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Guideline

2023 Indonesian Guidelines for Heart Failure Treatment: Working Group on Heart Failure and Cardiometabolic Diseases, Indonesian Heart Association

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Abstract
Heart failure represents a critical health problem with elevated mortality and morbidity rates in both advanced and emerging nations, including Indonesia. The increasing prevalence of heart failure is partly due to the progression from acute to chronic heart failure. This guideline aimed to provide practical guidance for the diagnosis, assessment, and management of acute and chronic heart failure in Indonesia, addressing the underutilization of Guideline-Directed Medical Therapy (GDMT) at recommended doses in patients with reduced ejection fraction (HFrEF). This update to the 2020 Guideline for the Management of Heart Failure by the Indonesian Heart Association incorporated numerous references and literature reviewed by contributors and the Evidence-Based Medicine (EBM) team. It underscored the high utilization of ACE inhibitors (ACE-I) and angiotensin receptor blockers (ARB) in Indonesia, while pointing out the country's low utilization of β-blockers and aldosterone inhibitors (Mineralocorticoid Receptor Antagonists, MRA) in contrast to the ASIAN-HF registry. The guideline aimed to reduce the prevalence and rehospitalization rates of heart failure through comprehensive management strategies. By providing updated, evidence-based recommendations, this guideline sought to enhance the management of heart failure in Indonesia, thereby improving patient outcomes and reducing the burden of the disease.

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Keywords: *guideline; heart failure; Indonesia; management*.

Introduction

Background

Heart failure presents a substantial public health challenge characterized by elevated mortality and morbidity rates across diverse socioeconomic settings, encompassing both developed and developing nations, including Indonesia. Although the occurrence of heart failure in Asian nations generally parallels that in Europe (1–3%), Indonesia reports a markedly higher prevalence exceeding 5%.[1] Notably, Indonesian patients with heart failure are generally younger than their counterparts in Europe and America, often exhibiting more severe clinical manifestations. The increasing prevalence of heart failure is attributed to the progression of acute heart failure to chronic stages. The World Health Organization (WHO) identifies escalating rates of smoking, obesity, dyslipidemia, and diabetes as significant contributors to the global rise in heart failure cases.[2] Additionally, comorbidities like ischemic heart disease significantly contribute to the onset of heart failure, particularly among individuals with suboptimal management of these underlying health conditions.[3]

Guideline-Directed Medical Therapy (GDMT) administered at the recommended levels was significantly underutilized in patients with heart failure who had reduced ejection fraction (HFrEF). Specifically, in Indonesia, despite the relatively high utilization rates of ACE inhibitors (ACE-I) or angiotensin receptor blockers (ARB), the country exhibited the lowest usage rates of β-blockers and aldosterone inhibitors, also known as Mineralocorticoid Receptor Antagonists (MRA), across the entire ASIAN-HF registry.[4] This discrepancy in medication usage highlighted a critical gap in the optimal treatment of heart failure within the region. In response to this issue, the development of this guideline was undertaken with the objective of providing detailed and practical guidance on the diagnosis, assessment, and comprehensive management of both acute and chronic heart failure. Therefore, this guideline aimed to address the underutilization of essential therapies and to standardize care practices in accordance with the latest evidence-based recommendations. The overarching goal of this guideline was to prevent the increasing prevalence of heart failure by ensuring that patients received complete and effective management. Additionally, it aimed to significantly reduce the rate of rehospitalizations, which was a common and costly consequence of inadequate heart failure management. By providing clear and actionable recommendations, this guideline sought to optimize patient outcomes and reduce the overall burden of heart failure within the Indonesian healthcare system.

Updates

The following table shows several updated concepts compared to the 2020 version.

Problems

- The rising incidence of heart failure and the growing population seeking treatment for chronic conditions ultimately contribute to high prevalence and mortality rates associated with heart failure.
- There are numerous challenges related to heart failure in Indonesia, encompassing both prevention and therapy.
- The diversity among healthcare professionals involved in treating heart failure, both in terms

Table 1.1 Updates concept.

• Definition and classification of heart failure with mildly reduced ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF)
• New algorithm for management of HFrEF
• New diagnostic algorithm and management recommendations for HFpEF
• Management recommendations for HFmrEF and HFimpEF
• Discussion of heart failure decompensation as a separate diagnosis
• Updates on heart failure comorbidities, including iron deficiency, diabetes, cardiorenal syndrome, obesity and frailty
• Update on optimizing heart failure management

Table 2.1 Classes of recommendation.

	Definition	Terms
Class I	Scientific evidence and/or general agreement that a therapy or procedure has been proven to be beneficial and effective	Recommended or indicated
Class II	Scientific evidence is contradictory and/or there is a diversity of opinion regarding the benefits or effectiveness of a therapy or procedure	
Class IIa	Scientific evidence or opinion shows more benefit or effectiveness	must be considered
Class IIb	Scientific evidence or opinion is insufficient to demonstrate benefit or effectiveness	might be considered
Class III	Scientific evidence or general agreement that a therapy or procedure is unhelpful or ineffective, and in some cases may be harmful	not recommended

of service provision and scientific expertise, has resulted in variations in healthcare delivery.
- Given the diversity of facilities, human resources, and tools/systems within each healthcare institution, standardized professional guidelines are essential to optimize the role of each institution in national heart failure treatment strategies.

Objectives

- Serve as a practical guideline for diagnosing, assessing, and managing acute and chronic heart failure.
- Enhance healthcare professionals' knowledge regarding heart failure treatment.
- Formulate evidence-based systematic guidelines to assist doctors and nurses in preventing and managing heart failure according to global standards.
- Offer evidence-based recommendations for primary to tertiary healthcare facilities within the national referral system, as well as for policymakers in developing local protocols.

Targets

- All medical professionals engaged in the treatment of heart failure in Indonesia, from primary to tertiary health facilities, include general practitioners, nurses, and cardiologists.
- The directors/heads of primary to tertiary health facilities are responsible for managing heart failure within their respective institutions.
- All stakeholders collaborating to enhance heart failure services in Indonesia.

Methods

Literature Review

The literature review conducted for this guideline encompassed a range of authoritative sources and consensus documents from prominent cardiovascular organizations. Key references included the 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure, which provide comprehensive recommendations on managing heart failure across different clinical settings. Additionally, the 2022 AHA/ACC/HFSA Focused Update and the 2021 ACC Expert Consensus Decision Pathway offered insights into optimizing treatment strategies for HFrEF. The Universal Definition and Classification of Heart Failure, jointly authored by the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Asia Pacific Society of Cardiology, and the Japanese Heart Failure Society, provided essential frameworks for understanding heart failure classification and diagnosis. Other notable contributions came from studies like the ASIAN-HF Registry, which explored multimorbidity patterns in heart failure across Asian regions, and consensus documents on specific issues such as fluid management and hyperkalemia in cardiovascular disease. These references collectively informed the development of this guideline, ensuring that it aligns with current global standards and addresses pertinent issues in the prevention, diagnosis, and management of heart failure.

Table 2.2 Levels of evidence.

Level of evidence A	Data come from many randomized studies or meta-analyses
Level of evidence B	Data come from single randomized studies or non-randomized studies with large sample sizes
Level of evidence C	Expert consensus and/or small studies, retrospective studies, registries

Table 2.3 Degrees of recommendation based on the level of validity of a study.

A	Scientific evidence comes from at least one meta-analysis, systematic review or randomized controlled trial at level 1++ and can be directly applied to the target population, or scientific evidence comes from several studies at level 1+ that show consistency of results and can be directly applied to the target population.
B	Scientific evidence comes from several level 2++ studies which show consistency of results, and can be directly applied to the target population, or extrapolation of scientific evidence from level 1++ or 1+ studies.
C	Scientific evidence comes from several level 2+ studies which show consistency of results, and can be directly applied to the target population, or extrapolation of scientific evidence from level 2++ studies.
D	Scientific evidence level 3 or 4 or extrapolation of scientific evidence from level 2+ studies.

Table 3.1 Signs and symptoms of heart failure.

Signs	Symptoms
Typical Shortness of breath Orthopnea Paroxysmal Nocturnal Dyspnea Decreased activity tolerance Easily tired Swelling in the ankles Swelling in other parts of the body besides the ankles Bendopnea	Specific Increased jugular venous pressure Hepatojugular reflux S3 heart sound (gallop rhythm) The apex of the heart shifts laterally Cheyne Stoke respiration in advanced heart failure
Less Typical Coughing at night Wheezing Bloating Reduced appetite Feelings of confusion (especially elderly patients) Depression Pounding Dizziness/dizziness Faint	Less Specific Peripheral edema (ankles, sacrum, scrotal) Pulmonary crepitus Weight gain (>2kg/week) Weight loss (in advanced heart failure) Cachexia Heart murmur Pleural effusion Tachycardia Irregular pulse Takipnoe Hepatomegaly Ascites Cold extremities Oliguria Narrow pulse pressure

Critical Appraisal

Critical appraisal was conducted individually by each contributor and subsequently reviewed by the EBM team. Specifically, for meta-analyses, guidelines, textbooks, and treatment protocols for heart failure, recommendations were directly established without undergoing further critical appraisal processes.

Levels of Evidence

The levels of evidence utilized were derived from the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, as outlined in Tables 2.1 and 2.2.

Degrees of Recommendation

The degrees of recommendation were illustrated in the table X.

Definition and Diagnosis

Definition

Heart failure is a multifaceted clinical condition that defies a singular pathological diagnosis. According to the Universal Definition of Heart Failure, it represents a disorder characterized by manifestations such as signs and symptoms, which stem from abnormalities in cardiac structure and/or function. This syndrome

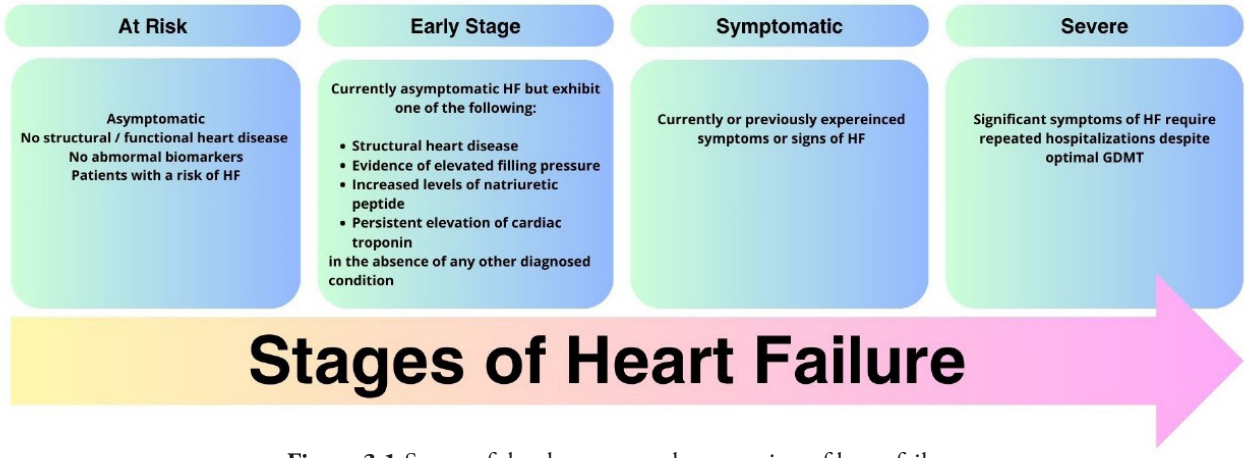

Figure 3.1 Stages of development and progression of heart failure

commonly presents with high levels of natriuretic peptides (NPs) and may also feature clear evidence of pulmonary or systemic fluid overload.[5]

Stages of Heart Failure

The stages of heart failure highlight its progression and clinical course, with advanced stages correlating with lower survival rates. Therapeutic strategies tailored to each stage are critical for effective management. Stage A focuses on modifying risk factors to prevent heart failure onset, while Stage B addresses established risk factors and structural heart disease to avoid symptomatic heart failure. In Stages C and D, interventions aim to alleviate symptoms, reduce morbidity, and enhance survival through targeted therapies that optimize cardiac function and manage complications associated with severe heart failure. This structured approach underscores the importance of early detection and comprehensive management in mitigating the impact of heart failure on patient outcomes.[5,6]

Classification

Heart Failure Classification by Ejection Fraction

Heart failure stratification according to left ventricular ejection fraction (LVEF) remains crucial due to its implications for prognosis and therapeutic response. Most clinical trials categorize patients according to LVEF, underscoring its role in defining treatment strategies and predicting outcomes. For instance, randomized clinical trials investigating heart failure therapies have predominantly enrolled patients with reduced LVEF, typically defined as <35% or <40%, known as HFrEF. These trials provide critical evidence supporting interventions aimed at improving survival rates and managing symptoms in this patient population.[5,7]

Classification of Heart Failure by Functional Status

The simplest way to assess functional capacity in heart failure is through the New York Heart Association (NYHA) classification system. This system classifies patients into four distinct groups based on their level of limitation during physical activity. Class I indicates minimal symptoms with no limitation during ordinary physical activity, while Class IV signifies severe symptoms even at rest. The NYHA classification provides clinicians with a standardized framework to gauge the extent of heart failure symptoms and tailor treatment plans accordingly, aiming to enhance patient care and quality of life.[7]

Diagnosis Algorithm

The diagnosis of heart failure necessitates the identification of signs and/or symptoms indicative

Table 3.2 Heart failure classification based on LVEF.

Types of Heart Failure	Criteria
HFrEF (Heart failure with reduced ejection fraction)	Signs + Symptoms LVEF <40%
HFmrEF (Heart failure with mildly reduced ejection fraction)	Signs + Symptoms LVEF >41 - 49%
HFpEF (Heart failure with preserved ejection fraction)	Signs + Symptoms LVEF >50% Objective evidence of structural and/or functional cardiac abnormalities consistent with left ventricular diastolic dysfunction/elevated left ventricular filling pressures, including increased natriuretic peptide.
HFimpEF (Heart failure with improved ejection fraction)	LVEF was <40% previously and there was an increase of more than 10% or increased to >40% on follow-up measurements

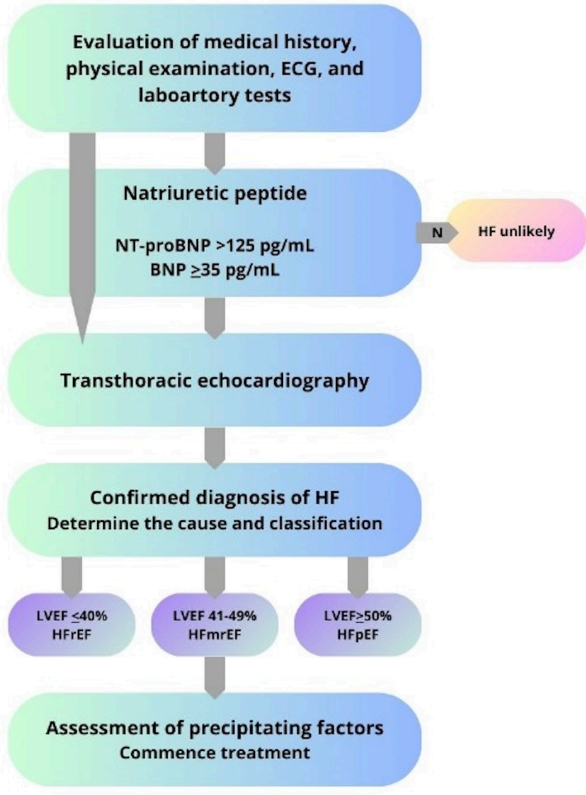

Figure 3.1 Stages of development and progression of heart failure

of heart failure, as outlined in Table 3.1, along with objective evidence demonstrating cardiac dysfunction.[5]

Electrocardiogram (ECG)

An electrocardiogram (ECG) is a standard diagnostic tool for assessing patients with a suspected diagnosis of heart failure. ECGs often reveal abnormalities that are commonly associated with heart failure. Despite their frequent occurrence in heart failure patients, these ECG abnormalities have limited predictive value in isolation for diagnosing the condition definitively.[8]

Chest X-Ray

Chest x-rays play a central role in diagnosing heart failure by providing valuable insights into cardiac and pulmonary abnormalities. This imaging modality is adept at identifying cardiomegaly, a hallmark sign of heart failure characterized by an enlarged heart. Additionally, chest x-rays can reveal signs of pulmonary congestion, such as vascular redistribution and interstitial edema, which indicate fluid buildup in the lungs. Furthermore, it can detect pleural effusions, an accumulation of fluid in the pleural space surrounding the lungs, which may also accompany heart failure. Beyond cardiac manifestations, chest x-rays can identify concurrent lung diseases or infections that could contribute to or mimic heart failure symptoms. Thus, integrating chest x-ray findings into the diagnostic process aids clinicians in confirming heart failure diagnosis and guiding appropriate treatment strategies to optimize patient care.[8]

Natriuretic Peptide (NP)

Plasma levels of NPs serve as valuable biomarkers in various aspects of heart failure management. They are instrumental in diagnosing heart failure, aiding in treatment decisions, determining discharge readiness, and identifying patients at risk of decompensation. NPs, including N-terminal pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP), increase when ventricular wall pressure rises, signaling

Table 3.3 Heart failure classification based on functional capacity.

Class I	There are no physical activity restrictions. Daily physical activity does not cause shortness of breath, fatigue, or palpitations.
Class II	There are few physical activity restrictions. Comfortable when resting, but daily physical activity causes shortness of breath, fatigue or palpitations
Class IIa	There are significant physical limitations. Comfortable when resting, but light physical activity that is less than daily physical activity causes shortness of breath, fatigue, or palpitations.
Class IIb	Unable to do physical activity without complaints. There are symptoms when resting. Complaints increase when doing physical activity.
Class III	Scientific evidence or general agreement that a therapy or procedure is unhelpful or ineffective, and in some cases may be harmful

Table 3.4 Upper limit values of natriuretic peptide for heart failure inclusion.

	Natriuretic Peptide	
	NT-proBNP	**BNP**
Acute	>300 pg/mL	>100 pg/mL
Chronic	>125 pg/mL	>35 pg/mL

cardiac stress and dysfunction. Unlike some biomarkers with short half-lives, NPs have a prolonged half-life, meaning that even after a sudden decrease in ventricular wall pressure, NP levels may not immediately return to baseline. This characteristic underscores their utility as persistent indicators of ongoing or recent cardiac stress, providing clinicians with critical information for monitoring and managing heart failure patients over time.

Echocardiography

Confirming the diagnosis of heart failure or assessing cardiac dysfunction through echocardiography is essential and should be promptly conducted in patients suspected of having heart failure. Transthoracic echocardiography (TTE) is a non-invasive diagnostic imaging method that offers comprehensive insights into the anatomy and performance of the heart. It enables the detection of myocardial, valvular, and pericardial abnormalities, providing crucial diagnostic information. Key assessments performed with TTE include measuring LVEF, assessing the sizes and volumes of the ventricles, evaluating the geometry of the heart chambers, identifying abnormalities in wall movement in specific regions, evaluating diastolic function, and estimating left ventricular and left atrial filling pressures. These parameters collectively aid in confirming the presence of heart failure, determining its severity, and guiding appropriate management strategies tailored to each patient's cardiac status.

Determination of Aetiology

Heart failure presents as a complex condition with diverse origins and underlying mechanisms, encompassing both cardiovascular and non-cardiovascular factors. Establishing the precise etiology is a crucial step in the diagnostic process to pinpoint the primary or secondary causes contributing to heart failure. This determination involves conducting standard evaluations to identify conditions such as myocardial ischemia, abnormal blood pressure responses to activity, chronotropic incompetence, and various types of arrhythmias originating from the atria or ventricles. Detecting these underlying conditions is pivotal as it directly influences treatment strategies. Additional diagnostic examinations relevant to identifying heart failure etiology are detailed in Table 3.9. Clarifying the etiology not only guides targeted therapeutic approaches but also plays a significant role in predicting the prognosis of heart failure based on its specific underlying causes.

Heart Failure With Reduced Ejection Fraction (HFrEF)

Non-Pharmacological Management

Multidisciplinary team-based heart failure management, implemented through specialized heart failure clinics, strives to lower readmission rates related to heart failure and cardiovascular mortality. These clinics are staffed by a diverse team including cardiologists, other specialist physicians, heart failure nurses, clinical pharmacists, nutritionists, and physiotherapists, all

Table 3.5 Conditions that cause an increase in natriuretic peptide values.

Cardiac Cause	Non-Cardiac Cause
• Heart failure, including right heart failure syndrome	• Elderly
• Acute coronary syndrome	• Anaemia
• Pulmonary embolism	• Ischemic stroke
• Myocarditis	• Subarachnoid haemorrhage
• Left ventricular hypertrophy	• Kidney failure
• Hypertrophic or restrictive cardiomyopathy	• Liver dysfunction, especially cirrhosis with ascites
• Valvular heart disease	• COPD, pulmonary hypertension
• Congenital heart disease	• Critical illness
• Atrial and ventricular tachyarrhythmias	• Severe burns
• Heart contusion	• Severe infections, including pneumonia and sepsis
• Electrical cardioversion, implantable cardioverter-defibrillator (ICD) shock	• Paraneoplastic syndromes
• Cardiac surgical procedures	• Severe metabolic and hormonal abnormalities (such as thyrotoxicosis and diabetic ketoacidosis)

collaborating closely to provide comprehensive care for heart failure patients. This multidisciplinary approach ensures that treatment plans are personalized to each patient's specific needs and circumstances. A study indicated that such personalized care delivered by a coordinated team might significantly reduce the risk of mortality by as much as 25%, underscoring the effectiveness of this model in improving outcomes for individuals with heart failure.[9]

Cardiac Rehabilitation and Self-Care Management

Data from numerous randomized clinical trials have consistently demonstrated that cardiac rehabilitation is a highly effective and cost-efficient intervention for individuals with heart failure. This structured program is associated with notable reductions in hospitalizations related to heart failure and all causes, along with improvements in patient-reported quality of life and decreased mortality rates among those with HFrEF. Concurrently, self-care management plays a pivotal role in heart failure treatment, encompassing actions aimed at maintaining physical stability, avoiding exacerbating behaviors, and early detection of worsening symptoms. Effective self-care management strategies significantly enhance heart failure symptoms, overall morbidity, quality of life, functional capacity, and long-term outcome. Key components of self-care management include patient adherence to prescribed therapies, independent monitoring of weight fluctuations, appropriate fluid intake management, and strategies for weight maintenance or loss as needed.[7]

Pharmacological Management

Renin-Angiotensin-Aldosterone System (RAAS) Blockers Angiotensin-Converting Enzyme Inhibitors (ACE-I)

ACE-Is are the preferred initial therapy for all symptomatic heart failure patients with an LVEF less than 40%, unless contraindicated. Indications for ACE-I administration in HFrEF include all patients, whether presenting with or without signs and symptoms of heart failure. However, several contraindications must be considered before initiating ACE-I therapy in HFrEF patients. These include a history of angioedema, serum potassium levels exceeding 5.5 mmol/L, severe aortic stenosis, pregnancy, bilateral renal artery stenosis, and elevated serum creatinine levels above 2.5 mg/dL, which are considered a relative contraindication. Proper assessment and consideration of these contraindications are crucial to ensuring safe and successful treatment of heart failure with ACE-I therapy.

Angiotensin Receptor-Neprilysin Inhibitor

Table 3.6 Echocardiographic abnormalities that are often found in heart failure.

Measurements	Abnormality	Clinical Implications
Left ventricular ejection fraction	Decreased (<40%)	Systolic dysfunction
Left ventricular function, global and focal	Akinesis, hypokinesis, dyskinesis	Myocardial infarction/ischemia, cardiomyopathy, myocarditis
End-diastolic diameter (EDD)	Increased (>55 mm)	Excessive volume, very likely heart failure
End-systolic diameter (ESD)	Increased (>45mm)	Excessive volume, very likely systolic dysfunction
Fractional shortening	Decreased (<25%)	Systolic dysfunction
Left atrium size	Increased (>40mm)	Increased filling pressure, mitral valve dysfunction, atrial fibrillation
Left ventricular thickness (>11-12 mm)	Hypertrophy Hypertension, aortic stenosis, hypertrophic cardiomyopathy	
Valve structure and function	Valve stenosis or regurgitation (especially aortic stenosis and mitral regurgitation)	Possible primary cause or as a complication of heart failure, gradient value and regurgitation fraction, hemodynamic consequences value, consider surgery
Mitral diastolic flow profile	Abnormalities in early and late diastolic filling patterns	Shows diastolic dysfunction and possible mechanisms
Peak velocity of tricuspid regurgitation (>3 m/sec)	Increased Elevated right ventricular systolic pressure, suspect for pulmonary hypertension	
Pericardium	Effusion, hemopericardium, thickening of the pericardium	Consider cardiac tamponade, uraemia, malignancy, systemic disease, acute or chronic or constrictive pericarditis
Inferior vena cava	Decreased (<15cm)	Low or reduced stroke volume
Aortic outflow velocity time integral	Dilation, retrograde flow	Increased right atrial pressure, right ventricular dysfunction, hepatic congestion

(ARNI)

The PARADIGM-HF study revealed that angiotensin receptor-neprilysin inhibitors (ARNI) are more effective compared to enalapril in lowering heart failure readmission rates and cardiovascular mortality in patients with chronic heart failure and an ejection fraction under 40%. The indications for ARNI administration in HFrEF encompass all patients, whether they exhibit signs and symptoms of heart failure or not. However, several contraindications must be considered before initiating ARNI therapy in HFrEF patients. These include a history of angioedema, serum potassium levels exceeding 5.5 mmol/L, severe aortic stenosis, pregnancy, bilateral renal artery stenosis, and elevated serum creatinine levels above 2.5 mg/dL, which are considered a relative contraindication. These criteria are crucial for the safe and effective administration of

Table 3.7 Additional examinations to determine the aetiology of heart failure.

Modality	Function
Cardiac Magnetic Resonance (CMR) Imaging	1. Assessing myocardial structure and function (especially in patients with a poor acoustic window) 2. Characterization of myocardial tissue in suspected infiltrative cardiomyopathy, Fabry disease, inflammatory cardiomyopathy (myocarditis), left ventricular non-compaction, amyloidosis, sarcoidosis, hemochromatosis, and other cardiomyopathies
Non-invasive imaging load test	Load testing with CMR, echocardiography, SPECT and PET to assess myocardial ischemia and viability in patients with heart failure and CHD
CT coronary angiography	Assessing the anatomy and presence/absence of coronary artery stenosis in heart failure patients with a low-moderate pre-test probability of CHD
SPECT	1. Technetium-99m to assess myocardial ischemia (if with pharmacological loading) as well as myocardial viability 2. Technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid (99mTc-DPD) scintigraphy; technetium-99 m pyrophosphate (99mTc-PYP) to identify cardiac amyloidosi
Right or left ventricular biopsy	Identification of various specific cardiac aetiologies such as amyloidosis, myocardial fibrosis, myocyte hypertrophy
Positron Emission Tomography Computed Tomography (PET-CT), specific genetic and laboratory tests	Confirm other specific aetiologies

ARNI therapy in heart failure management.

Angiotensin II Receptor Blockers (ARB)

ARBs are suggested for individuals afflicted with heart failure and an LVEF under 40%, and are also recommended for individuals who cannot tolerate ACE-I treatment. Indications for ARB administration in HFrEF include both symptomatic and asymptomatic patients who cannot tolerate ACE-I therapy. However, several contraindications must be taken into account before initiating ARB treatment in HFrEF patients. These include bilateral renal artery stenosis, pregnancy, serum potassium levels exceeding 5.5 mmol/L, severe aortic stenosis, and elevated serum creatinine levels above 2.5 mg/dL, which represents a relative contraindication. Additionally, ARBs should not be used concurrently with ACE-I and aldosterone antagonists due to potential risks, necessitating serial monitoring of kidney function and serum electrolytes when ARBs are used alongside ACE-I therapy. These considerations are crucial for optimizing the safety and efficacy of ARB treatment in managing heart failure.

Beta Adrenergic Receptor Blockers

Beta-blockers (BBs) are integral to the treatment of HFrEF, recommended alongside renin-angiotensin-aldosterone system (RAAS) inhibitors, aldosterone antagonists, and SGLT2 inhibitor drugs. Unless contraindicated, BBs should be prescribed to all HFrEF patients, regardless of the existence of heart failure signs and symptoms. Indications for BB administration in HFrEF include stable patients without recent changes in diuretic requirements, absence of need for intravenous inotropes, and no signs of severe fluid retention. However, several contraindications must be considered before initiating BB therapy in HFrEF patients. These include cardiogenic shock or hemodynamic instability, symptomatic bradyarrhythmias such as second or third-degree atrioventricular block and sick sinus syndrome without a permanent pacemaker, significant sinus bradycardia, pregnancy, and acute exacerbation of bronchial asthma (a relative contraindication for selective BBs). Non-selective BBs should be employed cautiously in patients with severe peripheral arterial disease. Careful assessment and adherence to these guidelines are crucial for the safe and effective use of

Table 4.1 Recommendations for Pharmacological Management of HFrEF.

Recommendations	COR	LOE
ACE-I is recommended for all HFrEF patients to reduce readmissions due to worsening heart failure, and increase patient survival rates.	I	A
-blockers are recommended for all stable HFrEF patients to reduce hospital admissions due to worsening heart failure, and reduce mortality	I	A
MRA is recommended for all HFrEF patients to reduce hospital admissions due to worsening heart failure, and improve patient survival rates.	I	A
ARNI is recommended as a replacement therapy for HFrEF patients who have received ACE-I or ARB to reduce the rate of rehospitalization due to heart failure and mortality.	I	B
Dapagliflozin or Empagliflozin is recommended for all HFrEF patients to reduce readmission rates due to worsening heart failure and mortality	I	A
ARB is recommended as a replacement therapy for HFrEF patients with signs and symptoms of heart failure who are intolerant to ACE-I or ARNI to reduce readmission rates due to worsening heart failure and mortality.	I	B
Loop diuretics are recommended in HFrEF to eliminate congestion	I	C
Ivabradine is recommended for HFrEF with signs and symptoms of heart failure, sinus rhythm and resting heart rate >70 beats per minute even after receiving the maximum dose of BB (the dose that the patient can tolerate), ACE-I and MRA to reduce the number of readmissions due to worsening heart failure and cardiovascular mortality	IIa	B
Ivabradine is recommended for HFrEF with signs and symptoms of heart failure, sinus rhythm and resting heart rate >70 beats per minute who cannot tolerate or are contraindicated to BB to reduce readmission rates due to worsening heart failure and cardiovascular mortality. The patient has also received ACE-I and MRA.	IIa	C

BBs in managing HFrEF.

Aldosterone Antagonists

Aldosterone antagonist drugs are essential components of the treatment regimen for HFrEF, recommended alongside renin-angiotensin inhibitors, β-blockers, and sodium glucose co-transporter-2 inhibitors (SGLT2 inhibitors). These medications are indicated for all HFrEF patients, regardless of the existence of heart failure signs and symptoms. However, several contraindications should be considered before initiating aldosterone antagonist therapy in HFrEF patients. These include serum potassium concentrations exceeding 5.5 mmol/L, the avoidance of concurrent use with other potassium-sparing diuretics or supplements, patients receiving both ACE-Is and ARBs, pregnancy, and elevated serum creatinine levels above 2.5 mg/dL (considered a relative contraindication). Additionally, a history of gynecomastia with spironolactone necessitates careful management, potentially requiring dose adjustment. Adherence to these guidelines ensures the safe and effective use of aldosterone antagonists in managing HFrEF.[10]

Sodium Glucose coTransporter-2 Inhibitor (SGLT-2 Inhibitor)

SGLT2 inhibitors represent a novel class of drugs recommended for managing HFrEF patients, regardless of their diabetic status. These medications are indicated for all HFrEF patients to help improve outcomes. However, certain contraindications should be noted before initiating SGLT2 inhibitor therapy in HFrEF patients. These include an estimated glomerular filtration rate (eGFR) below 20 mL/min/1.73 m^2, type 1 diabetes, and a history of diabetic ketoacidosis (requiring caution). Furthermore, the use of SGLT2 inhibitors during pregnancy and breastfeeding is not yet supported by sufficient evidence, warranting careful consideration. Adherence to these guidelines ensures the appropriate and safe use of SGLT2 inhibitors in the management of HFrEF.

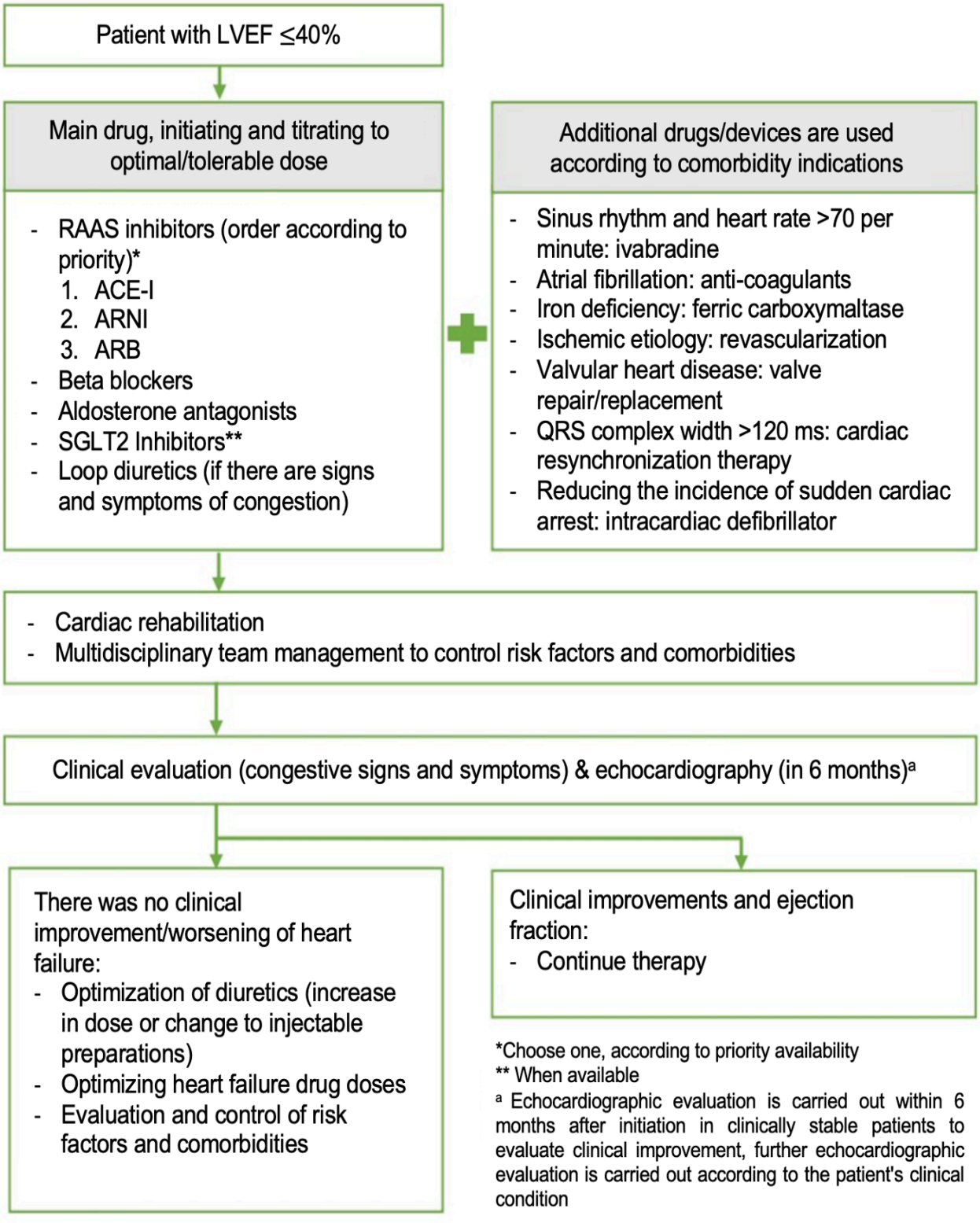

Figure 4.1 HFrEF management algorithm

Table 4.2 Main drug regimens in HFrEF.

Main drug regimens in HFrEF	Initiation Dose (mg)	Target Dose (mg)
ACE-Inhibitor		
Captopril	6.25 (3 times a day)	50 - 100 (3 times a day)
Enalapril	2.5 (twice a day)	10 - 20 (twice a day)
Lisinopril	2.5 - 5 (once a day)	20 - 40 (once a day)
Ramipril	2.5 (once a day)	5 (twice a day)
Perindopril	2 (once a day)	8 (once a day)
ARNI		
Sacubitril-Valsartan	50 (twice a day)	200 (twice a day)
ARB		
Candesartan	4-8 (once a day)	32 (once a day)
Valsartan	40 (twice a day)	160 (twice a day)
β-blockers		
Bisoprolol	1.25 (once a day)	10 (once a day)
Carvedilol	3.125 (twice a day)	25 (twice a day)
Metoprolol	12.5-25 (once a day)	200 (once a day)
Nebivolol	1.25 (once a day)	10 (once a day)
Aldosterone antagonist		
Spironolactone	25 (once a day)	50-100 (once a day)
Eplerenone	25 (once a day)	50 (oncea day)
SGLT2 Inhibitors		
Dapagliflozin	10mg (once a day)	10mg (once a day)
Empagliflozin	10mg (once a day)	10mg (once a day)
Loop Diuretic*		
Furosemide	According to clinical signs and symptoms of congestion	According to clinical signs and symptoms of congestion

* To find out more clearly about furosemide dose adjustments, see Consensus on Fluid Management in Heart Failure by Heart Failure and Cardiometabolic Working Group of Indonesian Heart Association 2020.

Loop Diuretics

Loop diuretics are crucial medications recommended for managing HFrEF to alleviate congestion. In heart failure with varying levels of ejection fraction, diuretics are strongly recommended (Class I) to mitigate the risk of readmission and improve symptoms associated with congestion. Indications for administering loop diuretics in HFrEF encompass all patients showing evidence of congestion, aiming to achieve fluid balance optimization. However, several relative contraindications necessitate cautious consideration before initiating loop diuretic therapy. These include hypotension with a blood pressure less than 90/50 mmHg, severe electrolyte disturbances, and indications of dehydration. By carefully assessing these factors, healthcare providers can ensure the appropriate use of loop diuretics while minimizing potential risks in managing HFrEF effectively.

Drugs and Additional Devices for HFrEF

Ivabradine

Ivabradine has demonstrated effectiveness in lowering mortality and hospitalizations among patients with HFrEF, as evidenced by findings from the SHIFT study. Resting heart rate serves as a modifiable risk factor, and achieving a target resting heart rate of less

Table 5.1 Markers of increased ventricular filling pressure using echocardiography modality.

Echocardiographic Markers	Sensitivity and Specificity	Pitfal
LAVI >32 ml/m^2 (SR) LAVI >40 ml/m^2 (AF)	sensitivity 49%; specificity 83%	LAVI underestimation in obesity Chronicity markers in AF
/e' >9 (resting) E/e' >13 (resting) E/e' >15 (exercise)	sensitivity 78%; specificity 59% sensitivity 46%; specificity 86%	
TR velocity >2.8 m/s TR velocity >3.4 m/s (exercise	probability: 92%	
RSVP >35 mmHg	used in the elderly, obesity and hypertension	
E/A ≥2		
Addition:		
RWT >0.42	absence of LVH is not exclusionary	
LVMI ≥115 g/m2 (male) LVMI ≥95 g/m2 (female)	HFpEF	
LV GLS<16%	sensitivity 62%; specificity 56%	

Table 5.2 Recommendations for management of HFpEF.

Recommendations	COR	LOE
HFpEF patients with hypertension must receive treatment according to blood pressure targets to prevent progression of heart failure	I	A
In HFpEF, SGLT2 inhibitors reduce cardiovascular death and heart failure hospitalization	I	A
In HFpEF, cardiac rehabilitation including aerobic exercise is recommended to improve functional capacity, in addition to pharmacological treatment	I	A
In HFpEF with obesity, weight loss with calorie restriction and aerobic exercise is recommended to improve the functional status and structure of the heart	I	A
In HFpEF, AF management can improve complaints	IIa	B
In HFpEF, spironolactone may be considered to reduce hospitalization in populations with a low risk of developing hyperkalaemia and creatinine values <2.5 mg/dl	IIb	B
In HFpEF, ARB or ARNI can be considered to reduce hospitalization at the lower end of the LVEF spectrum	IIb	B
In HFpEF, routine use of Nitrates or phosphodiesterase-5 inhibitors has not been shown to be effective in improving outcome	III	A

than 70 beats per minute is recommended. β-blockers are primary agents used to lower resting heart rate; however, in cases where patients do not reach this target despite receiving optimal or maximum tolerated doses of β-blockers, or exhibit intolerance to β-blockers, ivabradine should be considered as an adjunct therapy.[7,11]

Indications for the administration of ivabradine in HFrEF include patients in sinus rhythm with a resting heart rate above 70 beats per minute, even after receiving evidence-based optimal or highest tolerated doses of β-blocker therapy. Ivabradine is also suggested for patients who are in sinus rhythm who are intolerant to β-blockers or have failed β-blocker titration. However, several contraindications must be considered before initiating ivabradine therapy, such as hypotension with a blood pressure below 90/50 mmHg attributed to a slow heart rate, presence of rhythms other than sinus rhythm, heart conduction abnormalities including sinoatrial block, atrioventricular block, and sick sinus syndrome, severe liver disorders, and resting heart rates below 60

Table 6.1 Pharmacological therapy to consider in patients with heart failure (NYHA class II-IV) with mildly reduced ejection fraction.

Recommendations	Class	Level
Diuretics are recommended in patients with congestion and HFmrEF to relieve signs and symptoms.	I	C
ACE-I may be considered for patients with HFmrEF to reduce the risk of hospitalization and death due to heart failure.	IIb	C
ARBs may be considered for patients with HFmrEF to reduce the risk of hospitalization and death due to heart failure.	IIb	C
β-blockers may be considered for patients with HFmrEF to reduce the risk of hospitalization and death due to heart failure.	IIb	C
MRA may be considered for patients with HFmrEF to reduce the risk of hospitalization and death due to heart failure.	IIb	C
Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of hospitalization and death due to heart failure.	IIb	C

Table 6.2 Recommendations for heart failure with improved ejection fraction.

Recommendations	Class	Level
In HFimpEF after treatment, GDMT should be continued to prevent recurrence of heart failure and left ventricular dysfunction even in patients who may be asymptomatic.	I	C

beats per minute. Careful evaluation of these factors ensures the appropriate administration of ivabradine in HFrEF patients, optimizing therapeutic outcomes while minimizing risks.[7]

Digoxin

In patients experiencing symptomatic heart failure and an LVEF of less than 40% in sinus rhythm, digoxin serves as a therapeutic option to alleviate symptoms and reduce hospitalizations due to worsening heart failure. However, clinical trials have shown that digoxin does not significantly impact mortality rates in this patient population. Indications for administering digoxin in HFrEF include patients with atrial fibrillation (AF) characterized by rapid ventricular response, where digoxin effectively controls heart rate. Contraindications to the administration of digoxin in HFrEF encompass patients with bradyarrhythmia (such as second or third-degree heart block) and those with pre-excitation syndromes such as Wolff-Parkinson-White syndrome. These conditions pose risks of exacerbating arrhythmias when treated with digoxin, necessitating careful consideration and evaluation of alternative therapies in such cases.[7]

Cardiac Resynchronization Therapy (CRT)

One rationale for employing cardiac resynchronization therapy (CRT) in heart failure is its ability to synchronize the pumping action of the left and right ventricles. CRT involves the coordinated pacing of both the right ventricular endocardium and the left ventricular epicardium using a branch of the cardiac vein. Clinical trials have revealed that CRT enhances cardiac output, improves quality of life, increases functional capacity, and reduces mortality in patients with HFrEF who are already receiving pharmacological therapy. These benefits arise from improved efficiency in ventricular contraction and pump function.

CRT achieves these outcomes by maintaining atrioventricular synchrony, as well as inter- and intraventricular synchrony, which enhances left ventricular function and reduces functional mitral regurgitation. Additionally, CRT promotes reverse left ventricular remodeling, evidenced by increases in LVEF, along with decreases in end-systolic and end-diastolic volumes, mitral regurgitation, and septal dyskinesia. However, the specific mechanisms underlying the therapeutic effects of CRT can vary among patients and may even change over time within an individual patient. Predicting an individual patient's response to CRT

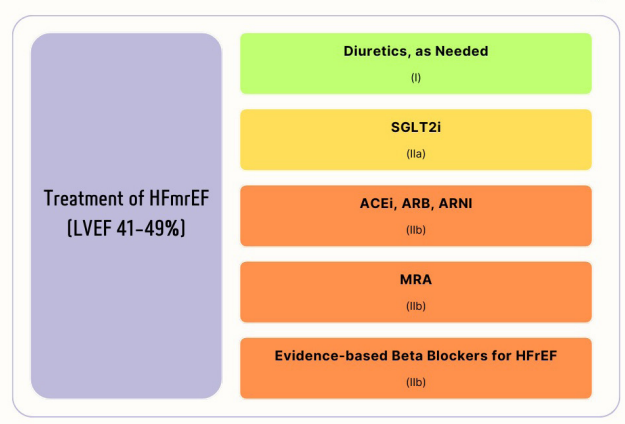

Figure 6.1 Proposed HFpEF diagnosis algorithm

remains challenging due to these variable mechanisms. Comprehensive guidelines for the implementation of CRT in heart failure are detailed in the Therapeutic Guidelines for Cardiac Implantable Electronic Devices (CIED) published by the Indonesian Heart Association in 2014. These guidelines provide clinicians with structured recommendations for the optimal use of CRT to improve outcomes among individuals suffering from heart failure.

Intracardiac Defibrillator

An implantable cardioverter defibrillator (ICD), also referred to as an intracardiac defibrillator, is a device placed in a patient's chest to address severe heart rhythm abnormalities that may result in sudden cardiac death. The Sudden Cardiac Death in Heart Failure (SCD-HeFT) study, a primary prevention trial involving patients with HFrEF, demonstrated that ICD therapy reduces the risk of all-cause mortality by 23% compared to placebo over a 5-year period. This benefit remained constant across patients with both ischemic and non-ischemic cardiomyopathy, which comprised the majority (70%) of the study population. However, the study did not observe any mortality benefit from ICD therapy in patients categorized as NYHA functional class III or IV. Comprehensive guidelines for the use of ICDs in heart failure are outlined in the Therapeutic Guidelines for CIED published by the Indonesian Heart Association in 2014, providing clinicians with detailed recommendations for optimal device placement and management to enhance patient outcomes.

Heart Failure With Preserved Ejection Fraction (HFpEf)

HFpEF Diagnosis Recommendations

The initial investigation of heart failure with preserved ejection fraction (HFpEF) involves assessing signs and symptoms indicative of heart failure, along with basic supportive examinations and their interpretation. This initial stage is typically conducted by primary care physicians or specialists managing individuals predisposed to heart failure. Recommended simple examinations include ECG, chest x-ray, and standard laboratory tests. These tests are crucial for identifying treatable causes, exploring other potential etiologies, and assessing comorbidities associated with heart failure. Additionally, they help evaluate therapeutic options in specific clinical contexts, guiding further management strategies aimed at optimizing patient outcomes.

Further Investigation of HFpEF

This stage involves confirming the diagnosis of HFpEF through ECG and, if available, NP testing. If the initial echocardiography yields inconclusive results, further investigations such as stress echocardiography or invasive hemodynamic assessment (right heart catheterization) may be necessary. These additional tests are essential for providing more detailed insights into cardiac function, hemodynamics, and ventricular performance, thereby aiding in the accurate diagnosis and subsequent management of HFpEF. They help clinicians tailor treatment strategies effectively, addressing the specific needs and conditions of each patient to optimize clinical outcomes.

Natriuretic peptides (NP)

The examination of NP exhibits a notable high negative predictive value (NPV) but a modest positive predictive value (PPV) across both acute and non-acute scenarios. Consequently, NP testing is primarily recommended for excluding heart failure rather than confirming its presence. Normal levels of NP plasma concentration do not definitively rule out HFpEF, particularly in individuals with obesity. NT-proBNP values are prone to elevation in cases of impaired kidney function, indicated by an eGFR below 60 mL/

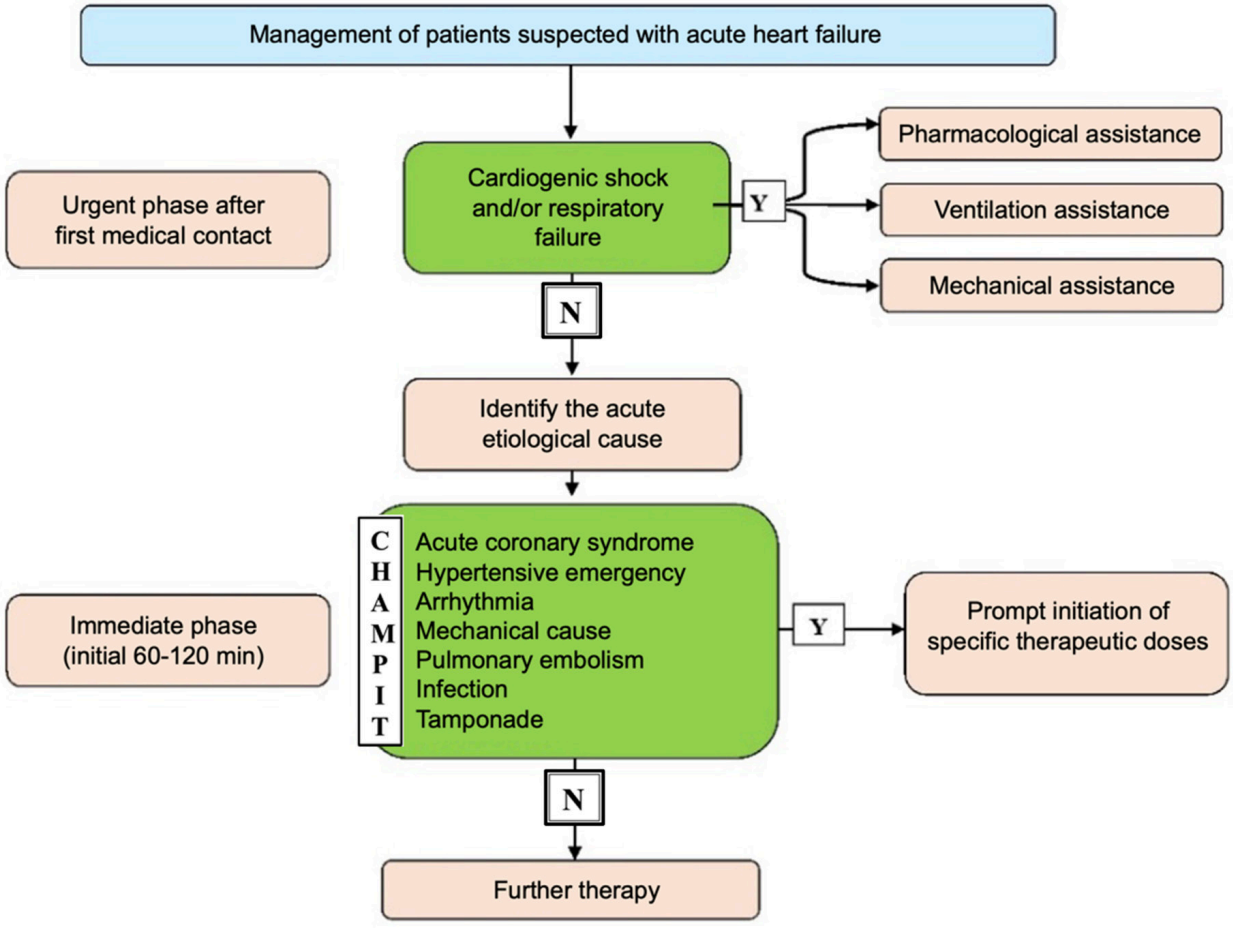

Figure 7.1 Management of patients with suspected acute heart failure

minute/1.73 m². Additionally, in obese individuals, the cutoff value for NP inclusion criteria is adjusted to 50% of the established standard criteria. These nuances underscore the importance of interpreting NP results cautiously, considering individual patient characteristics and clinical context when assessing for HFpEF.

Echocardiography

The primary diagnostic criterion for HFpEF revolves around elevated left ventricular filling pressure, which can manifest either at rest or during physical exertion. Echocardiography serves as a pivotal modality for identifying markers indicative of increased ventricular filling pressure in the diagnosis of HFpEF. Specific echocardiographic findings that signify elevated filling pressures are detailed in Table 5.

Diastolic Stress Echocardiography

Diastolic stress echocardiography plays a crucial role in detecting HFpEF by evaluating the increase in left ventricular filling pressure during exercise, particularly in patients who exhibit heart failure symptoms triggered by physical activity. This method involves assessing changes in E/e' ratio during exercise, which correlates well with invasive hemodynamic measurements and aids in differentiating between cardiac and non-cardiac origins of exertional dyspnea. Typically conducted using a supine bicycle or treadmill, the cycling protocol starts at 25 watts and increases incrementally every 3 minutes until reaching the target heart rate or symptomatic threshold. Alternatively, a treadmill can be used with adjustments to the protocol as needed. Key measurements include pulsed Doppler mitral flow,

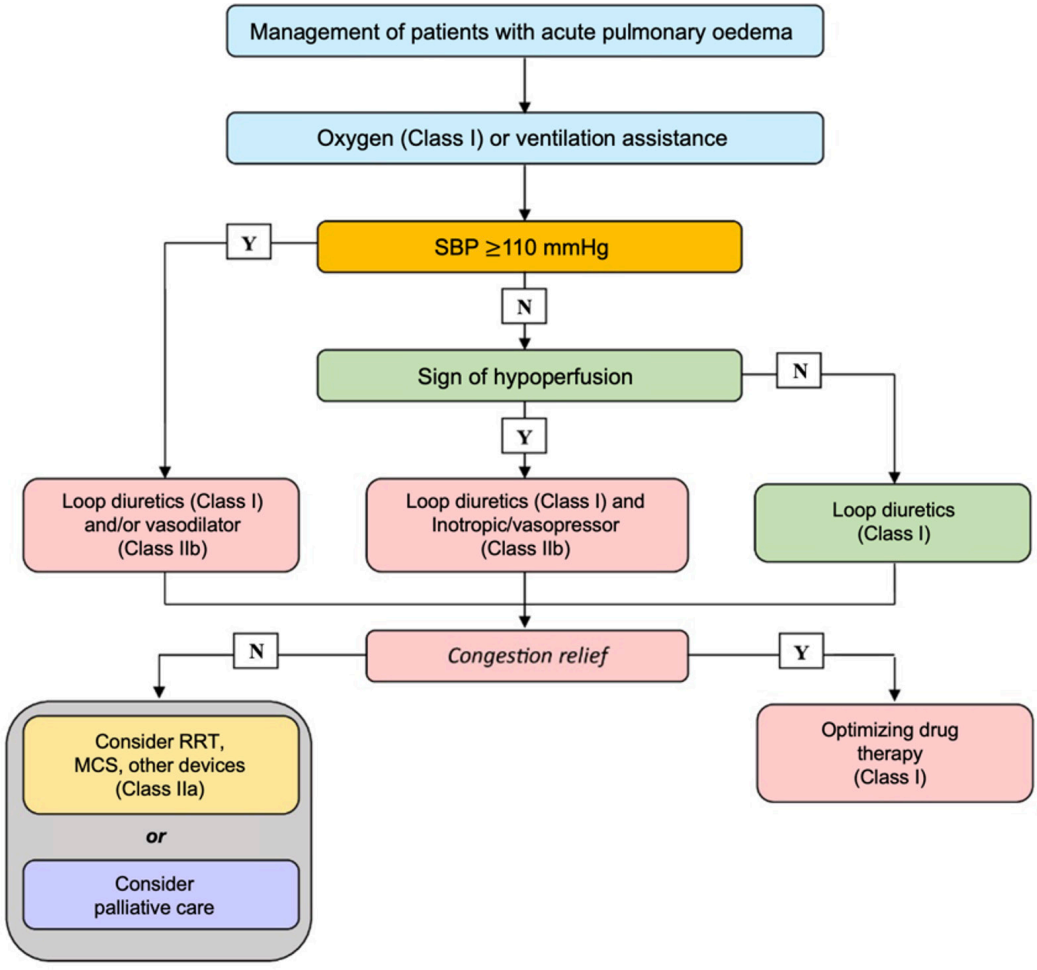

Figure 7.2 Management of acute pulmonary oedema

tissue Doppler imaging (TDI) of mitral annulus velocity, and continuous wave Doppler of tricuspid regurgitant jet, both before, during, and after exercise. Parameters such as septal E/e' ratio >15, mean E/e' >14, and peak tricuspid regurgitation velocity >2.8 m/s during exercise indicate diastolic dysfunction and elevated filling pressures associated with HFpEF, crucial for diagnosis and prognostication in these patients.

Invasive Hemodynamic Assessment

Left and right heart catheterization, while not routinely necessary for diagnosing HFpEF, can provide valuable insights in select cases. This procedure helps measure ventricular filling pressures, specifically cardiac filling pressures such as left ventricular end-diastolic pressure (LVEDP) and pulmonary capillary wedge pressure (PCWP), both at rest and during activity. Elevated thresholds (LVEDP ≥ 16 mmHg, PCWP ≥ 15 mmHg) are indicative of HFpEF. If these pressures are not initially elevated at rest, exercise hemodynamic testing may be warranted. Studies have revealed that a significant proportion of patients with normal resting filling pressures can exhibit abnormal hemodynamics during exertion, underscoring the utility of stress testing in assessing HFpEF. Furthermore, research has highlighted that right ventricular dysfunction in HFpEF is a reliable indicator of adverse outcomes, emphasizing the importance of comprehensive hemodynamic evaluation in managing these patients.

Management Recommendations

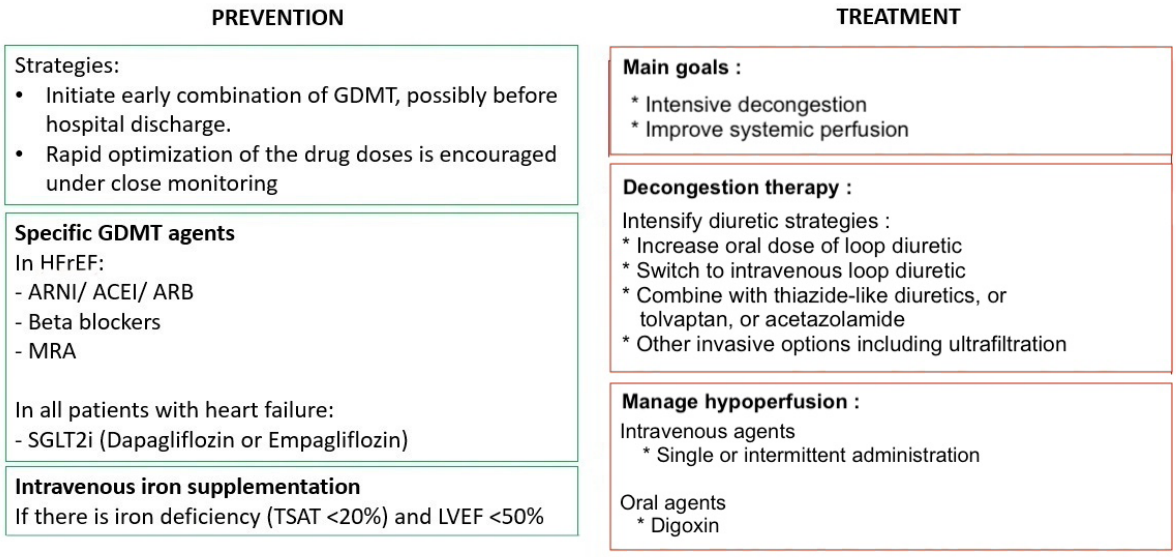

Figure 8.1 Management of worsening heart failure.

Treatment strategies for HFpEF encompass a multifaceted approach incorporating supportive care, weight reduction interventions tailored for obese individuals, structured rehabilitation through exercise programs, management of concurrent medical conditions, and targeted pharmacotherapy. The following recommendations are crucial considerations in the comprehensive management of HFpEF:

- Controlling blood pressure is critical to avoid the appearance of heart failure symptoms. In treating hypertension alongside HFpEF, RAAS blockers (such as ACE-Is, ARBs, or ARNIs) are often recommended as first-line therapy. BBs are frequently prescribed for individuals with high blood pressure and a history of coronary artery disease, myocardial infarction, or AF with rapid ventricular response. However, caution is advised when using β-blockers in HFpEF due to their potential to exacerbate chronotropic incompetence, a frequent finding in these patients.
- Supportive therapies such as aerobic exercise and weight loss programs are beneficial in improving exercise capacity, as evidenced by increased oxygen consumption and enhanced quality of life. Cardiac rehabilitation is universally suitable and has demonstrated efficacy in alleviating symptoms among HFpEF patients. Recommendations include engaging in moderate-intensity exercises such as walking or cycling for 20 to 60 minutes, three to five days per week, with adjustments for shorter durations as needed, particularly for elderly individuals. For obese HFpEF patients, reducing daily caloric intake by 400 kcal/day can achieve approximately a 6.6% reduction in body weight.
- Other pharmacological treatments aim to manage concurrent conditions, taking into account the potential adverse effects on heart failure. Careful selection of medications for these comorbidities is essential to avoid exacerbating the heart failure condition.
- The primary treatment approach for HFpEF currently involves diuretics for managing congestion and SGLT2 inhibitors. Diuretics such as furosemide reduce heart filling pressure and alleviate symptoms of dyspnea, but caution is necessary due to potential side effects like volume depletion, orthostatic hypotension, and the likelihood of acute kidney injury. Older HFpEF patients with left ventricular hypertrophy are particularly susceptible to these effects compared to younger individuals without hypertrophy, necessitating careful dose adjustments in this demographic. SGLT2 inhibitors like empagliflozin (for eGFR ≥20 ml/min/1.73m^2) or dapagliflozin (for eGFR ≥25 ml/min/1.73m^2) can be prescribed, but are contraindicated in type 1 diabetes, ketoacidosis, and recurrent genitourinary infections.

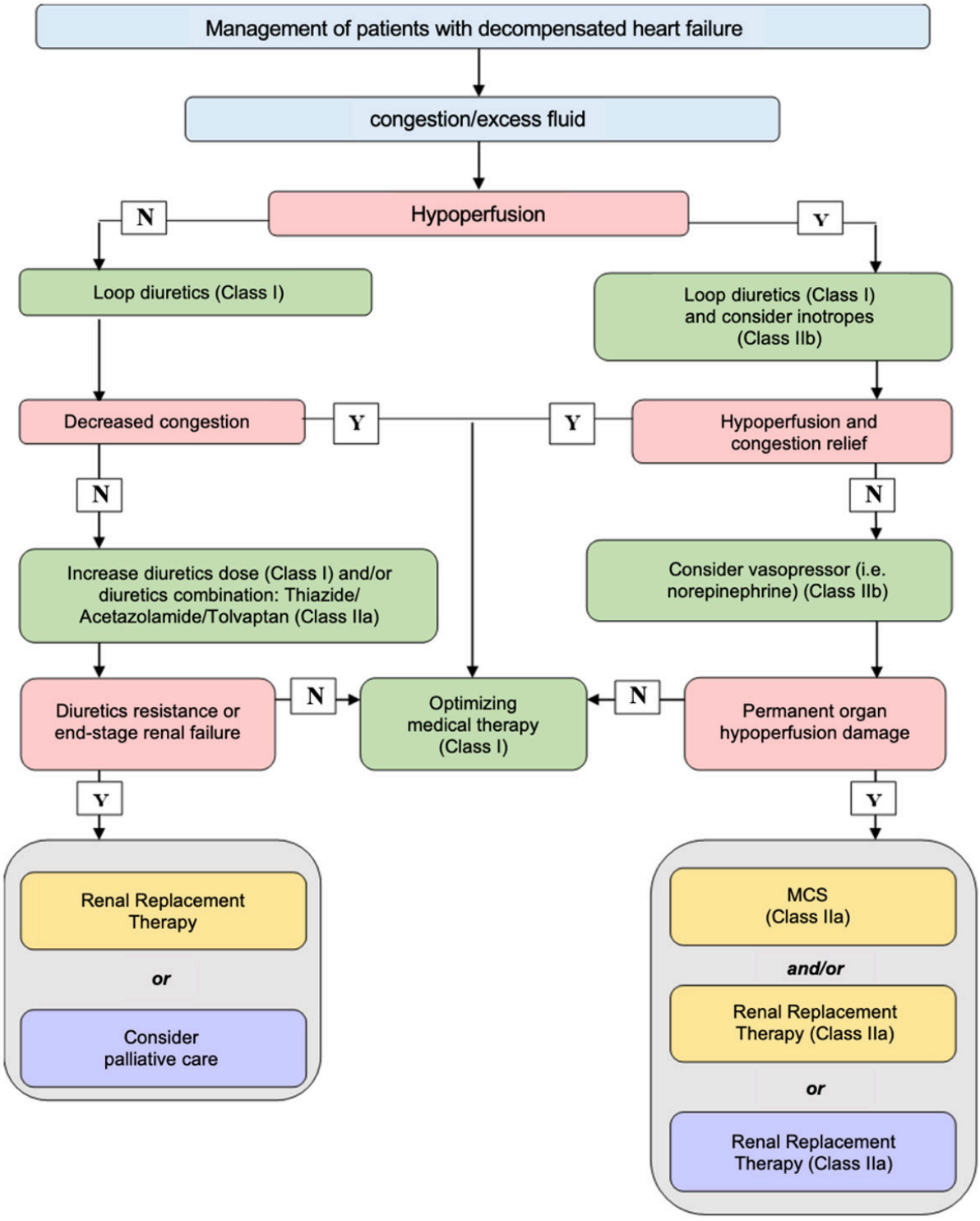

Figure 8.2 Treatment algorithm for decompensated heart failure.

Table 9.1 Pharmacological therapy to consider in patients with heart failure (NYHA class II-IV) with mildly reduced ejection fraction.

Step 1: β-blockers are the first line recommendation to reduce angina because these drugs also have advantages in the treatment of heart failure β-blockers alternatives: • Ivabradine, should be considered in patients with sinus rhythm who are intolerant of β-blockers for relief of angina • Oral or transcutaneous nitrates, should be considered in patients intolerant of β-blockers, to relieve angina • Amlodipine, should be considered in patients intolerant of β-blockers, for relief of angina • Nicorandil, may be considered in patients intolerant of β-blockers, for relief of angina
Step 2: Adding anti-anginal medication The following drugs can be added to β-blockers, if the combination is not recommended • The addition of ivabradine is recommended if angina persists despite treatment with β-blockers or alternatively, to relieve angina • The addition of oral or transcutaneous nitrates, recommended if angina persists despite treatment with β-blockers or alternatives, to eliminate angina • The addition of amlodipine, recommended if angina persists despite treatment with β-blockers or alternatives, to relieve angina • The addition of nicorandil may be considered if angina persists despite treatment with β-blockers or alternatively, to relieve angina.
Step 3: Coronary revascularization • Coronary revascularization is recommended if angina persists despite receiving two anti-anginal drugs • Coronary revascularization alternative: a third angina drug from those mentioned above can be considered if angina persists despite receiving two anti-anginal drugs • Diltiazem and verapamil are not recommended because they are negative inotropic and can worsen heart failure

Minor increases in creatinine (0.2-0.4 mg/dl), glucosuria, and a rise in hematocrit (approximately 2%) are expected and typically tolerated. However, if eGFR decreases by more than 40% from baseline within 4-5 weeks of SGLT2 inhibitor use, further evaluation is required. Continuation of therapy may involve a 50% dose reduction if eGFR decline persists, or discontinuation if eGFR falls below 20 ml/min/1.73m².

- Medical treatment using spironolactone has demonstrated improvement in diastolic function among HFpEF patients, despite the absence of notable differences in outcomes related to cardiovascular death, heart failure hospitalization, or cardiac arrest compared to those receiving a placebo. This suggests potential benefits of MRA in managing HFpEF in patients with LVEF ≥45%, raised BNP levels, or those recently treated. However, the use of spironolactone was linked to a greater occurrence of side effects, including hyperkalemia and elevated creatinine levels. It is not advisable for patients with an eGFR below 30 mL/min/1.73m², creatinine levels above 2.5 mg/dL, or potassium levels exceeding 5.0 mEq/L.
- Medical treatment using ARBs did not lead to a decrease in cardiovascular mortality. However, hospitalizations due to heart failure were less common among patients receiving candesartan compared to those receiving a placebo, particularly among individuals with the lowest LVEF values.
- Medical treatment using Sacubitril/Valsartan (Sac/Val) did not result in a reduction in cardiovascular mortality or hospitalization rates overall. However, a study indicated that among women with HFpEF and an LVEF ≤57%, Sac/Val decreased the likelihood of hospitalization or cardiovascular death by 60%.
- Medical treatment with nitrates did not show any beneficial effects in improving quality of life, exercise tolerance, or reducing BNP levels in patients with HFpEF.
- Phosphodiesterase-5 inhibition therapy did not demonstrate improvements in exercise tolerance or oxygen consumption in patients with HFpEF.
- More than 60% of HFpEF patients experience

Table 9.2 Recommendations for hypertension therapy for patients with NYHA fc II-IV heart failure and systolic dysfunction.

Step 1 One or more of ACE-I/ARB, β-blockers, and MRA are recommended as first-, second-, and third-line therapy, respectively, because of their interrelated benefits in heart failure.
Step 2 OThiazide diuretics or if the patient is being treated with a thiazide diuretic, switching to a loop diuretic is recommended if hypertension persists despite receiving combination therapy with ACE-I/ARB, β-blockers and MRA.
Step 3 • Amlodipine, recommended if hypertension persists despite receiving combination therapy with ACE-I/ARB, β-blockers, MRA and diuretics • Hydralazine, recommended if hypertension persists despite receiving combination therapy with ACE-i/ARB, β-blockers, MRA and diuretics • Alpha adrenoreceptor antagonists are NOT recommended, due to safety concerns (fluid retention, neurohormonal activation, worsening of heart failure)

Table 9.3 Recommendations for the management of heart failure in type II diabetes patients.

1.	ACE-I/ARB, β-blockers are recommended in diabetic patients with heart failure to reduce mortality and rehospitalization
2.	MRA, recommended in patients with diabetes and heart failure, who have received ACE-I/ARB, β-blockers who are still on NYHA II-IV to reduce the risk of worsening heart failure and rehospitalization
3.	Thiazolidinedione and saxagliptin should be avoided in diabetic patients with heart failure, as they may cause fluid retention
4.	Metformin or SGLT2 inhibitors are recommended as first-line therapy in heart failure patients with normal renal function and renal function should be evaluated periodically

comorbid AF at some stage before or after their HFpEF diagnosis. The management of AF in this context involves careful consideration of anticoagulant use and monitoring for associated risk factors such as sleep apnea, obesity, thyroid disease, or heart valve disease. Rhythm conversion strategies for AF may offer potential benefits in terms of reducing all-cause mortality or episodes related to heart failure treatment in HFpEF. β-blockers and non-dihydropyridine calcium channel blockers (CCBs) are among the pharmacological options available for managing AF in HFpEF.

Heart Failure Mildly Reduced Ejection Fraction (HFmrEF) And Heart Failure Improved Ejection Fraction (HFimpEF)

Definition of HFmrEF

Heart failure with an LVEF ranging from 41% to 49%, often referred to as heart failure with mid-range ejection fraction (HFmrEF), is diagnosed when patients exhibit symptoms and/or signs of heart failure alongside a slight reduction in LVEF.

Definition of HFimpEF

Heart Failure with Improved Ejection Fraction (HFimpEF) is characterized by heart failure where the initial LVEF was 40% or lower, with subsequent improvement by at least 10 percentage points from the baseline value, or a follow-up measurement showing an ejection fraction greater than 40%.

Management of HFmrEF (LVEF 41-49%)

The management of HFmrEF includes several key therapeutic approaches. First, diuretics are utilized if there is a need to manage fluid overload and congestion. Second, SGLT2 inhibitors are recommended due to their benefits in reducing cardiovascular events and heart failure progression. Third, ACE-Is, ARBs, or ARNIs are prescribed to manage blood pressure and reduce the workload on the heart. Fourth, aldosterone antagonists help in further reducing fluid retention and improving outcomes. Finally, β-blockers are administered based on evidence supporting their efficacy in treating HFrEF, aiming to optimize heart function and patient outcomes.[6]

HFmrEF Recommendations Based on Referenced Studies Supporting the Recommendations

- In patients with HFmrEF, SGLT2 inhibitors

Table 9.4 Cardiorenal syndromes based on pathophysiological mechanism.

Type	Syndrome	Pathophysiology
I	Acute Cardiorenal Syndrome	Acute decrease in heart function (acute cardiogenic shock or ADHF – acute coronary syndrome/ACS) which causes acute kidney injury (AKI)
II	Chronic Cardiorenal Syndrome	Chronic decline in heart function (congestive heart failure) which causes chronic kidney disease (CKD)
III	Acute Renocardiac Syndrome	Acute decrease in kidney function (ischemia or glomerulonephritis) causes acute heart problems (arrhythmia, ischemia, infarction)
IV	Chronic Renocardiac Syndrome	Decreased chronic kidney function (ischemic or chronic glomerulonephritis) causes chronic heart problems (LVH/left ventricular hypertrophy, heart failure)
V	Secondary Cardiorenal Syndrome	Systemic conditions (diabetes mellitus, sepsis) cause disruption of both organs

may offer benefits by reducing the incidence of hospitalization and cardiovascular death.

- Among symptomatic and asymptomatic HFmrEF patients (LVEF 41%–49%), the consideration of scientifically supported β-blockers for HFrEF, ARNI, ACE-I, or ARB, and aldosterone antagonists may help reduce the likelihood of hospitalization for heart failure and mortality from cardiovascular disease. This approach is particularly beneficial for patients with reduced LVEF, aiming to improve overall outcomes in heart failure management.[6]

HFimpEF Recommendations

In patients with HFimpEF who have undergone treatment according to GDMT, it is essential to maintain therapy to avoid the recurrence of heart failure and left ventricular dysfunction, even in those who are asymptomatic. The TRED-HF study, a small-scale investigation involving patients with HFimpEF, demonstrated a significant decrease in ejection fraction among individuals with dilated cardiomyopathy (initial LVEF 44%) within 6 months after discontinuing GDMT. Based on these findings, it is strongly advised to continue GDMT in patients with HFimpEF, including those without symptoms, to mitigate the likelihood of developing heart failure progression and deterioration in left ventricular function.[6]

Acute Heart Failure

Definition

Acute heart failure refers to a condition marked by a sudden or progressive onset or aggravation of symptoms and signs of heart failure, typically leading to hospitalization or an unplanned visit to the emergency department. This condition is categorized into two types based on its onset: de novo, which represents the initial manifestation of heart failure in patients previously asymptomatic, and acute decompensation, which occurs when there is a sudden worsening of symptoms in individuals with previously stable chronic heart failure.[7]

Management

Diagnostic management and the initiation of pharmacological and non-pharmacological therapies must be conducted concurrently in patients experiencing acute heart failure. Upon presentation, individuals are triaged based on the severity of hemodynamic instability and the critical nature of their illness. This triage helps prioritize interventions such as oxygen therapy, diuretics to relieve congestion, and vasodilators or inotropes to stabilize hemodynamics.[7]

Clinical Presentation

There are four major categories of patients who exhibit acute heart failure, each exhibiting symptoms and signs that can overlap: acute pulmonary edema, acute decompensated heart failure (ADHF), isolated right

Table 9.5 Examples of frailty status screening with the FRAIL questionnaire.

Characteristics	Measurement
FATIGUE	In the last 4 weeks, how much time/how often did you feel tired? Score 1 if the answer is "all the time" or "most of the time", otherwise score 0
RESISTANCE	Do you have difficulty climbing 10 steps independently without resting and without using tools? Yes: score 1, No score: 0
AMBULATION	Do you have difficulty walking several hundred meters alone and without assistive devices? Yes: 1 No:0
ILLNESS	Has a doctor ever told you about your illnesses (11 major illnesses: Hypertension, Diabetes, Cancer [other than minor skin cancer], chronic lung disease, heart attack, congestive heart failure, chest pain, asthma, joint pain, stroke and kidney disease?) 0-4 diseases : 0 5-11 diseases: 1
LOSS OF WEIGHT	"How much do you weigh barefoot right now? One year ago, how much did you weigh with clothes on and barefoot?" Information on calculating body weight in percent: Weight 1 year ago – current weight multiplied by 100% If the result is >5%: 1 If the result is <5%: 0

Interpretation of Results: Robust/Fit if score 0, Prefrail: score 1-2, Frail: Score 3-5
Adapted from: J Nutr Health Aging. 2012

heart failure, and cardiogenic shock. These categories are distinguished by the presence of either peripheral congestion or signs of hypoperfusion, necessitating distinct therapeutic approaches tailored to address these specific clinical manifestations. However, discussions pertaining to isolated right heart failure and cardiogenic shock fall outside the scope of this guideline, focusing instead on management strategies tailored to acute pulmonary edema and ADHF presentations.[7]

Acute Pulmonary Oedema

Acute pulmonary edema is characterized by significant pulmonary congestion, typically presenting with clinical features such as shortness of breath exacerbated by lying flat (orthopnea), respiratory distress including hypoxia and hypercapnia, rapid breathing exceeding 25 breaths per minute (tachypnea), and increased work of breathing. Immediate therapeutic interventions are crucial in managing this condition. Firstly, oxygen therapy using continuous positive airway pressure (CPAP), non-invasive positive pressure ventilation (NIPPV), or high-flow nasal cannula can be initiated to improve oxygenation. Secondly, intravenous diuretics are administered to alleviate pulmonary congestion by promoting fluid excretion. Thirdly, intravenous vasodilators may be considered if the patient's systolic blood pressure allows, aimed at reducing left ventricular afterload and thereby enhancing heart function. These interventions aim to stabilize respiratory distress and mitigate acute exacerbations of symptoms associated with heart failure in patients with acute pulmonary edema.[7]

Use of Other Diuretic Agents

Thiazide

The rationale behind using thiazides in acute heart failure stems from observations of heightened sodium retention in the distal nephron following prolonged use of loop diuretics. Research indicates thiazides' efficacy in patients with an eGFR decrease to less than 30 mL/minute, with greater benefits seen when eGFR exceeds this threshold. Hydrochlorothiazide is typically administered orally, ranging from 25 to 100 mg per day. This approach helps manage fluid overload by complementing the action of loop diuretics, particularly in cases where renal function allows for continued diuretic therapy.

Table 10.1 Individual approach based on the patient's clinical profile.

No	Patient profile	Therapy that must be given	Therapy that should be reduced or stopped temporarily	Therapy that should be added
1	Patients with ↓ blood pressure and ↑ heart rate	SGLT2i, MRA	BB, ACE-I/ARB/ARNI, diuretics	Ivabradine
2	Patients with ↓ blood pressure and ↓ heart rate	SGLT2i, MRA	BB, ACE-I/ARB/ARNI, diuretics	
3	Patients with normal blood pressure and ↓ heart rate	SGLT2i, ACE-I/ARB/ARNI, MRA, diuretics	BB	
4	Patients with normal blood pressure and ↑ heart rate	SGLT2i, ACE-I/ARB/ARNI, BB, MRA, diuretics		Ivabradine
5	Patients with AF and normal blood pressure	SGLT2i, ACE-I/ARB/ARNI, BB, MRA, diuretics		Anticoagulants, digoxin
6	Patients with AF and ↓ blood pressure	SGLT2i, ACE-I/ARB/ARNI, MRA	BB, diuretics	Anticoagulants
7	Patients with CKD and/or ↑ Potassium levels	SGLT2i, BB, diuretic	ACE-I/ARB/ARNI, MRA (based on eGFR dan K)	Hydralazine/ ISDN (CKD), potassium binder (↑ K)
8	Before discharge	SGLT2i, ACE-I/ARB/ARNI, BB, MRA	BB (if residual congestion remains)	Omecamtiv mecarbil* (in certain patients)
9	Patients with hypertension despite on GDMT	SGLT2i, ACE-I/ARB/ARNI, BB, MRA, diuretics		Hydralazine/ ISDN

*Not yet available in Indonesia

Acetazolamide

Acetazolamide acts as a carbonic anhydrase inhibitor, working to impede sodium reabsorption in the proximal tubule of the kidneys. The ADVOR study, a randomized controlled trial (RCT) focusing on ADHF patients with volume overload, demonstrated that supplementing optimal loop diuretic therapy with 500 mg of acetazolamide can enhance diuretic response. Typically, acetazolamide is prescribed at doses ranging from 250 to 375 mg per day, at the highest dosage reaching up to 500 mg daily. This approach aims to further alleviate fluid retention in ADHF patients by facilitating additional sodium and fluid excretion through the kidneys.

Tolvaptan

Vasopressin antagonists such as tolvaptan act by preventing water reabsorption in the distal nephron through antagonism of arginine vasopressin, which reduces the expression of luminal aquaporin channels in the renal collecting ducts. This mechanism promotes aquaresis, the excretion of water without causing significant loss of sodium. Currently, tolvaptan is indicated for use in patients experiencing acute heart failure or decompensated heart failure, with or without hyponatremia and renal dysfunction, to achieve notable reductions in weight, alleviation of shortness of breath, and resolution of edema. The initial dosage typically ranges from 7.5 to 15 mg, administered cautiously to avoid hypernatremia, which necessitates discontinuation of the medication.

Table 10.2 I-NEED-HELP acronyms.

	I-NEED-HELP
I	IV inotropic
N	NYHA IIIB/IV or persistent elevation of natriuretic peptide
E	End-organ dysfunction
E	Ejection fraction <35%
D	Defibrillator shocks
H	Hospitalization >1 kali
E	Edema despite escalation of diuretics
L	Low blood pressure, high heart rate
P	Prognostic medication: progressive intolerance or down-titration of GDMT

Decompensated Heart Failure

Decompensated Heart Failure denotes a progressive escalation of heart failure syndrome that leads to deteriorating clinical outcomes, necessitating aggressive evaluation and intervention. According to the latest consensus, this situation is categorized into two scenarios: worsening heart failure and ADHF.[5]

Worsening heart failure involves an exacerbation of symptoms and clinical signs in patients with a pre-existing diagnosis of heart failure, despite the continuation of treatment.[5] This definition excludes new-onset heart failure and conditions triggered by specific factors such as comorbidities or poor treatment adherence. Disease progression itself typically underlies this deterioration.[12] Outpatient management may involve periodic administration of intravenous diuretics or optimization of oral medications, while severe cases may necessitate emergency room visits or hospitalization. Early recognition of worsening heart failure is crucial as it indicates progression to an advanced stage. Management focuses on treating current clinical conditions and preventing future worsening through optimized therapy and proactive interventions.[13]

ADHF often arises from escalating congestion, sometimes accompanied by hypoperfusion, triggered by conditions such as infections, rapid AF, hypertensive emergencies, or non-compliance with fluid restrictions or medications.[5] Management primarily focuses on identifying and addressing precipitating factors, implementing strategies for decongestion, and improving hypoperfusion status to stabilize the patient's condition and prevent further deterioration.[7]

Heart Failure and Comorbidity

Management of Heart Failure and Comorbidity

Management of comorbidities is crucial in the care of patients with heart failure for several reasons. Firstly, comorbidities can impact the effectiveness of cardiac treatments. Secondly, therapy for comorbidities can alleviate symptoms and improve conditions of heart failure, such as the use of certain diabetes drugs like Thiazolidinediones. Thirdly, medications for heart failure and those for comorbidities can interact, which may reduce patient compliance; for example, the use of β-blockers in individuals suffering from severe asthma. Finally, most comorbidities are linked with the clinical state of heart failure and are linked with a poor prognosis, as seen in conditions like diabetes and hypertension.

Chronic Coronary Syndrome

In managing Chronic Coronary Syndrome, BBs are the primary choice of treatment. An alternative approach to this comorbidity is revascularization, which can also be evaluated depending on the patient's specific clinical condition.

Hypertension

Hypertension is linked to a higher likelihood of developing heart failure. Antihypertensive treatment markedly lowers the risk of heart failure, but alpha adrenoceptor blockers show lower effectiveness compared to other antihypertensive agents in achieving this reduction. CCBs with negative inotropic effects, such as verapamil and diltiazem, are not recommended for treating hypertension in patients with HFrEF, though they can still be used in HFpEF. If blood pressure remains uncontrolled despite treatment with ACE inhibitors, ARBs, β-blockers, MRAs, and diuretics, then hydralazine and amlodipine may be prescribed. Among individuals experiencing acute heart failure, the use of nitrates to lower blood pressure is recommended.

Type II Diabetes Mellitus

Diabetes is a very common comorbidity in heart failure and is associated with a worsening prognosis and

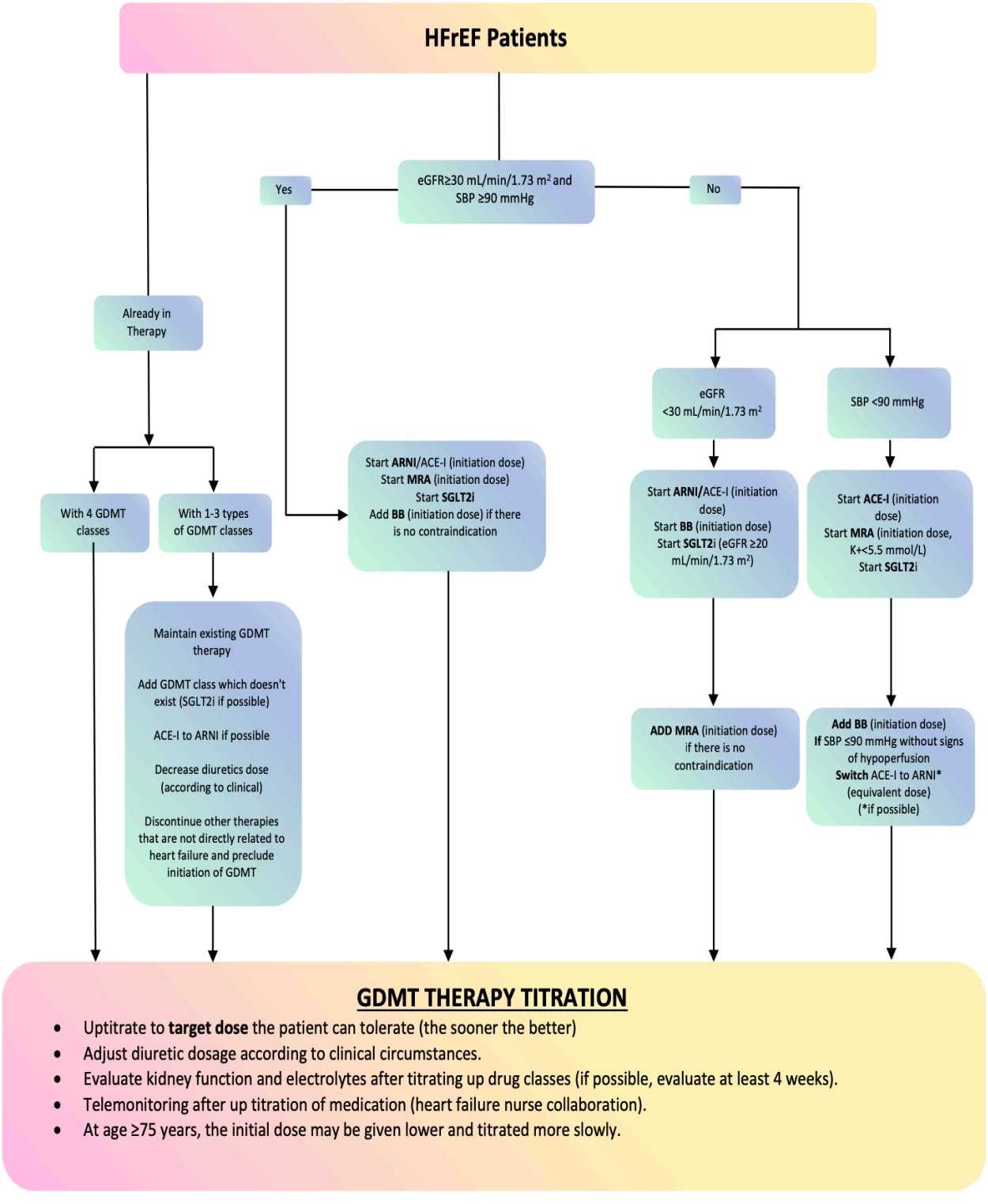

Figure 10.1 Management of acute pulmonary oedema.

Table 10.3 Referral guideline to comprehensive heart failure facilities.

Clinical scenario	1. New-onset heart failure (regardless of ejection fraction): to evaluate etiology, evaluation and management of guideline-recommended therapy, as well as assistance in disease management, including consideration of advanced imaging modalities, endomyocardial biopsy, invasive hemodynamic assessment (right heart catheterization/RHC) and genetic examination. 2. Chronic heart failure with high-risk characteristics due to the presence or persistence of one or more of the following risk factors: a. Continuous need for intravenous inotropes b. Persistent symptoms of congestion or significant fatigue (NYHA functional class III-IV) c. Systolic blood pressure <90 mmHg or symptomatic hypotension d. Creatinine level >1.8 mg/dL or BUN >43 mg/dL e. Onset of atrial fibrillation, ventricular arrhythmia, or recurrent ICD shock f. There have been >2 episodes of worsening heart failure in the last 12 months g. Inability to tolerate β-blockers, and/or ACE-I/ARB/ARNI, and/or optimal dose MRA h. Clinical deterioration characterized by worsening edema, elevated biomarkers (BNP, NT-proBNP), worsening exercise testing, decompensated hemodynamics, or evidence of progressive remodeling on imaging examination i. The risk of mortality is high using validated risk models in further assessment and consideration of advanced therapy such as the Seattle Heart Failure Model. 3. A low ejection fraction <35% that persists despite receiving GDMT for >3 months warrants consideration of implantable cardiovascular electronic device therapy (ICD or CRT), unless there is a contraindication or is inconsistent with general treatment goals. 4. Further investigation into the etiology of heart failure, such as: a. Coronary ischemia and possible revascularization b. Valvular heart disease and possible valve repair procedures c. Suspected myocarditis d. Suspicion or diagnosis of a specific cardiomyopathy (hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, Chagas disease, restrictive cardiomyopathy, cardiac sarcoidosis, amyloidosis, aortic stenosis) 5. Annual evaluation of patients with advanced heart failure, where the patient/family and clinician discuss current and potential therapies for both foreseeable and unexpected events, the likely course and prognosis of the disease, the patient's preferences for therapy, and follow-up care plans 6. Assessment of the possibility of patient participation in clinical studies

functional status. The progression of heart failure due to diabetes can be mitigated by administering ACE-I or ARB. β-blockers are not contraindicated in diabetes and improve prognosis similarly in both diabetic and non-diabetic patients. However, thiazolidinediones (glitazones) and saxagliptin should be avoided because they induce salt and fluid retention, leading to worsening heart failure and increased hospitalization. Metformin is not recommended for patients with significant renal or hepatic dysfunction due to the likelihood of developing lactic acidosis. On the other hand, SGLT2 inhibitors reduce mortality and rehospitalization rates due to heart failure in patients with and without diabetes.

Kidney Dysfunction and Cardiorenal Syndrome

Renal function is a robust standalone predictor of prognosis for individuals with heart failure. Renin-angiotensin-aldosterone inhibitors (ACE-I/ARB, MRA) typically cause a mild decrease in glomerular filtration rate, but this should not warrant discontinuation unless a very significant decrease occurs. If a substantial reduction in eGFR is noted, renal artery stenosis must be considered. Factors such as hypervolemia, right heart failure, and renal vein congestion can also impair kidney function. Additionally, drugs like NSAIDs, certain antibiotics (gentamicin, trimethoprim), digoxin, and thiazides can cause renal dysfunction. Cardiorenal

syndrome, a condition in which dysfunction in either the heart or kidneys causes impairment in the other organ, is classified based on underlying pathophysiological mechanisms as per the Acute Dialysis Quality Initiative (ADQI) Consensus. Of particular concern are cardiorenal syndrome types 1 and 2. It is crucial to differentiate between decreased kidney function due to underlying kidney disease and secondary impairment from heart complications. Kidney function decline can result from pre-renal disorders (conditions causing hypoperfusion to the kidneys, including worsening heart failure), renal causes (nephrotoxic drugs, glomerulonephritis, etc.), and post-renal issues (obstructive disorders along the urinary tract). Optimizing heart failure treatment is the primary approach for managing cardiorenal syndrome. This includes optimizing diuretics, using vasodilators, inotropes if blood pressure drops (cardiogenic shock), and considering ultrafiltration in patients with ADHF resistant to diuretic therapy. A multidisciplinary approach is essential for treating heart failure, especially in patients with compromised renal function.

Other Comorbidities

Iron deficiency

Iron deficiency is characterized by a ferritin level below 100 µg/L, or a ferritin level between 100-300 µg/L accompanied by transferrin saturation under 20%. This deficiency can lead to muscular dysfunction and anemia in heart failure patients. Multiple studies have indicated that intravenous iron replacement therapy improves the NYHA functional class, 6-minute walk test results, and overall quality of life. The FAIR-HF and AFFIRM-AHF studies have demonstrated that intravenous iron therapy decreases the rate of rehospitalization in heart failure. Conversely, the IRONOUT-HF study indicated that oral iron therapy did not yield positive results. Additionally, therapy with erythropoietin is not recommended for treating anemia in heart failure.

Chronic obstructive pulmonary disease (COPD), asthma, and interstitial lung disease

The lung diseases most commonly comorbid with heart failure are chronic obstructive pulmonary disease (COPD), asthma, and interstitial lung disease. These diseases can complicate the diagnosis of heart failure due to their similar clinical manifestations. It is suggested to perform screening heart failure patients for COPD and asthma through spirometry.[13-15] Patients with a combination of heart failure and either COPD, asthma, or interstitial lung disease have a poorer prognosis relative to those with only one of these conditions. COPD treatment includes adequate oxygen therapy, inhaled bronchodilators, inhaled corticosteroids, and antibiotics if there is an infection. Bronchodilators for COPD and asthma include anticholinergics, β2 agonists, and xanthines, though xanthines are less effective and have more side effects, making inhaled anticholinergics and β2 agonists the preferred options. If inhaled bronchodilators are unavailable, oral or intravenous bronchodilators can be used cautiously, starting with small doses and discontinuing if cardiovascular effects occur. Systemic corticosteroids can cause sodium and fluid retention, worsening heart failure. Administering β-blockers to these patients carries risks of acute bronchospasm, decreased lung function, and increased airway hyperresponsiveness; thus, cardioselective β-blockers are recommended. For interstitial lung disease, oral antifibrotics can be administered alongside heart failure medications.

Cancer

Certain chemotherapy drugs, such as anthracyclines and trastuzumab, can induce or exacerbate left ventricular dysfunction and heart failure. Dexrazoxane may offer cardioprotection for patients undergoing anthracycline therapy. It is crucial to evaluate ejection fraction before and after chemotherapy to monitor heart function. If chemotherapy patients develop heart failure, they should discontinue chemotherapy and receive standard heart failure therapy as appropriate.

Erectile dysfunction

Erectile dysfunction should be addressed with treatment appropriately. The use of phosphodiesterase-5 inhibitors, such as sildenafil, is generally not contraindicated, except for patients who are on routine nitrates. Several studies indicate that sildenafil can provide beneficial hemodynamic effects for patients with HFrEF. However, caution is advised when administering this drug to patients with HFpEF, as some studies

suggest it may cause disturbances in the left ventricle outflow tract (LVOT).

Obesity

Managing weight in heart failure patients presents unique challenges due to factors such as limited physical activity, anorexia, and potential fluid overload, which can complicate accurate measurements. Consequently, guidelines for weight management in heart failure patients with obesity include targeting a weight loss of 5-10%, making dietary modifications, implementing behavioral therapy, and considering anti-obesity medications or surgery. These approaches aim to address the complexities of weight management while improving overall health outcomes.

Dietary modifications for heart failure patients with obesity involve several key strategies. Severely obese patients should receive a caloric intake tailored to their needs, focusing on a healthy, balanced diet that includes increased consumption of fruits and vegetables while ensuring salt intake does not exceed one teaspoon per day. Patients are advised to avoid high-calorie, high-sugar, high-fat, and instant foods. Diet plans should be individualized, taking into account sociocultural values and personal preferences. If calorie restriction is necessary, it can be implemented at a rate of 500 kcal/day. However, ketogenic diets, intermittent fasting, and very low-calorie diets are not recommended due to their potential adverse effects.[16-18]

Behavioral therapy for weight management, also known as Behavioral Nutrition Counseling, encompasses a variety of strategies. This approach includes self-monitoring of food intake, physical activity, and body weight; setting specific goals; and providing education through face-to-face interactions or technological devices. It also involves problem-solving strategies, stimulus control, and behavioral contracting to support adherence to the weight management plan. Additional components include stress control, cognitive restructuring, motivational interviewing, and fostering social support. If needed, further evaluation, counseling, and psychological therapy may be conducted to address any underlying issues and support overall success in weight management.[17]

When medication is necessary for weight management, orlistat can be considered for patients with stable and non-severe heart failure. The recommended dosage is 120 mg taken orally three times a day before meals for the initial three months. Therapy can continue if there is a weight loss of more than 5% in patients without diabetes or more than 3% in those with diabetes. Regular liver function tests should be performed during the three-month evaluation period. Successful therapy is indicated by a decrease in body weight between 2.9% and 3.4% over one year. If the patient does not respond to the treatment or if liver function declines, the therapy should be discontinued.

Bariatric surgery, specifically sleeve gastrectomy, can be considered for heart failure patients with severe obesity (BMI >30 kg/m^2) who have NYHA Functional Class II-III, with or without a left ventricular assist device (LVAD). This surgical intervention may be appropriate when excessive adiposity could impact the process and outcomes of a planned heart transplant, improving overall treatment effectiveness and patient outcomes.

Geriatrics

Diagnosing heart failure in geriatric patients is complex due to their clinical characteristics and multiple comorbidities, which often result in atypical signs and symptoms. A thorough assessment, including detailed identification of all signs and symptoms and confirmation via echocardiography, is essential for accurate diagnosis. Management of heart failure in the elderly must address four domains: medical condition, functional status, cognitive and emotional status, and social environment. For pharmacological therapy, β1-selective blockers are the first-line treatment for systolic heart failure, starting with the smallest recommended dose to minimize side effects such as bradycardia or hypotension, and then titrated over at least two weeks to the optimal dose. ACE-I should be started at low doses, with ARBs used only if the patient is intolerant to ACE-I due to issues like cough, rash, or angioedema. ARNI and Ivabradine can be administered based on indications, as they have similar efficacy and side effect profiles across all ages. MRA require close monitoring to avoid hyperkalemia, kidney disorders, and hypotension. For HFpEF, diuretics are used symptomatically, but the evidence for ACE-I/ARB or β-blockers in reducing morbidity and mortality remains limited. ICDs

are effective in preventing all-cause death in older patients, similar to younger age groups, considering comorbidities, life expectancy, and quality of life. While evidence for CRT and LVAD in geriatrics is minimal, age alone is not an absolute contraindication for these procedures. Final treatment decisions should involve interdisciplinary discussions among medical personnel, patients, and families, using a value-based approach that balances expected health outcomes against the risks of side effects and costs.

Obstructive Sleep Apnoea (OSA)

Obstructive sleep apnea (OSA) is a specific type of sleep-related breathing disorder, alongside central sleep apnea (CSA). Both OSA and CSA are associated with poorer outcomes in heart failure, and they are more commonly observed in acute heart failure patients, affecting more than one-third of those with heart failure. OSA, in particular, is linked to a higher risk of developing heart failure in men.

Optimization Of Heart Failure Management

Algorithm for optimizing heart failure therapy

Optimizing heart failure therapy involves several key principles. First, it is crucial to initiate all four classes of GDMT as early as possible, even if starting with small doses. Secondly, the interval between initiating and titrating various drugs with different mechanisms should be minimized to ensure timely adjustments while considering patient safety. Recent evidence from the STRONG-HF study supports that rapid up-titration of GDMT can lead to improved outcomes.[19]

Profile 1. Patients with low blood pressure and elevated heart rate

Although there is no universally defined threshold for low blood pressure in HFrEF patients, a commonly used limit is a systolic blood pressure below 90 mmHg. In such cases, all non-heart failure medications should be reassessed. Nitrates, CCBs, and other vasodilators, which offer no prognostic benefit for heart failure patients, should be discontinued if possible. If the patient is in a euvolemic state, reducing or discontinuing diuretics may be considered, with close monitoring of fluid status to prevent fluid retention. Modifying GDMT or its dosage should only be considered if the patient experiences symptomatic hypotension.[20]

Lower heart rates in patients with HFrEF and sinus rhythm are associated with improved survival, with the best outcomes observed at heart rates around 60 beats per minute.[11] In cases of symptomatic hypotension, after evaluating and potentially discontinuing non-heart failure medications that lower blood pressure, it might be required to lower the dose or temporarily suspend β-blockers. In such situations, ivabradine, which reduces heart rate without affecting blood pressure, can be considered as an alternative treatment.[20] MRAs and SGLT2 inhibitors have minimal impact on blood pressure and can continue to be administered even in individuals with reduced blood pressure.[21,22]

Profile 2. Patients experiencing low blood pressure and a decreased heart rate

As with Profile 1, it is crucial to evaluate other causes of hypotension and assess the use of medications. Modifications to GDMT or its dosage should only be made if the patient experiences symptomatic hypotension. MRAs and SGLT2 inhibitors have minimal effect on blood pressure levels and can continue to be administered even in patients with low blood pressure. If the patient's heart rate drops below 50 beats per minute or if symptomatic bradycardia is present, it may be necessary to decrease the dose of β-blockers. For patients with limitations in GDMT options, omecamtiv-mecarbil might be considered as a potential therapeutic alternative.[20]

Profile 3. Patients with normal blood pressure and decreased heart rate

Negative chronotropic drugs, including non-dihydropyridine CCBs (such as diltiazem and verapamil), digoxin, and other antiarrhythmics, should be reassessed and, if possible, discontinued. If the patient is receiving ivabradine, the dose should be lowered or the medication should be discontinued if the heart rate remains below 50 beats per minute or if symptomatic bradycardia occurs. Additionally, patients experiencing

these conditions will likely need a reduction in the dose of their β-blocker.[20]

Profile 4. Patients with normal blood pressure and increased heart rate

Patients with this profile should receive β-blockers at target doses. If the heart rate remains elevated at over 70 beats per minute despite being in sinus rhythm, combining a β-blocker with ivabradine can enhance heart rate control and facilitate better titration of the β-blocker with a reduced frequency of side effects. Additionally, ACE-I, ARB, or ARNI should be adjusted to reach the target dose in patients with HFrEF, as study indicated that higher doses offered greater benefits compared to lower doses.[23]

Profile 5. Patients with AF and stable blood pressure

There is no well-defined optimal ventricular rate for heart failure patients with AF, but it is generally considered to be around 60-80 beats per minute.24 Unlike patients with sinus rhythm, heart rate does not correlate with mortality risk in individuals with heart failure and AF. Additionally, there is insufficient evidence showing a prognostic advantage of β-blockers for this population.[25] Efforts to escalate β-blocker doses to the maximum tolerated levels may lead to adverse effects, as a ventricular rate below 70 beats per minute is associated with poorer outcomes. Anticoagulants are always recommended for patients with AF, unless contraindicated or if the risks outweigh the potential benefits.[20]

Profile 6. Patients with AF and decreased blood pressure

Given the weaker evidence supporting the benefit of β-blockers in patients with HFrEF and concurrent AF, it may be appropriate to reduce or temporarily discontinue β-blockers if necessary. In such cases, digoxin may be administered as an alternative for heart rate control, particularly if the patient's heart rate remains above 70 beats per minute, as it does not impact blood pressure. This approach enables the start or escalation of medications that are effective in reducing mortality and morbidity, such as ACE-I or ARNI. MRAs and SGLT2 inhibitors, which have minimal effects on blood pressure, can continue to be administered.[20]

Profile 7. Patients with CKD and/or high potassium levels

Most RCTs involving HFrEF do not include patients with severe chronic kidney disease (CKD), therefore, data on the benefits and safety of medications in this population are limited. The administration of ACE-I, ARB, or ARNI should only be discontinued if creatinine levels increase by more than 100% from baseline, exceed 3.5 mg/dL, or if the eGFR falls below 20 mL/min/1.73 m². β-blockers are safe to use in patients with an eGFR of 30 mL/min/1.73 m² or lower. MRAs can be administered up to an eGFR of 30 mL/min/1.73 m², as long as potassium levels stay below 5.0 mEq/L and the risk of hyperkalemia is minimal. Potassium levels should be assessed at the start and four weeks after beginning or modifying the MRA dosage, with ongoing periodic evaluations thereafter. ARNI can be used until the eGFR drops below 30 mL/min/1.73 m². Additionally, dapagliflozin and empagliflozin have proven effective and safe in achieving better cardiovascular and renal outcomes for patients with an eGFR of 20 to 25 mL/min/1.73 m² or higher. A decrease in GFR shortly after starting SGLT2 inhibitors should not prompt discontinuation, as this decrease is reversible and associated with long-term renal benefits.26 The newest class of drugs, such as omecamtiv-mecarbil, can be used in patients with an eGFR above 20 mL/min/1.73 m². Medications that can exacerbate kidney function, like non-steroidal anti-inflammatory drugs, should be discontinued.[27] Potassium binders have demonstrated effectiveness in lowering serum potassium levels in heart failure and CKD patients on RAAS inhibitors, although their impact on patient prognosis remains unproven.[28]

Profile 8. Before being discharged

Some heart failure patients are discharged despite having persistent signs of congestion. In such cases, it is crucial to optimize diuretic therapy before starting β-blockers, particularly in patients who have not previously received treatment with this class of drugs. For patients who have been on ACE-I or ARNI regularly, these medications can be continued. On the other hand,

MRAs and SGLT2 inhibitors can be initiated relatively safely, even in the presence of ongoing congestion or low blood pressure.[20]

Profile 9. Patients with high blood pressure despite optimal medical treatment

In patients exhibiting hypertension, it is essential to verify that they are not using medications that could elevate blood pressure, such as non-steroidal anti-inflammatory drugs, bronchodilators, or corticosteroids. Ensuring patient compliance with treatment is crucial, and GDMT should be escalated to the maximum dose. If blood pressure remains high despite reaching the maximum GDMT dose, a combination of hydralazine and ISDN can be considered to achieve better blood pressure control.[20]

A comprehensive guide for when to refer a patient to a heart failure facility involves recognizing specific signs during the process of optimizing and intensifying therapy. If a patient demonstrates an inadequate response to treatment or experiences instability, acronyms can aid clinicians in deciding when to refer them to a specialized heart failure facility. For detailed criteria and decision-making processes, refer to tables 2 and 3, which provide structured guidance for such referrals.[29]

Key Messages

The final section of our updated review was presented as key messages rather than a conclusion, as there were numerous critical points that needed to be highlighted. These key messages encapsulated the main findings and important aspects of our review, ensuring that all significant information was clearly communicated.

- The latest update to the classification of heart failure based on LVEF currently consists of HFrEF, HFmrEF, and HFpEF. HFmrEF is defined as heart failure with an LVEF between 41% and 49%.
- The cornerstone therapies for HFrEF include four key drug recommendations: ACE-I or ARNI, BBs, MRA, and SGLT2 inhibitors.
- Due to SGLT2 inhibitors' ability to reduce cardiovascular death and heart failure hospitalization, this drug is recommended for HFpEF patients, with a degree of recommendation of I B.
- ICDs are advised for selected patients with HFrEF resulting from ischemic causes; for those with non-ischaemic aetiology, ICD use needs to be considered.
- CRT-P/D is advised for HFrEF patients who are in sinus rhythm with an LBBB duration greater than 150 ms, and it should be evaluated for those with an LBBB duration between 130-149 ms or a non-LBBB duration exceeding 150 ms.
- To diagnose HFpEF, an assessment must be made for cardiac abnormalities in structure or function, elevated plasma NP levels, and the existence of LV diastolic dysfunction or increased LV filling pressures. If these indicators are inconclusive, a diastolic stress test is advised.
- The clinical features of acute heart failure may present as ADHF, acute pulmonary oedema, RV failure, and cardiogenic shock, which are the four most common presentations.
- A patient hospitalized for worsening heart failure should be assessed for manifestations of congestion to confirm that they have resolved and can be ruled out before discharge. Additionally, oral treatment should be tailored for maximum benefit prior to discharge.
- Patients with type II diabetes mellitus and heart failure should be treated with SGLT2 inhibitors.
- Patients should be regularly tested for anemia and iron deficiency. Intravenous iron supplementation with ferric carboxymaltose is recommended for symptomatic individuals with an LVEF below 45% and iron deficiency, as well as for those discharged from the hospital following worsening heart failure, with an LVEF under 50% and iron deficiency.

List of Abbreviations

TACC	American College of Cardiology
ACE-I	Angiotensin Converting Enzyme Inhibitor
ADHF	Acute Decompensated Heart Failure
ADQI	Acute Dialysis Quality Initiative
AF	Atrial Fibrillation
AFFIRM AHF	Atrial Fibrillation Follow-up Investigation of Rhythm Management-Acute Heart Failure
AHA	American Heart Association
ARB:	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor-Neprilysin Inhibitor

AV	Atrio-Ventricular
BB	Beta Blocker
BNP	B-type Natriuretic Peptide
CCB	Calcium Channel Blocker
CIED	Cardiac Implantable Electronic Devices
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CRT-P/D	Cardiac Resynchronization Therapy-Pacemaker/Defibrillation
CSA	Central Sleep Apnea
DT	Deceleration Time
EBM	Evidence-Based Medicine
ECG	Electrocardiogram
EGFR	Estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
FAIR HF	Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure
GDMT	Guideline Directed Medical Therapy
HFA-PEFF	Heart Failure Association Pre-test assessment, Echocardiography & natriuretic peptide, Functional testing, Final etiology
HFimpEF	Heart Failure Improved Ejection Fraction
HFmrEF	Heart Failure Mildly Reduced Ejection Fraction
HFpEF	Heart Failure Preserved Ejection Fraction
HFrEF	Heart Failure Reduced Ejection Fraction
HFSA	Heart Failure Society of America
ICD	Implantable Cardioverter Defibrillator
ISDN	Isosorbide Dinitrate
LBBB	Left Bundle Branch Block
LVAD	Left Ventricular Assist Device
LVEDP	Left Ventricular End Diastolic Pressure
LVEF	Left Ventricular Ejection Fraction
LVOT	Left Ventricle Outflow Tract
MCS	Mechanical Circulatory Support
MRA	Mineralocorticoid Receptor Antagonist
NIPPV	Non-Invasive Positive Pressure Ventilation
NP	Natriuretic Peptide
NPV	Negative Predictive Value
NSAID	Non-Steroid Anti-Inflammatory Drug
NT-proBNP	N-Terminal pro-B-type Natriuretic Peptide
NTG	Nitroglycerin
NYHA	New York Heart Association
OSA	Obstructive Sleep Apnoea
PASP	Pulmonary Artery Systolic Pressure
PCWP	Pulmonary Capillary Wedge Pressure
PDE-5	Phosphodiesterase-5
PPV	Positive Predictive Value
RAAS	Renin Angiotensin Aldosterone System
RCT	Randomized Controlled Trial
RRT	Renal Replacement Theraps
SCD-HeFT	Sudden Cardiac Death in Heart Failure
SGLT-2	Sodium-Glucose Co-Transporters 2
SHIFT	Systolic Heart failure treatment with the If inhibitor Ivabradine Trial
STRONG-HF	Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure Trial
TDI	Tissue Doppler Imaging
TRED-HF	Therapy withdrawal in REcovered Dilated cardiomyopathy – Heart Failure Trial
TTE	Transthoracic Echocardiography
WHO	World Heart Organization.

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