibitors

The beneficial effect of SGLT-2 inhibitors on CV outcomes in subjects with type 2 diabetes mellitus and established HF was proven in several clinical trials and is independent of glycemic control.[5] Dapagliflozin has been shown to lower the risk of hospitalization for heart failure and CV-related death in HFrEF people (NYHA classes II–IV) by up to 55% with or without diabetes mellitus. Empagliflozin has been shown to have a cardio-protective effect on the combined risk of hospitalization for heart failure and cardiovascular death in subjects with HFpEF, an effect that is, independent of the presence of diabetes. EMPEROR-Preserved Trial demonstrated that the total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (407 with empagliflozin and 541 with placebo; hazard ratio, 0.73).[6] Canagliflozin has been shown to reduce the risk of HF hospitalization by up to 32% with diabetes mellitus.[7]

Dipeptidyl peptidase 4 inhibitors (DPP4i)

DPP4i are not drugs of choice for diabetes with heart failure and should be considered only after SGL2i, metformin, and GLP1RA.[3] However, sitagliptin and linagliptin can be considered for diabetes treatment in patients with HF due to their neutral effect on HHF risk.

Glucagon-like peptide 1 receptor agonist

In the LEADER Trial, GLP1RA liraglutide showed a significant reduction in the composite end point of occurrence of death from cardiovascular causes, nonfatal MI, or nonfatal stroke and did not increase the risk of HF or hospitalization for HF in patients with T2DM. Like liraglutide, in patients with type 2 diabetes who are at high cardiovascular risk, semaglutide has been shown to lower the rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.[9] This was related to improvements in SBP, non-HDL cholesterol, weight loss, and modification of atherosclerosis progression. In patients with HFpEF and obesity, treatment with semaglutide (2.4 mg, subcutaneous weekly) appears to result in larger

reductions in symptoms and physical limitations, greater improvements in exercise function, and greater weight loss compared to a placebo.

However, two small trials showed potential worsening of HF when individuals with existing HF are treated with GLP1RA.[10,11] Ferreira *et al.* suggested that after heart failure (HF) screening, the suggested GLP-1 receptor agonist (GLP-1 RA) treatment decisions are outlined as follows:[12]

1. T2D Without HF:
   - GLP-1 RAs are recommended for individuals with T2DM and without HF.
   - The use of GLP-1 RAs aims to reduce the risk of myocardial infarction and stroke.
   - There is a potential effect to lower the risk of HF hospitalizations.
2. HF with Preserved Ejection Fraction:
   - GLP-1 RAs do not appear to reduce HF hospitalizations significantly in patients with HF and preserved ejection fraction.
   - However, considering their potential to reduce atherosclerotic events, the use of GLP-1 RAs may be considered on an individualized basis.
3. HF with Reduced Ejection Fraction:
   - Caution is advised in using GLP-1 RAs in patients with HF and reduced ejection fraction.
   - There is concern about a potential risk of worsening HF events and arrhythmias.
   - Decision-making should be based on pending risk–benefit data from further studies.

Sulfonylureas

Sulfonylureas increase the risk of hypoglycemia and thus may indirectly increase HF risk in patients with diabetes.

Insulin

In type 2 diabetes, insulin therapy is added when lifestyle changes and oral medications are inadequate for glycemic control. Individuals on insulin therapy, often older, have a higher risk of HF.

FRAILTY IN HEART FAILURE

Definition

Frailty is defined as a decline in an individual's physical and cognitive reserve that prohibits regulatory bodily mechanisms to counter or recover from an acute stressor driven by the amplification of inflammatory mechanisms and sarcopenia.[1]

Epidemiology

Prevalence of frailty nears 40% in patients with heart failure, 90% in HFPEF, 30%–60% in HFREF, and 50% in WHF. Women have a 26% higher prevalence than men. Sarcopenia is present in 20% of patients with HF compared with patients to those without HF.[2]

Systemic inflammation has been shown to play a crucial role in worsening frailty with increased neutrophil-to-lymphocyte ratio.

Assessment

Validated HF frailty scores are still lacking. Current assessment scales to classify frailty in patients with HF include the Fried frailty phenotype and Rockwood Clinical Frailty Scale.

Clinical Implications

- Frailty has been associated with increasing age, female sex, ischaemic etiology, cardiovascular co-morbidities, higher NYHA class, quality of life, and drug discontinuation. Frail patients had a greater than twofold risk of 1-year mortality and a nearly twofold increased risk of 1-year all-cause readmissions
- Primary endpoint of HF hospitalizations and cardiovascular death was reduced with dapagliflozin in the high frailty group compared to the low frailty group with a difference in event rate per 100 person-years in high frailty of 7.9 in the DAPA-HF study and quality of life in DELIVER study[3]
- Structured physical rehabilitation program helps in enhancing recovery in elderly frail patients hospitalized for HF with significant improvements in 6-min walk distance.
- 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines denote a Class 1 indication for exercise training and Class 2a indication for a cardiac rehabilitation program for improving functional status, exercise tolerance, and health-related QOL.[4]
- Physical frailty was an independent predictor for nonuse of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and β-blockers in a multivariate model that included age and renal function. [5]

Conclusion

- Frailty is an important patient-level factor that negatively affects prognosis in HF and an independent variable for HF hospitalization even with consideration to the existent clinical characteristics.
- Frail patients with HF are often deprived of medical therapy, less optimized for the doses, and often with reduction of doses with a pre-existent concept of limitation of efficacy and side-effects including falls and fractures.
- Suboptimal treatment is associated with a higher risk of all-cause death or heart failure hospitalization, irrespective of the severity of physical frailty.

- Paradoxically, the elderly and frail have a better advantage than the less frail for outcomes and are denied the benefits they benefit from.

DEPRESSION AND ANXIETY IN HEART FAILURE

Introduction

- Heart failure (HF) patients are more likely to be affected by these mental health issues than cancer patients.
- Despite the well-known link between mental health issues like anxiety and depression and HF, this combined entity is underdiagnosed and undertreated

Prevalence

- About one in four patients of HF develop anxiety or depression
- The global prevalence of depression in patients with HF is between 20% and 30%.
- About 30% of HF patients exhibit anxiety clinically, whereas it should be remembered that symptoms of HF and anxiety overlap to some extent.

Prevalence in low- and middle-income countries:

- In low-and middle-income countries, the prevalence of depression and anxiety is likely to be higher. In a study from India, out of 541 patients attending cardiac out-patient services, 159 (30%) patients had mild-to-moderate depressive symptoms, and 144 (89%) of them were older than 50 years.[1]

Outcome

- Both depression and anxiety have been associated with poor outcomes. Various studies have established that HF when associated with depression and anxiety increases the risk of impaired quality of life, heart failure-related hospitalization, and mortality.

Heart Failure in Depression

- Nord-Trøndelag Health Study (HUNT 2) study of 62,567 healthy subjects followed for 11 years showed that the more severe the depression, the higher the risk of developing HF.[2]
- Depression is a strong independent risk factor for the development of HF in high-risk groups—old age, women, systolic hypertension, and coronary artery disease (CHD).[3]

Depression in Heart Failure

- HF increases the risk of depression.
- A population-based cohort study from the Netherlands showed that HF was associated with a greater risk of developing depression, and was an independent risk factor for incident depression. Other risk factors for depression are old age, female sex, the severity of symptoms of HF, and a previous history of CVD hospitalization.[4]

Pathophysiologic Mechanisms

- There are two pathways to explain adverse outcomes in these patients of HF and mental health issues—Physiologic and behavioral.
- Anxiety and depression are associated with the activation of the sympathetic nervous system (SNS).
- Inflammation, autonomic dysfunction, platelet aggregability, and endothelial dysfunction are the physiologic pathways.[5] Medication non-adherence and poor physical activity often seen with these patients are the behavioral mechanisms.

Predictors

- The predictors of depression in heart failure include advanced age, female gender, low socioeconomic status, previous depressive episode, smoking, a higher NYHA functional class, and unmarried status.[6]

Treatment

Screening

- HF patients should be routinely screened for depression and anxiety during hospital stay and follow-up. The clinician has to depend on clinical interviews and questionnaires for this. Validated questionnaires and diagnostic criteria are available.[7]

Non-pharmacologic treatment

- A meta-analysis of 21 randomized trials of HF involving 4563 patients showed significant improvement in symptoms with exercise training and cognitive-behavioral therapy (CBT, a composite psychological therapy). Even mild-to-moderate intensity of physical activity is beneficial.[8]

Pharmacologic treatment

Includes GDMT depression

- Tricyclic antidepressants are contraindicated in patients with heart disease because of the higher risk of hypotension, arrhythmia, worsening of HF, and myocardial infarction

- Depressive symptoms improve with selective serotonin reuptake inhibitors (SSRI)—sertraline and escitalopram—but show no significant benefit over placebo in improving symptoms and outcomes[9]

Newer modalities of treatment:[10]

- Brain stimulation: Transcranial magnetic stimulation (TMS), a modern brain stimulation technique, is an effective antidepressant monotherapy. It does not require anesthesia and rarely causes seizures. However, pacemakers and implanted devices form contraindications.
- N-methyl-D-aspartate (NMDA) receptor antagonists: Intranasal S-enantiomer of ketamine, esketamine, has been approved for the treatment of resistant depression. NMDA receptor antagonists have probably pleiotropic actions. However, there are major concerns with the use of these drugs, in patients with cardiovascular disease as they may increase BP and prolong QT interval.
- Omega-3 Fatty acid supplementation: Patients with depression have been shown to have a deficiency of omega-3 fatty acids. OCEAN randomized study of 108 HF patients (35% with HFpEF and 65% with HFrEF) with depression showed improvement in cognitive depressive symptoms.

PREGNANCY AND HEART FAILURE

Heart disease remains the primary contributor to maternal health issues and fatalities across the globe. Over the past decade, there was a 24% rise in the prevalence of women with cardiac conditions delivering babies, accompanied by an 18% increase in pregnancy-related complications in this demographic.[1] The maternal mortality rate due to cardiac causes stands at around 1.9%, with cardiac events occurring in about 15% of pregnancies involving heart disease. Among these events, new or aggravated heart failure (HF) ranks as the most common, followed by thromboembolic incidents, valve issues, and arrhythmias.[3] HF has been identified as the primary cause of over 9% of in-hospital deaths within pregnancy-related hospitalizations.[1]

Maternal Cardiovascular Physiology

In pregnancy, there is increased plasma volume, heart rate, stroke volume, and cardiac output, coupled with lowered blood pressure and systemic vascular resistance. Increased left ventricular dimensions, aortocaval compression, and hypercoagulability play a role in the dynamic alterations observed. Labor initiates a surge in preload and cardiac output due to uterine contractions, coupled with increased sympathetic activity from pain and anxiety. Post-delivery, heart rate and cardiac output return to pre-labor levels, followed by a notable decrease in stroke volume, heart rate, and cardiac output over the initial postpartum weeks.Atrial natriuretic peptide and B-type natriuretic peptide (BNP) levels further increase postpartum, mediating diuresis after delivery.

Cause of HF

1. Common causes of HF in pregnancy have been summarized in Figure 8.1.

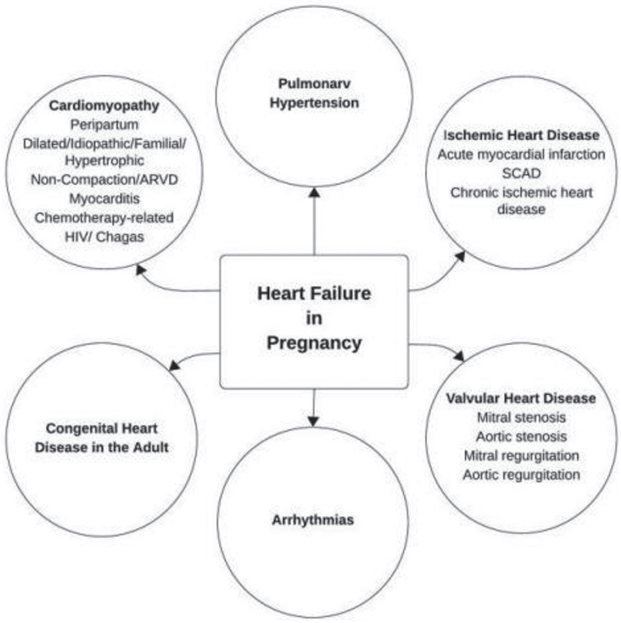


Figure 8.1: Cause of HF in pregnancy

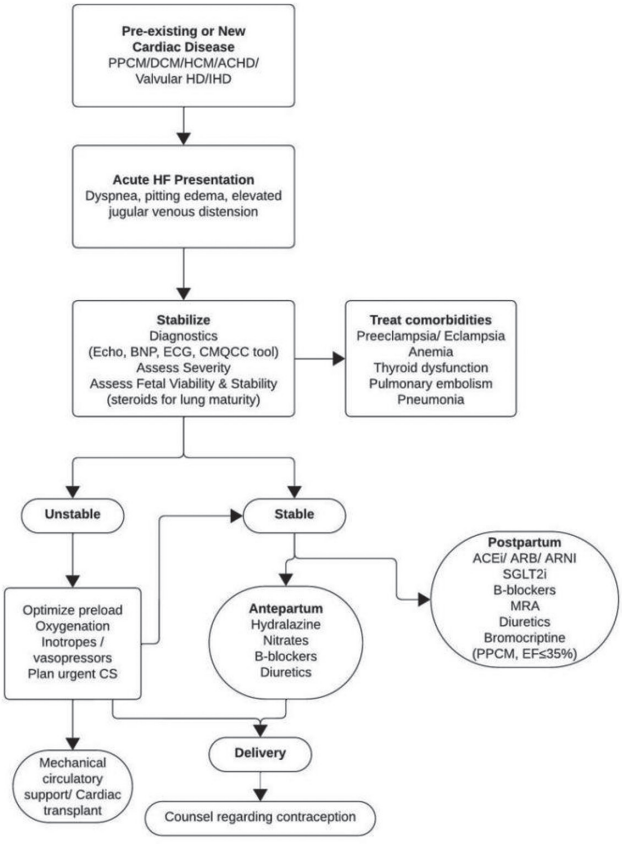


Figure 8.2: Risk factors and its management for maternal HF

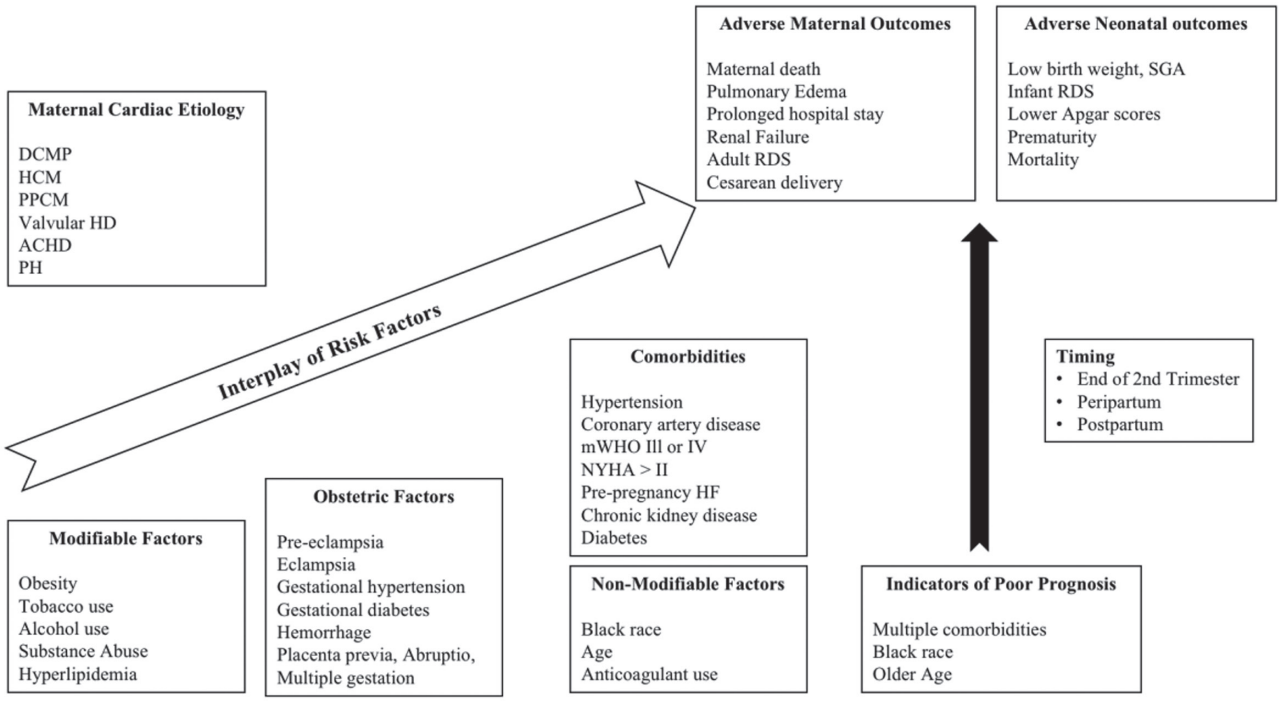


Figure 8.3: Comprehensive treatment pathways

Timing of HF

Timing of HF presentation varies: 60% postpartum, 27% at delivery, and 13% during pregnancy. In mothers with existing heart conditions, HF peaks at 23 to 30 weeks and postpartum. The valvular disease often develops HF across pregnancy, while cardiomyopathy mostly shows up around delivery. Shunt lesion patients experience HF around 25 weeks gestation. PPCM typically occurs in the last trimester or within 6 weeks postpartum, but late onset has been described up to a year after delivery

Risk Factors and Risk Stratification

Multiple studies have identified various risk factors for maternal HF, highlighted in Figure 8.2.[1,4,5]

Therapeutics and Principles of Management

1. Comprehensive treatment pathways are outlined in a concise Figure 8.3.

Delivery Considerations

Severe HF or persistent hemodynamic instability need urgent cesarean delivery regardless of gestational duration. For stable HF, vaginal delivery with epidural anesthesia is preferred. If vaginal delivery is chosen, instrumentation may be used to shorten the second stage of labor. Invasive hemodynamic monitoring, such as an intra-arterial line, may be employed during labor.

Lactation and Nursing

Lactation is encouraged in patients with heart disease whenever feasible but avoided in cases of severe LV dysfunction. Specific medications should be avoided during breastfeeding, as outlined in a summary chart below.

Medication	Safety during pregnancy	Safety during breastfeeding
ACE inhibitor/ ARB	Contraindicated	Captopril and enalapril are safe
ARNI	Contraindicated	Limited data
Beta-blockers (metoprolol, carvedilol, and bisoprolol)	Metoprolol is preferred due to its selectivity to avoid uterine relaxation; higher doses may be associated with intrauterine growth restriction	Compatible
Diuretics	Can reduce amniotic fluid, although generally considered safe (less data for torsemide and metolazone)	Can suppress lactation
MRA	Contraindicated	Spironolactone is safe; eplerenone has not been studied
SGLT2 inhibitor	Contraindicated	Contraindicated
Digitalis	Compatible	Compatible
Hydralazine	Compatible	Compatible
Nitrates	Compatible, risk of hypotension	Compatible
Ivabradine	Not recommended	Not recommended

Medication	Safety during pregnancy	Safety during breastfeeding
Bosentan	Not recommended	Not recommended
Sildenafil	Compatible	Compatible
CCBs	Verapamil is safe, Diltiazem is avoided	Possibly safe
Statins	Contraindicated	Contraindicated
Aspirin	Safe, high dose (>150 mg/day can cause ductus closure)	Compatible
Clopidogrel	Limited data, increased risk of maternal bleeding	Limited data
Adenosine	Compatible	Compatible
Flecainide and procainamide	Compatible	Compatible
Amiodarone	Not recommended	Not recommended
Warfarin	Not recommended	Compatible
UFH, LMWH	Compatible	Compatible
NOACs	Not recommended	Limited data

Postpartum Care

Despite the majority of HF cases being diagnosed postpartum, current practice often involves only one follow-up visit at 6 weeks postpartum, presenting a missed opportunity for early detection and intervention.

Preventing HF

Preventing HF is critical, given that nearly 73% of cardiac events in pregnant women are preventable. Comprehensive cardio-obstetric teams and broader training are the need of the hour. Key elements of prenatal visits involve symptom assessments, medication reviews, preconception health evaluations, maternal cardiovascular risk screenings using the mWHO scoring system, and comprehensive patient education, including advising against pregnancy for those in mWHO class IV. Patient education, including awareness of risks, recognition of warning signs, counseling on delivery options, and understanding the implications of HF diagnosis, is essential.[8]

HEART FAILURE—DISCHARGE PLANNING AND REVIEW PROTOCOL

Hospital Discharge after an acute heart failure (HF) episode marks the beginning of care, not the end. HF is a lifelong condition, and appropriate follow-up after discharge is critical to improve patient symptoms, quality of life, and survival.

HF guidelines emphasized the significance of pre-discharge and early post-discharge evaluation in patients hospitalized for an acute heart attack episode.[1] The safety and effectiveness of a strategy based on initiating and titrating oral medical therapy for HF within two days prior to hospital discharge were demonstrated by the STRONG-HF trial.[2] Early and quick intensification of oral HF treatment with ACE-I (or ARB) or ARNI, beta-blockers, and MRA was administered to patients in the high-intensity care group. Reaching at least half of the target doses of prescribed drugs was the aim of the initial titration visit, which took place 48 hours prior to hospital discharge. With the proper safety monitoring, titration to full target dosages of oral treatments was performed within two weeks after discharge. Compared to the usual care group, patients allocated to high-intensity treatment had a higher likelihood of receiving full doses of oral medications (renin-angiotensin system inhibitors 55% vs. 2%, beta-blockers 49% vs. 4%, and MRA 84% vs. 46%). While all-cause death by day 180 did not decrease (aRR = 0.84, 95% CI = 0.56–1.26; P = 0.42), readmissions for heart failure did (aRR = 0.56, 95% CI = 0.38–0.81; P = 0.0011). Each group reported similar rates of fatal adverse events (5% vs. 6%) and major adverse events (16% vs. 17%). Of course, the fundamental medications did not contain SGLT2i inhibitors. In order to lower HF readmission or all-cause mortality, high-intensity care for the initial period and quick up-titration of oral HF medications, as well as close follow-up during the first six weeks following discharge for an acute HF hospitalization, are advised based on the outcomes of STRONG-HF. NT-proBNP readings, potassium concentrations, heart rate, blood pressure (including monitoring for postural BP decline), symptoms and indicators of congestion, and eGFR should all be evaluated during the follow-up visits.

People leaving the hospital after an acute HF episode remain at high risk of hospital readmission and death. The 3 months following discharge from an acute HF episode are recognized as a peak period for rehospitalizations,[3]with a higher risk of mortality than during hospitalization.

Preventing Hospital Readmission Should be a Key Goal at Discharge

Recurrent hospitalizations are a serious event and contribute to decreased survival.[4] Rates of hospital readmission are about 25% within a month of discharge after a first episode of acute HF, rising to 50% in the first 6 months. The risk of death is also highest in the early period after discharge: mortality in the first 2–3 months after hospital discharge is around 7%–11%.[5]Preparing for discharge is a recognized phase of inpatient care. Ideally, discharge planning should be initiated as soon as the patient's condition is stable. It should ensure a seamless transition from inpatient to outpatient or primary care.

This includes sharing appropriate information between professionals in different care settings and putting steps in place to enable continuous monitoring and adjustments of treatment, so patients are supported in adhering to their medication and initiating lifestyle adjustments. Structured discussions may also help determine each patient's knowledge, health literacy, and available support networks. It is vital to engage patients, their carers, and families to ensure a sound understanding of the patient's needs and discharge plan after they have left the close supervision of the hospital.[6]

Discharge Criteria for Patients with Heart Failure

Address precipitating and exacerbating factors.

Transition from intravenous to oral diuretic successfully

Near-optimal/optimal volume status achieved.

Guideline-directed medical treatment

Stable renal function and electrolytes within normal range/near normal range based on patient's baseline

No symptomatic supine or standing hypotension or dizziness

Patient and family education completed regarding compliance with medicines

Dietary sodium restriction and understanding the rationale for adherence

Need for daily activity and graded exercise, and understands the rationale for both

Need for monitoring of daily weights and when to contact health care professional

Plan to reassess volume status, and electrolytes early after discharge

Plan to reinforce patient and family education post-discharge

Follow-up clinic visit scheduled within 7 days of hospital discharge

Referral to outpatient cardiac rehabilitation program if available. Oral medication regimen, stable for at least 24 h

REHABILITATION, EXERCISE, SEXUAL ACTIVITY, AND DIETARY ADVICE IN HEART FAILURE

Chronic heart failure as an entity has evolved rapidly into various sub-types including heart failure with preserved (HFpEF), mildly reduced (HFmrEF), and reduced (HFrEF) ejection fraction.

Cardiac Rehabilitation in Heart Failure

- World Health Organization (WHO) definition of cardiac rehabilitation (CR): "the sum of activities required to influence favorably the underlying cause of the disease, as well as to provide the best possible physical, mental, and social conditions, so that the patients may, by their own efforts, preserve or resume when lost as normal a place as possible in the community."[1]
- Two commonly used disease-specific health-related quality-of-life measures [Minnesota Living With Heart Failure (MLWHF) and Kansas City Cardiomyopathy Questionnaire (KCCQ)] are used.
- International heart failure guidelines recommend CR as a Class IA recommendation for patients with chronic heart failure regardless of left ventricular ejection fraction (with or without cardiac implantable electronic or ventricular assist devices).[2,3]
- Abysmally low (less than 20%) levels of CR are being received among patients across Europe and the USA for evidence-based cardiac rehabilitation intervention.
- A recent Cochrane review of 60 trials in HFrEF patients showed a 25%–30% relative risk reduction in all-cause and heart failure hospitalization, healthcare costs, and improvement in health-related quality of life though no reduction in mortality was seen.[4]
- The Cardiac Rehabilitation Outcome Study in Heart Failure (CROS-HF) study did not show a clear improvement in either mortality or hospitalization, it confirms the improvement in exercise capacity and health-related quality of life with participation in exercise-based cardiac rehabilitation.[5]
- A multidisciplinary team involvement (nurse specialists, physiotherapists, dietitians, and psychologists) is strongly recommended.
- Post COVID-19 era has seen the emergence of virtual and hybrid models of CR delivery.

Exercise in Heart Failure

The hallmark of heart failure is severe exercise intolerance which is likely to be multifactorial in its origin and mechanism. Both central and peripheral pathophysiological mechanisms lead to impaired cardiac and pulmonary reserve, enhanced systemic vascular resistance, and impaired vasodilatory capacity causing an abnormal redistribution of blood flow and muscle perfusion.

- Most data on the benefits of exercise exists for HFrEF patients. However, there is a paucity of data on HFpEF patients in whom the benefits of exercise as part of CR are based only on small, observational studies.
- A large multicentre HF-ACTION trial with 2331 patients evaluated exercise training and cardiac rehabilitation interventions for HFrEF.

- ExTraMATCH II study, a meta-analysis that evaluated data from 3990 patients and 13 randomized trials (including HF-ACTION trial) showed a reduced rate of hospitalization and improved quality of life (QOL) in HFrEF patients.[6]
- Another important aspect of CR is the impact of frailty in HF patients. Older people with HFrEF and HFpEF are associated with worse outcomes. Two substudies, one from the HF-ACTION trial and another from the EJECTION-HF trial, found benefits with aerobic exercise training in HF patients with baseline frailty.[7,8]
- Objective evidence can be derived from a 6-min walk test (6MWT), graded exercise testing with treadmill test (TMT), bicycle ergometry, and cardiopulmonary exercise testing (CPET). CPET is the gold standard for assessing CR, though it is expensive, needs specialized equipment, and training, and has limited availability. CPET gives insights into the mechanism of exercise intolerance, prognosis [percent-predicted peak VO2 and ventilatory efficiency (VE/VCO2)], therapeutic response, and can be combined with stress echocardiogram or even invasive monitoring.

Sexual Activity in Heart Failure

- Approximately 60%–87% of patients with HF report sexual dysfunction which includes a lack of interest or fear of having sex, orgasmic difficulties, or erectile dysfunction (ED) in men. On average, sexual activity is equivalent to mild to moderate physical activity (3–5 METS), depending on individual functional capacity. HF patients with poor peak VO2 <10 mL/kg/min (i.e., 2.8 MET) had impaired sexual function.[9]
- The first step of sexual counseling and treatment is a patient and empathetic assessment of sexual activity and level of satisfaction. An individualized approach is essential as the context, personality, or professional background influences sexual concerns and problems.
- The most common reported symptoms hampering sexual activity were shortness of breath (20%), fatigue (20%), medications (10%), and limited circulation (11%).[10]
- Smoking, Hypertension, diabetes, dyslipidemia, anabolic deficiency, andropausal symptoms, depression, performance anxiety, overweight and sedentary lifestyles, all play a part in sexual dysfunction.
- The second step is to assess any cardiac risk associated with sexual activity. Sexual activity is reasonable for patients with compensated and/or mild [New York Heart Association (NYHA) class I or II] HF (Class IIa; Level of Evidence B). Sexual activity is not advised for patients with decompensated or advanced HF (NYHA class III or IV) until their condition is stabilized and optimally managed (Class III; Level of Evidence C)[11]
- Drugs like beta blockers, thiazide diuretics, digoxin, and mineralocorticoid receptor blockers may all cause erectile dysfunction (ED) or sexual dysfunction.[12]
- The pathophysiology of ED in HF involves multiple mechanistic pathways like endothelial dysfunction, reduced cardiac output, neurohormonal activation, autonomic imbalance, and oxidative stress.
- The first-line pharmacological treatment for ED in HF patients with mild to moderate symptoms (NYHA classes I–II) is phosphodiesterase type 5 inhibitors (PDE5Is), which improve both sexual function and cardiopulmonary parameters. PDE5Is are contraindicated in patients who use nitrates or nitric oxide donors for angina relief. Non-pharmacological strategies like psychotherapy or couples therapy can also be advised in select cases.[13]

Dietary Advice in Heart Failure

- HF is known to be associated with chronic inflammation, coronary artery disease, hypertension, type 2 diabetes mellitus (T2DM), sarcopenia, obesity, etc. and nutrition interventions can aid in managing HF.
- Improper nutrition is a key lifestyle risk factor implicated in complicating HF. However, there is a paucity of data on the effects of macro- and micronutrients as well as dietary patterns on the progression and treatment of HF.
- Salt restriction: The guideline recommendations vary widely between 1.5 and 3 g per day. Moderate sodium restriction of up to 2.8 g/day is more beneficial in HF, compared to low sodium restriction of up to 1.8 g/day.[14]
- Dietary recommendations: The Mediterranean diet and Dietary Approaches to Stop Hypertension (DASH) diet are the two most recommended dietary patterns for both preventing the onset of HF as well as improving pre-existing HF. Both these dietary plans emphasize consuming more fruits, vegetables, whole grains, and legumes while limiting saturated fatty acids.
- The Mediterranean diet emphasizes on greater intake of unsaturated fatty acids (UFA), both monounsaturated (MUFA) and polyunsaturated fatty acids (PUFA) found in fatty fish, extra-virgin olive oil, canola oil, and mixed nuts. DASH diet advocates a high potassium intake while limiting sodium and total fat.[15]

END OF LIFE CARE IN HEART FAILURE

Heart Failure is associated with high morbidity and mortality. Recurrent hospitalization is a major problem encountered in patients with heart failure. While palliative care in terminal malignancies has been well studied and protocols established a similar approach to management of terminal heart failure is lacking.

Three Stages Identified in Heart Failure

Stage 1: chronic disease management phase.

Stage 2: Supportive and palliative care phase.

Stage 3: Terminal care phase.

WHO's statement on palliative care aims at providing relief from distressing symptoms, integrating psychological and spiritual aspects of patient care, providing support systems for continuing active life as far as possible with a team approach, and also aiming at enhanced quality of life.

Various terminologies have been proposed for palliative care in heart failure.

Terminal care: Care during the last few days or weeks of the patient's life.

End-of-life care is used interchangeably with palliative care or care of terminally ill patients.

Aims of Treatment

Stage 1

Effective Therapy, active monitoring, symptom control, and patient education.

Regular periodic monitoring.

Stage 2

Hospitalizations. Maintaining optimum symptom control and quality of life.

Multidisciplinary assessment of patient and career needs.

Stage 3

Various scoring systems are used in patients with heart failure for assessing the prognosis like the Heart Failure Survival Score, Seattle Heart Failure Score, and Cardiovascular Medicine Heart Failure Index (CVM-HF). But these are usually not required and simple clinical parameters mentioned above are sufficient Frequent hospitalizations, malignant arrhythmias intravenous drug requirement, and cardiac cachexia are also important prognostic markers.

Symptom Control

Dyspnea is the most common distressing symptom. Morphine has been found effective but the route and dose of administration are yet to be accepted unlike in oncology practice. Intravenous inotropes can be used in managing heart failure at the end of life, especially for transient clinical improvement.

Treatment of co-existing medical conditions needs to be done concomitantly and properly. Many patients are on ICDs or have CRT D implantations. Patients on end-stage palliative care should have their ICDs inactivated as they may have recurrent ICD discharges in the terminal phase, which may be distressing to the patient. In the case of a CRT D device, the defibrillator function may be disactivated.

Advanced Care Planning

This envisages a person's beliefs and values that will guide decision-making at the end of life.

There are three steps (1) identifying the substitute decision maker (SDM); (2) wishes related to health care; and (3) preparing the SDM for future decision-making as the patient may not be able to decide for himself.

Shared Decision Making

The patient and the family must understand the current condition, symptoms, quality of life, and goals of treatment and outcomes. The clinician should inform the patient and caregivers and the substitute decision maker regarding the prognosis, treatment outcomes, challenges, and decisions to be taken in the coming months. The psychosocial and spiritual needs of the patient are extremely important in end-of-life care.

The presence of a Palliative care physician in the specialized heart failure management team can facilitate interaction between the physicians, Caregivers, family, and the Substitute Decision Maker and often reduce hospitalizations. Many patients and caregivers may require spiritual and social support which may be supplied by the palliative care physician. While palliative care facilities are better in hospital settings, community-based support systems have to be developed to provide help for a larger number of patients who do not have access to advanced medical care.

Care of terminally ill cardiac failure patients especially those not being considered for transplantation is a challenge due to poor quality of life, frequent hospitalizations, socioeconomic issues, and psychological issues. A coordinated program involving heart failure specialists, palliative care physicians, caregivers, and substitute decision-makers will ensure smoother end-of-life care and avoid frequent hospitalizations.

Conclusions

Dear colleagues, in this document we have attempted to summarize the available scientific knowledge about the management of Heart failure in a concise form, which is easy to use and implement, for you to improve the care of patients of HF under your care. Attempts have been made to keep it as simple as possible, yet to help you to suspect and diagnose HF and use the therapies available today in your daily practice in a way that is easy to understand and put into practice. We earnestly request you to go through this document and let us know your suggestions to improve it in further editions. As knowledge expands, several new modalities of treatment may become available and it will

be our constant attempt to upgrade the recommendations to help you manage your patients.

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Conflicts of interest

There are no conflicts of interest.

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