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Review Article

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Focused Update of 2016 Korean Society of Heart Failure Guidelines for the Management of Chronic Heart Failure

Kyung-Jin Kim, MD, PhD[1], Hyun-Jai Cho, MD, PhD[2], Min-Seok Kim, MD, PhD[3], Jeehoon Kang, MD[2], Kyung-Hee Kim, MD, PhD[4], Darea Kim, MD, PhD[5], Suk Min Seo, MD, PhD[6], Jeong Hoon Yang, MD, PhD[5], Myung-Jin Cha, MD[2], Jong Il Choi, MD, PhD[7], and Dong-Ju Choi, MD, PhD[8]

[1]Division of Cardiology, Department of Internal Medicine, Ewha Womans University Medical Center, Ewha Womans University School of Medicine, Seoul, Korea
[2]Division of Cardiology, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea
[3]Division of Cardiology, Department of Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[4]Department of Cardiology, Sejong General Hospital, Incheon, Korea
[5]Division of Cardiology, Department of Internal Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[6]Department of Internal Medicine, Cardiovascular Center and Cardiology Division, Eunpyeong St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea
[7]Department of Cardiology, Cardiovascular Center, Korea University Anam Hospital, Seoul, Korea
[8]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

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Correspondence to
Hyun-Jai Cho, MD, PhD
Division of Cardiology, Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
E-mail: hyunjaicho@snu.ac.kr

ORCID iDs
Hyun-Jai Cho
https://orcid.org/0000-0002-2779-4037

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ABSTRACT

The incidence of heart failure (HF) is increasing in South Korea and devising the optimal care plan is crucial to promote appropriate and effective treatment of HF. To this end, the first Korean guideline for management of chronic HF was published in 2016 by the HF research group under the Korean Society of Cardiology (KSC). After this publication, considerable data have been accumulated and a new guideline for the management of HF was published in Europe, and an update regarding pharmacological therapy was published in the United States, which made it warrant to update the Korean guideline. Under this premise, The Clinical Practice Guidelines Committee under the Korean Society of Heart Failure (KSHF) founded in 2018 decided to publish a focused update management guideline for chronic HF and selected 15 topics that need an update regarding the diagnosis, definition, diagnostic algorithm, monitoring, novel biomarkers, drug therapy related to non-vitamin K antagonist oral anticoagulants and angiotensin receptor neprilysin inhibitors, and with respect to comorbidities changes in the guidelines of relevant institutions, such as new guidelines for the management of hypertension, a procedure used to treat severe aortic stenosis, information on sodium glucose co-transporter-2 inhibitor, and that about sleep apnea. Among nonpharmacological therapies, changes to the recommendations for implantable cardioverter defibrillator, cardiac resynchronization therapy, and cardiac rehabilitation were updated. Subsequent and continuous updates based on additional clinical research findings, with continual supervision by the KSHF will be needed.

Keywords: Heart failure; Guideline; Diagnosis; Treatment; Comorbidity

INTRODUCTION

To promote appropriate and effective treatment of heart failure (HF), the incidence of which is increasing in South Korea, devising the optimal care plan is the most crucial step to take. To this end, the HF research group under the Korean Society of Cardiology (KSC) published a guideline for the management of chronic heart failure (CHF) in 2016 and a guideline for the management of acute heart failure (AHF) in 2017[1-3] to direct clinical practice. Although the guideline has been developed over 4 years of preparation, there have been shortcomings regardless of the effort invested, possibly because it was the first guideline to be published in Korea. Both guidelines reflected Korean patient data as much as possible and referred to other European or US guidelines and relevant information. In 2016, a new guideline for the management of HF was published in Europe,[4] and an update regarding pharmacological therapy was published in the United States.[5] Further, considerable data have been accumulated over 2 years, and the change was substantial enough to warrant an update of the Korean guideline for the management of CHF.

The Korean Society of Heart Failure (KSHF) was founded in March 2018, and the Clinical Practice Guidelines Committee was established under this premise. Nine members of the committee discussed and selected topics and their scopes that need an update and comparatively analyzed European and US guidelines and relevant Korean and foreign data. As a result, the committee decided to publish a focused update on 15 topics.

The recommendations for diagnosis, definition, diagnostic algorithm, monitoring, and novel biomarkers were updated. Regarding drug therapy, the content related to non-vitamin K antagonist oral anticoagulants (NOACs) and angiotensin receptor neprilysin inhibitors (ARNIs) was updated. With respect to comorbidities, changes in the guidelines of relevant institutions, such as new guidelines for the management of hypertension, and a procedure used to treat severe aortic stenosis, were described, and information about diabetes medication, namely sodium glucose co-transporter-2 (SGLT-2) inhibitor, and that about sleep apnea was revised. Among nonpharmacological therapies, changes to the recommendations for cardiac rehabilitation or implantable cardioverter defibrillator (ICD), and cardiac resynchronization therapy (CRT) treatments were updated. The data collected were analyzed and recommendations for care were devised by classifying the level of evidence into 3 levels (A, B, and C).

Although we publish a focused update this year, a substantial portion of this guideline needs continuous updates based on additional clinical research findings, with continual supervision by the KSHF. Moreover, we hope the scheduled 2019 update for the guideline for the management of AHF is commenced based on a thorough collection of data and discussion among committee members as well as a detailed discussion between the KSHF and relevant academic societies. Finally, we hereby disclose that members who have participated in this focused update have not been subject to external influence and have strived to eliminate any conflict of interest.

DEFINITION AND TERMINOLOGY

Left ventricular ejection fraction (LVEF) is an index of left ventricular contractility and is used to classify HF. In general, patients with reduced in LVEF (<40%) is defined as heart

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Table 1. Definition of HF

Type of HF	HFrEF	HFmrEF	HFpEF
Diagnostic criteria			
1	Symptoms and/or signs	Symptoms and/or signs	Symptoms and/or signs
2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
3		1. Elevation of BNP or NT-proBNP	1. Elevation of BNP or NT-proBNP
		2. One or more additional findings	2. One or more additional findings
		- Structural heart disease (left ventricular hypertrophy and/or left atrial enlargement)	- Structural heart disease (left ventricular hypertrophy and/or left atrial enlargement)
		- Diastolic dysfunction	- Diastolic dysfunction

"Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129-200, DOI: 10.1093/eurheartj/ehw128." reproduced by permission of the European Society of Cardiology.[4]
BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Table 2. Clinical parameters according to LVEF in the KorAHF registry

Clinical parameters	Total population (n=5,374)	HF categories			
		HFrEF (n=3,140)	HFmrEF (n=880)	HFpEF (n=1,354)	p-value
Total mortality (including urgent heart TPL)	297 (5.5)	224 (7.1)	32 (3.6)	41 (3.0)	<0.001
Mortality	234 (4.4)	161 (5.1)	32 (3.6)	41 (3.0)	0.004
Urgent heart TPL	69 (1.3)	67 (2.1)	0 (0.0)	2 (0.1)	<0.001
In-hospital stay	9 (6–15)	9 (7–16)	9 (6–14)	8 (6–14)	<0.001
ICU/CCU admission	2,621 (48.8)	1,585 (50.5)	462 (52.5)	574 (42.4)	<0.001

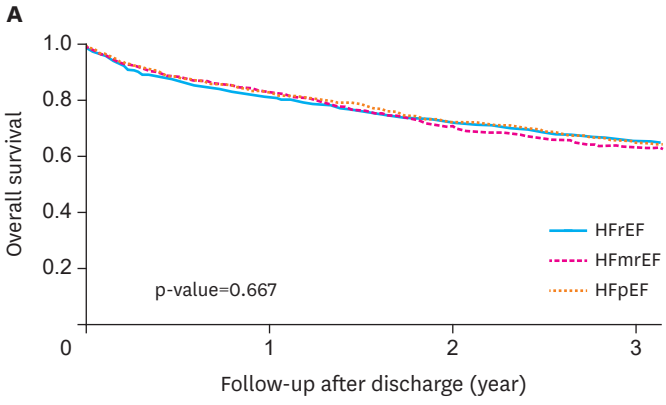
Values are presented as number (%) or median (interquartile range).
CCU, coronary care unit; ICU, intensive care unit; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; KorAHF = Korean Acute Heart Failure; TPL, transplantation; TPL = transplantation.

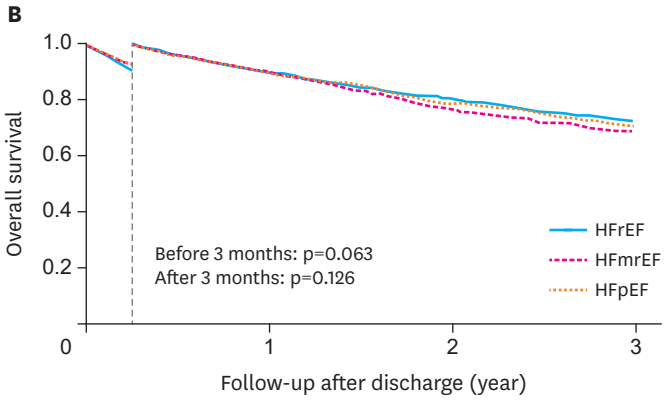
failure with reduced ejection fraction (HFrEF), and patients with LVEF of 50% or higher is defined as heart failure with preserved ejection fraction (HFpEF). Furthermore, patients with a marginal LVEF (40–49%) is defined as heart failure with mid-range ejection fraction (HFmrEF) (**Table 1**). HFmrEF patients are believed to show mild impairment of left ventricular contraction and relaxation, and patients without clear left ventricular myocardial disease may have other heart diseases, such as pulmonary hypertension or valvular disease.[4] When admitted for AHF, the hospital mortality rate was significantly higher in the HFrEF group, but there were no significant differences in the survival rates among the 3 groups during a long-term follow-up.

In the Korean Acute Heart Failure registry, 59.1% had HFrEF, 25.1% had HFpEF, and 15.8% had HFmrEF. The prevalence of ischemic heart disease was higher among patients with HFmrEF than among those with HFpEF, but in-hospital mortality was similar between the 2 groups (**Table 2** and **Figure 1**).

DIAGNOSTIC ALGORITHM

Diagnostic algorithms of non-acute onset and acute onset HF are illustrated in **Figures 2** and **3**, respectively. In the non-acute setting, the upper limits of normal of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) are 125 pg/mL and 35 pg/mL, respectively.[4] In AHF, a higher upper limit of 300 pg/mL for NT-proBNP and 100 pg/mL for BNP is used.[4]





No. at risk				
HFrEF	2,969	2,411	2,151	1,939
HFmrEF	844	699	596	534
HFpEF	1,308	1,080	950	843

Figure 1. Survival curves of patients with HFrEF, HFpEF, and HFmrEF (analyzed with KorAHF data). (A) Kaplan-Meier survival curve with reference to time of discharge. (B) Landmark Kaplan-Meier survival curve with reference to 3 months after discharge.
HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; KorAHF = Korean Acute Heart Failure.

REMOTE MONITORING OF PATIENTS WITH HEART FAILURE: TELEMEDICINE

1. For patients with symptomatic HF who have been admitted for HF symptoms in the past, the use of a wireless pulmonary artery pressure monitoring device (CardioMems) can curtail non-essential admissions for repetitive HF (class IIb, level of evidence B).
2. ICD-based monitoring (IN-TIME approach) may be considered to improve the clinical outcomes of patients with symptomatic HFrEF (ejection fraction ≤35%) (class IIb, level of evidence B).

Periodic follow-up and monitoring during the course of treatment are helpful for patients with HF. Such periodic follow-up and monitoring can prevent aggravation of AHF by

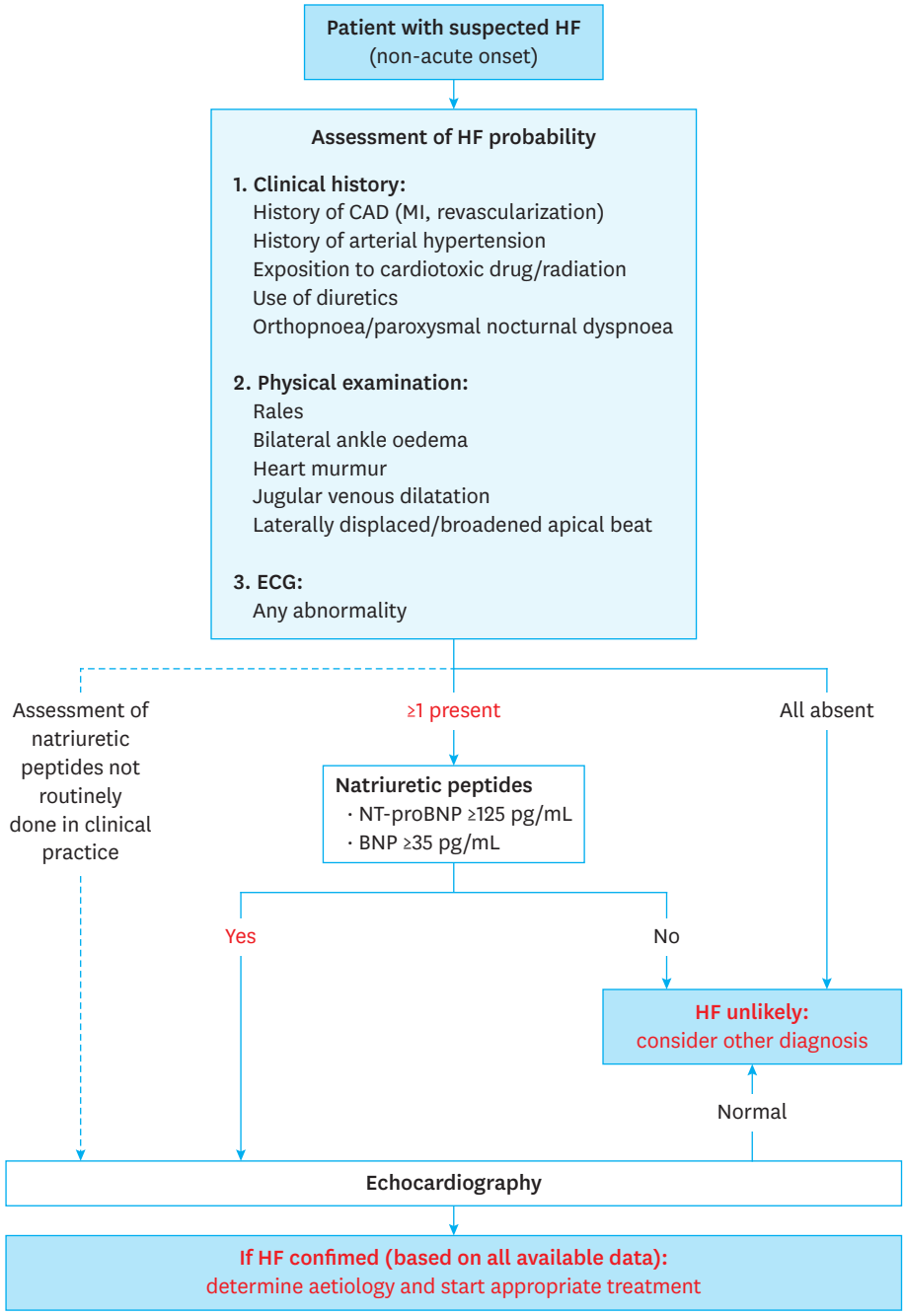


Figure 2. Diagnostic algorithm for a diagnosis of HF of non-acute onset.
"Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129-200, DOI: 10.1093/eurheartj/ehw128." reproduced by permission of the European Society of Cardiology.[4]
BNP = B-type natriuretic peptide; CAD = coronary artery disease; ECG = electrocardiogram; HF = heart failure; MI = myocardial infarction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

checking whether the patient is taking an appropriate dose of drugs, whether there are any adverse drug reactions, and whether the patient is showing symptoms of aggravation of HF and is in need of additional treatment. In particular, frequent monitoring would be clinically helpful in determining the appropriate time to adjust drug dosage and determining when there is an acute aggravation, as well as in cases of older patients with HF. The method of

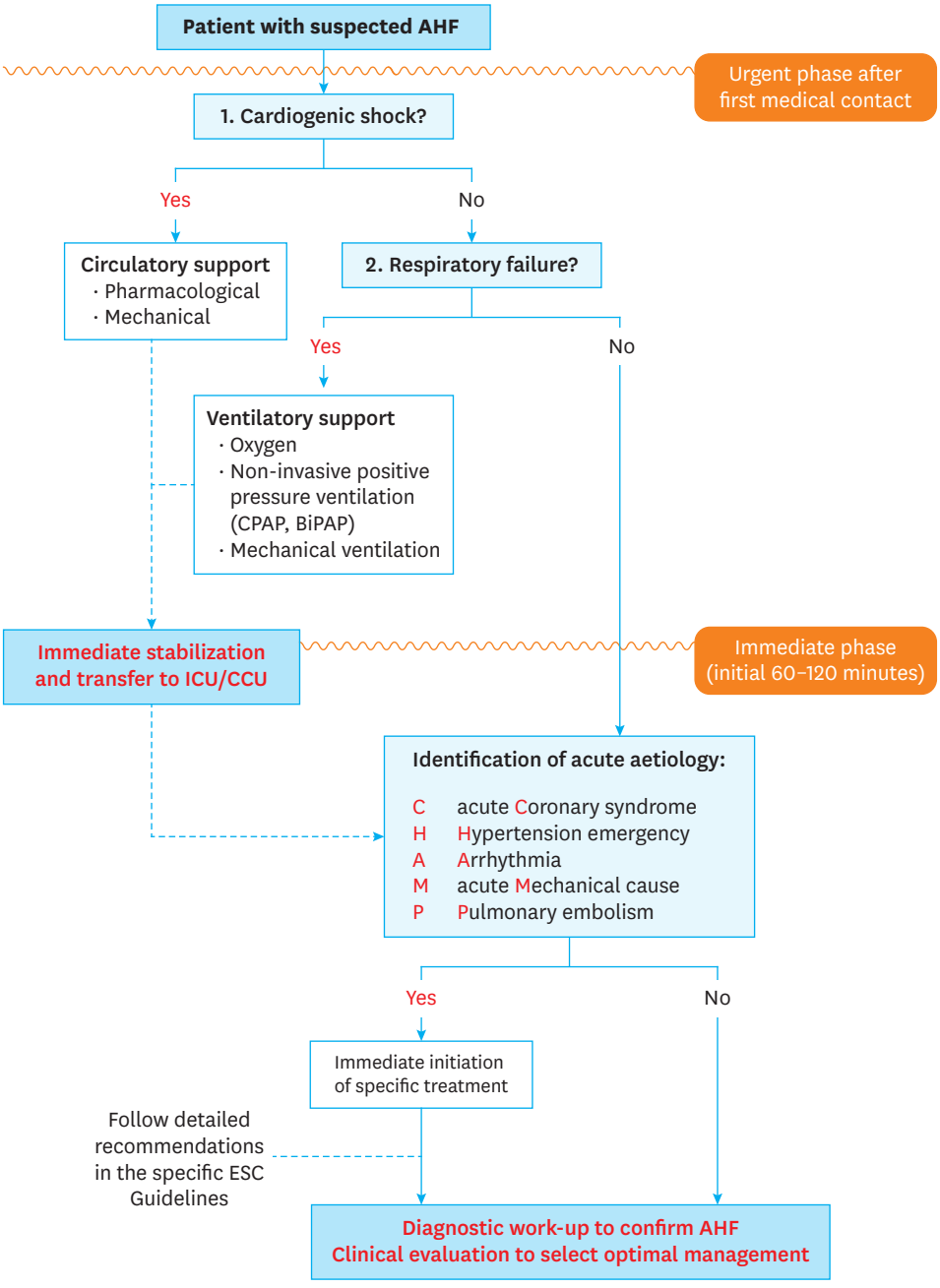


Figure 3. Diagnostic algorithm for a diagnosis and initial management of a patient with AHF.
"Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129-200, DOI: 10.1093/eurheartj/ehw128." reproduced by permission of the European Society of Cardiology.[4]
AHF = acute heart failure; BiPAP = bilevel positive airway pressure; CCU = coronary care unit; CPAP = continuous positive airway pressure; ICU = intensive care unit.
*Mechanical complications of acute myocardial infarction (acute mitral regurgitation, acute myocardial rupture, interventricular septal defect), chest trauma, acute valve failure caused by infectious endocarditis (native/prosthetic), aortic dissection.

periodic monitoring may differ depending on the surrounding environment and hospital, and recent clinical trials and systematic literature reviews on the effects of telemedicine or remote patient management reported diverse clinical outcomes.[6] Some systematic literature reviews reported that telemedicine was clinically effective, while most prospective clinical trials (Telemonitoring to Improve Heart Failure Outcomes [Tele-HF],[7] Telemedical Interventional Monitoring in Heart Failure [TIM-HF],[8] the Interdisciplinary Network for Heart Failure [INH],[9] Weight monitoring in patients with severe heart failure [WISH],[10] and the TElemonitoring in HeArt Failure [TEHAF][11] failed to prove significant clinical efficacy. Overall, there are several methods of employing telemedicine, with pros and cons for each method, so appropriate choice of method would increase the effectiveness of telemedicine.

A recent study on telemedicine (Implant-based multiparameter telemonitoring of patients with heart failure; IN-TIME) for patients with CRT/ICD[12] and a study on the use of CardioMems, a wireless pulmonary artery pressure monitoring device[13] reported that telemedicine was clinically useful for some patients with HF.

BIOMARKERS THAT AID DIAGNOSIS

1. BNP-based screening and collaborative care can be helpful for preventing HF in patients at risk of heart failure without left ventricular dysfunction (class IIa, level of evidence B).

According to the recent study (The St Vincent's Screening to Prevent Heart Failure; STOP-HF),[14] patients at risk of HF (hypertension, diabetes mellitus, vascular disease; Stage A HF) but without left ventricular dysfunction or symptoms of HF, it reduced the combined rates of left ventricular systolic dysfunction, diastolic dysfunction, and HF if the patients were seen by both a cardiovascular ultrasound specialist and a cardiologist when their BNP was 50 pg/mL or higher. In other words, BNP-based screening tests with interdisciplinary management are useful for preventing left ventricular dysfunction or HF.

ANGIOTENSIN RECEPTOR NEPRILYSIN INHIBITOR

1. In patients with HFrEF showing New York Heart Association (NYHA) class II or III symptoms and who tolerate angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), replacement of renin-angiotensin system-inhibitor by an ARNI is recommended to further lower mortality (class I, level of evidence B-R).

ARNI is a combination drug consisting of an ARB and inhibitor of an enzyme called neprilysin. Sacubitril (neprilysin inhibitor) elevates the concentration of natriuretic peptides by inhibiting neprilysin. ARNI lowered cardiovascular death or HF admission rate by 20% in patients with symptomatic HFrEF who tolerate ACE inhibitors or ARBs.[15] Based on this, replacement by an ARNI is recommended to further lower mortality in patients with HFrEF showing NYHA class II or III symptoms and who tolerate ACE inhibitors and ARBs.

ANTICOAGULANTS

1. If starting a new oral anticoagulant therapy, the use of NOAC (dabigatran, rivaroxaban, apixaban, or edoxaban) is recommended in preference to vitamin K antagonists (warfarin) in the absence of a contraindication for NOAC. (class I, level of evidence A).
2. In patients with HF and atrial fibrillation (AF) who do not have additional risk factors for thrombosis, it is recommended to choose the anticoagulation therapy after comprehensively evaluation considering of patient's characteristics and preference (class IIa, level of evidence B).

In the light of various data on the use of NOACs in recent years, their use has risen steeply. With large-scale studies on the effects and safety of NOACs in Korea as well, NOACs have become the standard treatment for preventing stroke in patients with AF.[16][17] Under the premise that there is no contraindication, NOACs are recommended in preference to warfarin for the prevention of stroke in patients with AF.[18][19] The currently available NOACs include dabigatran, a direct thrombin inhibitor, and coagulant factor Xa inhibitors apixaban, edoxaban, and rivaroxaban, and each drug must be selected depending on drug interactions based on different pharmacodynamic and pharmacological features as well as the patient's clinical features and preference.[20] Although it is yet difficult to identify a NOAC with a better drug profile in terms of stroke prevention and hemorrhagic complications, it is appropriate to replace warfarin with NOACs.

Anticoagulant therapy may be recommended for patients with HF and AF even in the absence of additional thrombotic risk depending on the patient's clinical condition.[19] Anticoagulation in patients with HF and sinus rhythm is not recommended.

CARDIAC REHABILITATION AND EXERCISE THERAPY

1. Exercise therapy (or regular physical activity) is recommended in patients with HFrEF in a stable state with NYHA functional class II–III (class I, level of evidence B).
2. Exercise therapy (or regular physical therapy) is reasonable in patients with HFpEF or HFmrEF in a stable state with NYHA functional class II–III (class IIa, level of evidence B).

Most data about exercise therapy for patients with HF show a strong recommendation of exercise for patients with HFrEF, but evidence for its use in patients with HFpEF is insufficient. Data about exercise therapy are also lacking for patients with an NYHA class IV.[21][22]

Exercise prescription

Exercise prescription must be coupled with an appropriate drug therapy. Exercise is prescribed by the dose, duration (how long), frequency (number of sessions per week), place (gym or home), type of exercise, importance, and progressiveness. Dose can be subdivided according to heart rate and speed on a treadmill. If AF or exercise-related ventricular extrasystole is anticipated, the patient should be monitored during exercise.

In general, 30–40 minutes of aerobic exercise is prescribed 3 times a week with an intensity at 60–70% of the heart rate reserve (maximum heart rate–resting heart rate). A 6–8-week

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program should be started with a well-trained exercise instructor, and exercise should be performed safely, with the intensity gradually increased while checking for physical functional state and signs of angina and/or dyspnea. After completing an exercise program with a well-trained exercise instructor, the patient may begin home training in addition to the exercise instructor program and gradually transition out from the instructor. Pulse rate during exercise may drop below the anticipated level in patients using a beta-blocker, but there is no report suggesting that increasing the intensity of exercise to 60–70% of the heart rate reserve has any adverse effects. Patients must be instructed to take their medication even when participating in a cardiac exercise program. Patients with HFrEF and patients with HFpEF are given similar exercise prescriptions.

Type of exercise

The exercise rehabilitation program is focused on aerobic exercise until the patient is more experienced.[21-24] Some programs include muscle-strengthening and respiratory muscle-strengthening exercises, but evidence for their efficacy is weak. In particular, muscle-strengthening exercise improves the capacity for daily living in patients with reduced upper limb muscle mass because most activities of daily living require the use of arm muscles. Respiratory muscle training ultimately increases intercostal muscle mass, and thus is effective for patients who have had endotracheal intubation or patients with chronic lung disease.

Aerobic exercise: Aerobic exercise refers to any type of "movement" exercise, such as walking, cycling, dancing, badminton, swimming, and stretching. Most patients cannot participate in a regular exercise program due to travel problems or other time constraints, such as those due to work. Therefore, patients are recommended to perform aerobic exercise, particularly walking, for 30–40 minutes a day and instructed to rest well. Patients are recommended to walk outside when the weather is nice or walk up the stairs or walk between rooms at home. Families should be involved to encourage patients to continue exercising. Recommendations are to wear light and comfortable shoes and clothing and to avoid outdoor activities when the weather is not good. Exercise should be performed in the day or afternoon when the patient is in a good mood, and should be avoided immediately after a meal. The patient may feel tired when first starting the program, but explanation should be provided to the patient that tiredness will get better over time if the patient is exercising in a stable state.

Muscle training: There is insufficient evidence on the effects of muscle training on patients with HF, but it may be included in exercise programs in this setting. Muscle training must be individualized, and monitoring of the patient's symptoms and blood pressure (BP) is crucial. Patients should be taught to breathe during muscle training in order to avoid the Valsalva maneuver, which can increase vascular resistance.

ATRIAL FIBRILLATION

1. Beta-blockers may be considered primarily for the purpose of rate control in the acute phase in patients with HF and AF (class I, level of evidence A).
2. Beta-blockers, digoxin, and calcium channel blockers (diltiazem, verapamil) may be considered for the purpose of long-term rate control in patients with HF and AF (class I, level of evidence B).

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3. The target heart rate should be below 110 beats/min in patients with HF and AF (class I, level of evidence B).
4. If a HF patient with AF is in need of a pacemaker or satisfies the criteria for CRT, then CRT following atrioventricular node ablation is reasonable (class IIa, level of evidence B).
5. Rhythm control may be additionally considered to control heart rate in patients with HF and AF (class IIb, level of evidence A).
6. Catheter ablation may be considered when considering rhythm control in patients with HF and AF (class IIb, level of evidence B).

Rate control may be helpful for patients with HF when they have AF.[25][26] The optimal heart rate is unknown, so the target rate and drug should be chosen depending on the patient's clinical status, symptoms, LVEF, and hemodynamic state. Based on research to date, the target rate can be set to a resting heart rate of below 110 beats/min. In patients with HF with an EF of below 40%, beta-blockers may be primarily used for the purpose of rate control, and digoxin may be added. For patients who are hemodynamically unstable or have severely impaired left ventricular function, amiodarone may be a better choice of drug. If drug therapy fails to control the heart rate and symptoms, an artificial pacemaker may be inserted after ablation of the atrioventricular node, but biventricular pacing (CRT) should be considered for patients with poor cardiac function.[27]

Amiodarone may be chosen as the antiarrhythmic agent for rhythm control in patients with HF and AF, but safety must be prioritized over therapeutic effect.[28] There is no completely reliable evidence on whether rhythm control strategy improves prognosis better than achieving rate control alone. However, most clinicians believe that rhythm control would be helpful. Recently, a study found that catheter ablation reduces mortality and improves prognosis to a significantly greater degree than does drug therapy alone in patients with HF.[29] The 2017 Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF)[30] study showed that catheter ablation may be more useful than drug therapy for patients with HF and paroxysmal AF who have an LVEF below 35%. Therefore, catheter ablation may be considered for rhythm control in patients with HF and AF if drug therapy fails or causes adverse reactions.

HYPERTENSION

1. Most calcium channel blockers (amlodipine and felodipine are recommended) must be used with caution, as they can aggravate HF (class III, level of evidence B).
2. The target BP for patients with HF should be set to a systolic BP of 130 mmHg and a diastolic BP of 80 mmHg (class I, level of evidence C).

In general, calcium channel blockers are not recommended for patients with HF.[4] However, amlodipine can be considered in patients with HF coupled with hypertension or coronary artery disease as it did not further increase morbidity and mortality rates and did not cause severe adverse reactions in these patients in a large-scale randomized controlled trial.[31] The target BP for patients with HF and hypertension varies across patients, but several guidelines[5][32-34]

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recommend lowering systolic BP to <130 mmHg and for patients with HF and hypertension with preserved contractile function as well as for patients with HF with cardiomegaly.

DIABETES MELLITUS

SGLT-2 inhibitors lower the mortality rate, the incidence of HF, and the admission rate in high-risk diabetic patients.[35] The results were similar in diabetic patients with HF.[36] However, these results must be interpreted with caution, as they were drawn from a subgroup analysis on patients with HF as a comorbidity in one study, as opposed to a study exclusively on patients with HF. Currently, multiple phase 3 clinical trials on the primary endpoint in patients with HF are underway, and their results will be published in 2020 or later.

SLEEP APNEA

Adaptive servo-ventilation is contra-indicated in patients with HFrEF who have central sleep apnea (class III, level of evidence B).

The Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure (SERVE-HF) study recently reported the effects of adaptive servo-ventilation (ASV). Adaptive servo-ventilation did not lower the primary endpoint (composite of all-cause mortality, cardiovascular intervention, or admission due to aggravated HF) and actually increased all-cause or cardiovascular mortality in patients with HFrEF who have central sleep apnea.[37] Therefore, ASV should be avoided in patients with HFrEF if they have central sleep apnea. However, some previous studies have reported that night time continuous positive airway pressure improved cardiac functions, sympathetic nervous activation, and quality of life in patients with HF who also have obstructive sleep apnea.[38-40]

IMPLANTABLE CARDIOVERTER DEFIBRILLATOR

1. ICD therapy is recommended for patients with symptomatic HF (NYHA class II–III), LVEF ≤35% despite ≥3 months of guideline-directed medical therapy, and if meaningful survival of greater than 1 year is expected, in non-ischemic etiology patients or ischemic etiology patients with at least 40 days after myocardial infarction and at least 90 days post-revascularization (class I, level of evidence B).
2. ICD therapy is recommended for primary prevention purposes to lower mortality in patients with ischemic HF 40 days after the onset of myocardial infarction who have a LVEF of <30%, NYHA functional class I symptoms despite appropriate drug therapy, and are anticipated to survive for more than 1 year (class I, level of evidence A).
3. The efficacy of ICD is unclear in patients with a risk of non-sudden death from other causes due to frequent admission, malignant tumor, and severe comorbidities such as renal dysfunction (class IIb, level of evidence B).

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4. ICD therapy may be helpful in patients with nonischemic cardiomyopathy caused by mutation in the Lamin A/C gene with 2 or more risk factors (non-sustained ventricular tachycardia, LVEF <45%, non-missense mutation, male sex) who are anticipated to survive for more than 1 year (class IIa, level of evidence B-NR).

Based on previous clinical trial results and their meta-analyses, implantation of an ICD is considered to be effective in lowering acute cardiac death and all-cause death in patients with non-ischemic cardiomyopathy.[41-47]

CARDIAC RESYNCHRONIZATION THERAPY

1. CRT is reasonable in patients with a LVEF of below 35%, sinus rhythm, left bundle branch block, QRS interval of 130–149 ms, and NYHA function class II–III and ambulatory IV despite appropriate drug therapy (class IIa, level of evidence B).
2. CRT is not recommended in symptomatic patients with NYHA functional class I–II when they have sinus rhythm, no left bundle branch block, and QRS duration of 150 ms or shorter (class III, level of evidence B).
3. CRT is not recommended in patients who are anticipated to survive no longer than 1 year (class III, level of evidence C).

Based on recent randomized studies in which CRT did not reduce mortality in patients with systolic HF and QRS duration less than 130 ms,[48][49] CRT is considered to be reasonable in patients with LVEF <35%, sinus rhythm, left bundle branch block, QRS interval of 130–149 ms, and NYHA function class II–III and ambulatory IV despite appropriate drug therapy. The results of recent clinical trials on the usefulness of CRT in patients with AF were clearly reflected in the guideline.[50-55] Moreover, it is clearly stated that CRT is not recommended in patients with NYHA functional class I–II when they are in sinus rhythm, there is no left bundle branch block, and QRS duration is 150 ms or shorter.[56-58] In addition, it was specified that CRT is also not recommended in patients who are anticipated to survive no longer than 1 year.[59] The recommended indications for CRT is summarized in **Figure 4**.

SURGICAL TREATMENT

1. Dobutamine stress echocardiogram should be considered in patients having symptomatic reduced LVEF with suspected aortic valve stenosis to screen patients for valve replacement and differentiate from “low flow-low gradient aortic stenosis” (class IIa, level of evidence C).
2. Transcatheter aortic valve implantation (TAVI) can be performed in patients with severe aortic stenosis who are, based on comprehensive cardiac care, anticipated to survive for more than one year, are inappropriate candidates for surgery, and can undergo TAVI (class I, level of evidence B).
3. Aortic valve replacement or aortic valvuloplasty is recommended in patients with severe symptomatic aortic regurgitation and in asymptomatic patients with a LVEF of below 50% with severe aortic regurgitation (class I, level of evidence C).

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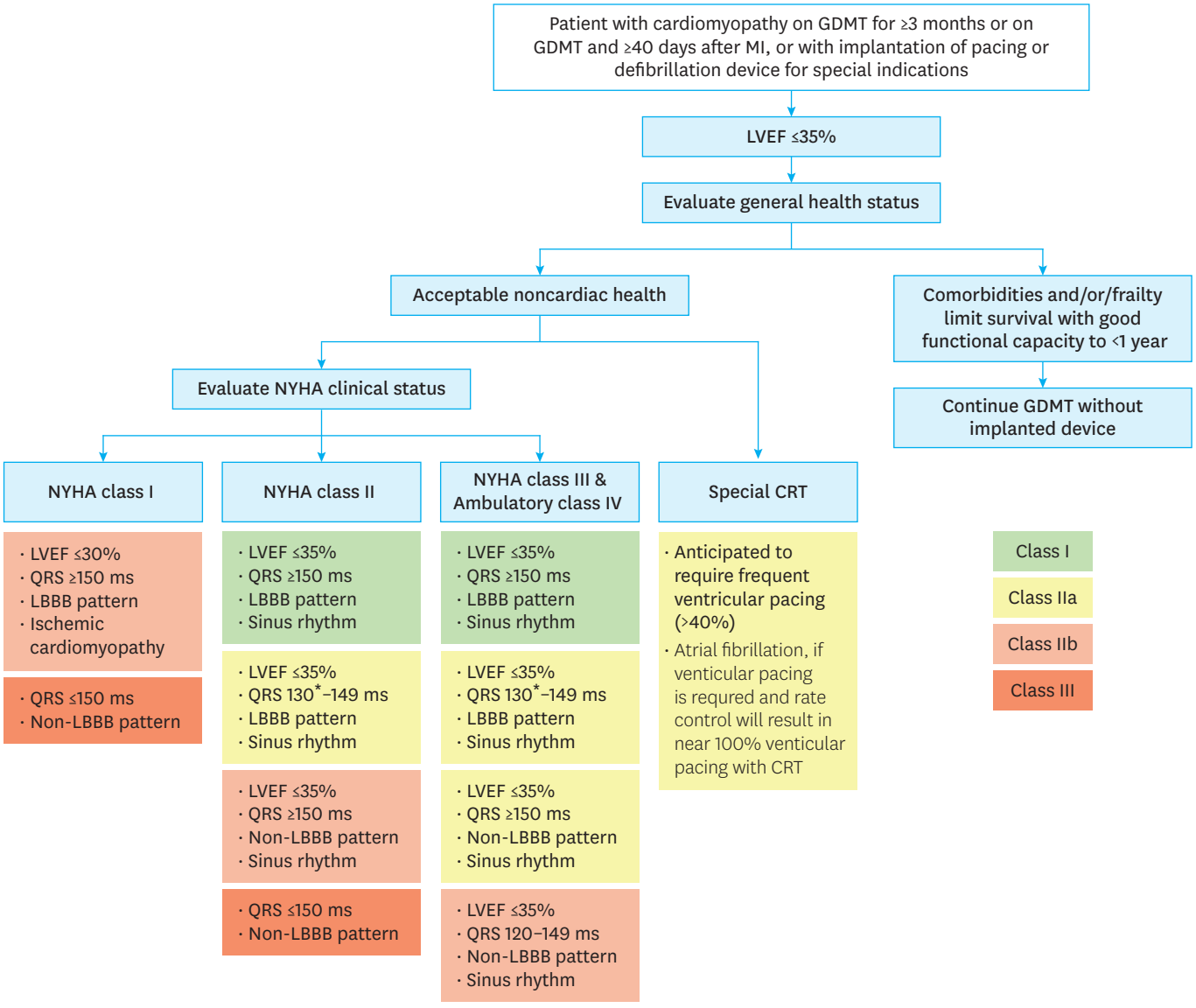

Figure 4. Algorithm of indications for cardiac resynchronization therapy.
"Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;62:e147-239, DOI: 10.1016/j.jacc.2013.05.019." reproduced by permission of the *Journal of the American College of Cardiology*.
CRT = cardiac resynchronization therapy; GDMT = guideline-directed medical therapy; LBBB = left bundle-branch block; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association.
*Updated based on Ruschitzka et al.[48] and Steffel et al.[49]

4. In patients with severe tricuspid regurgitation, surgical treatment can be considered for those who require surgical treatment of aortic valve or mitral valve abnormalities or those who have isolated primary tricuspid regurgitation without impaired right atrial function (class I, level of evidence C).
5. Optimal drug therapy must be considered first in patients with functional mitral regurgitation (class I, level of evidence C).

6. In patients with severe mitral regurgitation, surgical treatment should be considered, along with coronary artery bypass, when these patients are symptomatic and have reduced LVEF (class IIa, level of evidence C).
7. Surgery can be considered for patients with isolated severe mitral regurgitation with reduced left ventricular function (LVEF <30%) to replace or delay cardiac transplantation when there are no coronary artery lesions that induce ischemia (class IIB, level of evidence C).

Cardiac valvular disease is one of the most common causes of acute HF. Patients with HF and a cardiac valvular disease are classified as high-risk patients, so treatment of valvular disease must be decided after thoroughly examining the advantages and disadvantages of a global therapeutic approach. Regardless of the method of treatment, the optimal drug therapy must be administered to all patients, and particularly, ACE inhibitors, ARBs, calcium channel blockers, and nitrates must be used carefully in order to avoid reduction in BP.[4]

Aortic stenosis

For asymptomatic patients with reduced LVEF and suspected with aortic stenosis, it is important to appropriately screen for patients who are candidate for valve replacement. In particular, differentiating between moderate aortic stenosis and severe aortic stenosis with dobutamine stress echocardiogram is important for patients with "low flow-low gradient aortic valve stenosis (valve width <1 cm^2, LVEF <40%, mean gradient <40 mmHg)."

In patients with HF and severe aortic stenosis, there are no absolute criteria for TAVI. However, TAVI can be performed in patients who are anticipated to survive for more than one year and are inappropriate candidates for surgery, and those who are assessed to be able to undergo TAVI under consideration of risk factors and anatomical structures of the aorta and aortic valve. In particular, recent workers have performed TAVI not only in patients with high risk but also in patients with moderate or mild risk, so the indications for TAVI are projected to be changed in the future.[60][61]

Aortic regurgitation

Aortic valve replacement or aortic valvuloplasty is recommended in patients with severe symptomatic aortic regurgitation and in asymptomatic patients with a LVEF of below 50% with severe aortic regurgitation.[62]

Mitral regurgitation

In patients with symptomatic primary mitral regurgitation, surgical treatment should be considered for those without other surgical contraindications. Mitral valve replacement and mitral valvuloplasty must be decided upon depending on the anatomy of the mitral valve, the patient's clinical features, and the surgeon's experience.

Secondary mitral regurgitation occurs as a result of left ventricular enlargement and left ventricular remodeling, and these can also be substantially improved with optimal drug therapy. Surgical treatment must be considered along with coronary artery bypass in symptomatic patients with a reduced LVEF (< 30%). When AF is also present, surgical treatment and left atrial appendectomy can be considered. Although the effects of surgical therapy in isolated severe mitral regurgitation with reduced left ventricular function (LVEF <30%) in the absence of coronary artery lesions that induce ischemia are unclear,

surgery can be considered to replace or delay cardiac transplantation. Percutaneous mitral valve intervention may be considered in patients with HF and moderate or severe mitral regurgitation, but additional studies are needed to substantiate this.[63][64]

Tricuspid regurgitation

Tricuspid regurgitation aggravates HF by increasing the pressure and volume overload of the right atrium. Diuretics must be used to mitigate the symptoms of right HF caused by severe tricuspid regurgitation, and when liver congestion is also present, combined therapy with mineralocorticoid antagonists can be helpful.[4] The indications for surgical treatment of uncontrolled severe tricuspid regurgitation are as yet unclear, and surgical treatment may be considered in patients in need of surgical treatment of the mitral valve or aortic valve or patients with isolated primary tricuspid regurgitation without right atrial impairment.[65]

CARDIAC TRANSPLANTATION

1. Ventilatory gas analysis through cardiopulmonary exercise testing is useful for assessing patients with HF who are candidate for cardiac transplantation. Cardiac transplantation can be considered when peak oxygen consumption (VO_2) is 12 ml/kg/min or lower in patients taking beta-blockers and when it is 14 mL/kg/min or lower in patients who do not tolerate beta-blockers (class I, level of evidence: B).
2. Right ventricular catheterization must be performed in all adult cardiac transplant candidates, and it must be performed periodically prior to cardiac transplantation. (class I, level of evidence C). Periodic right ventricular catheterization must not be routinely applied to children (class III, level of evidence C).

Universally accepted indications and contraindications for cardiac transplantation are described in **Tables 3** and **4**.[66] Patients with indication for cardiac transplantation are registered in the Korean Network for Organ Sharing (KONOS) and priority status is determined according to the urgency of the patient. **Table 5** shows the newly revised (July 2017) Korean cardiac transplant urgency status.

Ventilatory gas analysis through cardiopulmonary exercise testing is useful for assessing patients with HF believed to be in need of cardiac transplantation and should be performed

Table 3. Universally accepted indications for cardiac transplantation

HFrEF with persistent symptoms despite appropriate medical therapy and instrumental therapy
NYHA class IIIb–IV
LVEF <35%*
VO_2max ≤12–14 mL/kg/min, or VO_2max <50% predicted, or VE/VCO_2 slope >35† in cardiopulmonary exercise test
Cardiogenic shock not anticipated to improve
Acute myocardial infarction
Acute myocarditis
Persistent angina without additional procedure or surgical options despite appropriate medical therapy, surgery, and procedure
Persistent ventricular arrhythmia despite use of antiarrhythmic agents or instruments or catheter ablation
Hypertrophic or restrictive cardiomyopathy with severe symptoms
Non-metastatic intracardiac tumor
Congenital heart disease without fixed pulmonary arterial hypertension

HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; VE/VCO_2 = minute ventilation/carbon dioxide production slope; VO_2max = maximal oxygen uptake.
*Low LVEF alone is not an indication for cardiac transplant. †Abnormal cardiopulmonary exercise testing findings without abnormal findings in NYHA class is not an indication for cardiac transplant.

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Table 4. Contraindications for cardiac transplantation

Contraindications	Descriptions
Age	Age of 70 years or older can be a relative contraindication depending on the underlying disease.
Obesity	Cardiac transplantation is recommended to patients with BMI ≤30 kg/m^2, and most centers perform cardiac transplantation in patients with BMI ≤35 kg/m^2*.
Cancer	Active cancer is an absolute contraindication. Transplantation can be discussed for patients with treatable low-grade cancer or treated cancer after consulting an oncologist.
Pulmonary hypertension	Pulmonary vascular resistance of 3 wood units or higher despite the use of vasodilators and pressors is a contraindication for cardiac surgery. These patients can be re-evaluated after trying a VAD.
Diabetes mellitus	Uncontrolled diabetes and relevant organ injury constitute an absolute contraindication for transplantation.
Renal dysfunction	Renal dysfunction related to diabetes is an absolute contraindication for transplantation (in such cases, consider simultaneous heart-kidney transplantation).
Hepatic cirrhosis	Hepatic cirrhosis caused by heart problems is an absolute contraindication for transplantation (in such case, consider simultaneous heart-liver transplantation).
Peripheral vascular anomaly	Lesions for which a bypass or recanalization is impossible are an absolute contraindication for cardiac transplant.
Infection	Active infection, HIV, and hepatitis C are contraindications in most institutions, but with the introduction of hepatitis C medications, some institutions still perform cardiac transplantation in such patients.
Drug abuse	Six months of abstinence from smoking and alcohol is required, and consultation with neuropsychiatry is advised for drug abusers.
Psychosocial problem	Patients with low medication adherence, who have no family to provide care, and who have dementia are absolute contraindications. Physical disability is a relative contraindication.

BMI = body mass index; HIV = human immunodeficiency virus; VAD = ventricular assist device.

periodically. The parameters measured with this analysis include VO_2 max, CO_2 output, minute ventilation, and ventilatory/anaerobic threshold, and among these, minute oxygen consumption is considered the best indicator for aerobic exercise capacity. The reliability and importance of ventilatory gas analysis data with exercise testing for evaluating patients with HF have already been established. This test is helpful in identifying patients with ambulatory HF with poor prognosis that warrants consideration of cardiac transplantation.[67]

Table 5. Korea's cardiac transplant urgency status

Urgency status		Item
Status 0	Patient must qualify for at least one of the following conditions (re-registration within 8 days).	1) Veno-arterial extracorporeal membrane oxygenation* 2) Mechanical ventilation due to HF 3) VT/VF requiring mechanical circulatory support* 4) ICU admission of a patient with an implantable VAD due to serious complication† 5) Non-implantable VAD‡
Status 1	Admitted patients who qualify for at least one of the following conditions with reference to the date of registration. However, non-admitted patients are included for condition 2 (re-registration within 8 days).	1) Artificial heart 2) VAD 3) IABP 4) Intravenous cardiotonic agent administration for more than 4 consecutive weeks 5) Require a single high-dose§ cardiotonic agent or 2 or more moderate-dose* cardiotonic agents for at least 1 week 6) Frequent recurrence of continuous VT/VF or frequent ICD shocks - On antiarrhythmic medication or had arrhythmia procedure with 3 or more VT/VF episodes or 3 or more ICD shocks within 24 hours (3 or more times within the re-application period)
Status 2	Patient must qualify for at least one of the following conditions (reapply every 30 days).	1) On cardiotonic agent for at least 1 week with reference to the date of registration but does not qualify for urgency status 1 2) On antiarrhythmic medication or had arrhythmia surgery and has VT/VF or ICD shock
Status 3	Not qualifying for statuses 0, 1, and 2	
Status 7	On hold for cardiac implantation	

IABP = intra-aortic balloon pump; ICD = implantable cardioverter defibrillator; VAD = ventricular assist device; VF = ventricular fibrillation; VT = ventricular tachycardia. *Mechanical circulatory devices with the exception of extracorporeal membrane oxygenation, such as IABP or VAD; †Serious complication: Thromboembolism, VAD infection, mechanical failure, recurrent ventricular arrhythmia; ‡Non-implantable right ventricular, left ventricular, biventricular assist device; §High-dose or moderate-dose cardiotonic agent (unit: μg/kg/min).

Category	Dopamine	Dobutamine	Milrinone	Epinephrine	Norepinephrine	Isoproterenol
High dose	10	10	0.75	0.1	0.1	0.05
Moderate dose	5	5	0.5	0.05	0.05	0.03

Right ventricular catheterization is an important test for evaluating patients waiting for a cardiac transplant. Although the recommendation is to perform the procedure every 3–6 months if the waiting period for cardiac transplant is extended, it must be individualized according to the patient's status and circumstances at the transplant center. For children, periodic right ventricular catheterization is not recommended. For patients with a pulmonary arterial systolic pressure of 50 mmHg or higher or transpulmonary gradient of 15 mmHg or higher or pulmonary vascular resistance (PVR) of 3 Wood units or higher (with systemic arterial pressure maintained at 85 mmHg or higher), vasodilator challenge should be performed to check whether PVR decreases.[67]

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