

Review Article



Korean Guidelines for Diagnosis and Management of Chronic Heart Failure

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ABSTRACT

The prevalence of heart failure (HF) is skyrocketing worldwide, and is closely associated with serious morbidity and mortality. In particular, HF is one of the main causes for the hospitalization and mortality in elderly individuals. Korea also has these epidemiological problems, and HF is responsible for huge socioeconomic burden. However, there has been no clinical guideline for HF management in Korea. The present guideline provides the first set of practical guidelines for the management of HF in Korea and was developed using the guideline adaptation process while including as many data from Korean studies as possible. The scope of the present guideline includes the definition, diagnosis, and treatment of chronic HF with reduced/preserved ejection fraction of various etiologies.

Keywords: Chronic heart failure; Guideline

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Conflict of Interest

The authors have no financial conflicts of interest.

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INTRODUCTION

The aim of the Korean guidelines for chronic heart failure (HF) is to provide practical guidance based on current evidence for the diagnosis and treatment of chronic HF in the real clinical setting. To ensure appropriate and effective treatment for HF in daily practice, it is of key importance that medical teams establish the best practice strategies for managing each individual patient. The present guidelines indicate the direction to be followed not only by general cardiologists or HF experts in the management of HF patients, but also highlight aspects important for education and consultation. However, while the present guidelines are meant to provide assistance in clinical practice, they should not be applied indiscriminately to all HF patients, and do not replace the medical code of conduct that defines the concepts of right and wrong in medical practice. Every physician is responsible for managing their HF patients on the basis of the individual clinical situations, and a physician's final decision has priority over the present guidelines.

The present guidelines provide the first set of practical guidelines for the management of HF in Korea and were developed using a guideline adaptation process while including as much data from Korean studies as possible. The guidelines will be revised periodically to ensure that recommendations are in line with the progress of diagnosis and treatment procedures for HF. The scope of the present guidelines includes the definition, diagnosis, and treatment of HF with reduced/preserved ejection fraction (EF) of various etiologies. The guidelines for the management of acute HF will be published separately.

The writing committee was composed of 19 HF experts from the Korean Society of Heart Failure, who decided on key aspects such as the form of the guidelines, the topics addressed, and the contributing authors. The development of the guidelines was initiated in June 2013, after the selection of topics and authors, and followed the PICO approach, which involves addressing key questions regarding the target population (P), suitable interventions (I), comparison among available strategies (C), and the therapeutic outcomes (O). The PICO questions helped organize and optimize the content relevant for each topic, which the writing committee then obtained from the selected authors. While the PICO questions and answers are not included in the guideline itself, this information was recorded during the development of the guidelines and remains available for use during further revision efforts. The present guidelines were completed with the supervision of the advisory committee composed of 10 councilors from the Korean Society of Heart Failure, and with the endorsement of the Korean Society of Cardiology, Korean Society of Hypertension, Korean Society of Interventional Cardiology, Korean Society of Echocardiography, and Korean Society of Lipidology and Atherosclerosis.

The recommendations are made based on clear evidence collected from studies describing real clinical experience and the outcome of surveys, as well as from epidemiologic, observational, and randomized clinical studies. The recommendations were intended to have a clear formulation, provide straightforward instructions, and be easily adapted to daily clinical practice. The level of evidence and class of recommendation (**Table 1**) were quoted from the guidelines put forth by the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA). The class of recommendation refers to clinical effectiveness, which was estimated based on weighing the benefit and risk associated with individual diagnostic or treatment methods.

Table 1. Criteria used to judge the level of evidence and establish the class of recommendation for HF

Criterion	Class I · Benefit>>>Risk · Procedure/Treatment SHOULD be performed	Class IIa · Benefit>>Risk · Additional studies with focused objectives needed · IT IS REASONABLE to perform procedure/administer treatment	Class IIb · Benefit>Risk · Additional studies with broad objectives needed; additional registry data would be helpful · Procedure/treatment MAY BE CONSIDERED	Class III · No benefit or harm · Procedure/treatment SHOULD NOT BE PERFORMED because they are not useful or potentially harmful
Level A · Multiple population evaluated · Data from multiple randomized clinical trials or meta-analysis	1) Recommendation that procedure or treatment is useful/effective 2) Sufficient evidence from multiple randomized trials or meta-analyses	1) Recommendation in favor of procedure or treatment being useful/effective 2) Some conflicting evidence from multiple randomized trials or meta-analyses	1) Recommendation's usefulness/efficacy less well established 2) Greater conflicting evidence from multiple randomized trials or meta-analyses	1) Recommendation that procedure or treatment is not useful/effective and/or may be harmful 2) Sufficient evidence from multiple randomized trials or meta-analyses
Level B · Limited populations evaluated · Data from a single randomized trial or non-randomized studies	1) Recommendation that procedure or treatment is useful/effective 2) Sufficient evidence from single randomized trials or non-randomized studies	1) Recommendation in favor of procedure or treatment being useful/effective 2) Some conflicting evidence from single randomized trials or non-randomized studies	1) Recommendation's usefulness/efficacy less well established 2) Greater conflicting evidence from single randomized trials or non-randomized studies	1) Recommendation that procedure or treatment is not useful/effective and may be harmful 2) Sufficient evidence from single randomized trials or non-randomized studies
Level C · Very limited populations evaluated · Only consensus opinion of experts, case studies, or standard of care	1) Recommendation that procedure or treatment is useful/effective 2) Only expert opinion, case studies, or standard of care	1) Recommendation in favor of procedure or treatment being useful/effective 2) Only diverging expert opinion, case studies, or standard of care	1) Recommendation's usefulness/efficacy less well established 2) Only diverging expert opinion, case studies, or standard of care	1) Recommendation that procedure or treatment is not useful/effective and may be harmful 2) Only diverging expert opinion, case studies, or standard of care

HF = heart failure.

Table 2. Formulations typically used with each class of recommendation

Class	Formulation
I	Should, is recommended, is useful/beneficial
IIa	Is reasonable, can be useful/beneficial
IIb	May/might be considered/reasonable
III	Is not recommended, should not be performed, potentially harmful

The 4 classes of recommendation are interpreted as follows (**Table 2**): class I, indicating that the approach should be performed, is recommended, or is useful/beneficial; class IIa, indicating that the approach is reasonable, or can be useful/beneficial; class IIb, indicating that the approach may/might be considered/reasonable; and class III, indicating that the approach is not recommended, should not be performed, or is potentially harmful. The level of evidence is used to indicate the type of scientific support for each class of recommendation, and was stratified by the writing committee into 3 grades as follows: A, indicating evidence from multiple populations evaluated via multiple clinical trials; B, indicating evidence from limited populations evaluated via non-randomized clinical trials; and C, indicating evidence from very limited populations evaluated via case studies, or opinion expressed as an expert consensus.

DEFINITIONS

Definitions and terminology

Definition of HF

According to the general definition, HF describes a state in which a cardiac problem leads to insufficient oxygen delivery to the peripheral organs. Clinically, HF is manifested as dyspnea

or fatigue due to the functional or structural impairment of ventricular filling or ejection of blood.¹⁾ This clinical syndrome is associated with general symptoms such as shortness of breath, leg swelling, and fatigue, as well as with somatic signs such as pulmonary rales (crackles on pulmonary auscultation) and increased pressure in the jugular veins. HF is rarely associated with a single illness, and typically develops as a result of several health problems. Previously, the Framingham criteria were used to diagnose HF in patients with characteristic symptoms and signs. However, recent approaches tend to avoid such numerical diagnostic criteria and rather consider the typical symptoms and signs in association with the left ventricular (LV) EF, which is assessed using echocardiography and by measuring the levels of B-type natriuretic peptide (BNP). HF affects not only the regions of the heart (epicardium, myocardium, endocardium, valves, and ventricles), but also the great arteries, rhythm, and cardiac conduction. Nevertheless, HF generally originates from a dysfunction in the LV. It is crucial to identify the cause of the disease not only to expedite the diagnostic process, but also to ensure optimal therapeutic management.

Terminology related to HF

If the symptoms and signs of HF last for a certain period of time, the condition can be defined as 'chronic HF.' The term 'stable' is used only when the symptoms are well-controlled for at least a month. The worsening of chronic stable HF is termed 'decompensated HF,' while a sudden outbreak or aggravation leading to hospitalization is termed 'acute HF.' The initial development of HF symptoms due to illnesses such as myocardial infarction or myocarditis is referred to as 'de novo HF.' The term 'compensatory HF' is used in HF patients who are asymptomatic or show an improvement in their condition for a certain period of time. The term 'congestive HF,' used more often in the United States, and indicates acute and chronic HF with signs of salt or fluid retention.

Definition of HF with reduced EF (HFrEF) and HF with preserved EF (HFpEF)

LVEF is calculated by dividing each stroke volume by the end-diastolic volume. If the contractile function deteriorates, the reduction in cardiac output can be compensated by increasing the end-diastolic volume, thereby increasing the stroke volume. However, although the stroke volume may be maintained, if the contractile force deteriorates, the EF will eventually decline and the heart will be dilated. In the past, HF was classified into 'systolic HF,' indicating deterioration of the contractile function, or 'diastolic HF,' originating from a diastolic dysfunction with intact contractile function. As LVEF is an indicator of the contractile function of the LV, reduced LVEF was classified as systolic HF.

However, there are cases in which reduced EF is accompanied with diastolic dysfunction, and moreover, not every type of contractile dysfunction can be explained in terms of the EF. Therefore, the terms 'HFrEF' and 'HFpEF' are currently used, rather than systolic HF and diastolic HF. While the HFrEF/HFpEF classification is useful in terms of clinical convenience and accessibility, it also implies aspects related to therapeutic outcomes. Most randomized prospective studies demonstrated that some drugs provide additional survival benefit in patients with HFrEF, but not in those with HFpEF.

Different guidelines use various values of the EF cut-off to further classify HF. For example, HFrEF is defined as LVEF $\leq 35\%$ – 40% , HFpEF as LVEF $\geq 50\%$, borderline HFpEF as LVEF between 41% and 49% , and HFpEF with improved EF as LVEF $> 40\%$.²⁾³⁾ The prognosis of borderline HFpEF may be similar to that of HFpEF, and the prognosis of HFpEF with

improved EF may be better than that of HFpEF.⁴ While LVEF can be easily measured using echocardiography, even normal echocardiographic findings might be associated with decreased LVEF, which can be verified using other imaging techniques such as magnetic resonance imaging (MRI). Thus, echocardiographic findings should be interpreted with caution.

Epidemiology

The prevalence of HF is skyrocketing worldwide, and is closely associated with serious morbidity and mortality.⁵ In particular, HF is one of the main causes for the hospitalization and mortality in elderly individuals aged over 65 years.⁶ According to the US National Health and Nutrition Examination Survey, more than 5.1 million individuals over 20 years old are believed to have HF;⁷ it is estimated that, by 2030, more than 8 million individuals over 18 years old will have HF, which represents a 46% increase in the prevalence of HF.⁸ In Asia, a 2010 report indicated that approximately 4 million people in China have HF, with a higher prevalence among women than men.⁹ In Japan, a 2005 report indicated that approximately 1 million individuals had HF, and estimated an expected increase of 35% by 2035.¹⁰

On the other hand, there have been few studies in Korea regarding the prevalence of HF, associated comorbidities, or cause of the disease. According to a recent analysis performed by the National Health Insurance Service using a sample cohort database, the prevalence of HF in 2013 was 1.5%; considering the latest census by the Statistics Korea, these findings indicate that approximately 750,000 Koreans have HF. Furthermore, reports for 2002 and 2013 suggest a gradual increase in the prevalence of HF among both men (from 0.54% to 1.24%) and women (from 0.96% to 1.72%). The prevalence of HF increases sharply with age, and is reported at 1.0% for individuals under the age of 60 years and 5.5% for those aged 60 years or older, with a spike to 12.6% for those aged 80 years or older. Based on these findings, age is considered the most important risk factor for HF, especially because the prevalence of HF among very elderly individuals (80 years or older) is more than 8-times higher than the prevalence in the overall population. Moreover, in the younger age group, men show a slightly higher prevalence of HF, with no substantial sex-specific difference; on the other hand, in the older age group, it is women who show a significantly higher prevalence of HF.

According to the Framingham study, 10 out of 1,000 elderly individuals (aged 65 years or older) are diagnosed with HF, and 75% of these patients have already been diagnosed as having high blood pressure prior to HF diagnosis.¹¹ An analysis of the 2013 database of the National Health Insurance Service in Korea indicated that ischemic heart disease and hypertension were the most common comorbidities noted among HF patients (45.4% and 43.6%, respectively), followed by valvular heart disease (5.6%) and cardiomyopathy (3.1%). A study from 2005 examined the cause of chronic HF in patients treated between 1998 and 2003 at 1 of 9 university hospitals in Korea, and found that ischemic heart disease was the most common etiology of chronic HF (32.3%), followed by cardiomyopathy (22.7%), hypertensive heart disease (16.5%), and valvular heart disease (13.5%); uncertain etiology and other causes such as congenital heart disease, endocarditis, or myocarditis accounted for up to 15%.¹² Another analysis included patients with HF hospitalized between 2004 and 2009, and also found that ischemic heart disease was the most common etiology (52.3%), followed by hypertensive heart disease (36.7%), cardiomyopathy (26.5%), and valvular heart disease (12.7%).¹³

DIAGNOSIS

Symptoms and signs

1. History should be taken and physical examination should be performed in patients with clinically suspected HF (class of recommendation I, level of evidence C).
2. History should be taken and physical examination should be performed in patients with known HF risk factors to identify HF (class of recommendation I, level of evidence C).
3. History should include the presence of orthopnea, and physical examination should include evaluation of serial vital signs, weight, jugular venous pressure, ventricular filling (S3) sound, and presence of peripheral edema to establish the severity and prognosis of HF (class of recommendation I, level of evidence B).

Careful assessment of the patient's medical history and physical status, with consideration of all symptoms and signs, is basic and vital in the assessment of a patient with HF. Patients with HF typically complain of various symptoms (**Table 3**). The most common symptom is dyspnea, which worsens with exercise. However, dyspnea is a non-specific indicator of cardiopulmonary diseases, as it is also commonly noted in patients with abnormalities of the airway, respiratory muscles, or chest wall, as well as in some healthy individuals performing low-intensity exercise. When decompensated HF is aggravated, the patient may complain of orthopnea, mentioning that it is easier to breathe while sitting up than when lying on their back, or of paroxysmal nocturnal dyspnea, but these symptoms are not very specific in patients with mild symptoms.¹⁴⁻²⁰ The reduction in cardiac output causes heavy fatigue, and patients with arrhythmia will complain of palpitation. Right ventricular dysfunction can lead to loss of appetite, indigestion, or the feeling of abdominal distention. The patients may also present with neurological symptoms such as confusion, dizziness, or depression, but such symptoms non-specific indicators of HF.

The severity of HF symptoms such as dyspnea is classified in terms of the amount of exercise that will induce the manifestation of the symptom (**Table 4**), which is helpful for monitoring the progress of the illness or the response to treatment, not for assessing the degree of cardiac dysfunction.²¹⁾²²⁾ It is also important to carefully scrutinize the patient's past medical history,

Table 3. Symptoms and signs of HF

Symptom		Sign	
Typical	Atypical	Specific	Nonspecific
Dyspnea	Nocturnal cough	Increase of jugular venous pressure	Peripheral edema
Orthopnea	Wheezing	Hepatojugular reflux	Pulmonary crepitations
Paroxysmal nocturnal dyspnea	Weight gain (2+ kg/week)	S3 sound	Dullness at lung base
Exercise intolerance	Weight loss	Displaced apical impulse	Tachycardia
Fatigue, delayed recovery from exercise	Satiety	Cardiac murmur	Irregular pulse
Ankle edema	Loss of appetite		Tachypnea (>16 breaths/min)
	Confusion		Hepatomegaly
	Depression		Ascites
	Palpitation		Cachexia
	Syncope		

HF = heart failure.

Table 4. NYHA functional classification for assessing the extent of HF

Class	Overview
I	No limitation of physical activity. Ordinary physical activity does not cause symptoms.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity causes symptoms.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity causes symptoms.
IV	Symptoms at rest. Any physical activity causes aggravation of symptoms.

HF = heart failure; NYHA = New York Heart Association.

as HF is rare in patients without medical history, while the risk of HF is significantly higher in patients who have had certain illnesses, especially myocardial infarction (**Table 5**).^{14-18,23} The presence of HF must be judged objectively, and a thorough physical examination is needed to understand its clinical course. The various symptoms of HF (**Table 3**), which result from pathophysiological mechanisms attempting to compensate for the low cardiac output, are non-specific and usually related to fluid retention. While edema is a common finding in patients with HF, it may also be a sign of another illness, as its presence is easily affected by the use of medication such as diuretics. Symptoms such as increased jugular venous pressure, pathological S3 sound, and displaced apical impulse are strongly associated with HF, but are not often manifested^{14,15,17,19,20,24-28} and difficult to detect in some patients, especially those with obesity, chronic obstructive pulmonary disease (COPD), or old age.^{23,29,30} Taken separately, each sign associated with HF may not be specific to HF,^{15,20,31} and, therefore, the diagnosis can be more accurate if several symptoms and signs are present. However, because other illnesses may manifest symptoms and signs similar to those of HF (**Table 6**), additional examinations are commonly required to establish a diagnosis of HF.

Once HF is diagnosed, it is important to consider the signs and symptoms in order to identify the cause, progression, and therapeutic response of HF. In patients with dyspnea, additional aspects should be monitored, including the presence of orthopnea and the change in symptoms indicative of the extent of HF according to New York Heart Association (NYHA) functional classification. In addition to monitoring changes in S3 sound and cardiac murmur, the severity of fluid retention should be determined based on measurements of weight, vital

Table 5. Findings indicative of suspected HF

Basis	Symptom
Past and present medical history	Hypertension Diabetes Obesity Coronary artery disease (especially myocardial infarction) Peripheral artery disease or cerebrovascular disease Valvular heart disease Family history of cardiomyopathy in direct ancestors Exposure to cardiotoxic agents Sleep apnea
Test findings	Frequent arrhythmia Abnormality on electrocardiography (LVH, LBBB, Q wave) Cardiomegaly on chest X-ray

HF = heart failure; LBBB = left bundle branch block; LVH = left ventricular hypertrophy.

Table 6. Symptoms and signs useful for the differential diagnosis of HF

Symptom and sign
Myocardial ischemia
Pulmonary disease (pneumonia, asthma, COPD, pulmonary embolism, pulmonary hypertension)
Sleep apnea
Obesity
Malnutrition
Anemia
Hepatic failure
Chronic kidney disease
Hypoalbuminemia
Venous congestion
Depression
Anxiety and hyperventilation syndrome
Hyper/hypothyroidism

COPD = chronic obstructive pulmonary disease; HF = heart failure.

signs, and jugular venous pressure, as well as on the outcome of the physical examination, including the presence of rales and peripheral edema. It is well-known that the increase in jugular venous pressure, especially for patients with advanced contractile dysfunction, is a good indicator of an increase in LV filling pressure.¹⁹⁾²⁴⁾²⁵⁾ These symptoms and signs hold information on the severity of the disease and the prognosis of the patient. Specifically, prognosis is known to be poor if HF is accompanied by other illnesses such as diabetes, anemia, or renal insufficiency, if orthopnea or pathologic S3 sound are present, or jugular venous pressure is elevated.²⁴⁾³²⁻³⁴⁾

Initial examination of patients with suspected HF

1. Electrocardiography (class of recommendation I, level of evidence B)
2. Echocardiography (class of recommendation I, level of evidence A)
3. Complete blood cell count (CBC) and blood chemistry (class of recommendation I, level of evidence C)
4. Chest X-ray (class of recommendation IIa, level of evidence C)
5. Natriuretic peptides (class of recommendation I, level of evidence A)

Electrocardiography

Electrocardiography should be conducted as an initial examination of a patient suspected of HF. The electrocardiographic examination facilitates not only the diagnostic process but also the identification of the cause of the disease, as well as the planning of the treatment. For example, ischemic heart disease may be considered HF etiology if a Q wave is noted; medical treatment for heart rate control may be considered if sinus tachycardia is noted; adjusting the drug dosage may be considered if excessive sinus bradycardia is noted; and cardiac resynchronization therapy (CRT) may be considered if left bundle branch block (LBBB) with wide QRS is noted. Electrocardiography can also be applied for the differential diagnosis of HF, because it is rare for a patient with acute HF symptoms and signs to have a normal electrocardiogram at rest. However, approximately 10%–15% of patients with chronic HF patients may have a normal electrocardiogram at rest. Therefore, the negative predictive value of electrocardiographic examinations is not very high.³⁵⁻³⁷⁾

Echocardiography

Echocardiography provides important information on several critical aspects such as the systolic and diastolic function of the LV, the ventricular wall thickness, and the morphology and function of the valves. Echocardiography also plays a critical role in future investigations required over the course of the treatment. For example, if the cause of HF is aortic stenosis, surgery should be indicated and, if dilated cardiomyopathy is suspected, medical treatment with beta-blockers or renin-angiotensin-aldosterone blocking agents should be considered. In patients with regional wall motion abnormality, further assessment of potential coronary artery disease is required. In patients with normal LV contractile function but thicker ventricular wall and severe diastolic dysfunction, infiltrative cardiomyopathy is suspected and the myocardial tissue should be analyzed.³⁸⁾³⁹⁾

CBC and blood chemistry

In addition to electrocardiography, blood tests including CBC, measurement of serum electrolyte levels, and assessment of renal and hepatic function should be conducted as part of the initial check-up of patients suspected of HF. Blood tests are useful not only for identifying the cause of HF, but also for deciding the treatment protocol and predicting the prognosis. For example, in patients with elevated levels of blood creatinine and potassium,

caution should be exercised when prescribing renin-angiotensin-aldosterone blocking agents; in patients with hyponatremia, prognosis is expected to be unfavorable. Detection of anemia or thyroid dysfunction potentially causing signs and symptoms similar to those of HF is also useful in the early diagnosis of HF.⁴⁰⁻⁴⁴⁾

Chest X-ray

While the chest X-ray examination does not generally have diagnostic value for HF, it should be performed as an initial examination to check for pulmonary edema, cardiomegaly, and other pulmonary diseases.⁴⁵⁾

Measuring the levels of BNP or N-terminal pro-BNP (NT-proBNP)

Measuring the levels of BNP or NT-proBNP is highly recommended in patients suspected of HF because it carries important information and its relevance has been established on the basis of many rigorous clinical studies. In patients with negative transthoracic echocardiography or who cannot undergo echocardiography, the BNP or NT-proBNP test can be conducted to check for HF. This investigation is also useful in the differential diagnosis of HF. Thus, if the patient has normal levels of BNP or NT-proBNP, there is a high possibility that the symptoms and the signs are not related to HF, prompting for investigations to identify other causes.

In daily clinical practice, the optimal cut-off value for BNP levels used for exclusion of HF is different for patients with acute-phase HF, who often manifest symptoms and signs strongly suggestive of HF, than for patients with chronic-phase HF, who manifest somewhat ambiguous symptoms and signs that progress slowly. Therefore, to minimize the rate of false negatives, it is recommended to use a low cut-off value for BNP levels if there are symptoms and signs of suspected HF, and high cut-off values if the opposite is true. Furthermore, it is important to keep in mind that BNP and NT-proBNP levels may have different cut-off values depending on the test reagents and methods used.

BNP and NT-proBNP levels are good indicators of LV end-diastolic pressure because loading of the LV is associated with enhanced secretion of BNP and NT-proBNP. However, caution should be used when interpreting the results, because BNP secretion also increases with loading of the right ventricle or atrium, which occurs in patients with atrial fibrillation (AF) or pulmonary thromboembolism. Furthermore, the NT-proBNP results should be adjusted for age, and certain exceptions should be considered in case where NT-proBNP levels increase in the absence of HF, as shall be explained below (see section biomarkers useful for diagnosis).⁴⁵⁻⁵⁵⁾

Phased approaches to diagnosis

It is important to keep in mind that HF is not a single disease, but a complex clinical syndrome resulting from a state where the heart is unable to provide the ultimate or relative blood volume that meets the oxygen demand of the peripheral organs. This insufficiency develops as heart disease of various etiology progresses, and systolic and diastolic function eventually deteriorates. Additionally, HF is associated with fluid retention resulting in pulmonary edema and systemic congestion, which leads to difficulty in performing activities of daily life.⁵⁶⁻⁵⁸⁾ Because of the ambiguous definition and complex clinical presentation, it remains challenging to diagnose HF in the clinical setting.¹⁹⁾⁵⁸⁾

Symptom and sign-based approaches

Characteristic symptoms of HF include dyspnea in an orthopneic position, paroxysmal nocturnal dyspnea, and ankle edema, while the characteristic signs include increased jugular

venous pressure, hepatojugular reflux, S3 gallop, and apical impulse displaced downward and to the left. However, these symptoms and signs are non-specific to HF and do not have high sensitivity and specificity because they tend to not appear during the early stages of HF. It is especially difficult to distinguish the cause of the symptoms and signs in patients with obesity, advanced age, or chronic lung disease.¹⁹⁾⁽⁵⁶⁻⁵⁹⁾

However, it is very important to understand the patient's symptoms and signs via thorough history and physical examination, which will not only facilitate diagnosis, but also help determine the cause of illness. Furthermore, if the symptoms and signs ameliorate too slowly after establishing the HF diagnosis and initiating treatment, it is recommended that additional treatment should be considered; if there is further deterioration, an aggressive treatment strategy including immediate hospitalization should be considered.¹⁷⁾

Several key investigations are helpful in discerning the presence of HF and thus overcome the difficulties in diagnosing HF. Specifically, electrocardiography and echocardiography should be performed to assess structural and functional cardiac impairment, and the levels of BNP or NT-proBNP should be measured to assess whether the secretion of such factors is enhanced because of ventricular loading. Echocardiography is especially important, as it facilitates the objective measurement of causative parameters and rapid detection of the organic or functional cardiac impairment.⁵⁶⁻⁵⁸⁾

Diagnostic algorithm

It is important to choose the appropriate order in which the investigative procedures will be performed, as it is not always clear whether transthoracic echocardiography should be performed before or after the measurement of BNP or NT-proBNP levels. Compared to outpatients with vague HF symptoms, patients in the emergency room and outpatients with acute HF symptoms may benefit from a different diagnostic protocol (**Figure 1**).⁵⁶⁻⁵⁸⁾

In patients with suspected HF presenting acute and relatively characteristic symptoms and signs, meticulous examination via transthoracic echocardiography should be performed to detect organic abnormalities, and appropriate treatment should be initiated according to the severity of the illness. If the patient is considered at high risk for HF (e.g., uncontrolled hypertension or history of myocardial infarction), transthoracic echocardiography is recommended to be performed in the early stages; if this is not possible, BNP (or NT-proBNP) measurements can be considered after obtaining the electrocardiogram and chest X-ray. To reduce the chance of a false-negative result in such cases, it would be better to use a lower cut-off value for the levels of BNP or NT-proBNP (e.g., HF can be excluded if BNP levels are <100 pg/mL and NT-proBNP levels are <300 pg/mL). If there are no abnormal findings on the electrocardiogram or chest X-ray and if the BNP or NT-proBNP levels are low, HF can be excluded with high probability, and echocardiography can be replaced by another, more relevant investigation in search for the cause of the symptoms and signs. On the other hand, if BNP levels are ≥ 100 pg/mL or NT-proBNP levels are ≥ 300 pg/mL, HF cannot be excluded, and echocardiography should be performed.

In patients with chronic and ambiguous symptoms and signs, it is recommended to consider echocardiography after obtaining the electrocardiogram, chest X-ray, and BNP or NT-proBNP results so as to exclude HF beyond a doubt. If the electrocardiogram shows no abnormalities and the levels of BNP or NT-proBNP are sufficiently low (considering high cut-off values to reduce false positives: <35 pg/mL for BNP, <125 pg/mL for NT-proBNP), HF can probably be

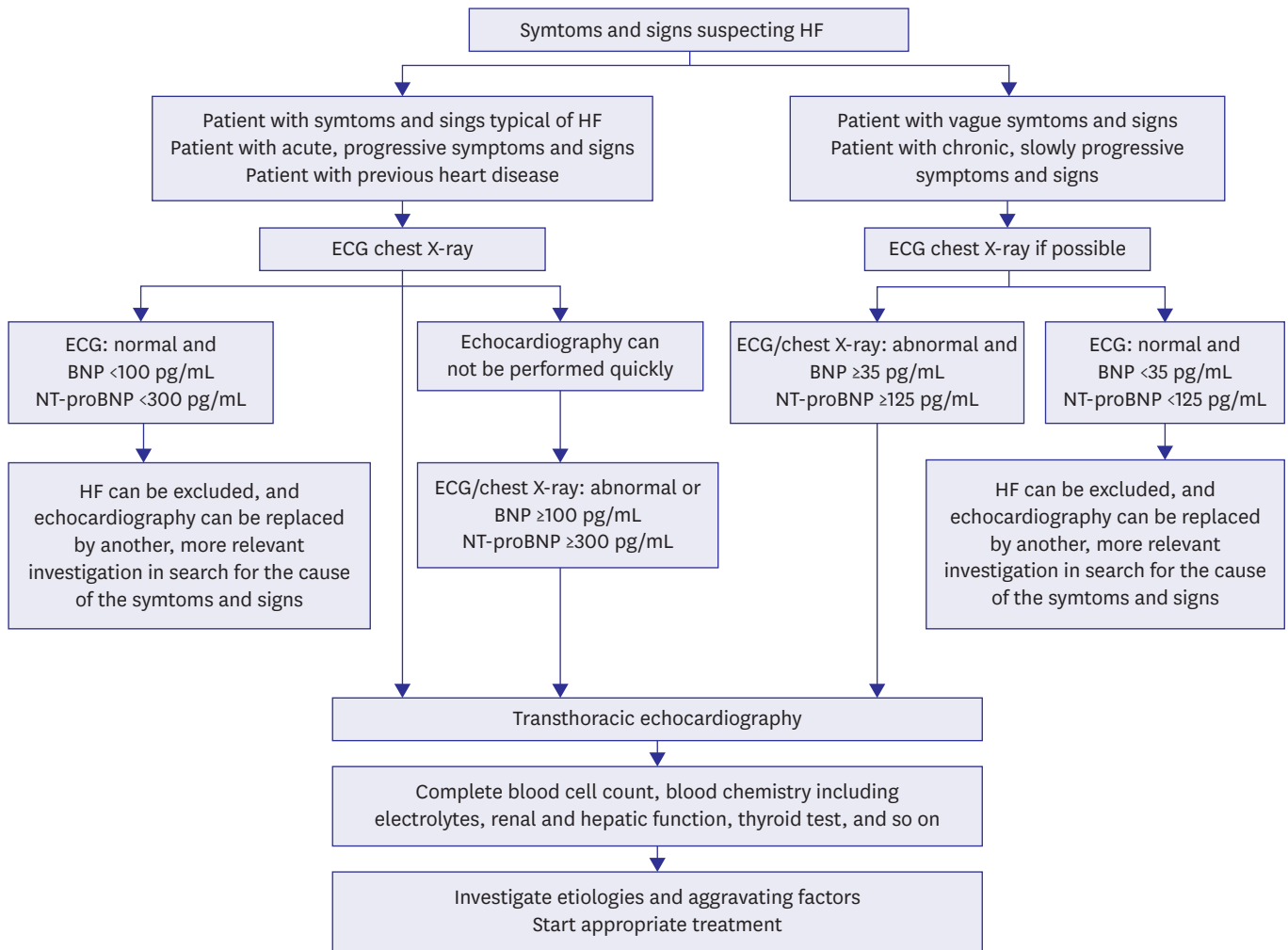


Figure 1. Algorithm for the diagnosis of HF. BNP = B-type natriuretic peptide; ECG = electrocardiogram; HF = heart failure; NT-proBNP = N-terminal pro B-type natriuretic peptide.

excluded, and echocardiography need not be performed. However, if the electrocardiogram and chest X-ray show abnormalities or if the BNP (or NT-proBNP) levels are high, HF cannot be excluded, and echocardiography should be considered.

What to check after diagnosis

Once HF is diagnosed, it is crucial to determine the cause and aggravating factors of the disease so that the treatment strategy may be planned or adjusted accordingly. For instance, if coronary artery disease is the suspected cause of HF, coronary angiography or an exercise test should be considered, and the potential benefits of adding reperfusion therapy to the treatment should be evaluated (see section ischemic heart diseases).

Biomarkers useful for diagnosis

The clinical standards for diagnosing HF do not have high sensitivity and specificity, and therefore additional procedures are required for differential diagnosis. Echocardiography is recognized as the gold standard and the most useful examination according to the guidelines for HF diagnosis; however, echocardiography is expensive, which limits its usage, and might not be as effective in some patients with obesity or chronic lung disease, who present with

dyspnea. Therefore, for a proper diagnosis of HF, one should use a biochemical indicator that can be easily measured and has high sensitivity in determining the presence and severity of HF, as well as in predicting prognosis.

The atrial, brain, and C-type natriuretic peptides represent such indicators. The atrial natriuretic peptide (ANP) and BNP are cardiac hormones usually synthesized in the atrium and ventricles, respectively, and present in the blood. The BNP precursor (proBNP) is present in the blood and reacts to hemodynamic stimuli such as ventricular pressure overload or increase in volume. As proBNP has a biologically active C-terminal and a biologically inert N-terminal (NT-proBNP), blood tests can measure the blood concentration of BNP and NT-proBNP. Many kits have been developed and are commercially available for this purpose. When conducting the analysis, either BNP or NT-proBNP can be measured, as they are equally useful as a prognostic factor; nevertheless, the pros and cons of each indicator should be considered, as their biological relevance and chemical reactivity differ, and therefore the range of standard values is also different. Therefore, it is necessary to interpret the result for each indicator separately, and the conclusions cannot be automatically extended from one indicator to another.

In some cases, the results of this measurement may conflict with the clinical state of the patient. It is important to remember that BNP levels vary with age, sex, the presence of comorbidities, and the use of medication. Therefore, one should be aware of the potential pitfalls of using a BNP-based investigation as the sole basis for diagnosis (**Table 7**). Ultimately, evaluation of BNP levels is not useful on its own, but represents an invaluable supportive tool for detection of HF, and it is important to consider the clinical context of the patient.⁴⁷⁾⁽⁶⁰⁾⁽⁶¹⁾

Significance of BNP and NT-proBNP levels for diagnosis or differential diagnosis of HF
 Measuring BNP or NT-proBNP levels has recently become a mandatory examination in patients with suspected HF, as many studies have proven its crucial clinical relevance in the differential diagnosis with acute respiratory distress. In patients presenting at the emergency room or the outpatient department with dyspnea, it is important that the diagnosis approach be timely and precise, with particular emphasis on the negative predictive value. If the cut-offs are set at 100 pg/mL for BNP and 162 pmol/L for NT-proBNP, the diagnostic accuracy of this investigation is almost 90%, with a high negative predictive value (90%). In a Korean study with a national sample, the accuracy of the diagnosis based on BNP measurements was the highest (98%) at a cut-off of 108 pg/mL, and the receiver operator characteristic curve indicated a sensitivity of 92.5% and specificity of 88.9%, which are similar to

Table 7. Situations in which the levels of BNP or NT-proBNP are inadequate for diagnosing HF

Situation	Symptom
High BNP levels in patients without HF	Advanced age Anemia Renal failure Acute coronary syndrome Certain pulmonary conditions (sleep apnea, severe pneumonia, pulmonary hypertension) Bacterial sepsis Severe burns
Low BNP levels in patients with HF	Obesity (BMI >30 kg/m ²) Fulminant pulmonary edema (within 1–2 hours) Valvular heart disease (acute mitral regurgitation, mitral stenosis) Chronic stable HF

BMI = body mass index; BNP = B-type natriuretic peptide; HF = heart failure; NT-proBNP = N-terminal pro B-type natriuretic peptide.

findings reported in foreign studies.⁶²⁻⁶⁸⁾ This type of measurement is not only useful for the differential diagnosis of acute dyspnea, but can also be applied in patients with chronic illnesses. Cowie et al.⁵⁰⁾ found that a cut-off of 76.4 pg/mL for the levels of BNP could be used to diagnose HF with 97% sensitivity and 84% specificity in a sample of patients visiting their clinic. Interestingly, compared to chest X-ray, the BNP-based investigation provided better diagnostic accuracy for HF. However, Tang et al.⁷³⁾ reported that approximately 21% of outpatients with chronic stable HF showed relatively low levels of BNP (below 100 pg/mL), suggesting that the results of these measurements should be interpreted with care if the patient has relatively stable HF. In addition, BNP levels represent a useful biological marker for detecting LV hypertrophy or cardiac abnormalities in individuals with no suspected HF, but the cost effectiveness of the investigation in such cases must be considered.⁶⁹⁻⁷⁴⁾

Significance of BNP and NT-proBNP levels for predicting the severity and prognosis of HF

As BNP concentration is closely related to not only the presence of HF but also its severity, BNP serum levels increase with NYHA class, which is very helpful in predicting prognosis and planning the treatment strategy. BNP levels have also been demonstrated to serve as an independent predictor not only of HF but also of the prevalence of myocardial infarction and associated mortality. The Valsartan Heart Failure Trial (Val-HeFT) study, which involved patients with severe or chronic HF, reported a higher incidence of cardiac events in patients with high levels of BNP, and that the mortality rate increased by 1.2% for every 10 pg/mL increment in BNP levels. Therefore, it is clinically relevant to measure the levels of BNP or NT-proBNP to estimate the severity and predict the prognosis of HF.⁶⁶⁾⁷⁵⁻⁸¹⁾ Furthermore, BNP levels can be used as an indicator of clinical improvement as a response to medical treatment with both currently available and newly developed medications intended to alleviate the symptoms of HF. Several multinational prospective clinical studies have assessed the effectiveness of medical treatment based on the levels of BNP as indicators of clinical improvement, but the results regarding prognosis are inconsistent. Moreover, it remains unclear how to apply the information provided by BNP levels in deciding the actual treatment protocol and dosage. Further study is warranted in this direction.⁸²⁻⁹⁰⁾

Imaging diagnosis

Echocardiography

1. Echocardiography should be performed at the initial evaluation of HF (class of recommendation I, level of evidence B).
2. In patients with HF, regular follow-ups with echocardiography can help decrease the rate of mortality, morbidity, and hospitalization related to HF (class of recommendation IIa, level of evidence B).

In patients with dyspnea and suspected HF, echocardiography is the most effective radiologic examination for HF diagnosis,⁹¹⁾ as it facilitates the assessment of the cardiac structure (volume, mass) and function, including ventricular systolic/diastolic function, regional wall motion, valve motion, and hemodynamic parameters. Furthermore, echocardiography can be used to diagnose asymptomatic HF and predict the risk of subsequent events,⁹²⁻⁹⁶⁾ thus playing an important role in establishing an accurate diagnosis and choosing an appropriate treatment strategy.⁹⁷⁾

If the contractile function of the LV is deteriorated or if there is a structural anomaly, a comprehensive echocardiography is needed for the quantitative evaluation of the LVEF, LV

Table 8. Common abnormal echocardiographic findings in patients with HF

Variable	Parameters	Abnormality	Clinical implications
Variables associated with systolic function	LVEF	Reduced (<50%)	LV global systolic dysfunction
	LV fractional shortening	Reduced (<25%)	LV radial systolic dysfunction
	LV regional function	Hypokinesis, akinesis, dyskinesis	Myocardial infarction/ischemia Cardiomyopathy, myocarditis
	LV end-diastolic size	Increased (diameter, ≥55 mm; diameter/BSA, >34 mm/m ² ; volume/BSA, >81 mL/m ²)	Volume overload HF likely
	LV end-systolic size	Increased (diameter, >36 mm; diameter/BSA, >22 mm/m ² ; volume/BSA, >33 mL/m ²)	Volume overload HF likely
Variables associated with diastolic function	LV outflow tract velocity time integral	Reduced (<15 cm)	Reduced LV stroke volume
	LV diastolic dysfunction parameters	Abnormalities of the mitral inflow (e' or E/e' ratio)	Indicate LV diastolic dysfunction degree and suggest level of filling pressure
	Left atrial volume index	Increased (volume/BSA >34 mL/m ²)	Increased LV filling pressure (past or present) Mitral valve disease
Variables associated with valvular function	LV mass index	Increased (females, >96 g/m ² ; males, >100 g/m ²)	Hypertension, aortic stenosis, hypertrophic cardiomyopathy
	Valvular structure and function	Valvular stenosis or regurgitation (especially aortic stenosis and mitral regurgitation)	May be the cause of HF, a complicating factor, or the result of HF (secondary mitral regurgitation) Assess dysfunction severity and hemodynamic consequences Consider surgery
Other variables	RV function (e.g., TAPSE)	Reduced (TAPSE <16 mm)	RV systolic dysfunction
	Tricuspid regurgitation peak velocity	Increased (>3.4 m/s)	Increased RV systolic pressure
	Systolic pulmonary artery pressure	Increased (>50 mmHg)	Pulmonary hypertension likely
	Inferior vena cava	Dilated, with no respiratory collapse	Increased right atrial pressure RV dysfunction, volume overload Pulmonary hypertension possible
	Pericardium	Effusion, hemopericardium, calcification	Consider tamponade, malignancy, systemic diseases, acute or chronic pericarditis, constrictive pericarditis

BSA = body surface area; E/e' = ratio of the mitral inflow E-wave to the tissue Doppler e'-wave; e' = early diastolic myocardial velocity; HF = heart failure; LV = left ventricular; LVEF = left ventricular ejection fraction; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion.

size, wall thickness, and LV volume. LVEF is used as a clinical performance measure for quality of care in HF patients.⁹⁸⁾ It is necessary to evaluate not only the LV, but also the size and function of the right ventricle and atrium, as well as any morphological or functional abnormalities of the valves and the severity of mitral or tricuspid insufficiency, which are considered secondary changes associated with HF. Echocardiography provides a useful solution in this direction, as it allows the non-invasive measurement of hemodynamic data. The mitral and pulmonary vein inflow patterns, as well as the mitral annular velocity provide additional information on the LV filling pressure and left atrial pressure. The systolic pulmonary artery pressure and the central venous pressure can be estimated based on the peak velocity of tricuspid regurgitation and its calculated pressure gradient, the diameter of the inferior vena cava, and the respiratory variation of this diameter. An overview of abnormal echocardiographic findings commonly found in HF is provided in **Table 8**.⁹⁹⁾

1) Evaluating LV systolic function

While LVEF is commonly considered an indicator of ventricular systolic function, it should not be used as a sole estimator because its magnitude is influenced by the ventricular volume, preload, and afterload, as well as by the heart rate and valve function. Furthermore, LVEF is not equivalent to stroke volume. Specifically, if LV expands, stroke volume is constant even in the presence of HF. Similarly, the stroke volume is reduced when HFpEF is accompanied by concentric LV hypertrophy. Furthermore, in patients with significant mitral regurgitation, the LVEF is constant while the ejection volume is reduced. Therefore, the LVEF must not be evaluated just in terms of its numerical value, but in the overall clinical context.

Simpson's rule is recommended when calculating LVEF based on echocardiographic measurements.³⁸⁾³⁹⁾¹⁰⁰⁾ However, in order to perform precise calculations using Simpson's rule, at least 80% of the endocardial border has to be visible during the evaluation.¹⁰¹⁾ Other methods for LVEF assessment such as the Teichholz and Quinones methods, which measure the LV diameter, are inaccurate in patients with regional wall motion abnormalities; fractional shortening, a method evaluating LV systolic function, has the same limitation. Therefore, methods such as the Teichholz method, the Quinones method, fractional shortening, and visual approximation are not recommended.¹⁰¹⁾ Three-dimensional echocardiography can determine the LV volume and EF more precisely.¹⁰²⁾ Other methods appropriate for evaluating LV systolic function involve assessing aortic valve plane systolic excursion or systolic tissue Doppler velocities. Finally, the myocardial strain or strain rate, which can be estimated via myocardial deformation imaging, represent more sensitive indicators than LVEF, as they can detect the smallest changes in LV systolic function; however, deformation imaging is not currently used in routine clinical practice because significant issues related to reproducibility and standardization remain. Stroke volume and cardiac output can be calculated using the velocity-time integral of the LV outflow tract.

2) Evaluating LV diastolic function

Measuring LV diastolic function is essential in diagnosing HFpEF. The LV diastolic function index is influenced by age, heart rate, and physical size.¹⁰³⁾¹⁰⁴⁾ Therefore, it is recommended to evaluate LV diastolic function after calculating several other echocardiographic indicators.^{103),104)} The tissue Doppler imaging-derived early diastolic myocardial velocity (e'), which is measured at the mitral annulus, is used as an indicator of myocardial relaxation. Patients with HF rarely have normal e' (septal e', >8 cm/s; lateral e', >10 cm/s; or average e', >9 cm/s). The E/e' ratio is related to the LV filling pressure.¹⁰³⁾¹⁰⁴⁾

An overview of common abnormal findings and their clinical significance in terms of LV diastolic function, as mentioned in the HF treatment guidelines put forth in 2012 by the European Heart Association, is provided in **Table 9**.

Patients with suspected HF who underwent repeated and follow-up echocardiographic investigations were found to have improved HF-related mortality, morbidity, and hospitalization rates compared to the corresponding values noted in patients who did not undergo echocardiography.⁹²⁻⁹⁶⁾ However, at present, there is insufficient research to establish clearly whether or not echocardiography should be conducted often for monitoring the

Table 9. Common abnormal findings and clinical implications of parameters associated with LV diastolic function in patients with HF

Parameter	Abnormality	Clinical implication
e'	Reduced (<8 cm/s septal, <10 cm/s lateral, or <9 cm/s average)	Delayed LV relaxation
E/e' ratio	High (>15)	High LV filling pressure
	Low (<8)	Normal LV filling pressure
	Intermediate (8-15)	Gray zone (additional parameters necessary)
Mitral inflow E/A ratio	Restrictive (>2)	High LV filling pressure Volume overload
	Impaired relaxation (<1)	Delayed LV relaxation Normal LV filling pressure
	Normal (1-2)	Inconclusive ('pseudonormal' pattern)
Mitral inflow during Valsalva maneuver	Change of the 'pseudonormal' pattern to the 'impaired relaxation' pattern (with a decrease in E/A ratio of ≥0.5)	High LV filling pressure (unmasked during Valsalva)
(A _{pulm} -A _{mitral}) duration	>30 ms	High LV filling pressure

A_{pulm}-A_{mitral} = time difference between the duration of the pulmonary vein flow A-wave and that of the mitral flow A-wave; E/A = ratio of early to late diastolic mitral inflow waves; e' = early diastolic myocardial velocity; E/e' = ratio of the mitral inflow E-wave to the tissue Doppler e'-wave; HF = heart failure; LV = left ventricular.

progress of HF patients, and no current guidelines explicitly recommend such a strategy. Repeated echocardiography is currently indicated only if there was a meaningful change in the clinical status, a clinical event occurred, recovery occurred, the patient received surgical or medical treatment with significant effect on cardiac function, or the patient is undergoing therapy with a cardiac device. However, if there are no significant changes in the clinical status or no special therapy was initiated, repeated evaluation of LV function is unnecessary.

Cardiac computed tomography (CT) and MRI

1. Patients with suspected HF should undergo a chest X-ray for assessing heart size and pulmonary congestion (class of recommendation I, level of evidence C).
2. Radionuclide ventriculography or MRI can be useful for assessing LVEF and LV volume when echocardiography is inadequate (class of recommendation IIa, level of evidence C).
3. To detect ischemic heart disease, it is reasonable to perform noninvasive imaging using single photon emission CT with thallium-201 or technetium-99m, using coronary CT, or using cardiac MRI (class of recommendation IIa, level of evidence C).

When treating patients with HF or LV dysfunction, it is of key importance to identify the etiology, which is typically classified as ischemic or non-ischemic. This distinction is important because HF caused by ischemic heart disease can be treated using coronary artery revascularization. The traditional approach is to use electrocardiography, echocardiography, and nuclear medicine imaging to evaluate the damage related to previous myocardial infarctions or perfusion defects. Cardiac MRI can now provide late gadolinium enhancement images, stress perfusion scans, and coronary artery images, which enables detection of ischemic HF via simultaneous assessment of previous myocardial infarctions, myocardial perfusion state, and arterial stenosis.¹⁰⁵⁻¹⁰⁸ In patients with preserved renal function, CT imaging is helpful to detect coronary arterial stenosis (see section *ischemic heart diseases*).¹⁰⁹

Non-ischemic cardiomyopathy includes conditions such as dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, and arrhythmogenic right ventricular dysplasia. The underlying cause of individual conditions can be evaluated using specific MRI techniques such as delayed gadolinium enhancement, T1-weighted imaging, and T1/T2 mapping.¹¹⁰⁻¹¹⁵ It may be difficult to identify the specific etiology in the terminal stage of non-ischemic cardiomyopathies because infiltration and fibrosis affect the entire myocardium. While successful revascularization therapy has been described as the most important positive predictor of prognosis in patients with ischemic HF, not every patient gains benefit from revascularization therapy. The viability of the myocardium is an important predictor of the recovery of myocardial contractility and can be assessed using transmural measurements based on delayed gadolinium enhancement and dobutamine stress MRI. Basing the indication for revascularization therapy on the findings of such MRI techniques is helpful in improving the prognosis and symptoms of patients with HF.¹¹⁶⁻¹²³

Linear delayed contrast enhancement in the intermediate layer of the myocardium is reported to be a predictor of natural recovery or re-hospitalization related to the deterioration of ventricular arrhythmia or HF.¹²⁴⁻¹²⁵ Furthermore, the presence and extent of delayed gadolinium enhancement were reported to be predictors of mortality related to the outbreak of ventricular tachycardia in patients with hypertrophic cardiomyopathy, and findings indicate high risk for complications during implantable cardioverter defibrillator (ICD)

therapy.¹²⁶⁾¹²⁷⁾ However, the results of small-scale studies are inconsistent in this respect, and investigations with a larger number of subjects and long-term follow-up are warranted before gadolinium enhancement MRI can be incorporated in the guidelines.

Cardiac MRI is used to measure the left and right ventricular EF, as well as the LV volume and mass as indicators of the therapeutic effect of various treatments. Compared to echography, cardiac MRI is accepted as a standard approach for measuring such parameters because of higher repeatability, accuracy, and reproducibility.¹²⁸⁾¹³⁰⁾ An increasing number of researchers are using cardiac MRI rather than echocardiography or nuclear imaging because cardiac MRI has the advantage of providing highly reproducible measurements even when the study sample is limited.¹³¹⁾¹³³⁾

The survival rate of children and adolescents with congenital heart disease has improved with the progress of surgical techniques and medical treatment strategies. Cardiac MRI provides important diagnostic information in patients with congenital heart disease with involvement of the great arteries related to the right ventricle, as well as information regarding post-operative pulmonary artery perfusion of a surgically corrected congenital heart disease, the connection between blood vessels, and the function and histological changes of the left and right ventricles.¹³⁴⁾¹⁴⁰⁾

In heart transplant recipients, coronary allograft vasculopathy represents a fatal complication of chronic rejection and requires re-transplantation. While invasive coronary angiography is typically performed to detect coronary allograft vasculopathy at an early stage, recent studies suggest that coronary stenosis can be efficiently detected using high-resolution CT.¹⁴¹⁾¹⁴²⁾

PHARMACOLOGICAL TREATMENT

Pharmacological treatment to improve survival

Inhibitors of the renin-angiotensin and renin-angiotensin-aldosterone systems

1. Unless contraindicated, angiotensin-converting enzyme (ACE) inhibitors are recommended in order to reduce morbidity and mortality in patients with HFrEF with current or prior symptoms (class of recommendation I, level of evidence A).
2. Unless contraindicated, angiotensin-receptor blockers (ARBs) are recommended in order to reduce morbidity and mortality in patients with HFrEF with current or prior symptoms who are intolerable to ACE inhibitors (class of recommendation I, level of evidence A).
3. To reduce morbidity and mortality, use of ARBs represents a reasonable first-line therapy alternative to ACE inhibitors in patients with HFrEF, especially in those already taking ARBs for other indications (class of recommendation IIa, level of evidence A).
4. Addition of an ARB may be considered in patients with HFrEF who are intolerant to mineralocorticoid antagonists and are already being treated with an ACE inhibitor and a beta-blocker (class of recommendation IIb, level of evidence A).

1) ACE inhibitors

ACE inhibitors are known to ameliorate the symptoms of HFrEF patients and lower the mortality and re-hospitalization rate, and these effects were observed regardless of the time of symptom presentation at treatment (current or prior HF symptoms), the severity of the symptoms, and the presence of coronary artery diseases.

In 1987, enalapril (Vasotec[®]; Valeant Pharmaceuticals International, Inc., Steinbach, Canada) was first identified to significantly improve survival in HFrEF patients, as it reduced mortality by 27% in patients with NYHA class IV (Cooperative North Scandinavian Enalapril Survival Study [CONSENSUS] trial),¹⁴³ and by 16% in those with NYHA class II–III (Studies of Left Ventricular Dysfunction [SOLVD] trial).¹⁴⁴ In a study comparing the effect of low and high doses of lisinopril (Zestril[®]; AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA) in patients with HFrEF and NYHA class II–IV, the high-dose group exhibited a 15% reduction in the mortality and re-hospitalization rate (Adjuvant Tamoxifen Long Against Short [ATLAS] trial).¹⁴⁵

Furthermore, the use of enalapril reduced the mortality and re-hospitalization rate by 20% in asymptomatic patients with HFrEF (SOLVD trial).¹⁴⁶ A meta-analysis indicated that enalapril reduced mortality and re-hospitalization by 27% in patients with HF after myocardial infarction.¹⁴⁷ Various ACE inhibitors (captopril [Capoten[®]; Par Pharmaceutical Companies, Inc., Spring Valley, NY, USA], lisinopril, perindopril [Aceon[®]; Patheon Pharmaceuticals, Inc., Cincinnati, OH, USA], ramipril [Altace[®]; Pfizer Inc., New York, NY, USA], quinapril [Accupril[®]; Pfizer Inc.], andtrandolapril [Mavik[®]; Halo Pharmaceutical Inc., Whippany, NJ, USA]) have demonstrated effectiveness in patients with HF, and there are no significant differences noted between the benefits of these drugs in terms of reducing mortality (Table 10).¹⁴⁸ Such drugs are contraindicated in patients with a history of serious angioedema and in pregnant women; indication and dosage should be carefully evaluated in patients with: low systolic blood pressure (≤ 80 mmHg), serum creatinine levels ≥ 3 mg/dL, stenosis of both renal arteries, or serum potassium levels ≥ 5 mEq/L. ACE inhibitors should be started from a low dose in the early stages, with a gradual increase, followed by evaluation of serum potassium levels and renal function after 1–2 weeks of treatment.

Drug-related adverse effects mostly originate from angiotensin and kininase inhibition. Coughing is most commonly observed, manifested in almost 20% of the medicated patients. Severe angioedema may occur, but most patients with HF show drug tolerance. Among Koreans, coughing is also known to be the most common adverse effect. The target dose is not determined as the dose that shows amelioration of HF symptoms but as the initially suggested dose that demonstrated an increase in survival rate in randomized studies. Therefore, if HFrEF patients with current or prior symptoms do not have contraindications, ACE inhibitors should be used, and the dose must be increased as much as possible to the level reported to reduce the incidence of cardiovascular events (captopril, 50 mg three times per day; enalapril, 10–20 mg twice per day; lisinopril, 20–35 mg once per day; and ramipril, 5 mg twice per day).

Regarding the increasing population of patients with HFpEF, no drugs have been confirmed to be effective at reducing mortality rate, although some have been shown to improve clinical symptoms. However, a study involving elderly patients with HFpEF (age, >70 years; average age, 76 years) followed up for 1 year, perindopril was shown to reduce mortality and

Table 10. Starting and target doses of ACE inhibitors in patients with HF

ACE inhibitor	Starting dose	Target dose
Captopril	6.25 mg 3 times a day	50 mg 3 times a day
Enalapril	2.5 mg twice a day	10–20 mg twice a day
Fosinopril	5–10 mg once a day	40 mg once a day
Lisinopril	2.5 mg once a day	20–35 mg once a day
Perindopril	2 mg once a day	8–16 mg once a day
Ramipril	2.5 mg once a day	5 mg twice a day
Trandolapril	0.5 mg once a day	4 mg once a day

ACE = angiotensin-converting enzyme; HF = heart failure.

re-hospitalization related to cardiovascular events by 31%, and overall re-hospitalization rate by 37% (Perindopril in Elderly People with Chronic Heart Failure [PEP-CHF] trial).¹⁴⁹⁾ While the reduction in mortality and re-hospitalization rate over the course of 1 year was not statistically significant, it is expected that the long-term benefits will be more significant in this patient population; nevertheless, further research is warranted to clarify this hypothesis. Generally, use of ACE inhibitors may be considered in patients with HFpEF.

2) ARBs

ARBs are renin-angiotensin system inhibitors that theoretically overcome the limitations of ACE inhibitors. Specifically, even if ACE inhibitors block the renin-angiotensin system, angiotensin II is continuously produced via other pathways such as the non-converting enzyme-dependent pathway. Furthermore, ACE inhibitors have adverse effects of coughing and angioedema due to the inhibition of kinin degradation. In a study performed in 2001, valsartan (Diovan[®]; Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA) did not reduce the overall mortality of HFrEF patients with NYHA class II–IV, but it was effective at reducing the composite endpoint of mortality/re-hospitalization rate by 13% (Val-HeFT trial).¹⁵⁰⁾ The benefit was most pronounced in patients who had not used ACE inhibitors before, and was also noted in patients using either an ACE inhibitor or a beta-blocker; however valsartan was ineffective and showed more adverse effects in patients using both ACE inhibitors and beta-blockers. Candesartan was also found effective at reducing the overall mortality and morbidity in patients with HFrEF, regardless of whether or not ACE inhibitors were used (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity [CHARM]-Overall program trial).¹⁵¹⁾ A particularly important observation was that candesartan (Atacand[®]; AstraZeneca Pharmaceuticals LP) was effective at reducing the composite endpoint of cardiovascular mortality and re-hospitalization rate by 40% in patients who could not be administered ACE inhibitors because of the side effects (CHARM-Alternative trial).¹⁵²⁾ In a study assessing the dose-dependent of losartan (Cozaar[®]; Merck & Co., Inc., Whitehouse Station, NJ, USA) in HFrEF patients with NYHA class II–IV, the mortality/re-hospitalization rate in patients receiving high-dose treatment was 10% lower than the rate noted in patients receiving low-dose treatment (Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan [HEAAL] trial).¹⁵³⁾

As in the case of ACE inhibitors, ARBs should not be administered during pregnancy, and indication and dosage must be carefully evaluated in patients with: low systolic blood pressure (≤ 80 mmHg), serum creatinine levels ≥ 3 mg/dL, stenosis of both renal arteries, or serum potassium levels ≥ 5 mEq/L. If ACE inhibitor administration is difficult because of angioedema or coughing, an ARB may be used as an alternative, although the side effects may not resolve. Randomized studies have reported that ARBs were effective in improving survival rate when administered at the target dose (candesartan, 32 mg once per day; valsartan, 160 mg twice per day; losartan, 150 mg once per day) (**Table 11**).

Thus, ARBs should be the treatment of choice in patients with HFrEF who exhibit or have a history of symptoms related to intolerance to ACE inhibitors and have no contraindication to ARBs.

Table 11. Starting and target doses of ARBs in patients with HF

ARB	Starting dose	Target dose
Candesartan	4–8 mg once a day	32 mg once a day
Valsartan	40 mg twice a day	160 mg twice a day
Losartan	50 mg once a day	150 mg once a day

ARB = angiotensin-receptor blocker; HF = heart failure.

However, no studies have demonstrated ARB effects related to improving survival in patients with HFpEF. Candesartan did not reduce the mortality rate in such patients but was effective at reducing the overall HF-related hospitalization rate by 16% (CHARM-Preserved trial),¹⁵⁴ whereas irbesartan reduced neither mortality nor re-hospitalization rate (Irbesartan in Heart Failure with Preserved Systolic Function [I-PRESERVE] trial).¹⁵⁵ Further research is necessary to clarify the benefits of ARBs in patients with HFpEF.

It is currently not recommended to preemptively use ARBs instead of ACE inhibitors in patients with HFrEF. Specifically, many small-scale studies have demonstrated the positive effect of preemptive ARB administration on not only the HF symptoms but also the change in hemodynamic factors and levels of neurohormonal substances. However, the valsartan study was the only large-scale investigation on the preemptive administration of ARBs instead of ACE inhibitors (Val-HeFT),¹⁵⁰ and the positive effect of the ARB valsartan was demonstrated mostly in patients who could not receive ACE inhibitors because of the adverse effects. Valsartan was demonstrated to be just as effective as captopril at reducing the mortality rate after acute myocardial infarction (VALsartan In Acute myocardial infarcTion [VALIANT] trial),¹⁵⁶ which was also confirmed for losartan (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan [OPTIMAAL] trial).¹⁵⁷ Therefore, if ARBs are already administered for other indications, it is reasonable to continue their use.

3) Combination of ACE inhibitors and ARBs

Adding candesartan to the prescription of patients with HFrEF who already received ACE inhibitors was found to reduce cardiovascular mortality/re-hospitalization rate by 15% compared to the rate noted in patients who received only ACE inhibitors (CHARM-Added trial).¹⁵⁸ In this study, 55% and 17% of patients were already using beta-blockers and spironolactone, respectively. As already mentioned, valsartan reduced the rate of mortality/hospitalization by 13% in patients with HFrEF and NYHA class II–IV, and was particularly effective in patients who had not received ACE inhibitors prior to the study, as well as in patients using either an ACE inhibitor or a beta-blocker, but was ineffective in patients using both types of drugs and manifested more adverse effects (Val-HeFT trial).¹⁵⁰ In another study where valsartan was added to the prescription of patients with HFrEF taking ACE inhibitors but not beta-blockers, valsartan was not effective in lowering the mortality/hospitalization rate (a sub-study based on the Val-HeFT trial).¹⁵⁹ A study comparing the effects of valsartan, captopril, and combined administration in patients with post-acute myocardial infarction found no difference in the mortality/hospitalization rate between patients who received combined therapy and those who received either valsartan or captopril (VALIANT trial).¹⁵⁶ Therefore, in patients with HFrEF who are already receiving ACE inhibitors and beta-blockers, adding ARBs to the prescription may be considered.

Beta-blockers

1. Continuous use of beta-blockers (e.g., bisoprolol, carvedilol, and sustained-release metoprolol succinate) has been shown to reduce mortality is recommended in all patients with HFrEF, unless contraindicated, to reduce mortality and prevent the deterioration of HF (class of recommendation I, level of evidence A).
2. Administration of nebivolol can be useful in patients with HFrEF aged over 70 years (class of recommendation IIa, level of evidence B).

Several large-scale clinical studies have shown that, in patients who received ACE inhibitors, beta-blockers are effective at prolonging life and preventing the deterioration of HF. To date,

Table 12. Starting and maintenance doses of beta-blockers in patients with HF

Beta-blocker	Starting dose	Maximum dose	Maintenance dose achieved in clinical trials
Bisoprolol	1.25 mg once a day	10 mg once a day	8.6 mg once a day
Carvedilol	3.125 mg twice a day	50 mg twice a day	37 mg once a day
Metoprolol	12.5–25 mg once a day	200 mg once a day	159 mg once a day
Nebivolol	1.25 mg once a day	10 mg once a day	7.7 mg once a day

HF = heart failure.

improved prognosis was demonstrated in patients using bisoprolol (Cardiac Insufficiency Bisoprolol Study II [CIBIS-II]),¹⁶⁰⁾ sustained-release metoprolol,¹⁶¹⁾ carvedilol (Carvedilol Prospective Randomized Cumulative Survival [COPERNICUS] and Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction [CAPRICORN] trials),¹⁶²⁻¹⁶⁴⁾ or nebivolol,¹⁶⁵⁾ and these are the only drugs approved for patients with HFrEF (Table 12). Unlike ACE inhibitors, there is no “class effects” when using beta-blockers. First-generation beta-blockers such as propranolol and atenolol, as well as short-acting metoprolol tartrate, did not improve the prognosis of patients with HF, and their use should be avoided. Bisoprolol and sustained-release metoprolol inhibit beta-1 receptors selectively, while carvedilol inhibits the alpha-1, beta-1, and beta-2 receptors.

It is recommended to initiate treatment with ACE inhibitors before starting administration of beta-blockers. However, the optimal timing for adding beta-blockers to the prescription of patients receiving ACE inhibitors remains unclear. When beta-blockers are used, it is not necessary to use a high dose of ACE inhibitors or ARBs, and it is better to add beta-blockers as soon as possible even if the patient is receiving a low dose of ACE inhibitor.¹⁶⁶⁾

Beta-blockers are to be started at a very low dose and gradually increased to reach the target dose over the course of several weeks or months. Fluid retention should be monitored during the increase of beta-blocker dose, and diuretics should be added or increased if necessary. If HF worsens during the administration of beta-blockers, all attempts should be made to keep the patient on the beta-blocker, even in patients with acute decompensated HF, perhaps with an increased dose of diuretics. However, if low cardiac output is the reason for HF aggravation, the beta-blocker should be reduced or stopped temporarily, and inotropics such as phosphodiesterase inhibitor (milrinone) should be administered. If the patient is stable, re-administration of beta-blockers should be considered before discharging the patient.

Mineralocorticoid antagonists

1. Unless contraindicated, mineralocorticoid receptor antagonists in addition to ACE inhibitors (or ARBs) and beta-blockers are recommended to reduce morbidity and mortality in patients with HF and NYHA class II–IV who have LVEF ≤35% (class of recommendation I, level of evidence A).
2. Unless contraindicated, mineralocorticoid receptor antagonists in addition to ACE inhibitors (or ARBs) and beta-blockers are recommended to reduce morbidity and mortality following an acute myocardial infarction in patients with LVEF ≤40% who develop symptoms of HF or have a history of diabetes mellitus (class of recommendation I, level of evidence B).

Widely used mineralocorticoid antagonists include spironolactone and eplerenone, but eplerenone is difficult to obtain in Korea. Aldosterone plays an important role in the pathophysiology of HF as it hinders the balance of the autonomic nervous system, accelerates collagen production, and participates in remodeling of the cardiovascular system. This complex effect cannot be inhibited by using renin-angiotensin system inhibitors alone,¹⁶⁷⁾

and mineralocorticoid antagonists must add in the prescription of patients receiving ACE inhibitors (or ARBs) and beta-blockers. In the RALES study involving patients with HF, addition of spironolactone (25–50 mg) to the prescription of patients with LVEF $\leq 35\%$ and NYHA class III–IV led to a 30% decrease in mortality rate, 35% decrease in hospitalization rate, and improvement in the hemodynamic variables and symptoms.¹⁶⁸⁾¹⁶⁹⁾

In the EMPHASIS-HF study involving patients with dyspnea, NYHA class \geq II, and LVEF $\leq 30\%$ ($\leq 35\%$ for QRS of >130 ms), adding eplerenone to the prescription of patients already taking ACE inhibitors (or ARBs) and beta-blockers induced a 37% reduction in the rate of cardiovascular mortality and HF-related hospitalization.¹⁷⁰⁾ The beneficial effect was also noted for the HF-related hospitalization rate among elderly patients (65 years or older) with LVEF $\leq 35\%$.¹⁷¹⁾ Therefore, in patients hospitalized for HF, use of mineralocorticoid antagonists before discharge helps to reduce mortality and morbidity.

A positive effect of eplerenone was noted in patients with HF and acute myocardial infarction (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study [EPHESUS] trial), as the use of 25–50 mg eplerenone led to a 15% decrease in the rate of cardiovascular death and a 13% decrease in the rate of cardiovascular death or hospitalization among patients with diabetes or HF, LVEF $\leq 40\%$, and treated within 3–14 days of the infarction event.¹⁷²⁾

Regarding hemodynamic effects other than clinical prognosis in patients with HFpEF, limited data are available on the LV-remodeling effect of eplerenone, but spironolactone was shown to inhibit ventricular remodeling after HF or myocardial infarction, improve laboratory findings, and improve LVEF.

To date, little research has focused on the use of mineralocorticoid antagonists for HFpEF. In small-scale studies, eplerenone demonstrated amelioration of hemodynamic or laboratory findings, and spironolactone showed improvement in quality of life when used in elderly patients (aged 65 or older). Several large-scale studies have been conducted to confirm these effects. The Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction (RAAM-PEF) trial¹⁷³⁾ reported that eplerenone did not reduce the rate of mortality/hospitalization in elderly patients with HFpEF and LVEF $\geq 40\%$. Similarly, in the Aldo-DHF study,¹⁷⁴⁾ spironolactone did not improve the quality of life related to dyspnea in patients with LVEF $\geq 50\%$ and NYHA class II–III. Finally, in the TOPCAT study involving symptomatic patients with HF and LVEF $\geq 45\%$, spironolactone did not significantly reduce the composite endpoint of cardiovascular death, cardiac arrest, and hospitalization related to HF, although it did reduce the HF-related hospitalization rate by 17%.¹⁷⁵⁾

Spironolactone (Aldactone[®]; Pfizer Inc.) may be started at 12.5–25 mg per day, and eplerenone at 25 mg, which can be increased up to 50 mg (**Table 13**).¹⁷⁰⁾¹⁷²⁾¹⁷⁶⁾ However, blood electrolyte concentrations should be carefully monitored because hyperkalemia is the main side effect of using mineralocorticoid receptor antagonists. Blood potassium levels

Table 13. Dosing of mineralocorticoid antagonists according to renal function in patients with HF

Drug	Estimated GFR (>50 mL/min/1.73 m ²)		Estimated GFR (<30 –49 mL/min/1.73 m ²)	
	Starting dose	Maintenance dose	Starting dose	Maintenance dose
Spironolactone	12.5–25.0 mg once a day	25 mg once or twice a day	12.5 mg once a day or once every 2 days	12.5–25.0 mg once a day
Eplerenone	25 mg once a day	50 mg once a day	25 mg once every 2 days	25 mg once a day

GFR = glomerular filtration rate; HF = heart failure.

must be preserved under 5.0–5.5 mmol/L, and renal function should be assessed before and after drug administration. The parameters of renal function allowing safe use of such drugs are: blood creatinine levels were <2.9 mg/dL for men and <2.5 mg/dL for women; predicted glomerular filtration rate (GFR) was >30 mL/min/1.73 m²;⁵⁷⁾ and contraindication for combined administration of ACE inhibitors, ARBs, and mineralocorticoid antagonists. Furthermore, it has been reported that arrhythmia-induced mortality may be noticeably higher among patients with AF, reduced renal function, and LV dysfunction (LVEF, <35%). Other adverse effects of spironolactone include gynecomastia or breast pain not associated with breast cancer.

Hydralazine and isosorbide dinitrate

1. Unless contraindicated, the combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality in self-identified black patients with HFrEF and NYHA class III–IV who receive optimal therapy with ACE inhibitors and beta-blockers (class of recommendation I, level of evidence B).
2. Unless contraindicated, the combination of hydralazine and isosorbide dinitrate can be useful to reduce morbidity or mortality in patients with current or prior symptomatic HFrEF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency (class of recommendation IIa, level of evidence B).

The V-HeFT I randomized clinical trial started in 1980 following research reports that vasodilators such as hydralazine and isosorbide dinitrate improved hemodynamics, HF symptoms, and exercise intolerance. Adding the combination of hydralazine and isosorbide dinitrate to the standard HF treatment available at the time of the study, which involved the use of diuretics and digoxin (beta-blockers or ACE inhibitors were not used), was found to be associated with a significant decrease in all-cause mortality, an amelioration of exercise capacity, and LVEF improvement in 642 male patients with HFrEF over the entire follow-up (expected average of 2.3 years).¹⁷⁷⁾ However, in the V-HeFT II study, which compared the effect of ACE inhibitors (enalapril) to those of hydralazine/isosorbide dinitrate on HFrEF, patients receiving ACE inhibitors had significantly lower mortality rates.¹⁷⁸⁾

On the other hand, the post-hoc analysis of specimens from the V-HeFT I and II studies suggested very interesting results.¹⁷⁹⁾ The patients were grouped by race. In V-HeFT I, black patients showed significantly lower mortality when treated using the combination of hydralazine and isosorbide dinitrate, but there was no significant difference between the effect of the therapy and that of the placebo in white patients.¹⁷⁹⁾ On the other hand, in V-HeFT II, use of an ACE inhibitor (enalapril) reduced the mortality rate significantly only in white patients, whereas there was no difference between the mortality rate in black patients who received the ACE inhibitor and the mortality rate in black patients who received the combination therapy.¹⁷⁹⁾ Thus, it can be inferred that ACE inhibitors are effective particularly in white patients, while hydralazine-isosorbide dinitrate combination therapy is particularly effective in black patients. The A-HeFT trial, which was conducted based on this information, demonstrated that combination therapy with hydralazine-isosorbide dinitrate is only effective for black patients with HFrEF.¹⁸⁰⁾ Specifically, among the 1,050 black patients with HFrEF, those who received therapy with hydralazine-isosorbide dinitrate in addition to standard drug therapy for HF (beta-blockers ACE inhibitors or ARBs, including aldosterone antagonists) showed significantly lower mortality rate than that noted in black patients receiving standard therapy alone (6.2% vs. 10.2%; relative risk, 0.57). The mortality rates of the 2 groups started

diverging from the 6th month of treatment and remained significantly different throughout the remaining observation period; a significant difference was also noted between the 2 groups regarding the rate of hospitalization related to HF (16.4% vs. 22.4%), and the study was terminated early on ethical grounds, after an average follow-up of 10 months.¹⁸⁰⁾

The treatment starts with hydralazine at 37.5 mg and isosorbide dinitrate at 20 mg three times per day. The dosage can be doubled over the course of the treatment. Limitations associated with this type of combination therapy are related to patient discomfort, as there are many pills to take, doses have to be taken too frequently, and the incidence of adverse effects is high. Common adverse effects include headaches, dizziness, and digestive discomfort. However, we expect that drug tolerance will increase if dosage is increased gradually.

Pharmacological treatment to improve symptoms

Diuretics

Diuretics are recommended to maintain adequate volume status in patients who have symptoms (orthopnea, dyspnea, and edema) or signs (increased jugular venous pressure, peripheral edema, hepatomegaly, and pulmonary rales) of fluid retention (class of recommendation I, level of evidence B).

Evaluation of body fluid volume and preservation of the fluid balance are mandatory in the management of patients with HF, regardless of whether systolic dysfunction is present or not. However, unlike renin-angiotensin-aldosterone blockers or beta-blockers, there is limited evidence regarding the effectiveness of diuretics in improving the prognosis of patients with HF because of the lack of randomized studies in this direction. According to studies involving a small number of patients and using a placebo control, diuretics may lower the mortality rate and the risk of hospitalization due to deterioration of symptoms.¹⁸¹⁾¹⁸²⁾ However, a series of observational studies suggested that use of a large dose of diuretics is a predictor of increased mortality, and the use of non-potassium-sparing diuretics is associated with elevated risk of death by arrhythmia.¹⁸³⁾ Nevertheless, as these findings originate from an observational study, the increase in mortality may be a reflection of the clinical condition requiring the use of a high dose of diuretics, rather than a reflection of adverse effects of diuretics.

1) General principles for the use of diuretics

Primary treatment for HF starts by restricting the patient's fluid and salt intake, and prescribing diuretics. Loop diuretics are commonly prescribed (**Table 14**). In Korea, available loop diuretics include mainly furosemide (Lasix[®]; Sanofi-Aventis U.S. LLC, Bridgewater, NJ, USA), torasemide (Demadex[®]; Roche Farma S.A., Leganes, Spain), and torasemide with prolonged release.¹⁸⁴⁾ Typical findings indicating fluid retention include pulmonary congestion, peripheral edema, and elevated jugular venous pressure. Patients with acute HF exhibiting such findings are administered loop diuretics by intravenous injection. The dose (high or low) of loop diuretics and injection method (continuous infusion or intermittent dosing) will be described in detail in the guideline for the management of acute HF; however, according to the recent Diuretic Optimization Strategies Evaluation (DOSE) trial, there is no evidence that one administration regimen is superior to any other.¹⁸⁵⁾

It is common to use loop diuretics for body fluid control and alleviation of symptoms, but loop diuretics may cause electrolyte imbalance, leading to states of hypokalemia or hypomagnesemia, which may increase the risk of death due to arrhythmia. Aldosterone antagonists may improve the survival rate of patients with HFrEF and prevent hypokalemia in patients receiving loop diuretics.

Table 14. Oral diuretics used in patients with HF

Diuretic	Starting dose	Commonly used maintenance dose	Maximum dose	Duration of diuresis (hours)
Loop diuretics				
Furosemide	20–40 mg once or twice a day	40–240 mg	600 mg	6–8
Torsemide	10–20 mg once a day	10–20 mg	200 mg	12–16
Bumetanide*	0.5–1.0 mg once or twice a day	1–5 mg	10 mg	4–5
Thiazide diuretics				
Hydrochlorothiazide	25 mg once or twice a day	12.5–100 mg	200 mg	6–12
Chlorthalidone	12.5–25.0 mg once a day	25–100 mg	100 mg	24–72
Indapamide	2.5 mg once a day	2.5–5 mg	5 mg	36
Metolazone	2.5 mg once a day	2.5–10 mg	20 mg	12–24
Potassium-sparing diuretics†				
Spironolactone	12.5–25 mg once a day	12.5–50 mg	50 mg	1–3
Amiloride	5 mg once a day	5–10 mg	20 mg	24
Triamterene*	50–75 mg twice a day	100 mg	200 mg	7–9
Combination (add to loop diuretics)				
Metolazone*	2.5–10 mg once a day			
Hydrochlorothiazide	25–100 mg once or twice a day			

HF = heart failure.

*Not available in Korea, †Need to monitor serum potassium levels.

2) Choosing the appropriate diuretics

Loop diuretics are commonly used to promote the excretion of excessive fluid in HF. The saluretic effect of thiazide-type diuretics is expected to disappear within a week, followed by blood pressure regulation as the vascular resistance decreases. Therefore, it is appropriate to use loop diuretics for the control of body fluid volume. However, if thiazide-type diuretics are used in combination with loop diuretics, sodium reabsorption at the distal tubule is prevented (sequential blocking), which can be beneficial in patients who cannot achieve sufficient diuretic effect using loop diuretics alone.¹⁸⁴⁾¹⁸⁶⁾

Few studies have compared the effect of several loop diuretics. While furosemide is the most widely used loop diuretic, its bioavailability is only 50%. Moreover, bioavailability varies largely with each patient and condition, and may be much lower (<10%) if there is edema. Therefore, the effect is not proportional to the dose, and changing the administration regimen (e.g., increasing dosage or changing to intravenous injection) should be considered if the clinical response does not reach the target level.¹⁸⁴⁾

Compared to furosemide, torsemide has higher and more stable bioavailability, as well as longer-lasting effects.¹⁸⁷⁾ A non-blinded, randomized study involving 234 patients with chronic HF found that torsemide therapy (average, 72 mg) was associated with significantly lower HF-related re-hospitalization rate, which was the primary endpoint, compared to the rate noted in patients receiving furosemide (average, 136 mg).¹⁸⁸⁾ An observational study involving 1,377 patients with HF also showed that torsemide therapy (10 mg) was associated with significantly lower mortality rate than that noted for furosemide therapy (40 mg) (2.2% vs. 4.4%).¹⁸⁹⁾ Therefore, although torsemide is more expensive than furosemide, it may ultimately represent a more cost-effective therapy, as it may reduce the rate of re-hospitalization.

3) Dose of diuretics

Loop diuretics are excreted from the glomerulus to the renal tubule and exert their biologic activity in the tubular lumen. The diuretic effect is manifested only when the amount of biologically active compound has surpassed a certain threshold value, and no effect is noted for lower doses. Therefore, if there is no response to the initial dose, it is more effective

to provide a double dose in a single injection than to repeat injection with the same dose, because the bioavailability is expected to be approximately 50%. A dose-dependent effect, whereby the diuretic effect increases with the dose of diuretics provided, is observed up to a certain dose, but no further increase in diuretic effect is noted after reaching the concentration of maximum diuretic effect.¹⁹⁰⁾

Furosemide can be started at 20–40 mg once or twice per day (10–20 mg once per day for torasemide), and the daily dose should typically not exceed 240 mg. If the patient cannot urinate because of renal dysfunction, a maximum of 600 mg can be administered, but it is more common to use combination therapy with thiazide-type diuretics or to perform ultrafiltration.

4) Precautions for the use of diuretics

The most important thing to keep in mind while using diuretics is to carefully monitor the patient's fluid balance. While it is important to relieve congestion, reduced body fluid volume due to excessive diuretic effect may lead to low cardiac output, low blood pressure, and deterioration of renal function. States of electrolyte imbalance such as hypokalemia, hypomagnesemia, and hyponatremia are more often associated with the use of diuretics, with hypokalemia noted most commonly. Therefore, in patients who show hypokalemia before initiating treatment with diuretics (potassium levels ≤ 3.5 mEq/L), the indication and dosage should be carefully assessed and potassium-sparing diuretics should be used, or potassium supplementation should be administered concomitantly. Furthermore, in patients with creatinine levels >2.5 mg/dL or an expected GFR <30 mL/min/1.73 m², renal function should be monitored carefully to minimize the risk of renal function deterioration. Aldosterone antagonists in particular increase the risk of hyperkalemia in patients with deteriorated renal function, and therefore it is preferable not to use aldosterone antagonists in such patients.

5) Treatment of patients with insufficient diuretic effect

In some patients, pulmonary congestion and edema may not improve after injection of a high dose of oral diuretics. The first step in the management of such patients is to accurately assess their water and salt intake and to effectively restrict the salt intake. It is also important to perform a detailed review of their medical history, because such patients may be taking non-steroidal anti-inflammatory drugs or long-term adrenocortical hormone therapy for pain control. Patients with severe edema may have insufficient intestinal absorption of furosemide, and therefore long-term intravenous therapy or change to torasemide may be considered. As mentioned before, one resistance mechanism to therapy with loop diuretics consists of accelerated sodium reabsorption in the distal convoluted tubules, against which combination therapy with thiazide-type diuretics may provide an effective treatment.¹⁹¹⁾ If diuretic resistance cannot be controlled using such therapy, a physical method such as ultrafiltration may be used.

Digoxin

Unless contraindicated, digoxin can be used to decrease the rate of HF-related hospitalization in patients with HFrEF (class of recommendation IIa, level of evidence B).

Digoxin has traditionally been used in combination with diuretics to treat patients with LV systolic dysfunction. However, as the understanding of the HF pathophysiology deepened and especially as renin-angiotensin-aldosterone system inhibitors became widely used,

the clinical utility of digoxin has been repeatedly called into question; however, there is insufficient evidence from clinical studies to clarify this issue. Taking together the results of small-scale randomized studies describing the effect of 1–3 month administration of digoxin, there is consensus that digoxin use was related to improvement in quality of life, symptoms, and exercise capacity.¹⁹²⁻¹⁹⁶⁾ However, these findings have limited clinical application as those studies were conducted before the establishment of the current standard treatment guidelines that stipulate the use of renin-angiotensin-aldosterone system inhibitors, beta-blockers, and mineralocorticoid antagonists. The DIG trial is a representative, large-scale clinical study on the effects of digoxin use, which involved 6,800 patients (digoxin group vs. control group) with HF, NYHA class II–IV, and LVEF \leq 45%, who were followed-up for an average of 3 years. The DIG study demonstrated that there was no difference in the survival rate between the digoxin group and the control group, but digoxin use showed significant improvement in the rate of re-hospitalization, particularly that related to worsening of HF.¹⁹⁷⁾ Similar conclusions were reported in a meta-analysis of other small-scale, randomized studies.¹⁹⁸⁾

Compared to those receiving low-dose digoxin or having low blood concentrations of digoxin, patients with HFrEF who receive a high dose of digoxin or have a high blood concentration of digoxin present more adverse effects without additional clinical gain.¹⁹⁹⁻²⁰¹⁾ Therefore, digoxin should be started at a low dose (0.125 mg per day or once every two days) and increased to 0.25 mg per day while monitoring for toxicity-related adverse effects. Typical symptoms of digoxin toxicity include gastrointestinal disturbance (loss of appetite, nausea, vomiting), neurological disturbance (visual impairment, disorientation, confusion), and fatal arrhythmia. Digoxin is particularly toxic in patients with advanced age (70 years or older), renal failure, low body weight, electrolyte abnormality, and concomitant use of drugs that could influence digoxin metabolism, including macrolide antibiotics, itraconazole, cyclosporine, amiodarone, and quinidine. Because it is not possible to predict or exclude the risk of adverse reactions based on the blood concentration of digoxin,²⁰²⁾²⁰³⁾ it is crucial to start with a low dose and monitor the clinical course of the patient for manifestations of toxicity, rather than measuring the blood levels of digoxin.

Intravenous inotropics

1. Patients with cardiogenic shock should receive intravenous inotropic support temporarily to maintain systemic perfusion and preserve other end-organ functions (class of recommendation I, level of evidence C).
2. Continuous usage of intravenous inotropic support is reasonable in patients with advanced HF who are waiting for mechanical circulatory support (MCS) or cardiac transplantation (class of recommendation IIa, level of evidence B).
3. Use of intravenous inotropic support is harmful in patients without documented severe systolic dysfunction, low blood pressure, or hypoperfusion (class of recommendation III, level of evidence A).

Patients with refractory or terminal HF (also termed end-stage HF) may reach a critical condition of systemic hypoperfusion with cardiogenic shock due to acute exacerbating factors. In such situations, intravenous inotropes are used to improve the unstable hemodynamic state, resolve the acute exacerbating factors, and preserve blood circulation until the patient may undergo further treatment such as coronary revascularization, MCS, or cardiac transplantation.²⁰⁴⁻²⁰⁶⁾ While intravenous inotropes can improve the patient's hemodynamic condition temporarily, such therapy provides no benefit in terms of the overall

clinical course. Oral inotropic agents with various action mechanisms have been developed, but long-term use has generally been found to increase the incidence of arrhythmia-related death.²⁰⁷⁻²¹⁶ Therefore, inotropic therapy should only be used as temporary treatment limited to patients with severe systolic dysfunction, low blood pressure, or hypoperfusion, or as a bridging therapy in patients with refractory HF waiting for heart transplantation or mechanical support.

Commonly used intravenous inotropic agents include dobutamine, which is a type catecholamine, and milrinone, which is a phosphodiesterase inhibitor. Compared to dobutamine, milrinone has a stronger vasodilatory, reducing pulmonary artery pressure and systemic vascular resistance to a greater extent. Milrinone is also less likely to increase heart rate or myocardial oxygen consumption, but there is a high incidence of hypotension associated with milrinone use. Nevertheless, no significant difference between the effects of individual inotropic drugs has been reported with respect to the overall clinical course of patients with HF who require intravenous inotropic support. Therefore, each treating physician may choose the inotropic regimen based on the condition of the patient.^{205,217}

Other medications

Anticoagulants

1. An oral anticoagulant is recommended in HF patients with AF who have additional thromboembolic risk factors (class of recommendation I, level of evidence A for warfarin; level of evidence B for dabigatran, rivaroxaban, and apixaban).
2. The choice of oral anticoagulant (warfarin, dabigatran, apixaban, rivaroxaban) in patients with HF and AF should be based on clinical characteristics such as risk factors, costs, tolerability, patient's preference, and drug interactions (class of recommendation I, level of evidence C).
3. It is reasonable to prescribe an anticoagulant in patients with HF and AF without additional thromboembolic risk factors (class of recommendation IIa, level of evidence A for warfarin; level of evidence B for dabigatran, rivaroxaban, and apixaban).
4. Anticoagulation therapy is not recommended in HF patients without AF, previous thromboembolic events, or intracardiac thrombus (class of recommendation III, level of evidence B).

AF is an important risk factor of thromboembolic events, which have a prevalence of 13%–27% in patients with HF.²¹⁸ Current guidelines for the management of AF stipulate the use of the CHA₂DS₂-VASc score for estimating the risk of thromboembolic events including stroke based on the number of accompanying risk factors.^{219,220} Thromboembolic risk factors include HF; hypertension; advanced age (≥ 75 years), which carries a very high risk (included in the score with a weight of 2 points); diabetes mellitus; previous history of stroke, transient ischemic attack (TIA), or thromboembolism, which also carries a very high risk (included in the score with a weight of 2 points); vascular disease including previous history of myocardial infarction, peripheral artery disease, or aortic plaque; advanced age (65–74 years); and female sex. An oral anticoagulant is recommended in patients with CHA₂DS₂-VASc score ≥ 2 ^{219,220} and such use is also reasonable in patients with CHA₂DS₂-VASc score 1.²¹⁹ Because HF on its own corresponds to a CHA₂DS₂-VASc score of 1, patients with HF and AF who have one or more additional thromboembolic risk factors (hypertension, age ≥ 65 years, diabetes mellitus, stroke, TIA, vascular disease, or female sex) are regarded to have a CHA₂DS₂-VASc score of ≥ 2 , whereas patients with HF and AF but no additional risk factors are regarded to have a CHA₂DS₂-VASc score of 1.

The direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors rivaroxaban and apixaban are classified as new oral anticoagulants (NOACs), which are distinguished from conventional oral vitamin K antagonists. Although the efficacy and safety vary with each NOAC, the overall clinical effectiveness of NOACs was found to be superior or non-inferior to that of the vitamin K antagonist warfarin.²²¹⁻²²⁸⁾ Therefore, NOACs are recommended (class of recommendation I, level of evidence A) in patients with CHA₂DS₂-VASC score ≥ 2 , and can be used (class of recommendation IIa, level of evidence A) in patients with CHA₂DS₂-VASC score 1; moreover, according to the 2012 European guidelines for the management of AF, NOACs are recommended in preference to the use of a vitamin K antagonist.²¹⁹⁾ However, NOAC indication cannot be categorized by class because each NOAC has a different efficacy and safety profile.²²⁶⁾²²⁷⁾ The 2014 American guidelines for the management of AF recommend the use of an oral anticoagulant in patients with CHA₂DS₂-VASC score ≥ 2 (class of recommendation I, level of evidence B), without any preference.²²⁰⁾ According to the same guideline, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered in patients with CHA₂DS₂-VASC score 1.

There is insufficient evidence as to whether anticoagulation should be recommended or not and what type of drug should be recommended (e.g., aspirin, warfarin, or NOACs) in patients with HF and AF who do not have any additional thromboembolic risk factors (i.e., with a CHA₂DS₂-VASC score of 1). However, the use of warfarin or NOACs is reasonable even in patients with HF and AF who do not have other additional thromboembolic risk factors, as warfarin was found to be superior to aspirin in terms of stroke prevention,²²⁹⁻²³¹⁾ while NOACs were not inferior to warfarin in terms of stroke prevention, and superior to warfarin in terms of reducing the risk of bleeding. On the other hand, there was no significant difference in clinical outcome among aspirin, clopidogrel, and warfarin in patients with HF and sinus rhythm who do not have a history of AF, whereas the rate of adverse events including bleeding was significantly higher in patients who received warfarin.²³²⁻²³⁴⁾ The thromboembolic risk was as low as 1%–3%/year in patients with clinically stable HF, and was low even in patients with very low LVEF or intracardiac thrombus.²³⁵⁻²³⁸⁾ Therefore, if there is no specific indication regarding the risk of bleeding, routine use of warfarin or aspirin is not recommended in patients with systolic HF.

Statins

In the absence of specific indications, routine use of statins to improve HF outcomes is not recommended (class of recommendation III, level of evidence A).

Statins are recommended to reduce cardiovascular risk and to control hypercholesterolemia in patients with atherosclerotic cardiovascular disease.²³⁹⁻²⁴¹⁾ However, routine use of statins to improve HF outcome is not recommended. Although some studies reported beneficial effects of statin in patients with HF, such findings were mostly obtained from observational or retrospective studies.²²⁷⁾²⁴²⁻²⁴⁵⁾ The two large randomized trials CORONA and GISSI-HF, which evaluated the effect of statin treatment in patients with chronic HF, did not demonstrate any improvement in long term outcome.²⁴⁶⁾²⁴⁷⁾ Moreover, there are several reports describing increased mortality in patients with HF and low cholesterol levels.²⁴⁸⁾²⁴⁹⁾ Therefore, in the absence of specific indications, routine use of statins to improve HF outcomes is not recommended.

Ivabradine

1. Administration of ivabradine is reasonable in symptomatic patients (NYHA functional class II–IV) with LVEF \leq 35%, sinus rhythm, and a resting heart rate of \geq 70 beats per minute (bpm) despite treatment with an ACE inhibitor and beta-blocker (class of recommendation IIa, level of evidence B).
2. Ivabradine may be considered in patients with LVEF \leq 35%, sinus rhythm, and a resting heart rate of \geq 70 bpm if there is intolerance or contra-indication to beta-blockers (class of recommendation IIb, level of evidence C).

Heart rate is an important prognostic factor in patients with HF.²⁵⁰⁻²⁵² Ivabradine slows the heart rate in patients with sinus rhythm through inhibition of the I_f channel in the sinoatrial node. Given the selective effect on the I_f channel, ivabradine selectively decreases heart rate without loss of myocardial contractility or disturbance of intracardiac conduction in patients with HFrEF. Ivabradine reduced the composite endpoint of cardiovascular mortality and HF-related hospitalization in patients receiving evidence-based HF treatment including beta-blocker therapy.²⁵³ A post hoc analysis indicated that the improvement in prognosis was significantly related with heart rate reduction.²⁵⁴ Therefore, ivabradine may be considered for symptomatic patients with HF, NYHA class II–IV, LVEF \leq 35%, sinus rhythm, and a resting heart rate of \geq 70 bpm despite receiving evidence-based HF medications. Although there is insufficient evidence from randomized controlled studies as to whether ivabradine can replace beta-blockers in patients who have intolerance or contraindications to beta-blockers, ivabradine was found to significantly reduce cardiovascular death and HF-related hospitalization in a sub-group analysis of the SHIFT trial, in which 10% of patients could not use a beta-blocker.²⁵⁰ Therefore, ivabradine may be considered in symptomatic patients with HF, NYHA class II–IV, LVEF \leq 35%, sinus rhythm, and a resting heart rate of \geq 70 bpm despite receiving evidence-based HF medications if such patients have intolerance or contraindications to beta-blockers.

Vasopressin antagonists

Use of a vasopressin antagonist may be considered in patients with HF and refractory hyponatremia (class of recommendation IIb, level of evidence B).

Hyponatremia-related cognitive dysfunction can cause attention deficit, increasing the risk of fall and loss of consciousness.²⁵¹ Vasopressin V2-receptor antagonists were found to improve cognitive function in patients with hypervolemic hyponatremia.²⁵² It is important to identify the specific cause of hyponatremia, which may include the syndrome of inappropriate antidiuretic hormone secretion (SIADH), hypothyroidism, or hypoaldosteronism. If no specific cause is identified, free water restriction and angiotensin II inhibition can be attempted. Although vasopressin antagonists can increase serum sodium concentration in patients with hypervolemic hyponatremia,²⁵²⁾²⁵³ long-term use of vasopressin antagonists did not improve survival in patients with HF.²⁵⁴ Tolvaptan, which is an oral vasopressin V2-receptor antagonist, may be considered in patients with HF and hyponatremia accompanied by cognitive dysfunction. However, the long-term efficacy and safety of vasopressin antagonists have not been established to date. Because vasopressin antagonists have a distinct mechanism of action, their use may benefit patients with HF and diuretics resistance and is recommended for treating cardiogenic edema in Japan.²⁵⁵

Angiotensin receptor-neprilysin inhibitor (ARNI): LCZ696

LCZ696 (Entresto™; Novartis Pharmaceuticals Corporation) was the first dual inhibitor acting on both the angiotensin receptor and neprilysin. LCZ696 combines the biologically active moieties of the ARB valsartan and of the neprilysin inhibitor sacubitril (AHU377). The neutral endopeptidase neprilysin inactivates endogenous vasoactive peptides such as the natriuretic peptides and bradykinin. By inhibiting neprilysin, the concentration of endogenous vasoactive peptides is increased because of reduced degradation, leading to vasodilation, natriuresis, decrease in apoptosis, prevention of fibrosis, and inhibition of unfavorable overactivation of neurohormones.²⁵⁶⁾²⁵⁷⁾ The Prospective Comparison of ARNi with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) randomized trial compared the outcomes of therapy with the ACE inhibitor enalapril (10 mg twice a day) to those of therapy with LCZ696 (200 mg twice a day), and involved 8,442 symptomatic patients with HF, NYHA class II–IV, and LVEF ≤40%. In this study, LCZ696 reduced cardiovascular mortality by 20%, HF-related hospitalization by 21%, and all-cause mortality by 16%. It is of note that the control group received enalapril, which was demonstrated to reduce mortality and hospitalization rate. The PARADIGM-HF study was terminated early for ethical reasons, after 27 months of follow-up.²⁵⁸⁾ Compared to the outcomes noted in patients receiving a placebo, LCZ696 was associated with a significant reduction in the risk for cardiovascular mortality and HF-related re-hospitalization (reduction of 34% and 49%, respectively, in the SOLVD-T trial; reduction of 32% and 46%, respectively, in the CHARM-Alternative trial).²⁵⁹⁾²⁶⁰⁾ The current American, European, and Canadian guidelines for HF management recommend the use of an ARNI in patients with mild to moderate HFrEF who have elevated BNP, were hospitalized because of HF within the previous 12 months, have serum potassium levels <5.2 mmol/L, and have an estimated GFR of ≥30 mL/min/1.73 m²; the guidelines specify preference over ACE inhibitors and ARBs based on high-quality evidence, but are phrased in the form of a conditional recommendation because of limited commercial availability ARNI.²⁶¹⁾ Further clinical observation is needed to confirm the effect of such drugs on blood pressure and electrolyte levels, as well as to confirm their long-term safety. Nevertheless, it is expected that LCZ696 will be included in the recommendation as first-line therapy or in place of ACE inhibitors or ARBs.

Treatment of HFpEF

1. Hypertension should be treated according to the guidelines for hypertension to reduce the risk of complications (class of recommendation I, level of evidence B).
2. Diuretics should be used in patients with volume overload (class of recommendation I, level of evidence C).
3. Coronary revascularization is reasonable in patients with HF that remain symptomatic despite receiving evidence-based medical therapy, or with a history of angina or myocardial ischemia (class of recommendation IIa, level of evidence C).
4. Treatment of AF according to specific guidelines is reasonable for improving HF symptoms in patients with HFpEF (class of recommendation IIa, level of evidence C).
5. The use of ACE inhibitors, ARBs, and beta-blockers is reasonable to control blood pressure (class of recommendation IIa, level of evidence C).
6. The use of ARBs and aldosterone antagonists may be considered to improve HF symptoms (class of recommendation IIb, level of evidence B).

While the normal range of LVEF depends on the definition, 40%–50% of patients with HF have preserved LVEF.²⁶²⁾²⁶³⁾ While normal LVEF ranges have been defined differently in

various studies (i.e., $\geq 40\%$, $\geq 45\%$, or $\geq 50\%$), it is typically considered that patients with LVEF between 40% and 50% have HFpEF.⁵⁶⁾¹⁵⁴⁾¹⁵⁵⁾¹⁷⁵⁾²⁶²⁾²⁶⁴⁾²⁶⁵⁾ Because LVEF is regarded as a representative marker of LV systolic function, the terminology ‘HF with normal LV systolic function’ and ‘diastolic HF’ have been used. Even if it results in HF, diastolic dysfunction is often difficult to evaluate precisely, and the term HFpEF is currently preferred. Female sex, advanced age, hypertension, diabetes mellitus, ischemic heart disease, obesity, hypercholesterolemia, and AF have been identified as major risk factors for HFpEF.²⁶³⁾²⁶⁶⁻²⁶⁷⁾ Whereas the survival rate in HFpEF is comparable or slightly higher than that in HFrEF, the rate of hospitalization for HF and exercise capacity of patients with HFpEF are similar to those noted in patients with HFrEF.²⁶²⁾

Although several large clinical trials have been conducted to evaluate the effectiveness of medical treatment for HFpEF, no single drug was found to improve prognosis.¹⁵⁵⁾¹⁷⁵⁾²⁶⁷⁾²⁶⁸⁾ Therefore, the current therapies for patients with HFpEF focus mainly on controlling symptoms and treating comorbidities. Diuretics are recommended to improve congestive symptoms in patients with volume overload, while antihypertensive agents including ACE inhibitors, ARBs, beta-blockers, and calcium channel blockers should be used to control high blood pressure and prevent worsening of HF.²⁶⁹⁾²⁷⁰⁾ There is no specific target for blood pressure in patients with HF, and generally guidelines for the management of hypertension should be followed. Recent clinical trials using aldosterone antagonists did not demonstrate improvement in HF-related mortality, but did indicate decreased hospitalization for worsening HF. Mineralocorticoid receptor antagonists should be added with caution because of the risk of hyperkalemia and increase in serum creatinine levels.¹⁷⁵⁾

Ischemic heart disease is a common comorbidity in patients with HFpEF; however, there is no direct evidence that percutaneous coronary intervention or surgical revascularization can improve the clinical outcomes. Thus, patients with HFpEF and ischemic heart disease should be treated according to the current guidelines for the management of ischemic heart disease. Aggressive management including an interventional procedure or surgical treatment should be considered if coronary artery stenosis contributes to HF aggravation.

Use of calcium channel blockers and beta-blockers may be considered to prolong the LV diastolic filling time by lowering the heart rate in patients with AF and rapid ventricular response.²⁷¹⁾²⁷²⁾ In general, medications contraindicated in HFrEF are also contraindicated in HFpEF, but calcium channel blockers can be used exceptionally to lower blood pressure or to control heart rate.

NON-PHARMACOLOGICAL MANAGEMENT

Holistic management and multidisciplinary approach

1. Team management and a multidisciplinary approach should be used to improve cardiac function and quality of life in patients with HF (class of recommendation I, level of evidence A).
2. Team management and a multidisciplinary approach should be applied to reduce the rate of mortality, morbidity, and readmission due to HF in patients with HF (class of recommendation I, level of evidence A).

Although therapeutic approaches for HF continue to improve, the overall prognosis of patients with HF remains poor. Therefore, a multidisciplinary approach that considers

medical, psychosocial, and behavioral factors should be considered. Patient education through team management, appropriate medical treatment, cardiac rehabilitation, psychosocial support, and better accessibility to medical facilities and health care systems can improve clinical outcomes. Implementing such an approach requires good organization and cooperation among the HF specialists (cardiologists, HF specialist nurses) and other healthcare professionals (general physicians, pharmacists, dietitians, exercise prescribers, physical therapists, psychiatrists, and social workers). Furthermore, the approach should be adjusted according to the social, cultural, and economic conditions of the region or country. Specific components of a multidisciplinary approach include: appropriate medication and device therapy; appropriate patient education for HF; improving patient compliance with evidence-based treatment strategies; training in self-management and self-monitoring of symptoms to allow flexible use of diuretics; regular outpatient follow-up after discharge in the form of outpatient visits, home visits, or telephone interviews (telephone tracking), and remote management programs; enhanced access to health care systems; rapid access to medical centers to investigate acute exacerbation of HF; assessment of sudden weight gain without specific causes, nutritional status, and quality of life; clinical evaluations; and education on current treatment strategies and psychosocial support for patients and their families. The main challenges include the detection of HF and education regarding various key aspects of life style adaptations to cope with HF, including HF etiology, symptom monitoring, self-management, drug effects, drug adverse effects, treatment compliance, diet, cessation of alcohol consumption, smoking cessation, activities (including exercise, traveling, and leisure), sexual life, occupational choice, vaccination, sleep (especially in relation to respiratory distress), and aspects related to mental and psychological health.

High-risk patients in particular should undergo such comprehensive HF management. High-risk groups include patients with renal impairment, low cardiac output, diabetes mellitus, COPD, persistent symptoms of NYHA functional class III–IV, frequent hospitalization, the presence of multiple comorbid diseases, cognitive impairment, inadequate social support, or lack of knowledge about health, as well as patients who fail to follow the treatment plan consistently. As mortality and morbidity are high in patients with HF and structural heart disease, symptomatic patients, and patients with a history of hospital admission, such patients could benefit from education about self-management.²⁷³⁻²⁷⁷ Education includes awareness of the changes in symptoms and body weight, restriction of salt intake, and compliance with the prescribed medications and recommended physical activities. Education involves counseling not only for patients, but also for their families and caregivers, and covers topics such as patient self-management, follow-up, rapid response training for signs and symptoms of water retention, and communication with primary care facilities.

A multidisciplinary team approach can lower the hospitalization and mortality rates of patients with HF. Education focused on self-management achieved improved drug compliance, enhanced self-monitoring, reduced time to readmission, and reduced duration of hospitalization.²⁷³ Applying a multidisciplinary approach in the management of chronic HF has been reported to reduce readmission rates, while applying such an approach during follow-up has also been reported to reduce readmission rates and mortality.^{278,279} Furthermore, such multidisciplinary approaches were shown to minimize the rate of unexpected hospitalization.²⁸⁰ Finally, a comprehensive analysis of the outcomes of studies involving multidisciplinary approaches showed that patients with HF who are managed by a team with a specialized multidisciplinary approach exhibit reduced mortality and hospitalization rates.²⁸¹ Therefore, high-risk patients should be advised to undergo

multidisciplinary HF management programs.²⁸¹⁻²⁸³ This approach is necessary in patient selection, treatment, and follow-up and when performing surgical treatment or applying MCS, and also requires a multidisciplinary team involving internal medicine, surgery, anesthesiology, and various other departments.⁵⁶⁾⁵⁸⁾ Particularly, in the case of heart transplantation, patient selection must be carried out by a multidisciplinary team including cardiologists specialized in heart transplantation, cardiothoracic surgeons, nurses, social workers, and palliative care specialists.⁵⁶⁾

General measures

Diet, nutrition, and weight control

Sodium restriction reduces congestive symptoms in patients with symptomatic HF (class of recommendation IIa, level of evidence C).

Evidence regarding the importance of diet and nutrition in patients with HF is currently insufficient. However, a small randomized study showed that dietary control and graded exercise therapy 3–5 times a week improved the exercise capacity and psychologically stability in patients with HF and NYHA functional class II–III.²⁸⁴⁾ Moreover, it is important to limit dietary salt intake in patients with chronic HF. The 2013 ACCF/AHA guideline for the management of HF recommended salt intake restriction in order to reduce congestion symptoms in symptomatic patients.⁵⁶⁾ On the other hand, excessive salt restriction may activate the neurohormonal system, and several randomized studies showed that excessive salt restriction can aggravate the clinical course of patients with HFrEF.²⁸⁵⁾²⁸⁶⁾

Because Koreans traditionally use high amounts of salt, it is very difficult to ensure that Korean patients comply with salt restriction recommendations. In one Korean study including 232 patients with HF, NYHA functional class III–IV, and LVEF <30%, patients with more than 3 g of urinary sodium excretion exhibited more severe symptoms and higher incidence of cardiovascular events.²⁸⁷⁾ Despite controversies, it is recommended that patients with moderate-to-severe HF consume less than 2 g of sodium per day (7–8 g of salt).

Obesity is associated with other risk factors for HF such as hypertension, obstructive sleep apnea, LV hypertrophy, and relaxation abnormalities. Thus, weight control is helpful to prevent the development of HF.²⁸⁸⁾²⁸⁹⁾ However, in patients who have already been diagnosed with HF, both overweight and underweight status are associated with worse prognosis. Patients with HF and a body mass index (BMI) in the range of 30–35 kg/m² were consistently reported to have lower mortality and hospitalization rates compared to those noted in patients with BMI indicating normal weight, with cardiac cachexia being reported as a factor for poor prognosis. Patients with a BMI of less than 18.5 kg/m² were also reported to have poor prognosis.²⁹⁰⁻²⁹⁴⁾

Patients with severe HF symptoms should weigh themselves at regular intervals during the day in order to check for excessive fluid accumulation. If a patient gains more than 2 kg of body weight in a single day, there is a high risk of acute exacerbation of HF. Such patients should contact a health care provider as soon as possible, reduce their daily activity, and strictly limit their daily salt intake.

Smoking and alcohol consumption

Smoking is an important risk factor for cardiovascular disease²⁹⁵⁾ and HF,²⁹⁶⁻²⁹⁸⁾ and represents a major risk factor for pulmonary disease and malignant tumors in elderly patients with

HF. Smoking is also associated with reduced quality of life.²⁹⁹⁾ Because smoking cessation improves HF symptoms and reduces mortality,³⁰⁰⁾³⁰¹⁾ it should be strongly recommended in patients with HF. However, smoking cessation education is not appropriately performed in current clinical practice.³⁰²⁾ Therefore, the medical practitioner should continuously educate patients with HF regarding the risks associated with smoking and should support the patient in complying with smoking cessation.⁵⁸⁾

Excessive alcohol consumption is an important risk factor for developing HF.²⁹⁶⁾³⁰³⁾³⁰⁴⁾ Although the relevance of sex-related differences in alcohol intake is uncertain in the context of HF, excessive alcohol consumption is a recognized risk factor for the development and progression of HF. Therefore, it is recommended to continuously educate HF patients to avoid excessive intake of alcohol, and strict avoidance of alcohol intake should be suggested when alcoholic cardiomyopathy is suspected.

Vaccination and prevention of infective endocarditis

Influenza is the common cause of hospitalization and death worldwide. In the presence of cardiovascular disease or diabetes, complications such as influenza-related hospitalization and death are more common, especially in patients aged 65 years or older.³⁰⁵⁾ Although there has not yet been a randomized study to confirm the effectiveness of vaccination in patients with HF, influenza vaccination has been reported to reduce 1-year cardiovascular mortality³⁰⁶⁾ and hospitalization in elderly patients with HF.³⁰⁷⁾ On the other hand, there are also no reports to date showing an increase in cardiovascular events associated with vaccination.³⁰⁸⁾ Although the effect of vaccination was not evident in young patients with cardiovascular disease,³⁰⁹⁾ observational studies involving elderly patients (aged 65 years or older) with chronic heart disease have shown a reduction in the incidence of cardiovascular disease after vaccination.³¹⁰⁾ Therefore, elderly patients (older than 65 years) with HF should be vaccinated against pneumococcal infection and influenza every year, unless there is a contraindication.⁵⁸⁾

In the absence of indications such as valvular heart disease, endocarditis prophylaxis is not necessary in patients with HF and no other comorbidities.³¹¹⁾ Endocarditis prophylaxis is indicated in patients with HF and prosthetic heart valve, history of endocarditis, or congenital heart defect corrected using artificial tissue (especially within 6 months after the procedure/surgery), as well as in patients waiting for heart transplantation for valvular heart disease.⁵⁸⁾

Other medications

Patients with HF may have deficiencies of vitamins and other nutrients because of reduced oral intake of vitamins and the use of diuretics. Although several nutritional and hormonal therapies have been proposed as combination therapies for patients with HF, there has not yet been a clinical study showing improvement in the survival of such patients.³¹²⁻³¹⁸⁾ However, several randomized studies demonstrated that the intake of omega-3 fatty acids reduced mortality, morbidity, and, especially, readmission rates,³¹⁹⁾³²⁰⁾ while a small-sized randomized trial showed that intake of omega-3 fatty acids was effective in increasing LVEF by more than 10%.³²¹⁾

Because atrial and ventricular arrhythmias increase the morbidity and mortality of HF, several clinical studies have been conducted to assess the effect of various antiarrhythmic agents for controlling arrhythmias.³²²⁻³²⁴⁾ However, most drugs investigated have been shown to increase mortality rate, with only amiodarone and dofetilide having a neutral effect on mortality in patients with HF.³²⁵⁻³²⁷⁾

Although calcium channel blockers were thought to be beneficial for patients with chronic HF by reducing peripheral vasoconstriction and LV afterload, it was found that most such drugs lowered myocardial contractility and exacerbated HF symptoms.²⁷¹⁾³²⁸⁾³²⁹⁾ A large study showed that only amlodipine had a neutral effect on HF morbidity and mortality and may therefore be considered for additional blood pressure control in patients with HF.³³⁰⁾ In general, calcium channel blockers are not recommended in patients with HF_{rEF}.

Furthermore, because nonsteroidal anti-inflammatory drugs inhibit prostaglandin synthesis and vasodilatation in the kidneys, but do not inhibit sodium reabsorption in the ascending limb of the loop of Henle and the collecting ducts, such drugs can cause sodium and water retention and ultimately reduce the effectiveness of diuretics. In several observational studies, nonsteroidal anti-inflammatory drugs have been shown to increase morbidity and mortality in patients with HF.³³¹⁻³³⁴⁾

Finally, thiazolidinediones increase insulin sensitivity by activating the peroxisome proliferator-activated receptor γ in the nucleus, which is also expressed in the collecting duct of the kidneys, leading to sodium reabsorption. Indeed, the use of thiazolidinediones is associated with increased incidence of hospitalization and worsening of HF in patients with de-novo or chronic HF.³³⁵⁻³³⁹⁾

Occupation and activity

To date, no study has confirmed that restricting job choice for patients with chronic HF reduces mortality or readmission rate compared to the rates noted in patients who are free to make occupational choices according to their preference. However, it is reasonable to expect that an occupation is chosen based on the physical demands of the job. If patients with chronic HF experience sudden symptomatic deterioration, functional exercise capacity and even the possibility of not working should be reviewed after clinical stabilization has been achieved. After evaluating exercise capacity, it is desirable to maintain the existing occupation, even if the work time or work amount is temporarily adjusted based on the result of the evaluation.

In principle, there is no major limitation to sexual activity in chronic HF if the patients do not experience difficulty in daily activities (walking, stair climbing, light activities inside the home), but this can vary from person to person.³⁴⁰⁾ In general, although about 60%–85% of patients with HF have sexual problems such as decreased sexual desire and activity or have stopped sexual activity entirely,³⁴¹⁻³⁴³⁾ the mortality rate related to sexual activity remains unclear. However, epidemiologic studies have reported that sudden death related to general sexual activity occurs in approximately 0.6% of HF patients.³⁴⁴⁾ Moreover, compared to the general population, high-risk patients with a history of myocardial infarction showed a similar mortality rate associated with sexual activity (1.0% vs. 1.1%, respectively).³⁴⁵⁾ Thus, there is no evidence that a sexual life in itself increases mortality related to HF. Factors associated with the risk of sexual intercourse are related to the clinical symptoms (NYHA functional class or 6-minute walking test) rather than LV contractile function.³⁴²⁾ The likelihood of death or worsening of HF due to sexual activity is low in patients with NYHA functional class I. In addition, patients receiving appropriate HF medications can maintain a safe and satisfying sexual life.³⁴⁶⁾ Patients with NYHA functional class II have moderate risk, and the assessment of exercise capacity is helpful in such patients. There is little risk associated with an active sexual life in patients exerting more than 5 metabolic equivalents during the exercise stress test and exhibiting no significant decrease in LV systolic function

on echocardiographic examination. However, patients with NYHA functional class III–IV are at high risk and should undergo careful evaluation and counseling by HF specialists before engaging in an active sexual life. The use of 5-phosphodiesterase antagonists such as sildenafil for erectile dysfunction is relatively safe in patients with stable HF, and the drug is known to be effective in improving cardiac function, especially regarding exercise capacity.³⁴⁷⁾ However, such drugs should not be administered to patients using nitrates.

For patients with chronic HF, travel and leisure are important issues related to quality of life. There is no particular restriction for going on flights lasting up to 7 hours for patients with NYHA functional class I–II under appropriate pharmacotherapy.^{348–350)} However, patients with NYHA functional class III–IV, or those who exhibit HF symptoms in everyday life, should be restricted from going on long-duration flights and from traveling to places with high temperature, high humidity, or high altitude. Exposure to travel by flight and to high temperature environments increases water loss, and therefore appropriate fluid balance must be ensured. Finally, while traveling, the patient should carry a written record of the current medication and clinical history including HF, as well as carry all current medication and additional medications potentially required under unexpected circumstances.

Cardiac rehabilitation and exercise therapy

1. Exercise therapy (or regular physical activity), as a safe and effective way to improve functional status, is recommended for patients with HF who are able to perform such activities (class of recommendation I, level of evidence A).
2. Cardiac rehabilitation is advisable for improving exercise capacity and duration, improving quality of life, and reducing mortality in patients with clinically stable HF (class of recommendation IIa, level of evidence B).

The role of exercise in the treatment of patients with HF has been addressed in the 2001 guidelines for HF management, put forth by the Canadian Heart Association.^{351–353)} Until the late 1980s, patients with HF were advised to avoid physical activity to minimize their symptoms and to protect the injured heart. However, a decrease in exercise capacity is known to aggravate HF itself, which is explained by various mechanisms. In addition to increased intracardiac pressure and contractility of the LV, peripheral arteries and fitness are also important factors in determining exercise capacity. Because exercise training programs improve both peripheral abnormalities and exercise capacity, appropriate exercise regimens can reduce exacerbation of HF. In addition, exercise therapy has the advantage of preventing rehospitalization due to HF because it improves vascular endothelial function, restrains and stabilizes the excessive catecholamine reaction, and increases the release of oxygen from the peripheral circulation.^{354–357)}

Some studies have shown that a regular combination of aerobic exercise (e.g., bicycling or running) and muscle strengthening exercises is safe and effective in improving symptoms and enhancing exercise performance by 15%–25% in patients with HF and NYHA functional class II–III.³⁵⁸⁾³⁵⁹⁾ A meta-analysis (ExTraMATCH trial) has examined the role of exercise training in patients with chronic HF, but the study had several limitations, especially in terms of the sample size and the fact that only pathophysiologic outcomes were considered.³⁶⁰⁾ A meta-analysis including 800 patients found that exercise prescription reduced the mortality rate of patients with HF by 32% and the cumulative outcome (death or re-admission) by 23%.³⁵⁴⁾³⁶¹⁾³⁶²⁾ In another large study including 2,331 patients with HF divided into an exercise

intervention group and a control group found that patients who underwent a 3-month exercise program had lower mortality (by 11%) and significantly lower cardiovascular mortality or readmission rate after adjustment of other factors.³⁵⁵⁾ Another meta-analysis showed an increase in maximum oxygen demand and a decrease in mortality after exercise.³⁶³⁾ Therefore, exercise (or regular physical exercise) should be prescribed in patients with HF because it can safely and effectively improve the physical state. Cardiac rehabilitation should also be prescribed, as it improves the physical status, exercise capacity, LV contractility, quality of life, and survival.

The amount of exercise beneficial for patients with HF is about 30–45 minutes per day, 3–5 days per week. The activity should consist of moderate exercise including a warm-up and a cool-down exercise. A preparatory phase should be implemented before starting the exercise program, during which the intensity is gradually increased until the target level, and the physical condition, anginal symptoms, and the most appropriate target heart rate are evaluated. Training should start with a moderate intensity activity combining aerobic exercise and strength training. Finally, it is better to start in the presence of a specialized trainer, and, if possible, a defibrillator should be prepared before the activity.

Education and counseling

Education and supportive therapy to enhance compliance

Patients with HF should receive specific education to improve self-management skills for HF (class of recommendation I, level of evidence B).

In a number of studies regarding the relevance of HF education in patients with HF, it was demonstrated that education improved understanding, self-monitoring, and adherence to medications, as well as reduced re-admission rates and the length of hospital stay.²⁷³⁾ Those who were educated before discharge had a much better understanding of HF at discharge and at 1 year after discharge.³⁶⁴⁾ In-hospital training with several forms of education has shown good results in reducing mortality within 6 months of discharge.²⁷⁴⁻²⁷⁶⁾³⁶⁵⁾³⁶⁶⁾ Patient and family education programs at discharge and during outpatient treatment improved many aspects of patient management, including: compliance with treatment plans, diet, fluid restriction, and weight monitoring; recognition of physical symptoms associated with HF worsening; prediction of prognosis; assessment of quality of life; palliative care; cardio-pulmonary resuscitation training for family members; and support from the community. Several studies regarding post-discharge, home-based self-care in patients with HF were conducted in the late 1990s and early 2000s,³⁶⁷⁻³⁷⁸⁾ and their findings suggest that a framework should be constructed for a comprehensive and integrated treatment in addition to the treatment of home-based patients, either in the form of self-management of care provided by a family member. Comprehensive approaches are needed, involving the use of appropriate pharmacotherapy, education and counseling of patients and family members, clinical follow-up, early detection of symptoms and physical findings indicating volume overload, quality of life management, and access to medical institutions. While recent studies have reported, encouraging findings regarding monitoring via ICDs (using thoracic impedance, or pulmonary artery pressure, etc.) and remote monitoring by telephone, there is a lack of objective evidence, and further studies are needed.³⁷⁹⁾³⁸⁰⁾ Overall, educating patients with HF and their family helps improve compliance with treatment, can reduce mortality and re-hospitalization rates, and is important in terms of quality of life. Thus, such strategies should be actively considered.

Management of comorbidities

AF

1. Beta-blockers should be used first to control heart rate in patients with HF and AF (class of recommendation I, level of evidence A).
2. The CHA₂DS₂-VASc scoring system is the recommended tool for estimating the risk of stroke, and should be used in the decision of the treatment modalities in patients with HF and AF (class of recommendation I, level of evidence B).
3. Atrioventricular node catheter ablation followed by CRT is an acceptable treatment strategy in patients with HF and AF requiring CRT or the implantation of a cardiac pacemaker (class of recommendation IIa, level of evidence B).
4. Rhythm control can be considered in addition to heart rate control in patients with HF and AF (class of recommendation IIb, level of evidence A).
5. Catheter ablation of the pulmonary vein may be considered in order to restore sinus rhythm in patients with HF and AF (class of recommendation IIb, level of evidence B).

AF is the most common arrhythmia in HF, increases the risk of systemic thromboembolic complications (particularly stroke), and worsens the symptoms of HF by impairment of cardiac function. The Korean national registry of acute HF reported an incidence of 27% for AF,³⁸¹⁾ indicating that a substantial number of HF patients require treatment for AF, which should be performed in consideration of the risk of thromboembolic events (particularly stroke), as well as in consideration of the treatment for heart rate control and rhythm control related to HF management.

Beta-blockers should be used as the first-line treatment to control ventricular rate in patients with HF and AF. Because digoxin has a limited effect in reducing heart rate at rest, beta-blockers are preferred.³⁸²⁾ Moreover, beta-blockers have favorable effects in terms of reducing mortality and morbidity.¹⁶⁰⁻¹⁶²⁾³⁸³⁾

Rhythm control strategy in addition to rate control has not been shown to reduce mortality or morbidity in patients with HF and atrial fibrillation.³⁸⁴⁾ However, aggressive rhythm control can be beneficial in patients with tachycardia-induced cardiomyopathy.³⁸⁵⁾³⁸⁶⁾ Amiodarone is the only proven antiarrhythmic agent with beneficial effect in patients with reduced LV systolic function.³⁸⁷⁾³⁸⁸⁾ Because catheter-based pulmonary vein isolation represents a rhythm control strategy that can reduce symptoms and improve LV systolic function, it can be considered in patients with persistent symptoms despite the use of medications.³⁸⁹⁻³⁹¹⁾

The CHA₂DS₂-VASc scoring system is recommended to assess the risk of systemic thromboembolic events and stroke in patients with HF and AF (**Table 15**).³⁹²⁾ The CHA₂DS₂-VASc scoring system considers vascular disease, age (65–74 years), and female sex in addition to the risk factors included in the previous CHADS₂ score, and it is recommended in the recent American and European guidelines.²²⁰⁾³⁹³⁾ Similar to the CHA₂DS₂-VASc scoring system, the modified CHADS₂ scoring system was described in Korea and includes chronic kidney disease in addition to female sex, coronary artery disease, and age (65–74 years).³⁹⁴⁾ Because the majority of patients with HF and AF have a CHA₂DS₂-VASc score of more than 2, anticoagulant treatment is recommended. However, the anticoagulant treatment should be decided based on the bleeding risk, which can be assessed using the HAS-BLED score, a tool that takes into consideration hypertension, abnormal liver and kidney function, previous stroke, previous bleeding, labile international normalized ratios, age (>65 years), and use

Table 15. Overview of the CHA₂DS₂-VASc scoring system for assessing the risk of stroke in patients with AF

Risk factor	Score
Congestive HF or reduced LVEF (<40%)	1
Hypertension	1
Age (≥75 years)	2
Diabetes mellitus	1
Stroke, TIA, or thromboembolism	2
Vascular disease*	1
Age (65–74 years)	1
Sex (female)	1
Total	9

AF = atrial fibrillation; HF = heart failure; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack.
*Previous history of myocardial infarction, peripheral arterial disease, or severe calcification of the aorta.

of drugs/alcohol (**Table 16**). Anticoagulants should be used cautiously in patients with high bleeding risk indicated by a HAS-BLED score of more than 3 (see section anticoagulants).³⁹⁵⁾

Ischemic heart disease

1. The presence of coronary artery disease should be assessed in all patients with HF, and non-invasive imaging tests or coronary angiography should be performed in patients with HF of unknown etiology and uncertain aggravating factors (class of recommendation I, level of evidence C).
2. It is reasonable to detect ischemic heart disease using single-photon emission CT with thallium-201 or technetium-99m, using cardiac CT, or using cardiac MRI (class of recommendation IIa, level of evidence C).
3. It is reasonable to perform reperfusion therapy with coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention in patients with ischemic cardiomyopathy and viable myocardium (class of recommendation IIa, level of evidence B).
4. CABG surgery can be an option to manage coronary artery disease in patients with HF and LVEF <35% (class of recommendation IIa, level of evidence B).

In Korea, the reported prevalence of ischemic cardiomyopathy is 38%,³⁸¹⁾ and obstructive coronary artery disease is a known predictor of poor prognosis in patients with HF.^{396–402)} Autopsies of patients with sudden cardiac death have reported a high incidence of myocardial infarction and acute coronary syndrome in patients with ischemic HF or HF with obstructive

Table 16. Overview of the HAS-BLED scoring system for assessing the risk of major bleeding in patients with AF

Risk factor	Score
Hypertension*	1
Abnormal renal [†] or liver function [‡]	1 or 2
Stroke	1
Bleeding [§]	1
Labile INRs	1
Elderly (>65 years)	1
Drug use [¶] or alcohol abuse	1 or 2
Total	9

AF = atrial fibrillation; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; INR = international normalized ratio.

*Systolic blood pressure >160 mm Hg, [†]Presence of chronic dialysis, renal transplantation, or serum creatinine levels ≥200 μmol/L, [‡]Chronic hepatic disease or biochemical evidence of significant hepatic dysfunction (e.g., bilirubin levels more than twice over the maximum normal limit, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase levels more than three times over the maximum normal limit), [§]Previous bleeding history and/or predisposition to bleeding (e.g., bleeding diathesis, anemia), ^{||}Unstable or high INRs or prothrombin time in the sub-therapeutic range (e.g., <60%), [¶]Concomitant use of drugs such as antiplatelet agents or nonsteroidal anti-inflammatory drugs.

coronary artery disease, and a lower incidence of such conditions in patients with HF but without coronary artery disease. So, there can be different mechanisms of death in 2 groups.⁴⁰³⁾ Once coronary artery disease has been detected, medications such as aspirin and statins, which reduce acute coronary syndrome, should be used in patients with HF and coronary artery disease. However, there are several controversies as to whether additional tests to detect coronary artery disease should be performed, which tests are optimally suited for this purpose, and whether revascularization therapy can improve prognosis in patients with coronary artery disease. Moreover, no study has evaluated whether coronary angiography should be performed in all patients to exclude coronary artery disease, or only in patients with specific risk factors or ischemic symptoms. Several reports have confirmed the high sensitivity and negative predictive value of myocardial perfusion imaging with radionuclides to screen for ischemic cardiomyopathy.⁴⁰⁴⁻⁴¹⁰⁾ Although one study found different patterns of myocardial distribution for ¹¹C-labeled palmitate, few studies have investigated the potential role of positron emission tomography in discriminating between ischemic and non-ischemic HF.⁴¹⁰⁾ In studies using 64-slice multidetector CT, the scan showed a sensitivity of 92%–97% and a specificity of 98% for differentiating between ischemic and non-ischemic cardiomyopathy.⁴¹¹⁾⁴¹²⁾ Cardiac MRI can evaluate regional myocardial systolic function and detect ischemic segments using late gadolinium enhancement.¹¹⁰⁾⁴¹³⁻⁴¹⁵⁾

It is known that myocardial hibernation is an important mechanism of HF caused by coronary artery disease.⁴¹⁶⁻⁴¹⁸⁾ Methods for detecting hibernating myocardium include the low-dose dobutamine stress test for evaluating the recovery of myocardial contractility, single-photon emission CT with thallium-201 or technetium-99m for assessing cell membrane permeability, and positron emission tomography for evaluating metabolic activity.⁴¹⁹⁾⁴²⁰⁾ Cardiac MRI can also be used, as described above.¹¹⁸⁾ It has been reported that reperfusion therapy can increase the survival rate in patients with HF and hibernating myocardium.⁴¹⁹⁾ However, no report has yet compared the above described imaging techniques regarding their ability to detect hibernating myocardium and predict its recovery. On the other hand, a recent sub-study of the Surgical Treatment for Ischemic Heart Failure (STICH) trial revealed that the presence of ischemia induced by the stress test with radionuclide or via dobutamine stress echocardiography was not related to survival.⁴²¹⁾ In the STICH trial assessing whether CABG surgery for coronary artery disease increases the survival rate of patients with HF and LVEF \leq 35%, there was no statistically significant benefit of CABG in overall mortality. However, the mortality rate tended to decrease, and there was a significant difference in the cumulative outcome involving all-cause mortality, re-admission due to cardiovascular disease, and cardiovascular mortality.⁴²²⁾

Hypertension

1. ACE inhibitors (or ARBs), beta-blockers, and aldosterone antagonists should be used as first-, second-, and third-line therapy, respectively (class of recommendation I, level of evidence A).
2. If ACE inhibitors (or ARBs), beta-blockers, and aldosterone antagonists fail to control blood pressure, thiazide diuretics should be added. If the patient is already receiving thiazide diuretics, these should be changed to loop diuretics (class of recommendation I, level of evidence C).
3. If combination therapy with ACE inhibitors (or ARBs), beta-blockers, aldosterone antagonists, and diuretics does not control blood pressure, then either amlodipine or hydralazine should be added (class of recommendation I, level of evidence A).
4. If blood pressure is not controlled by the combination of ACE inhibitors (or ARBs), beta-blockers, aldosterone antagonists, and diuretics, the administration of felodipine should be considered (class of recommendation IIa, level of evidence B).

5. Alpha-blockers should not be used because of risks associated with neurohormonal activation, water retention, and deterioration of HF.

Elevated blood pressure increases afterload on the LV, impairing systolic and diastolic function and promoting LV remodeling. The increased LV wall stress also exacerbates myocardial dysfunction by inducing myocardial ischemia as a result of increased oxygen consumption, microcirculatory impairment, and coronary arterial endothelial dysfunction. In patients with HF, elevated blood pressure causes an additional increase in hemodynamic load on the functionally impaired heart.

Hypertension is an important risk factor for the development and worsening of HF in all age groups,⁴²³⁾ and similar data were reported in a large-scale registry study in Korea.³⁸¹⁾ The optimal management of systolic and diastolic blood pressure can reduce the risk of HF by approximately 50%,⁴²⁴⁾⁴²⁵⁾ and appropriate management of blood pressure can restore myocardial contractility.⁴²⁶⁾ Although blood pressure is often lowered in patients with advanced HF, control of hypertension in addition to the general management of HF is also important. The choice of antihypertensive medication is based on the treatment of HF with a suitable target for blood pressure.

ACE inhibitors and ARBs can regress LV hypertrophy in patients with hypertension and LV hypertrophy, and this effect is known to be greater than that of beta-blockers.⁴²⁷⁾⁴²⁸⁾ Therefore, ACE inhibitors and ARBs should be used as a first-line therapy in patients with HF and hypertension.⁵⁷⁾

Generally, the use of calcium channel blockers is not recommended in patients with HF. However, large randomized trials of amlodipine did not indicate increased mortality or morbidity in patients with HF, and revealed no significant side effects. Therefore, the use of amlodipine can be considered in patients with HF and hypertension or coronary artery disease.

Although the target blood pressure varies individually in patients with HF and hypertension, various treatment guidelines recommend that the systolic blood pressure should be lowered to under 130 mmHg.⁵⁸⁾⁴²⁹⁾⁴³⁰⁾ Additionally, it is recommended to control blood pressure below 130/80 mmHg in patients with HF, hypertension, and preserved LVEF and/or LV hypertrophy.

Diabetes mellitus

Insulin resistance and diabetes mellitus represent important risk factors for developing HF. Impaired glucose tolerance and diabetes mellitus are very common in patients with HF,³⁸¹⁾ and diabetes mellitus is associated with worse functional status, hospitalization rate, and mortality rate.

Because there was no prospective randomized controlled trial regarding the optimal blood glucose levels in patients with HF and diabetes, it is difficult to provide clear target values for blood glucose in such patients. However, according to one observational study, the relationship between glycated hemoglobin levels and mortality is U-shaped in patients with diabetes mellitus; moreover, the mortality rate was the lowest in patients with HbA1C levels between 7.1% and 7.8%, and increased rapidly at extremely high or low levels of HbA1C.⁴³¹⁾ While it is recommended that HbA1C levels should be controlled to 7.0% or lower in general, less strict glycemic control (HbA1C levels \leq 8.0%) is required when the accompanying

diseases are severe.⁴³²⁾ Therefore, glycosylated hemoglobin levels can be controlled to within 8.0% in patients with severe HF and diabetes mellitus.⁴³³⁾

In patients with diabetes, ACE inhibitors or ARBs can reduce the incidence of HF by preventing the development of other risk factors for HF, including renal dysfunction. Indeed, ACE inhibitors and ARBs improved survival and reduced hospitalization rates in patients with HF and diabetes.⁴³⁴⁻⁴³⁶⁾ Beta-blockers have various effects on blood glucose levels and are not contraindicated in patients with diabetes mellitus, and improve prognosis in these patients to the same extent as in patients without diabetes mellitus.⁴³⁷⁻⁴³⁹⁾ The survival benefit of aldosterone antagonists did not differ with the presence of diabetes mellitus.¹⁷⁰⁾⁴⁴⁰⁾ However, the clinical course should be closely monitored to detect the development of hyperkalemia or worsening of renal function when aldosterone antagonists are prescribed.

The safety and efficacy of diabetic agents have not been established yet in patients with HF. However, the use of metformin was associated with lower incidence of admission, death, and cardiovascular events compared to the values noted for the use of sulphonylureas or insulin.⁴⁴¹⁻⁴⁴³⁾ Because thiazolidinediones may cause fluid retention,⁴⁴⁴⁾⁴⁴⁵⁾ they should not be used in patients with HF and NYHA functional class II or higher. The effect of glucagon-like peptide-1 and dipeptidyl peptidase-4 has not been proven in patients with HF.

Chronic kidney disease

More than 40% of patients with HF have chronic kidney disease.⁴⁴⁶⁾ Known etiologies of renal failure include hypotension, excess fluid, right HF, renal vein congestion, and sodium and water deficiency due to vomiting, diarrhea, or excessive use of diuretics.²⁾ Decreased renal function itself has a great influence on the prognosis of HF, especially when severely deterioration is present.⁴⁴⁷⁾ In general, cardiorenal syndrome worsens due to the interaction between HF and renal dysfunction and involves, in addition to decreased blood flow to the kidney because of HF, various mechanisms including central venous congestion, neurohormonal changes, anemia, and activation of the renal sympathetic system.⁴⁴⁸⁾ The principle of selecting medications in patients with HF and impaired renal function was described in previous chapters (see section inhibitors of the renin-angiotensin and renin-angiotensin-aldosterone systems; see also section mineralocorticoid antagonists).

Ultrafiltration may be considered if patients with acute decompensated HF do not respond to any diuretics. Ultrafiltration removes excess fluid and filters out low- and medium-weight solutes through a semipermeable membrane. While diuretics make the urine more hypotonic, ultrafiltration produces isotonic urine and removes a relatively higher amount of sodium in the urine. In a randomized study published in 2007 and involving 200 patients with acute decompensated HF, the ultrafiltration group showed more pronounced weight loss at 18 hours after the procedure and a lower 90-day admission rate compared to the values noted in the control group.⁴⁴⁹⁾ However, another randomized study involving 188 patients with acute decompensated HF and cardiorenal syndrome showed no significant benefit of ultrafiltration, which is contrary to the previous findings.⁴⁵⁰⁾ Specifically, there were no significant differences between the intervention and the control groups regarding the extent of weight loss after 96 hours or in the rate of hospitalization and mortality at 60 days. In fact, the ultrafiltration group tended to show a higher incidence of complications at 60 days. Adverse effects associated with ultrafiltration therapy include hypotension, hemorrhage, hemolysis, catheter-related complications, allergic reactions, and air embolism.⁴⁵¹⁾ Therefore, cardiologists without sufficient experience with ultrafiltration should seek advice from the nephrologist prior to prescribing ultrafiltration therapy.

The favorable effects of ACE inhibitors or ARBs in patients with chronic HF are well known. However, there is insufficient evidence regarding the effectiveness of these drugs in patients with chronic renal dysfunction accompanied by high incidence of cardiovascular events. This is because most clinical studies exclude patients with serum creatinine levels >2.0–2.5 mg/dL and no sub-group analysis has included patients with chronic renal impairment.⁴⁵²⁻⁴⁵⁴ The CONSENSUS study,¹⁴³ which included many patients with renal impairment and serum creatinine levels of up to 3.4 mg/dL, indeed showed improved survival in patients who received enalapril. A similar finding was reported in a sub-analysis that involved patients with renal insufficiency (estimated GFR, <60 mL/min/1.73 m² and serum creatinine levels, <2.5 mg/dL).⁴⁵⁵ Therefore, a favorable effect of ACE inhibitors can be expected in patients with renal impairment without dialysis. As a small randomized study has shown that the use of ARBs can reduce the incidence of cardiovascular events in patients receiving hemodialysis (not in patients with HF), this finding can be interpreted as indirect evidence for the use of ARBs in patients with HF undergoing hemodialysis.^{456,457} In the case of beta-blockers, the benefit is more evident in patients with HF and renal failure without dialysis. Randomized studies and subgroup analyses investigating the effects of using metoprolol, carvedilol, and bisoprolol showed a survival benefit of beta-blockers regardless of the degree of renal insufficiency.⁴⁵⁸⁻⁴⁶⁰ Finally, a placebo-controlled trial showed that patients receiving carvedilol had significantly lower cardiovascular mortality than that noted in patients receiving the placebo (29.3% vs 67.9%, respectively).⁴⁶¹

COPD

COPD makes diagnosis of HF difficult and is associated with worse functional status and prognosis.^{462,463} While beta-blockers have demonstrated efficacy in improving prognosis in patients with HF, these drugs should be used cautiously because they can exacerbate bronchospasm. However, beta-blockers are contraindicated in patients with asthma, but not in patients with HF and COPD. It is recommended to start with a low dose of beta-blockers and then gradually increase the dose. Selective beta 1-blockers (e.g., bisoprolol, metoprolol, nebivolol) can be used safely.⁴⁶⁴⁻⁴⁶⁶

Oral beta 2-blockers used as bronchodilators in COPD not only increased the incidence of HF⁴⁶⁷ but also increased mortality in patients with HF.⁴⁶⁸ Although inhaled beta 2-blockers have fewer systemic effects and improve pulmonary function in patients with HF,⁴⁶⁹ they are associated with an increased rate of hospitalization due to HF and thus should be used cautiously.⁴⁷⁰

While oral steroids can cause salt and water retention and deteriorate HF, inhaled steroids have not been reported to be associated with worsening HF.

Anemia

1. It is appropriate to administer intravenous iron in patients with HF and iron deficiency anemia (class of recommendation IIa, level of evidence A).
2. The use of erythropoietic stimulants may be harmful in patients with chronic HF and unexplained anemia (class of recommendation III, level of evidence B).

Anemia is commonly associated with chronic HF. Although there is a difference in the way anemia is defined in each study and therefore it is difficult to assess the exact prevalence, it is estimated that anemia is found in approximately 25%–40% of patients with HF, and

the prevalence of anemia increases with the severity of HF. Anemia is also more common in women and is found in both HFrEF and HFpEF.⁴⁰⁾⁴⁷¹⁻⁴⁷⁵⁾ In patients with HF, anemia is associated with increased mortality, decreased exercise capacity, high re-admission rate, and poor quality of life.⁴⁰⁾⁷⁶⁾⁴⁷¹⁾⁴⁷⁶⁾⁴⁷⁷⁾ However, there is controversy as to whether anemia correction can reduce HF symptoms, improve quality of life, and ultimately decrease the rate of HF-related re-hospitalization or death. The most important aspects related to the correction of anemia in HF are as follows: the effect of the correction of iron deficiency anemia in reducing the patient's symptoms and improving prognosis; and the role of erythropoietic stimulants in patients with anemia of non-specific etiology.

Small studies have shown that administration of erythropoietin can correct anemia and improve the exercise capacity.⁴⁷⁸⁻⁴⁸²⁾ A relatively large-scale, randomized study assessing the effect of darbepoetin in 165 patients found that darbepoetin improved indicators of quality of life but did not improve exercise capacity or LVEF. However, there was no death among the 55 patients in the control group, whereas 6 of the 110 patients receiving darbepoetin died of treatment-unrelated problems. These results raise safety concerns related to the use of erythropoietic stimulants in patients with HF.⁴⁸³⁾ Moreover, the STAMINA-HeFT study including 319 patients failed to demonstrate drug efficacy, although no safety concerns were raised.⁴⁸⁴⁾ On the other hand, 2 meta-analyses regarding the efficacy of erythropoietic stimulants revealed conflicting conclusions.⁴⁸⁵⁾⁴⁸⁶⁾ Based on these controversies, a randomized controlled trial (RED-HF) evaluated the efficacy and safety of darbepoetin in a large population of 1,142 patients. While the symptoms and prognosis of patients who received darbepoetin did not improve significantly, the risk of thromboembolism was significantly higher in the treatment group.⁴⁸⁷⁾ Therefore, the use of erythropoietic stimulants is not recommended in patients with chronic HF and anemia of non-specific cause.

Bolger et al.⁴⁸⁸⁾ reported that intravenous iron supplementation improved symptoms and exercise capacity in 16 patients with HF and iron deficiency anemia. Several studies have demonstrated that intravenous iron administration improved exercise capacity, quality of life, and HF symptoms,⁴⁸⁹⁻⁴⁹¹⁾ while some studies have reported it can reduce re-admission rate and mortality.⁴⁸⁹⁾⁴⁹²⁾ On the other hand, intravenous iron administration can be beneficial even in patients with iron deficiency but without anemia.⁴⁹⁰⁾⁴⁹³⁾ The FAIR-HF study is the largest multi-center randomized trial involving intravenous iron administration. They compared the effect of iron and saline intravenous administration in 459 patients with systolic HF and iron deficiency anemia (hemoglobin levels, 9.5–13.5 g/dL). Iron supplementation was associated with improvement in symptoms, exercise capacity, and quality of life after 6 months of treatment.⁴⁹³⁾ Therefore, intravenous administration of iron is feasible in patients with HF and iron deficiency anemia.

Depression

Depression is frequently noted and usually underdiagnosed in patients with advanced HF. As HF itself can cause depression, it is difficult to distinguish between somatic symptoms of HF and depression. If depression is not treated appropriately, survival and quality of life in patients with HF are markedly decreased. Therefore, active treatment for depression is needed in these patients.

While possible mechanisms underlying the association between depression and HF include alterations in the autonomic nervous system, inflammation, arrhythmia, and changes in platelet function, the exact cause of the depressive symptom is largely unknown.⁴⁹⁴⁾ Patients

with HF and depression have poor quality of life, are unable to manage themselves, and have poor clinical outcomes.⁴⁹⁵⁻⁴⁹⁷⁾ Depression also decreases drug compliance and promotes social isolation. Although depression is most common during admission,⁴⁹⁸⁾ 63% of patients with HF who have been hospitalized for 3 months have complained of depression.⁴⁹⁹⁾

The diagnosis of depression in patients with HF is based on various physical symptoms, decreased appetite and sexual desire, decreased energy, and insomnia. However, physical symptoms such as loss of appetite due to physical illness, fatigue, or insomnia caused by uncontrolled pain may interfere with the diagnosis of depression. Therefore, in patients with physical illness, the diagnosis of depression should be focused on cognitive and emotional symptoms rather than on physical symptoms.

The treatment of depression in patients with HF can be combined with supportive psychotherapy, cognitive-behavioral therapy, and antidepressant therapy. Psychosocial treatment is offered for individuals, families, and groups, with the ultimate goal to improve overall coping skills through education, behavioral, or psycho-dynamic approaches. Psychopharmacological therapy is used mainly for the treatment of moderate to severe depression, and the safety and effectiveness of antidepressant treatment has been confirmed in many experimental and clinical studies. Selective serotonin re-uptake inhibitors are known to be relatively safe, while tricyclic antidepressants should not be used because of side effects such as orthostatic hypotension, cardiac conduction abnormality, and arrhythmia.⁵⁰⁰⁾ In addition, selective serotonin re-uptake inhibitors have strong protein binding capacity, which can increase blood levels of warfarin, digoxin, and cisplatin. Although treatment of depression can improve prognosis, the optimal approach for patients with HF remains unclear. Supportive care for patients and their families is complex but important, especially during the transition period. There are reports that the 30-day rate of HF-related re-admission and mortality are higher if such support is not properly understood and provided.⁵⁰¹⁾⁵⁰²⁾

Sleep apnea syndrome

The use of continuous positive airway pressure therapy is reasonable to increase LVEF and improve functional status in patients with HF and obstructive sleep apnea syndrome (class of recommendation IIa, level of evidence B).

Many patients with HF have difficulty breathing when sleeping. The contributing factors vary. For example, orthopnea and paroxysmal nocturnal dyspnea may be due to pulmonary congestion, while nocturia may be related to the use of diuretics. Anxiety and other psychiatric problems also contribute to sleep disorders.²⁾ Moreover, it has been reported that patients with HF often have obstructive sleep apnea (30%–69%),⁵⁰³⁾⁵⁰⁴⁾ even though symptoms such as daytime sleepiness are rare.⁵⁰³⁾⁵⁰⁵⁾⁵⁰⁶⁾ Obstructive sleep apnea is diagnosed using polysomnography. When the airflow is stopped for more than 10 seconds, the condition is termed apnea. When the airflow is not completely stopped, but decreases by more than 50%, the condition is termed hypopnea.⁵⁰⁷⁾ The severity of obstructive sleep apnea is assessed by the apnea-hypopnea index.

The primary treatment for obstructive sleep apnea involves the use of continuous positive airway pressure therapy at night. In addition to improving pharyngeal closure, continuous positive airway pressure therapy can also alleviate the degree of central sleep apnea

syndrome.⁵⁰⁷⁾⁵⁰⁸⁾ The CANPAP trial, published in 2005, is the largest study showing the effect of nighttime continuous positive airway pressure therapy in patients with HF and obstructive sleep apnea.⁵⁰⁹⁾⁵¹⁰⁾ In this study, 258 HF patients with a mean LVEF of $24.5\% \pm 7.7\%$ were randomly assigned to either a control group or a treatment group, which involved nighttime continuous positive airway pressure therapy for 3 months. In the treatment group, there was a decrease in the apnea-hypopnea index, increase in the LVEF, improvement in the norepinephrine levels, and increase in the performance during the 6-minute walk test. The subgroup analysis showed that, after 3 months of treatment, the survival rate was higher in patients with an apnea-hypopnea index <15 .⁵⁰⁹⁾ Other studies, although small in scale, have reported that nighttime continuous positive airway pressure therapy improves ventricular function, activation of sympathetic nervous system, and quality of life in patients with HF and obstructive sleep apnea.⁵⁰⁴⁾⁵¹¹⁾⁵¹²⁾

Malignant neoplasms

Certain anticancer agents can cause or worsen HF. Anthracyclines and trastuzumab are well-known anticancer agents associated with HF.⁵¹³⁾⁵¹⁴⁾ In addition, high-dose cyclophosphamides, taxoid, mitomycin-C, 5-fluorouracil, and interferons are known to have cardiotoxicity.⁴⁴⁶⁾⁵¹⁵⁻⁵²²⁾ A meta-analysis showed that dexrazoxane has cardioprotective effect in patients receiving chemotherapy with anthracyclines.⁵²³⁾ Trastuzumab-induced decrease in cardiac function can often be reversed by discontinuing the drug. In an observational study involving 38 patients with congestive HF caused by use of trastuzumab, 37 patients showed recovery of the reduced LVEF within a mean period of 1.5 months after trastuzumab discontinuation.⁵¹⁸⁾ The HERA study, which involved 3,386 patients, demonstrated that, although the incidence of symptomatic HF was higher in the trastuzumab group (2.15%) than in the placebo group (0.12%), most patients with HF recovered ventricular function within 6 months after trastuzumab discontinuation. Therefore, the most important current strategy for preventing the onset and worsening of HF associated with trastuzumab is to stop the administration of trastuzumab at appropriate points during the follow up.⁵²⁴⁾ Several international treatment guidelines recommended that LVEF should be checked using echocardiography after 4–8 cycles of trastuzumab or every 3 months after the treatment, and that trastuzumab should be discontinued in patients with $LVEF \leq 45\%$ and even in patients with normal LVEF provided that LVEF decreased by 10%–15% from the baseline value. LVEF should always be checked after discontinuation of trastuzumab.⁵²⁰⁾⁵²⁴⁾ However, there is insufficient data on the specific methods for monitoring the deterioration of cardiac function during chemotherapy and the optimal approach for preventing cardiotoxicity due to anticancer drugs. In the present guidelines, we recommend that concomitant cardiovascular risk factors for developing HF, such as coronary artery disease or hypertension, be identified and managed at the time of initiating cardiotoxic chemotherapy.²⁾⁵¹³⁾⁵²⁴⁾⁵²⁵⁾

Pregnancy

Pregnant women with chronic HF have a high mortality rate, and normal pregnancy and delivery may be difficult. Pregnant women with hemodynamically unstable acute HF symptoms have high risk for developing cardiac events and may require preterm delivery. There is a risk that pregnancy will exacerbate HF even in mild chronic HF; therefore, patients who desire to become pregnant should receive adequate education and counseling regarding the associated risks. Patients with LVEF less than 40% are considered to be at high risk and should be monitored at a tertiary medical center. If a patient with LVEF less than 20% is pregnant, the attending physician should consider the termination of pregnancy because high maternal mortality rates have been reported for such clinical conditions.⁵²⁶⁾

Pregnant patients with HF are treated similarly to non-pregnant patients, with the exception of certain medications that are contraindicated during pregnancy. ACE inhibitors and ARBs are contraindicated during pregnancy because of teratogenicity, and may be replaced with hydralazine and nitrates to lower afterload. Beta-blockers should be used in all patients with HF, and selective beta 1-blockers are recommended. However, atenolol is contraindicated because it can cause hypoglycemia, bradycardia, and respiratory depression in the newborn. Although diuretics are the only medication that can be used in patients with pulmonary edema, indication and dosage should be prescribed cautiously because such drugs can reduce placental blood flow. Furosemide and hydrochlorothiazide (Teva Czech Industries s.r.o., Opava-Komarov, Czech Republic) can be used predominantly. Spironolactone is contraindicated in the first trimester because of its anti-androgenic effects. The effect of eplerenone in pregnancy has not yet been studied. Generally, aldosterone antagonists are not recommended during pregnancy.

Vaginal delivery is preferred in patients with hemodynamically stable HF. In this case, intensive hemodynamic monitoring is necessary and epidural anesthesia is recommended. However, urgent delivery should be considered regardless of gestational age in patients with hemodynamically unstable advanced HF, and cesarean section is recommended.

DEVICE THERAPY AND SURGICAL TREATMENT

ICD therapy

1. ICD implantation is recommended for primary prevention of sudden cardiac death and to reduce total mortality when applied at least 40 days post-myocardial infarction in selected patients with non-ischemic or ischemic cardiomyopathy, LVEF $\leq 35\%$, NYHA class II or III while receiving optimal guideline-directed medical therapy, and with an estimated meaningful survival of more than 1 year (class of recommendation I, level of evidence A).
2. ICD implantation is recommended for primary prevention of sudden cardiac death and to reduce total mortality when applied at least 40 days post-myocardial infarction in selected patients with LVEF $\leq 30\%$, NYHA class I while receiving optimal guideline-directed medical therapy, and an estimated meaningful survival of more than 1 year (class of recommendation I, level of evidence C).

There is an increased risk of developing ventricular arrhythmias and sudden cardiac death as a consequence of sustained ventricular tachyarrhythmia in patients with reduced LV systolic function. Several studies demonstrated the beneficial role of ICD in the primary prevention of cardiac death in patients with systolic HF. In the Multicenter Automatic Defibrillator Implantation Trial (MADIT) study,⁵²⁷⁾ ICD therapy reduced all-cause mortality in patients with asymptomatic, non-sustained ventricular tachycardia, a prior history of myocardial infarction, LVEF $\leq 35\%$, and inducible ventricular tachyarrhythmias during electrophysiological testing that could not be suppressed with procainamide. In the MADIT-II study, ICD implantation decreased the risk of all-cause mortality after myocardial infarction by 31% in patients with LVEF $\leq 30\%$.⁵²⁸⁾ MADIT-II only enrolled patients who had no previous episode of sustained ventricular arrhythmia or inducible arrhythmia on electrophysiological study. In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), ICD therapy improved survival in patients with ischemic and non-ischemic cardiomyopathy, HF with NYHA functional class II or III and LVEF $\leq 35\%$ while managed using a guideline-directed medical therapy.⁵²⁹⁾

Table 17. Reimbursement criteria of the Korean National Health Insurance Service regarding the use of ICD devices

Reimbursement criterion

ICD can be used in patients with high risk of sudden cardiac death if ICD implantation is expected to decrease the risk of cardiac death and improve survival. The National Health Insurance Service will approve reimbursement if the conditions given below are fulfilled, but will decline reimbursement if the ICD was implanted in violation of the conditions outlined below, and the patient will be liable to pay the full cost (100/100).

- (1) Patients with ischemic cardiomyopathy and a history of myocardial infarction (more than 40 days), NYHA functional class II–III on optimal guideline-directed medical therapy, expected meaningful survival for more than 1 year, and fulfilling one of the following criteria:
 - a) LVEF \leq 30%
 - b) LVEF of 31%–35% with non-sustained ventricular arrhythmias or inducible sustained arrhythmias during electrophysiological studies
- (2) Patients with non-ischemic cardiomyopathy, NYHA functional class II–III on optimal guideline-directed medical therapy for more than 3 months, expected meaningful survival for more than 1 year, and fulfilling one of the following criteria:
 - a) LVEF \leq 30%
 - b) LVEF of 31%–35%, with non-sustained ventricular arrhythmias or inducible sustained arrhythmias during electrophysiological studies

ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

However, compared to conventional treatment, ICD therapy provided no clinical benefit in high-risk patients with LVEF of 35%–40% within 40 days after myocardial infarction.⁵³⁰⁾⁵³¹⁾ Specifically, while ICD implantation reduced the incidence of cardiac death, it increased mortality from other causes, which effectively canceled the beneficial effect of ICD therapy in this patient population. Based on these findings, ICD therapy should be considered after careful re-evaluation of the patients at least 40 days after myocardial infarction. Moreover, in patients with HFrEF, adequate medical treatment should be attempted for at least 3 months before making the decision to implant an ICD as a primary prevention approach.

ICD implantation should be considered in patients with sustained reduction in LV systolic function at the re-evaluation conducted after 3 months of optimal medical treatment. The reimbursement criteria of the Korean National Health Insurance Service regarding ICD implantation are listed in **Table 17**.

Appropriate management should be continued after ICD implantation. Almost all patients treated with ICD receive an electric shock within 1–3 years after the implantation, and about one third of the shocks are inappropriate.⁵³²⁾ Frequent electric shocks can cause post-trauma stress disorder⁵³³⁾ and may increase mortality.⁵³⁴⁾⁵³⁵⁾ Therefore, proper pharmacologic treatment should be undertaken to reduce the necessity of electric shock, and cooperation with an electrophysiology specialist is needed to set up an appropriate program for the implanted ICD.

ICD therapy may not be beneficial in elderly patients with multiple other comorbidities and recurrent hospital admissions.⁵³⁶⁾ Thus, ICD therapy is not recommended in patients with expected survival of less than 1 year related to the presence of other medical conditions.

CRT

1. CRT is indicated in patients with LVEF \leq 35%, sinus rhythm, LBBB, QRS duration \geq 150 ms, and NYHA functional class II–III or ambulatory functional class IV symptoms despite receiving optimal guideline-directed medical therapy (class of recommendation I: for NYHA functional class III–IV, level of evidence A; for NYHA functional class II, level of evidence B).
2. CRT can be useful in patients with LVEF \leq 35%, sinus rhythm, LBBB, QRS duration of 120–149 ms, and NYHA functional class II–III or ambulatory functional class IV symptoms despite receiving optimal guideline-directed medical therapy (class of recommendation IIa, level of evidence A).
3. CRT can be useful in patients with LVEF \leq 35%, sinus rhythm, non-LBBB pattern, QRS duration \geq 150 ms, and NYHA functional class III or ambulatory functional class IV symptoms despite receiving optimal guideline-directed medical therapy (class of recommendation IIa, level of evidence A).

4. CRT can be useful in patients with AF and LVEF $\leq 35\%$ despite receiving optimal guideline-directed medical therapy, and who require ventricular pacing or otherwise meet the CRT criteria, provided that atrioventricular nodal ablation or pharmacologic heart rate control is expected to allow near 100% ventricular pacing with CRT (class of recommendation IIa, level of evidence B).
5. CRT can be useful in patients with LVEF $\leq 35\%$ despite receiving optimal guideline-directed medical therapy, who are receiving a new or replacement device with an anticipated requirement for significant ($>40\%$) ventricular pacing (class of recommendation IIa, level of evidence C).
6. CRT may be considered in patients with LVEF $\leq 30\%$, ischemic cardiomyopathy, sinus rhythm, LBBB, QRS duration ≥ 150 ms, and symptoms worse than those characteristics of NYHA functional class I despite receiving optimal guideline-directed medical therapy (class of recommendation IIb, level of evidence C).
7. CRT may be considered in patients with LVEF $\leq 35\%$, sinus rhythm, non-LBBB pattern, QRS duration of 120–149 ms, and NYHA functional class III or ambulatory functional class IV despite receiving optimal guideline-directed medical therapy (class of recommendation IIb, level of evidence B).
8. CRT may be considered in patients with LVEF $\leq 35\%$, sinus rhythm, non-LBBB pattern, QRS duration ≥ 150 ms, and NYHA functional class II symptoms despite receiving optimal guideline-directed medical therapy (class of recommendation IIb, level of evidence B).

Many patients with HF have increased QRS duration following the exacerbation of LV systolic dysfunction, which is associated with poor prognosis. CRT improves LV systolic function by sending tiny electrical stimuli to the cardiac muscle to reduce ventricular dyssynchrony, decrease the degree of mitral insufficiency, and improve myocardial remodeling. The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study, published in 2002, revealed that CRT is associated with significant clinical improvement in patients with HF that present with moderate-to-severe symptoms associated with LVEF $\leq 35\%$ and QRS duration of ≥ 130 ms.⁵³⁷⁾ Later, the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial showed that, when used in combination with an implantable defibrillator, CRT decreased the cumulative risk of all-cause death or first hospitalization, and significantly reduced mortality in patients with advanced symptoms (NYHA functional class III–IV) and a QRS interval of ≥ 120 ms.⁵³⁸⁾ The Cardiac Resynchronization-Heart Failure (CARE-HF) study, published in 2005, showed that CRT improved symptoms, increased quality of life, reduced the incidence and severity of complications, and decreased mortality in patients with HF and cardiac dyssynchrony.⁵³⁹⁾ These clinical benefits are provided by CRT in addition to those afforded by standard medical therapy. The reimbursement criteria of the Korean National Health Insurance Service were put together based on the above-described evidence (**Table 18**).

However, there are difficulties in the prediction of CRT outcomes in patients who meet some criteria including a QRS interval of ≥ 120 ms and LVEF $\leq 35\%$. **Figure 2** provides an overview of the indications for CRT based on evidence from clinical studies.

In 2009, the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT) study demonstrated a favorable effect of CRT in patients with LBBB and QRS interval of ≥ 150 ms.⁵⁴⁰⁾ CRT now has an indication corresponding to class of recommendation I for patients with LVEF $\leq 35\%$, sinus rhythm, LBBB, QRS duration of ≥ 150 ms, and NYHA functional class II–III or ambulatory functional class IV despite receiving optimal guideline-directed medical therapy. CRT may also be useful in patients with a QRS interval of 120–149 ms or non-LBBB in addition to LVEF $\leq 35\%$, sinus

Table 18. Reimbursement criteria of the Korean National Health Insurance Service for CRT

Reimbursement criterion
<p>CRT can be performed when there is evidence that HF will improve by resynchronization of the ventricle. The National Health Insurance Service will approve reimbursement if the conditions given below are fulfilled, but will decline reimbursement if CRT was performed in violation of the conditions outlined below, and the patient will be liable to pay the full cost (100/100).</p> <p>(1) CRT with a pacemaker Patients with significant HF symptoms on optimal guideline-directed medical therapy* more than 3 months, as well as fulfilling all the following criteria: a) LVEF $\leq 35\%$ b) QRS interval ≥ 120 ms c) Sinus rhythm d) NYHA functional class III or ambulatory functional class IV</p> <p>(2) CRT with a defibrillator Patients meet all conditions for receiving CRT with a pacemaker, as well as those for receiving an implantable cardioverter-defibrillator.</p>

ARBs = angiotensin-receptor blocker; CRT = cardiac resynchronization therapy; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

*Optimal guideline-directed medical therapy involves the use of angiotensin-converting-enzyme inhibitors or ARBs, combined with diuretics and beta-blockers.

rhythm, and NYHA functional class II–III or ambulatory functional class IV despite receiving optimal guideline-directed medical therapy.

Moreover, the beneficial effect of CRT has been demonstrated in patients with AF. CRT can be useful in patients with AF and LVEF $\leq 35\%$ if ventricular pacing is required or the CRT are

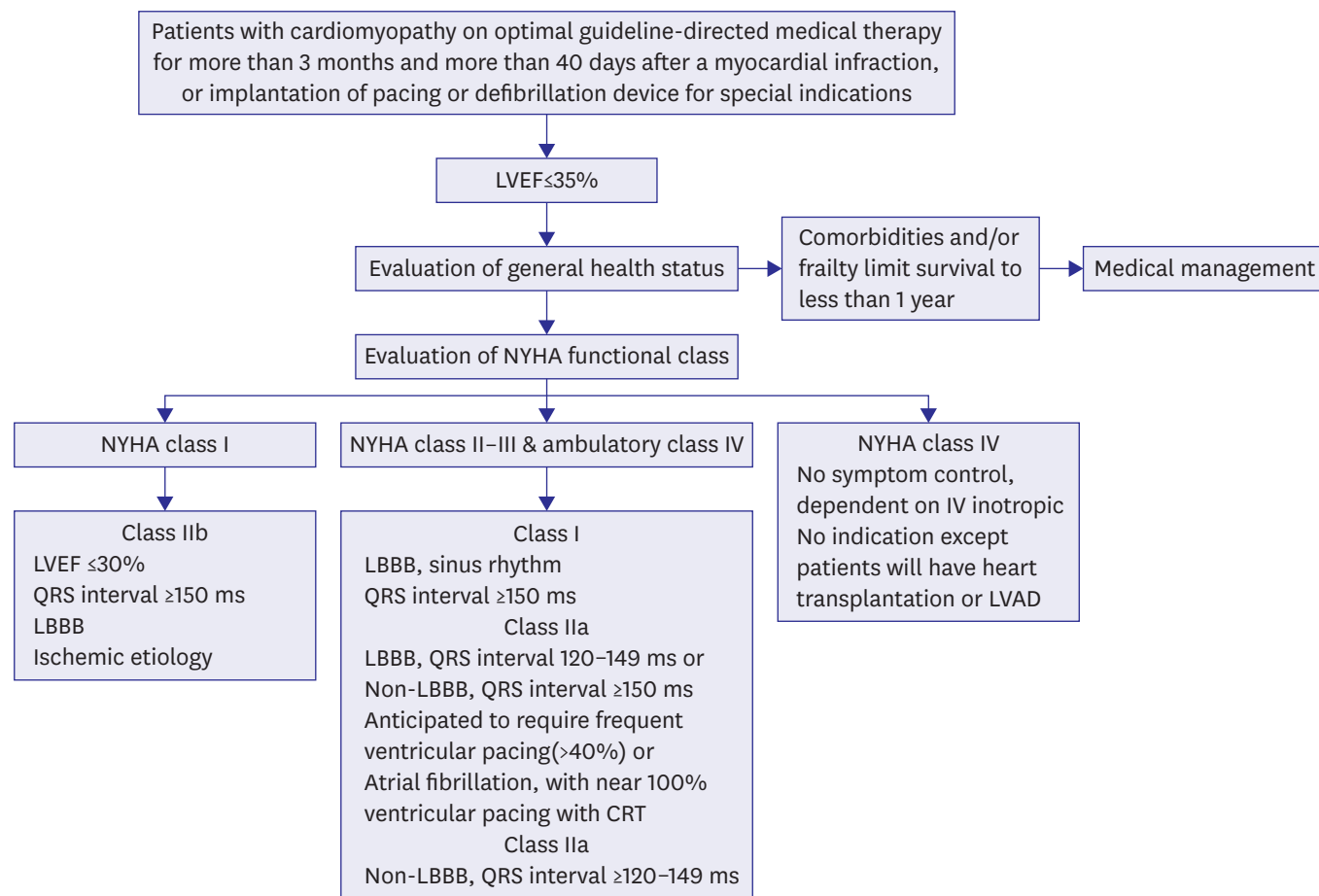


Figure 2. Indications for CRT.

CRT = cardiac resynchronization therapy; LBBB = left bundle branch block; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

otherwise met, provided that atrioventricular nodal ablation or pharmacologic heart rate control is expected to allow near 100% ventricular pacing with CRT.⁵⁴¹⁾⁵⁴²⁾ However, because these indications are not included in the current reimbursement criteria of the Korean National Health Insurance Service, this patient selection algorithm should be applied with caution in clinical practice.

CRT should be considered in patients with significant HF symptoms despite receiving optimal guideline-directed medical therapy for more than 3 months. Regular monitoring and medical management are required after device implantation. Moreover, a specialized electrophysiologist and a specialist in cardiac imaging should be included in the treatment team for adjusting the CRT mode in patients without response to CRT.

MCS of the LV

1. Nondurable, that is, transient, MCS is beneficial in carefully selected patients with decompensated, hemodynamically unstable, stage D systolic HF for whom cardiac transplantation is planned (class of recommendation IIa, level of evidence B).
2. Durable MCS is reasonable to prolong survival in carefully selected patients with stage D systolic HF, who are refractory to medical therapy, require continuous intravenous inotropes, and for whom cardiac transplantation is not indicated (class of recommendation IIa, level of evidence B).

Heart transplantation is the gold standard for the management of patients with refractory, end-stage systolic HF. MCS has been developed to overcome the shortage of cardiac donors and increase, over the past 50 years, in the population of patients with end-stage HF. After the first successful implantation of a LV assist device (LVAD), which was performed in 1966 by Dr. DeBakey and involved a 37-year-old woman as the recipient, and with the approval of the Heartmate IP by the United States Food and Drug Administration, a wide array of studies describing clinical experience with MCS. A ventricular assist device (VAD) provides MCS to increase cardiac output and induce reverse remodeling with partial or complete replacement of cardiac function by passing blood from either the LV to the aorta or from the right ventricle to the pulmonary artery. VADs can be categorized by the flow characteristic (pulsatile vs. continuous), pump mechanism (volume displacement, axial vs. centrifugal), implant location (intracorporeal vs. extracorporeal), approach method (percutaneous vs. surgical), and supported ventricle (left, right, biventricular). VADs can also be defined based on their intended period of use, as short-term (hours to days) non-implantable VADs and long-term (months to years) implantable VADs.

The most common clinical situations requiring MCS include: 1) bridge therapy in patients planning heart transplantation, 2) destination therapy in patients without indications for cardiac transplantation, and 3) bridge to recovery in patients for whom it is difficult to determine the indication.

Bridge to transplant has been the most common indication of VADs. In a recently reported multicenter prospective study with the second-generation VAD HeartMate II, 79% of the participants survived to heart transplantation, until recovery of cardiac function, or for at least 180 days of continuous MCS.⁵⁴³⁾ Because similar benefits of VADs have been reported in several studies with long-term follow-up periods (≥ 18 months), VADs are commonly used in western countries with organ shortage and longer waiting periods for heart transplantation.⁵⁴⁴⁻⁵⁴⁶⁾

MCS, and especially permanent MCS, was initially invented to improve long-term survival of patients with end-stage HF who were not candidates for heart transplantation. Studies of MCS as a definite therapy had been started earlier. One randomized controlled trial published in 2001 evaluated the survival benefit of the long-term use of MCS as a definitive therapy over the benefits provided by optimal established medical management approaches.⁵⁴⁷⁾ In the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, LVAD implantation resulted in improved 2-year survival and quality of life. However, complications occurred more frequently in the LVAD group and included infection, bleeding, neurologic abnormalities, and complications associated with the implanted device. Nevertheless, LVADs beyond the second generation showed reduced device-related complication rates and significant survival benefit in patients ineligible for heart transplantation, which has resulted in an increasing use of LVADs as long-term definitive therapy.⁵⁴⁸⁾⁵⁴⁹⁾

Surgical management

Because medical treatment has traditionally been the cornerstone of HF management, surgical management was originally applied only in selected patients. Currently, heart transplantation is the gold standard in selected patients with end-stage HF refractory to medical therapy. However, donor shortage has inevitably led to the need for developing some type of surgical management approaches to handle the increasing number of patients waiting for a donor and patients ineligible for transplantation.

In the STICH trial including patients with LVEF \leq 35% and coronary artery disease amenable to CABG surgery, there was no significant difference in all-cause mortality between medical therapy alone and medical therapy in combination with CABG. However, the CABG group had significantly lower rates of cardiovascular death or hospitalization for cardiovascular causes.⁴²²⁾ Retrospective studies have indicated that, in patients with ischemic cardiomyopathy and viable myocardium, coronary revascularization provides a survival benefit and is associated with myocardial recovery.⁴¹⁹⁾⁵⁵⁰⁾

The clinical benefit of CABG over that of percutaneous coronary intervention has not been demonstrated in patients with HF and ischemic heart disease. However, compared to CABG, percutaneous coronary intervention had inferior outcomes, as many retrospective studies suggested a reduced rate of complete revascularization.⁵⁵¹⁻⁵⁵³⁾ There are controversies regarding the benefits of surgical ventricular reconstruction. Specifically, the prospective STICH trial⁵⁵⁴⁾ as well as retrospective studies⁵⁵⁵⁻⁵⁵⁷⁾ demonstrated that addition of surgical ventricular reconstruction to CABG was not associated with improvement in symptoms or better clinical outcomes compared to those provided by CABG alone. However, earlier studies showed that surgical ventricular reconstruction surgery can increase LVEF and improve clinical symptoms in patients with HF and dysfunctional scarred myocardium and/or infarcted territories.⁵⁵⁸⁻⁵⁶⁰⁾ Surgical ventricular reconstruction is not indicated in non-ischemic cardiomyopathy because of higher mortality and reduced benefit expected. Based on the results of current studies, surgical ventricular reconstruction may be considered in selected patients with severe ischemic cardiomyopathy and reduced extent of viable myocardium.

Valvular heart diseases can cause and worsen HF. When appropriately indicated, surgical management of valvular heart diseases can improve clinical symptoms of HF. Mitral valve repair may have symptomatic benefit in patients with functional mitral regurgitation. However, to date, no survival benefit has been reported in such patients.

Because of the current lack of evidence regarding surgical management of HF, further studies will be needed to develop up-to-date treatment strategies. Technical advances in LVADs and application of appropriate surgical management strategies will be necessary in patients with end-stage HF who are not candidates for heart transplantation.

Heart transplantation

Heart transplantation is the therapy of choice for the treatment of end-stage HF refractory to medical therapy. After the first successful heart transplantation, which was performed in 1967 by Dr. Barnard,⁵⁶¹⁾ advances in immunosuppressive therapy have markedly improved long-term survival of the recipients, especially since the United States Food and Drug Administration approved cyclosporine in 1983. The currently reported 1-, 3-, and 5-year post-transplant survival rates in adults are 87.8%, 78.5%, and 71.7%, respectively.⁵⁶²⁾ The 1- and 5-year post-transplant survival rates reported by a Korean single-center study were 94% and 84%, respectively.⁵⁶³⁾

However, organ donor shortage remains a major problem, along with the marked increase in the prevalence of end-stage HF. Indeed, about 20% of patients waiting to receive heart transplantation die before undergoing the procedure.⁵⁶⁴⁾ MCS can be used as a bridge therapy in such patients or as a definite therapy to assist ventricular function in patients deemed not eligible for heart transplantation.

In the HVAD study, the 2-year survival rate was 80% in patients with LVADs,⁵⁴⁷⁾⁵⁶⁵⁾ which is similar to the survival rate reported for recipients of heart transplant.⁵⁶¹⁾ However, LVADs were associated with a 5-year survival rate of about 40%, which is significantly lower than that of transplant recipients. Moreover, because MCS can be associated with increased risk of complications including hemorrhage, infection, and thrombus formation,⁵⁶⁶⁾ heart transplantation should be considered as a first-line definitive therapy in patients with refractory end-stage HF.

Heart transplantation prolongs long-term survival and promotes improvement of exercise capacity and quality of life.⁵⁶⁷⁻⁵⁶⁹⁾ Additionally, there is significant improvement in maximal oxygen consumption, and ventilation capacity recovers to the normal values within 6 months after transplantation.⁵⁷⁰⁾ Moreover, active cardiac rehabilitation can significantly improve exercise capacity.⁵⁷¹⁾

The recommended indications of heart transplantation include: 1) cardiogenic shock requiring either continuous inotropic support or mechanical support, 2) coronary artery disease with severe or intractable angina symptoms not amenable to percutaneous or surgical revascularization, and 3) intractable life-threatening ventricular arrhythmias unresponsive to catheter ablation and/or ICD therapy.⁵⁷²⁾

Heart transplantation can only increase survival in high-risk patients with end-stage HF. Deng et al.⁵⁷³⁾ reported that heart transplantation was associated with a survival benefit only in the high-risk patients awaiting transplantation, and no reduction in mortality was noted in low- or medium-risk patients.

Cardiopulmonary exercise testing is helpful for refining the selection for transplantation candidates. Generally, the maximal rate of oxygen consumption, expressed as peak VO_2 max, is associated with maximal cardiac output and reflects the maximal oxygen carrying

capacity and maximal consumption in peripheral tissues. Patients with HF presenting with peak VO_2 max of ≥ 14 mL/min/kg have similar prognosis to that of heart transplanted patients. However, the 1-year survival rate in patients with peak VO_2 max of ≤ 14 mL/min/kg was about 70%, which is significantly lower than that of heart transplantation.⁵⁷⁴⁾ Thus, the prognosis should be calculated based on the severity of the end-stage HF and on the peak VO_2 max, which should be considered in the selection of candidates for heart transplantation from among patients with end-stage HF.

Cell therapy

Cell therapy has not yet been fully evaluated for the treatment of HF. Cell therapy has typically been applied in patients with mild to moderate LV systolic dysfunction of ischemic etiology. However, there is little evidence regarding the benefit related to short- and long-term prognosis or to the ventricular remodeling effect of cell therapy because most investigations focused on cell therapy are small-sized clinical studies.⁵⁷⁵⁻⁵⁷⁷⁾ Specifically, clinical studies have investigated the use of autologous and homologous bone marrow mononuclear cells, bone marrow progenitor cells, mesenchymal stem cells, and cardiac stem cells to treat patients with HF. Of these, autologous bone marrow mononuclear cells are the most actively investigated for cell therapy. A meta-analysis showed that autologous bone marrow mononuclear cell therapy significantly improved LV systolic function and reduced the LV volume in patients with ischemic cardiomyopathy.⁵⁷⁸⁾ Furthermore, there is some low-quality evidence regarding the reduction in 12-month mortality and hospital admission due to HF. Although each clinical study and meta-analysis demonstrate that cell therapy has beneficial effects on cardiac function, ventricular remodeling, and clinical parameters, there is insufficient evidence regarding the recommendation of cell therapy to patients with HF. Despite the debate about the effect of cell therapy on HF, there is a consensus that cell therapies are relatively safe, based on data from short- and long-term observational studies.

At present, caution should be exercised when considering cell therapy in patients with HF, and such treatment should be performed as an investigational trial, in a research center with plenty of biologic knowledge and clinical experience. Based on the outcomes of previous studies, cell therapy can be more effective in patients with above-moderate LV systolic dysfunction than in those with mild LV systolic dysfunction.⁵⁷⁹⁾ However, most studies excluded patients with unstable HF symptoms and severely decreased LV systolic function, and these exclusion criteria should be taken into account when considering the use of cell therapy in patients with HF.

The most favorable results of cell therapy are associated with the use of stem cells, precursor cells with high colony-forming capacity, and bone marrow mononuclear cell fraction with high concentration of stem cells.⁵⁸⁰⁾⁵⁸¹⁾ Because the fraction of stem cell and cellular function are highly influenced by the individual characteristics, the function of stem cells is decreased in high-risk patients (i.e., patients with advanced age, chronic kidney disease, or diabetes), and the proportion of stem cells is lower than that noted in lower-risk patients.⁵⁸²⁾ Although there is no phase III trial of cell therapy in patients with HF, there is such a trial in patients with acute myocardial infarction. Specifically, The Effect of Intracoronary Reinfusion of Bone Marrow-derived Mononuclear Cells on All Cause Mortality in Acute Myocardial Infarction (BAMI) trial is a multinational, multi-center, randomized open-label, controlled, parallel-group phase III study aiming to provide more definitive data on the safety and efficacy of stem cell therapy.

FUTURE DIRECTIONS

The present guidelines are the first practical guidelines for the management of HF in Korea. There have been many guidelines for HF up to this time, however each set of guidelines provides slightly different recommendations for various issues. Furthermore, previous guidelines do not fully take Korean society into account. Thus, there was a need for the development of HF guidelines for Koreans. These guidelines include as much data as possible from Korean-specific studies. The next revision is expected to include more Korean data from Korean HF registry data. In addition, these guidelines will be revised with future perspectives as follows.

In the present guidelines, HF was classified into HF_rEF and HF_pEF based on LVEF. However, the characteristics of HF with improved or borderline EF were not fully defined. These veiled HF fields can be clarified with further research data. In addition, current diagnostic flow is based on patient's symptoms or signs, BNP, and echocardiographic tests. However, it is necessary to consider whether other biomarkers or imaging modalities could be helpful for the diagnosis of HF. New diagnostic algorithms using multi-modality tests may be updated in line with the development of various imaging tools. In terms of pharmacological treatment, the recommendations about new agents such as NOACs or ARNI should be revised. During the development of these guidelines, the data about these new agents were insufficient. However, clinical evidence is accumulating that shows that the drugs have some benefit for HF patients. Thus, our attention is directed towards future clinical studies. Among non-pharmacological treatments, as of recent, cardiac rehabilitation is now reimbursed by the Korean National Health Insurance Service. The evidence supporting cardiac rehabilitation in HF are concrete. However, further studies should assess which type(s) of multidisciplinary rehabilitation programs are beneficial under current Korean circumstances. Regarding the surgical treatments of HF, the use of MCS is expected to increase in Korea. Korean data about the indication and management of MCS are needed.

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