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Clinical Practice Guideline

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Korean Society of Heart Failure Guidelines for the Management of Heart Failure: Treatment

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AUTHOR'S SUMMARY

This paper aims to provide physician with the latest evidence-based recommendations for the management of patients with heart failure (HF). In this paper, we discuss pharmacotherapy, cardiac implantable electronic devices, treatment for specific cardiomyopathies, and multidisciplinary care to improve the prognosis and provide the best care for patients with HF, based on previous HF research in the Korean population and international guidelines.

ABSTRACT

The Korean Society of Heart Failure (KSHF) guidelines aim to provide physicians with evidence-based recommendations for the management of patients with heart failure (HF). After the first introduction of the KSHF guidelines in 2016, newer therapies for HF with reduced ejection fraction, HF with mildly reduced ejection fraction, and HF with preserved ejection fraction have since emerged. The current version has been updated based on international guidelines and research data on Korean patients with HF. Herein, we present Part II of these guidelines, which comprises treatment strategies to improve the outcomes of patients with HF.

Keywords: Heart failure; Guideline; Treatment; Pharmacotherapy

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INTRODUCTION

Globally, heart failure (HF) is a major public health issue that involves high medical costs. In Korea, the prevalence of patients with HF is 2.25%, and given the increasing older adult population, the burden of HF is expected to rise. Since the introduction of the Korean guidelines for the diagnosis and management of chronic HF in March 2016,[1] newer strategies have emerged to improve outcomes of patients with HF. Angiotensin receptor-neprilysin inhibitors (ARNI) is more beneficial for patients with heart failure with reduced ejection fraction (HFrEF) and heart failure with mildly reduced ejection fraction (HFmrEF). Sodium-glucose co-transporter 2 (SGLT2) inhibitors were effective in improving the prognosis of patients with HF, irrespective of the left ventricular (LV) ejection fraction (EF). Furthermore, tafamidis has demonstrated clinical benefit in patients with cardiac transthyretin amyloidosis (ATTR). This article aims to provide the most up-to-date evidence to improve outcomes in patients with HF and assist shared decision making in clinical practice. The current guidelines have been established based on previous HF research in the Korean population and international guidelines with a focus on providing the best possible care for patients with HF.[2-5]

PHARMACOTHERAPY

Heart failure with reduced ejection fraction

Treatment algorithm of HFrEF

1. In patients with HFrEF, ARNI or angiotensin-converting enzyme inhibitors (ACEI) (or angiotensin receptor blockers [ARBs], in case of intolerance), beta-blockers, mineralocorticoid receptor antagonists (MRA; aldosterone antagonists), and SGLT2 inhibitors are the standard of care for reducing cardiovascular mortality and HF hospitalization. (Class I, LOE A)
2. Even if HF symptoms improve after the guideline directed medical therapy (GDMT) and LVEF improves to >40%, maintaining the GDMT is recommended. (Class I, LOE B)

The key treatment goals for patients with HFrEF are as follows: 1) reduced mortality rate; 2) reduced readmissions due to worsening HF; and 3) improved functional clinical status and quality of life.[4-7] The typical treatment strategies to achieve these goals are illustrated in **Figure 1**.

Patients with symptoms and signs of HF and LVEF ≤40% may be classified as HF with recovered EF in the following scenarios: if the EF is >40% on post-treatment follow-up; if the EF is improved by >10% compared with the previous examination; or if the EF is improved to ≥50%. However, the term "recovery" may be inappropriate because an improvement in LV EF does not necessarily mean complete recovery of the dysfunction, and ascertaining if the patient has completely recovered from HF is often difficult.[4-7] In a clinical study, comprising a small group of patients with improved EF after HF treatment, the LV function, HF symptoms, or HF worsened in 45% of patients who were randomly assigned to discontinue HF medications, within 6 months after discontinuations.[8] Thus, even if the EF is improved post-treatment, HFrEF may be considered as an "improved" condition, rather than classifying it as an independent disease group, and continuation of the standard treatment is recommended.

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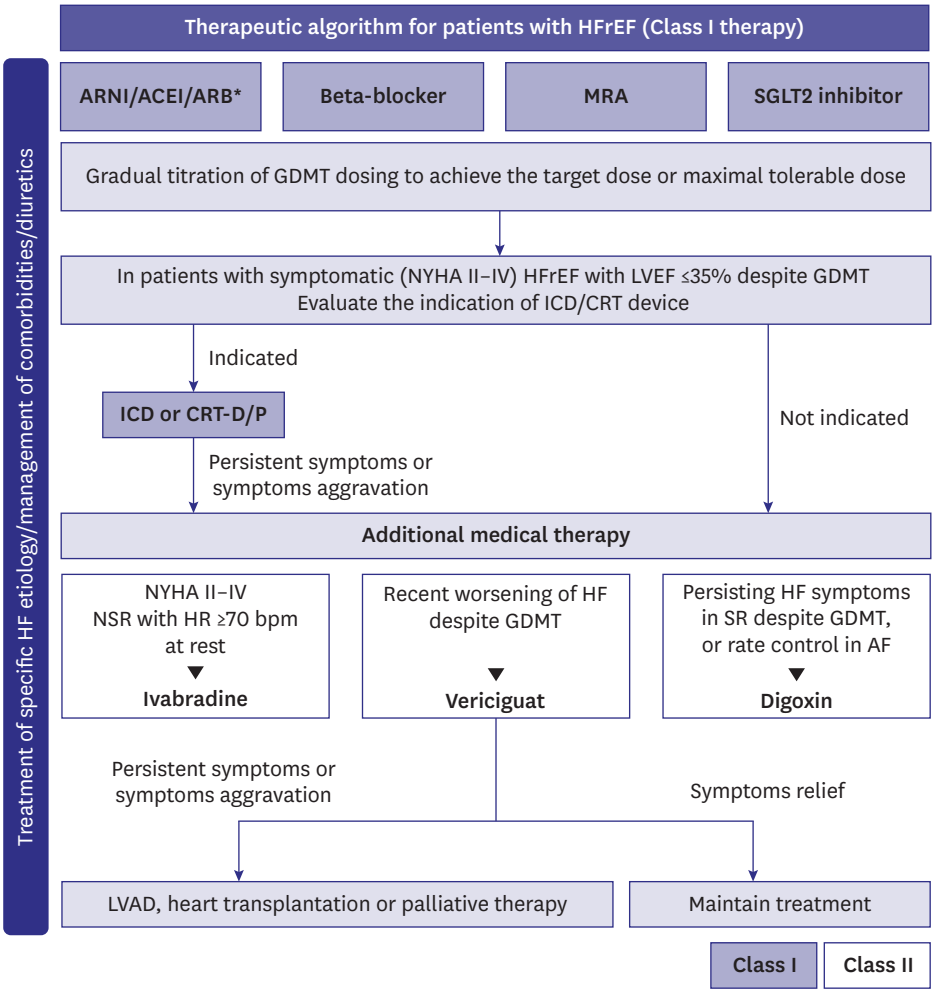

Figure 1. Therapeutic algorithm for HFrEF.
ACEI = angiotensin converting enzyme inhibitors; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitors; CRT = cardiac resynchronization therapy; D/P = defibrillator/pacemaker; GDMT = guideline directed medical therapy; HR = heart rate; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonists; NSR = normal sinus rhythm; NYHA = New York Heart Association; SGLT2 = sodium-glucose co-transporter 2; SR = sinus rhythm.
*If patients with chronic HFrEF are intolerant to ACEI because of cough or angioedema and when the use of ARNI is not feasible, the use of ARB is recommended to reduce morbidity and mortality.

(1) Renin-angiotensin system inhibitor

1. In patients with HFrEF, ARNI is recommended as the standard of care to reduce cardiovascular mortality and HF hospitalization. If ARNI is intolerable or unavailable, the use of ACEI is recommended. (Class I, LOE A)
2. If both ARNI and ACEI are intolerable or unusable, ARBs are recommended as alternatives. (Class I, LOE A)
3. Even If the patient is stable with ACEI or ARBs, the replacement with ARNIs is recommended to further reduce the risk of HF-related cardiovascular mortality and hospitalization. (Class I, LOE B)
4. If acutely exacerbated hospitalized HFrEF patients recovered to be hemodynamically stable, treatment with ARNI, instead of ACEI or ARBs, is reasonable. (Class IIa, LOE B)

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In patients with HFrEF, ACEIs improve symptoms, reduce mortality, and readmissions. These effects have been found to be consistent regardless of previous or current symptoms of HF, severity of symptoms, and irrespective of coronary artery disease.[4-7]

ARB can theoretically overcome some limitations of ACEI. ACEIs do not completely block angiotensin II formation due to presence of non-ACE pathway which continuously product low level of angiotensin II. ACEIs inhibit the breakdown of bradykinin and increase circulating bradykinin levels which is implicated in pathogenesis of cough and angioedema. According to the Korean Acute Heart failure Registry (KorAHF), there was no difference in all-cause mortality between HFrEF patients on ARBs and ACEIs during 27 months of follow up (29.1% vs. 28.9%), while ARBs significantly reduced all-cause mortality when compared to those without renin-angiotensin blockers (adjusted hazard ratio, 0.71; p<0.001). ARBs were more tolerable than ACEIs within one year follow up as discontinuation rates were lower in ARB group compared to ACEI group (20.8% vs. 33.6%, p<0.001).[9]

Previously, if symptoms persisted despite standard treatment (including ACEI), ARNI was recommended as an alternative; however, recent studies have consistently confirmed the reduction in mortality and readmission rates; therefore, ARNI is currently recommended as a first-line treatment over ACEI (Class I).[10-14]

Based on the results of recent studies, ARNI may be used as a first-line treatment in patients hospitalized for acute HF exacerbations, including newly-diagnosed HF, or in patients who have never used ACEIs or ARBs.[15][16] Contraindications or precautions of ARNI are similar to that when using ACEIs or ARBs. In particular, if the patient is already using ACEIs, a washout period of 36 hours is required before switching to ARNI, to avoid the risk of angioedema.

(2) Beta-blockers

1. Beta-blockers are recommended for administration in patients with stable HFrEF to improve symptoms and reduce mortality and HF hospitalization. (Class I, LOE A)
2. Beta-blockers proven to reduce mortality in randomized clinical trial include bisoprolol, carvedilol, and metoprolol sustained-release tablets. (Class I, LOE A)
3. In patients aged ≥70 years, the use of nebivolol can be beneficial. (Class IIa, LOE B)

Beta-blockers reduce mortality and HF hospitalization in patients with HFrEF.[17-21] In a domestically conducted registry, beta-blockers improved the prognosis in patients with HF,[22] and reduced the risk of death, particularly older patients with HFrEF.[23] In another nationwide prospective study, beta-blockers combined with renin-angiotensin-aldosterone antagonists reduced overall mortality at discharge in patients with HFmrEF (EF 40–49%).[24] A higher adherence to beta-blockers indicates a better prognosis.[25]

High-dose ACEIs or ARBs are not necessarily required when beta-blockers are being used, and even if low-dose ACEIs are used, prompt addition of beta-blockers is recommended.[26] According to data from the KorAHF, even in patients hospitalized with decompensated HF requiring vasopressors, the use of beta-blockers after recovery and before discharge improves the prognosis.[27] Beta-blockers prescribed before discharge reduced mortalities by 24% after one year, if the heart rate (HR) was ≥70 beats/min at discharge; however, beta-blockers were ineffective if the HR was <70 beats/min.[28] In a study based on a HR of 60 beats/min

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at discharge, a pre-discharge HR ≥60 beats/min was effective in reducing overall mortality; however, a HR <60 beats/min was ineffective.[29] Comparative studies between beta-blockers are rarely reported; however, in a comparative study of carvedilol and bisoprolol in patients with acute HFrEF, there was no difference in the mortality rates between the two drugs.[30]

(3) Mineralocorticoid receptor antagonists

1. The use of MRA (aldosterone antagonists) is recommended to reduce HF hospitalization and mortality in patients with HFrEF. (Class I, LOE A)

Aldosterone antagonists or MRA reduce mortality and readmission and improve HF symptoms in patients with HFrEF.[31-33] Spironolactone is initiated at a dose of 12.5–25 mg/day and eplerenone at 25 mg/day; both drugs can be increased to 50 mg/day. Since hyperkalemia may occur as a side effect of aldosterone antagonists, a blood test should be performed before initiating the medication to check for abnormalities in kidney function and electrolyte balance, and if the estimated glomerular filtration rate (eGFR) is <30 mL/min/1.73 m^2 or serum potassium concentration is >5.0 mEq/L, subsequent drug administration should be cautious.

(4) Sodium-glucose co-transporter 2 inhibitors

1. In patients with HFrEF with or without diabetes, administration of SGLT2 inhibitors (empagliflozin or dapagliflozin) is recommended to reduce HF hospitalization or cardiovascular mortality. (Class I, LOE A)

SGLT2 inhibitors were developed as antidiabetic drugs. However, in randomized clinical trials, irrespective of diabetes, SGLT2 inhibitors have been demonstrated to reduce HF hospitalization[34)35] and improve the quality of life[36)37] in patients with HFrEF. Before initiating SGLT2 inhibitors, kidney function should be evaluated at an early stage and regularly monitored. The eGFR slightly decreases during treatment initiation; however, this is reversible and discontinuing the drug is not recommended. Moreover, SGLT2 inhibitors have been confirmed to have a protective effect on kidney function. Caution is advised when using SGLT2 inhibitors because SGLT2 inhibitors increase risk of urogenital infection, and may contribute to volume depletion. Although rare, hypoglycemia and ketoacidosis may occur in patients with diabetes.[4)5]

(5) Diuretics

In patients with HF with fluid retention, diuretics is recommended to maintain adequate fluid volume, regardless of LV systolic function. (Class I, LOE B)

Assessment of volume status and maintenance of proper fluid balance are essential components in the treatment of patients with HF, regardless of LV systolic function. Initial treatment involves the use of diuretics, such as loop diuretics, in addition to water and salt intake restrictions.[4)5] Prolonged use of excessive diuretics may cause a state of low cardiac output (CO) due to reduced body fluid, hypotension, or deterioration of kidney function; therefore, adequate care is needed. In case when high doses of oral diuretics do not improve pulmonary congestion or swelling, limiting salt intake is necessary. Furthermore, it is

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necessary to ensure that the patient is not receiving non-steroidal anti-inflammatory drugs or corticosteroids. In patients with severe edema, furosemide may have insufficient intestinal absorption; therefore, short-term intravenous administration or replacement with torsemide may be considered. If resistance to loop diuretics is exhibited, short-term combination therapy of thiazide diuretics may be considered to inhibit salt reabsorption in the distal tubules.[36]

(6) Ivabradine

1. In symptomatic HFrEF (LVEF ≤35%) patients who are in sinus rhythm (SR) and a resting HR ≥70 beats/min, ivabradine can be useful to reduce the risk of HF hospitalization and cardiovascular mortality; if HF symptoms persist despite the use of beta-blockers, ACEI (or ARNI) and MRA. (Class IIa, LOE B
2. In symptomatic HFrEF (LVEF ≤35%) patients who are in SR and a resting HR ≥70 beats/min, ivabradine can be useful to reduce the risk of hospitalization and cardiovascular mortality, if beta-blockers cannot be used. (Class IIa, LOE C)

HR is an important prognostic factor in patients with HFrEF. Ivabradine lowers the HR by inhibiting the I*f* channel of the sinoatrial node. Ivabradine specifically reduces HR without affecting myocardial contractility or other cardiac ionic current in patients with HFrEF. In symptomatic HFrEF (LVEF ≤35%) patients despite GDMT including beta blockers at maximally tolerated dose and who are in SR and a HR of ≥70 beats/min, ivabradine significantly reduced cardiovascular mortality and HF hospitalization.[37][38]

(7) Vericiguat

1. Vericiguat may be used to reduce cardiovascular mortality or HF hospitalization in selected high-risk patients with HF (LVEF <45%) and recent worsening of HF already on GDMT. (Class IIa, LOE B)

Vericiguat is a soluble guanylate cyclase receptor stimulator that enhances the cyclic guanosine monophosphate pathway and restores nitric oxide sensitivity. According to the Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) study, vericiguat significantly reduced cardiovascular death or hospitalization in high risk pateints with HF (LVEF <45%) with recent worsening HF (35.5% vs. 38.5%; hazard ratio, 0.90; 95% confidence interval, 0.82–0.98; p=0.02).[39] The absolute risk reduction by vericiguat was 4.2% per year. Vericiguat was approved by the United States Food and Drug Administration (FDA) in January 2021, the European Union European Commission in July 2021, and Korean Ministry of Food and Drug Safety in November 2021. Vericiguat may be considered in selected high-risk patients with HFrEF and recent worsening of HF already on GDMT, to reduce HF hospitalization and cardiovascular death.

(8) Digoxin

1. In patients with HFrEF with atrial fibrillation (AF), if the use of beta-blockers does not provide good HR control, or if beta-blockers are contraindicated, digoxin can be beneficial. (Class IIa, LOE B)

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2. In patients with symptomatic HFrEF despite GDMT, digoxin may be used to reduce HF hospitalization. (Class IIb, LOE B)

Digoxin inhibits the sodium/potassium (Na/K) ATPase pump of sarcoplasmic reticulum and increases intracellular calcium concentration even as intracellular sodium concentration decreases. In addition, it sensitizes the Na/K ATPase in afferent vagal nerves to enhance parasympathetic activity and reduce sympathetic activity by reducing plasma norepinephrine.[40] The Digitalis Investigation Group (DIG) trial reported that digoxin provided no overall mortality benefit and only a modest reduction in hospitalizations among patients with HFrEF. The post hoc analysis of DIG trial demonstrated higher serum digoxin levels were associated with increased mortality.[41] Digoxin is conventionally initiated at a low dose and subsequently, continued at a maintenance dose of 0.125 or 0.25 mg/day. Attention should be paid to the occurrence of side effects due to toxicity. Typical symptoms of digoxin toxicity include digestive (loss of appetite, nausea, and vomiting) and nervous (visual and cognitive impairments, and confusion) system symptoms; fatal arrhythmias, especially in older adults (aged >70 years) and patients with renal failure, low body weight, or electrolyte abnormalities. Side effects occur when digoxin is co-administered with drugs that can affect digoxin metabolism (macrolide antibiotics, itraconazole, cyclosporin, amiodarone, quinidine, etc.).[42-44]

(9) Tolvaptan

1. The use of vasopressin V_2-receptor antagonists (tolvaptan) may be considered in patients with HF in a state of volume overload with hyponatremia refractory to other treatments. (Class IIb, LOE B)

Hyponatremia causes cognitive impairment, which can easily cause falls, and in severe cases (Na <125 mEg/L), can alter consciousness.[45] In hyponatremia accompanied by volume overload, vasopressin V_2-receptor antagonists have been reported to significantly improve cognitive function associated with hyponatremia.[45-48] In hyponatremia, ensuring the absence of other causes, such as syndrome of inappropriate antidiuretic hormone secretion, hypothyroidism, or hypoaldosteronism, is crucial; if not, fluid intake can be limited (800–1,000 mL/day) or drugs that inhibit angiotensin II can be used. Vasopressin V_2-receptor antagonists may increase serum sodium levels in hyponatremia with volume overload[46-48]; however, they have not improved survival in patients with HF.[47][48]

Heart failure with mildly reduced ejection fraction and heart failure with preserved ejection fraction

1. Screening and treatment for comorbidities (cardiovascular diseases such as hypertension and AF; non-cardiovascular diseases such as diabetes and renal failure) are needed. (Class I, LOE C)
2. Diuretics are necessary, if symptoms of congestion are present. (Class I, LOE C)
3. SGLT2 inhibitors (empagliflozin or dapagliflozin) are recommended for patients with HF with or without diabetes to reduce hospitalization or cardiovascular mortality. (Class I, LOE B)

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4. ARNI can be beneficial to reduce hospitalization or cardiovascular mortality due to HF. (Class IIa, LOE B)
5. MRA can be useful to reduce the risk of HF hospitalization. (Class IIa, LOE C)
6. ARBs or ACEIs may be considered to reduce hospitalization or cardiovascular mortality due to HF. (Class IIb, LOE C)
7. Beta-blockers may be considered to reduce cardiovascular mortality. (Class IIb, LOE C)

Until recently, no prospective randomized clinical trials have been conducted in patients with HFmrEF, although some evidence can be gathered from sub-analyses of studies in patients with heart failure with preserved ejection fraction (HFpEF). The survival rate of patients with HFpEF is marginally higher than that of patients with HFrEF, although it is low; furthermore, hospitalization and disease burden due to worsening HF are known to be similar.[49)50)] Various drugs and device treatments have been developed for HFrEF to gradually improve survival; however, no treatment has clearly demonstrated improvement in survival rates for HFpEF. Patients with HFpEF are mainly older women with concomitant cardiovascular (hypertension, AF, and ischemic heart disease) and non-cardiovascular (diabetes and renal failure) diseases.[51-53)] The clinical phenotypes of HFpEF are diverse due to varied etiologies. In particular, lung disease, anemia, and obesity may exhibit similar symptoms; therefore, first, each causative disease entity has to be diagnosed and treated individually.[51-53)] Until recently, treatment recommendations to improve the course of HFpEF were insufficient, and conventional treatments were aimed at alleviating symptoms. Diuretics should be appropriately used; loop diuretics are initially recommended for congestive symptoms,[54)55)] thiazide diuretics may be useful in case of concomitant hypertension.[56)] In patients with obesity, weight loss and exercise therapy can help alleviate symptoms and improve athletic performance.[57)58)]

A prespecified meta-analysis including EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved)[59)] and Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER)[60)] showed that SGLT2 inhibitors reduced the risk of cardiovascular death and hospitalizations for HF irrespective of EF and the clinical benefit extended to HF patients with LVEF ≥60%.[61-63)] DELIVER trial demonstrated clinical benefit in broad spectrum of HF patients, including HF with improved EF and regardless of recent HF hospitalization.[60)] The SGLT2 inhibitors, empagliflozin or dapagliflozin, are recommended for reducing cardiovascular mortality and HF hospitalization in patients with HFpEF and HFmrEF, regardless of diabetes.[58-62)]

The FDA recently approved ARNI and MRA for patients with HF and EF below normal, which include both HFmrEF and HFpEF. Although primary outcomes were not met in Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial, from the exploratory analysis, there was a significant benefit for the ARNI for HF hospitalizations in patients with LVEF below the median (45–57%) compared to valsartan.[63-66)] Regarding MRA, the subgroup analysis of the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) study suggested benefit for hospitalization for HF in symptomatic HF patients with LVEF <55%.[67-70)] Post hoc analyses of TOPCAT study suggest a possibility of benefit in appropriately selected patients with symptomatic HFpEF (LVEF ≥45%, elevated B-type natriuretic peptide [BNP] level or HF admission within 1 year, eGFR >30 mL/min/1.73 m^2, creatinine <2.5 mg/dL, and potassium

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<5.0 mEq/L).[69][70] The KorAHF studies have reported that the use of ARBs, ACEIs, and beta-blockers reduced in-hospital mortality, post-discharge mortality in patients with HFpEF[71]; therefore, the use of these agents may be considered to improve prognosis.

Cardiac implantable electronic device

(1) Implantable cardioverter-defibrillator

1. In patients who recovered from hemodynamically unstable ventricular arrhythmias, in the absence of reversible causes or unless if the ventricular arrhythmia occurred within 48 hours after myocardial infarction, and survival is expected for >1 year, an implantable cardioverter-defibrillator (ICD) is recommended to reduce the risk of sudden death and all-cause mortality. (Class I, LOE A)
2. In patients with symptomatic HF (New York Heart Association [NYHA] II–III) of ischemic origin, if LVEF is ≤35% despite ≥3 months of GDMT, and survival is expected for >1 year, an ICD is recommended to reduce sudden death and all-cause mortality. (Class I, LOE A)
3. In patients with symptomatic HF (NYHA II–III) of non-ischemic origin, if LVEF ≤35% despite ≥3 months of GDMT and survival is expected for >1 year, an ICD is reasonable to reduce the risk of sudden death and all-cause mortality. (Class IIa, LOE A)
4. Experienced cardiologists should reassess the patient before generator replacement, because the patient's needs and clinical status may have changed. (Class IIa, LOE B)
5. An ICD insertion is not recommended within 40 days of myocardial infarction, since it does not improve clinical outcome. (Class III, LOE A)
6. In patients with NYHA class IV symptoms who do not respond to medical therapy, an ICD is not recommended, unless they are candidates for cardiac resynchronization therapy (CRT), ventricular assist devices or transplantation. (Class III, LOE C)

Patients with HF experience more sudden cardiac deaths than the general population; this is the leading cause of death in HF patients with NYHA class II and III.[72] An ICD prevents sudden death and reduces the risk of mortality in such patients.[72] ICDs reduce the risk of sudden cardiac death and all-cause mortality in patients who experienced sustained symptomatic ventricular arrhythmias. Therefore, an ICD is recommended for secondary prevention in patients with HF in absence of reversible cause or unless the ventricular arrhythmia occurred within 48 hours of myocardial infarction and survival is expected for >1 year. An ICD for primary prevention is recommended in symptomatic patients (NYHA II-III) with HFrEF (EF ≤35%) despite ≥3 months of GMDT. ICDs are not recommended in severe symptomatic patients (NYHA IV) who are refractory to medical treatment, unless they are candidates for mechanical circulatory support, CRT or heart transplant.

(2) Cardiac resynchronization therapy

CRT uses pacemaker leads to induce coordinated contraction of the left and right ventricles (ventricular resynchronization) simultaneously, thereby improving the quality of life, reducing HF hospitalization and mortality, and inhibiting the process of LV remodeling.[73-75] In symptomatic patients (NYHA III–IV) with chronic HF who did not respond to appropriate medical treatment, CRT was confirmed to be a crucial non-pharmacological treatment, which improved HF symptoms and quality of life; in cases HFrEF with electrical dyssynchrony, CRT significantly reduced HF hospitalization and mortality.[73-75] The algorithm for the indications for CRT, which reflects the results of recent trials, is presented in **Figure 2**.

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Figure 2. Indications for cardiac resynchronization therapy.
AF = atrial fibrillation; AV = atrioventricular; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; GDMT = guideline directed medical therapy; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; SR = sinus rhythm.

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Treatment for specific cardiomyopathies

(1) Cardiac amyloidosis

1. Tafamidis is recommended to reduce symptoms, cardiovascular-related hospitalizations and mortality in NYHA I-II patients with wild-type or hereditary (genetic mutation) ATTR-CM. (Class I, LOE B)

Amyloidosis is a disorder where misfolded proteins accumulate and cause organ dysfunction. It has an age-standardized incidence rate of 0.5 persons per 100,000 persons. Although it is a relatively rare disease, cardiac amyloidosis is under-recognized cause of HF. The diagnosis is often difficult and delayed.[76-80] The typical amyloid proteins that cause cardiac amyloidosis include light chain immunoglobulin amyloidosis (AL) and transthyretin (TTR). The clinical symptoms and signs of cardiac amyloidosis are listed in **Table 1**. The algorithm for diagnosing cardiac amyloidosis is presented in **Figure 3**. In AL cardiac amyloidosis, chemotherapy or autologous stem cell transplantation is the main treatment. For TTR cardiac amyloidosis (ATTR-CM), TTR stabilization and reduction of TTR production is the basis of treatment. Tafamidis reduced all-cause mortality and cardiovascular hospitalization in hereditary and wild-type TTR cardiac amyloidosis, in patients with NYHA I or II.[81][82]

(2) Myocarditis

1. In cases of acute severe HF of unknown cause that rapidly progress despite treatment, endocardial biopsy is recommended to diagnose myocarditis. (Class I, LOE B)
2. If giant cell or eosinophilic myocarditis are suspected, endocardial biopsy can be useful for diagnostic and prognostic evaluation. (Class IIa, LOE C)
3. Cardiac magnetic resonance (CMR) imaging can be beneficial in patients with suspected myocarditis. (Class IIa, LOE C)
4. In patients with myocarditis, immunosuppressive treatment may not improve survival. (Class III, LOE B)

The reported cases of HF due to myocarditis vary depending on age and region. The incidence ranges from 0.5–4%.[83-85] The etiology of acute myocarditis is varied and includes viral diseases, toxins or drugs, or systemic autoimmune diseases. Acute myocarditis typically presents with nonspecific symptoms including chest pain, dyspnea, palpitations,

Table 1. Clinical symptoms and signs of cardiac amyloidosis

		Signs and symptoms
Cardiac	Clinical symptoms	Heart failure, intolerance to beta blockers or ACE inhibitors, hypotension or normotensive if previously hypertensive
	ECG	Pseudo-infarct pattern, low QRS voltage to degree of LV thickness, AV conduction disease
	Echocardiography	Myocardial walls-granular sparkling, increased thickness of RV wall, increased valve thickness, pericardial effusion, decreased longitudinal strain, and apical sparing pattern
	CMR	Subendocardial /transmural LGE, increase in native T1 value and ECV in extracellular volume
	Blood test	Disproportionately elevated NT-proBNP, sustainably elevated troponin
Extracardiac	Peripheral neuropathy	
	Autonomic neuropathy	
	AL	Proteinuria, renal failure, bruises/periorbital purpura, macroglossia, MGUS
	ATTR	Lumbar spinal stenosis, family history of ATTR, vitreous deposit, biceps tendon rupture, bilateral carpal tunnel syndrome

ACE = angiotensin converting enzyme; AL = light-chain amyloidosis; ATTR = transthyretin amyloidosis; AV = atrioventricular; CMR = cardiac magnetic resonance; ECG = electrocardiogram; ECV = extracellular volume; LGE = late gadolinium enhancement; LV = left ventricle; NT-proBNP = N-terminal pro B-type natriuretic peptide; MGUS = monoclonal gammopathy of undetermined significance; RV = right ventricle.

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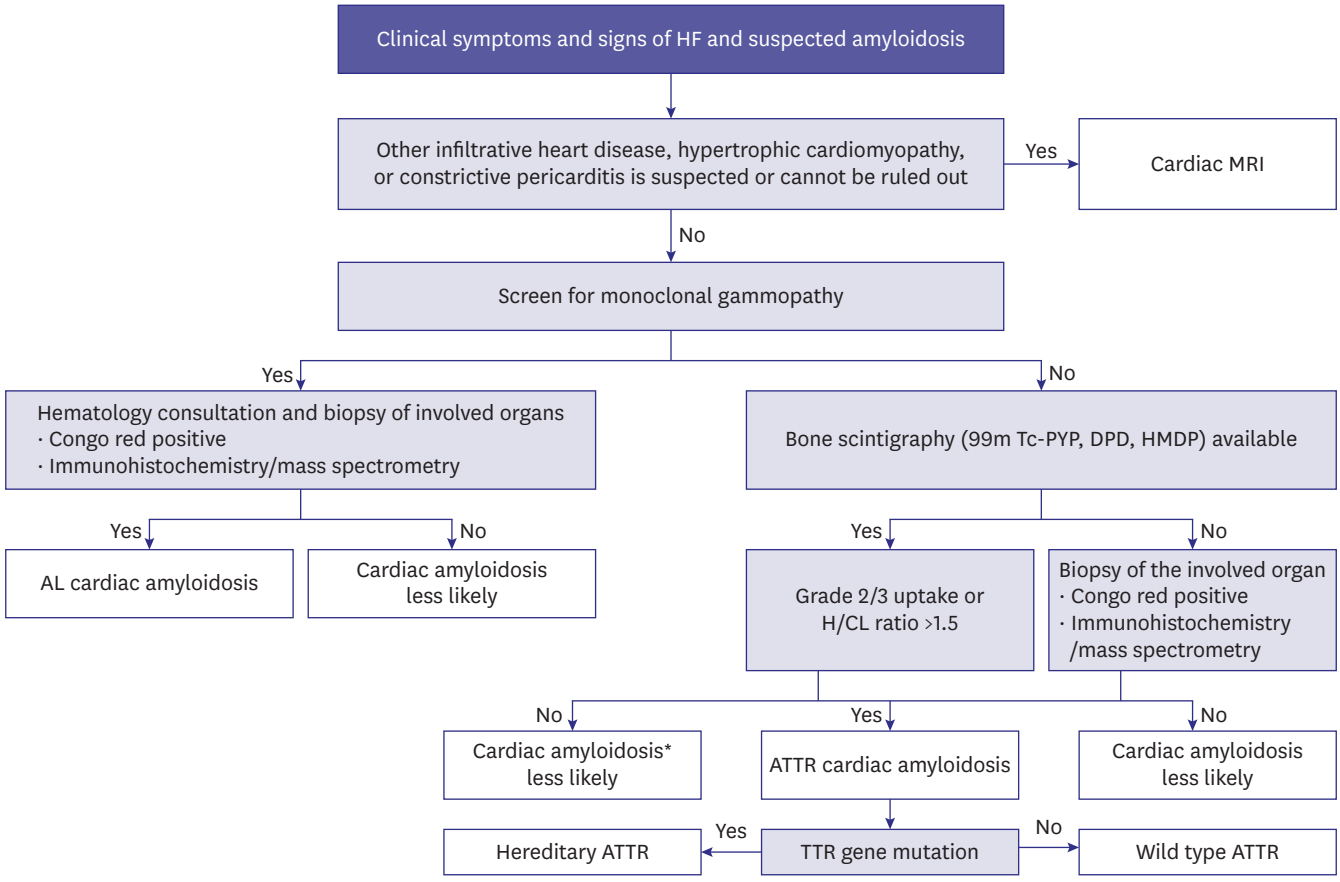

Figure 3. Diagnostic algorithm for cardiac amyloidosis.
AL = light chain immunoglobulin; ATTR = transthyretin amyloidosis; CMR = cardiovascular magnetic resonance; H/CL = heart-to-contralateral lung; HF = heart failure; Tc-DPD = technetium 3,3-diphospho-1,2-propanodicarboxylic acid; Tc-HMDP = technetium-hydroxymethylene diphosphonate; Tc-PYP = technetium pyrophosphate; TTR = transthyretin.
*Consider cardiac biopsy if clinical suspicion is high.

and fainting; in severe cases, cardiogenic shock may occur. Since myocarditis has various clinical manifestations depending on the degree and etiology, diagnosis and treatment are performed according to hemodynamic status and risk (**Figure 4**); furthermore, myocardial biopsy can be helpful in differential diagnosis and risk stratification.[83-88] Approximately 40–60% of patients with myocarditis fully recover after the acute phase; however, approximately 20% of patients develop HF and subsequently, dilated cardiomyopathy within a few years.[89] Therefore, HF treatment is recommended for at least 6 months after heart function is recovered (LVEF >50%) and the arrhythmia disappears; additionally, electrocardiogram (ECG) annual follow-up with echocardiograms are recommended for 4 years.[86-90]

(3) Right heart failure

1. Coronary revascularization should be performed in patients with acute ST-segment elevation myocardial infarction with right ventricular myocardial infarction. (Class I, LOE A)
2. The use of vasodilators in patients with group 1 pulmonary arterial hypertension is recommended to improve survival. (Class I, LOE A)

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3. During mitral valve surgery, severe tricuspid valve regurgitation should be concomitantly corrected. (Class I, LOE C)
4. In patients with right HF with congestive symptoms, diuretics are recommended. (Class I, LOE C)
5. For right HF with unclear diagnosis, hemodynamic evaluation via right cardiac catheterization is recommended. (Class I, LOE C)
6. In patients with arrhythmia-induced right ventricular cardiomyopathy, a defibrillator is recommended if there is a high probability of sudden cardiac death. (Class I, LOE C)
7. For families of patients with arrhythmia-induced right ventricular cardiomyopathy, clinical screening and genetic testing are recommended. (Class I, LOE C)
8. In patients with HF with hypotension and decreased peripheral perfusion, vasopressors and/or cardiac agents may be used. (Class IIb, LOE C)

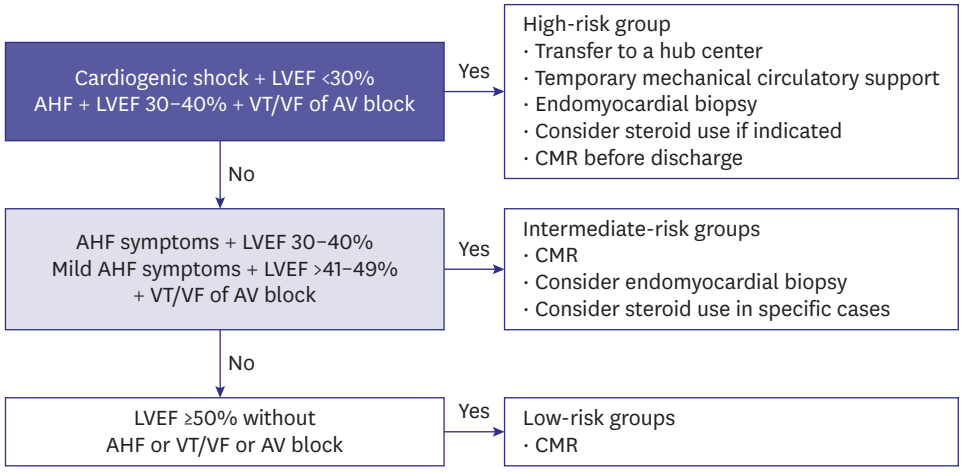

Figure 4. Risk-based approach for acute myocarditis.
AHF = acute heart failure; AV = atrioventricular; CMR = cardiovascular magnetic resonance; LVEF = left ventricular ejection fraction; VF = ventricular fibrillation; VT = ventricular tachycardia.

Right HF is associated with increased pressure in the right ventricle and atrium. Right HF can cause problems with LV filling, ultimately reducing systemic CO.[91)92)] Mechanisms and etiology of right HF are varied, relieving venous congestion is the treatment priority. Diuretics are often the first line of therapy for venous congestion. Inotropes and vasopressors are indicated for low CO and hemodynamic instability. Inotropes reducing that cardiac filling pressures are preferred (e.g., levosimendan, milrinone). Since these inotropic agents may aggravate arterial hypotension, they may be combined with norepinephrine, if needed (**Figure 5**).

Multidisciplinary care

(1) Improving the quality of non-drug treatment and medical care - a multidisciplinary approach

1. A multidisciplinary approach is recommended to reduce HF hospitalization or mortality. (Class I, LOE A)
2. Patient self-management is recommended to reduce HF hospitalization or mortality. (Class I, LOE A)

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Figure 5. Assessment and treatment of right HF.

ARVD = arrhythmogenic right ventricular dysplasia; AV = atrioventricular; BP = blood pressure; CI = cardiac index; CO = cardiac output; CVP = central venous pressure; CVVH = continuous veno-venous hemofiltration; DCCV = direct current cardioversion; HF = heart failure; IV = intravenous; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; PA = pulmonary artery; PADP = pulmonary artery diastolic pressure; PAH = pulmonary arterial hypertension; PASP = pulmonary artery systolic pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RV = right ventricle; SV = stroke volume; SVI = stroke volume index; UO = urine output; PTE = pulmonary thromboembolism; TR = tricuspid regurgitation.

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3. Home- or office-based HF management programs is recommended to reduce HF hospitalization or mortality. (Class I, LOE A)

A multidisciplinary HF treatment approach should be patient-centered, based on sufficient discussion and communication, and adaptable to local- and national-level social, cultural, and economic conditions. Several clinical studies have demonstrated that compared with the standard HF treatment, a multidisciplinary approach reduces HF hospitalization and mortality and improves the quality of life.[93-99]

(2) Cardiac rehabilitation

1. Exercise therapy is recommended to improve exercise performance and the quality of life and reduce HF hospitalization in all patients with HF. (Class I, LOE A)
2. In patients with severe disease, frailty, or with multiple comorbidities, supervised exercise-based cardiac rehabilitation programs can be beneficial. (Class IIa, LOE C)
3. Measures to increase participation in cardiac rehabilitation programs can be beneficial. (Class IIa, LOE B)
4. Home-based cardiac rehabilitation, telehealth, and mobile health intervention may be considered to increase long-term participation in cardiac rehabilitation programs. (Class IIb, LOE B)

The goals of cardiac rehabilitation in patients with HF are to improve the quality of life by improving cardiorespiratory endurance, and to reduce readmissions and mortalities due to worsening HF.[100][101] The contents of cardiac rehabilitation programs includes multidisciplinary access through the followings: 1) patient evaluation; 2) diet; 3) weight management; 4) blood pressure management; 5) blood lipid management; 6) diabetic disease management; 7) smoking cessation; 8) psychosocial management; 9) physical activity counseling; and 10) all sections in cardiac rehabilitation exercise therapy should be included. Inpatient-cardiac rehabilitation programs can be initiated after stabilization of patients' symptoms, cardiac enzymes, N-terminal pro B-type natriuretic peptide (NT-proBNP; or brain natriuretic peptide) levels, and ECG findings for >48 hours. Outpatient-cardiac rehabilitation is recommended within the first 1 week post-discharge, and approximately 4 weeks after thoracotomy.[100][101] If the patient is unable to participate in hospital-based cardiac rehabilitation program, a tele-cardiac rehabilitation program using home-based cardiac rehabilitation, monitoring devices, and information and communication technology may be considered.[100-103] Supervised rehabilitation should be considered in patients with ICD, CRT, or LV assist device, or those who underwent high-risk open-heart surgery or heart transplant, or those with cancer or frailty.[104-107]

(3) Performance measures or clinical quality indicators for quality improvement in patients with heart failure

1. In patients with HF, assessment of treatment outcomes and clinical quality indicator can be beneficial to improve the quality of HF treatment and patient prognosis. (Class IIa, LOE B)

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In the United States, standardized performance indicators were applied to improve readmission and mortality rates, and society-led performance indicators and checklists for HF programs revealed improvement in patient prognosis by applying quality improvement programs for each institution.[108] Furthermore, the HF practice guidelines published by the European Society of Cardiology emphasize the effective applications of the guidelines and performance evaluation of quality management of HF.[4] Although standardized quality management indicators have not yet been developed in Korea, verifying their usefulness while developing and applying performance indicators to Korean HF patients are essential.[109] To successfully improve the quality of HF treatment and patient prognosis through Korean clinical quality indicators in the future, institutional efforts are needed to integrate health care system and medical information among HF institutions.

CONCLUSION

In this part of the guideline, we have discussed pharmacotherapy, cardiac implantable electronic devices, treatment for specific cardiomyopathies, and multidisciplinary care to improve the prognosis and provide the best care for patients with HF. We have evaluated and summarized up-to-date evidences for novel drugs including ARNI, SGLT2 inhibitors, and tafamidis. These guidelines will facilitate treatment decision making for patients with HF. Furthermore, we recognize the importance of multidisciplinary care and the necessity for assessing and reporting the quality of HF care for the best possible patient outcomes.

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