# JCS 2017/JHFS 2017 Guideline on Diagnosis and Treatment of Acute and Chronic Heart Failure
## — Digest Version —

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# Abbreviations

| | |
|---|---|
| ACC | American College of Cardiology |
| ACCF | American College of Cardiology Foundation |
| ACE | angiotensin converting enzyme |
| ACP | advance care planning |
| ACS | acute coronary syndrome |
| ADL | activities of daily livings |
| AHA | American Heart Association |
| AHI | apnea hypopnea index |
| ANP | atrial (A-type) natriuretic peptide |
| ARB | angiotensin II receptor blocker |
| ASV | adaptive servo-ventilation |
| BNP | brain (B-type) natriuretic peptide |
| CABG | coronary artery bypass grafting |
| CKD | chronic kidney disease |
| COPD | chronic obstructive pulmonary disease |
| CPAP | continuous positive airway pressure |
| CRT | cardiac resynchronization therapy |
| CS | clinical scenario |
| CSA | central sleep apnea |
| CSR | Cheyne-Stokes respiration |
| CT | computed tomography |
| DOAC | direct oral anticoagulant |
| ECMO | extracorporeal membrane oxygenation |
| ESA | erythropoiesis stimulating agent |
| ESC | European Society of Cardiology |

| | |
|---|---|
| $FiO_2$ | fraction of inspiratory oxygen |
| HF | heart failure |
| HFmrEF | heart failure with mid-range ejection fraction |
| HFpEF | heart failure with preserved ejection fraction |
| HFrecEF | heart failure with recovered ejection fraction |
| HFrEF | heart failure with reduced ejection fraction |
| IABP | intra-aortic balloon pump |
| ICD | implantable cardioverter defibrillator |
| IL | interleukin |
| JCS | Japanese Circulation Society |
| LVAD | left ventricular assist device |
| LVEF | left ventricular ejection fraction |
| MBP | mean arterial pressure |
| MRA | mineralocorticoid receptor antagonist |
| MRI | magnetic resonance imaging |
| NPPV | noninvasive positive pressure ventilation |
| NSAID | nonsteroidal anti-inflammatory drug |
| NT-proBNP | N-terminal pro-brain (B-type) natriuretic peptide |
| NYHA | New York Heart Association |
| OSA | obstructive sleep apnea |
| $PaO_2$ | arterial partial pressure of oxygen |
| PCI | percutaneous coronary intervention |
| PCPS | percutaneous cardiopulmonary support |
| PDE | phosphodiesterase |
| QOL | quality of life |

| SBP | systolic blood pressure |
|---|---|
| SDB | sleep-disordered breathing |
| SGLT | sodium glucose cotransporter |
| SPECT | single-photon emission computed tomography |

| $SpO_2$ | oxygen saturation |
|---|---|
| TAVI | transcatheter aortic valve implantation |
| TAVR | transcatheter aortic valve replacement |
| VAD | ventricular assist device |

**Table 1. History of Heart Failure Guidelines in Japan and Western Countries**

| Year | Japan (The Japanese Circulation Society) | U.S. (ACC/AHA) | EU (ESC) |
|---|---|---|---|
| 1995 | | ACC/AHA guidelines for the evaluation and management of heart failure (Chair: Williams)[2] | Guidelines for the diagnosis of heart failure (The Task Force on Heart Failure of the European Society of Cardiology)[9] |
| 1997 | | | The treatment of heart failure (Task Force of the Working Group on Heart Failure of the European Society of Cardiology)[10] |
| 2000 | Guidelines for Treatment of Chronic Heart Failure (Chair: Matsuzaki) Guidelines for Treatment of Severe Acute Heart Failure (Chair: Takekoshi) | | |
| 2001 | | ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult (Chair: Hunt)[3] | Guidelines for the diagnosis and treatment of chronic heart failure (CoChair: Remme and Swedverg),[11] covering both diagnosis and treatment |
| 2005 | Guidelines for Treatment of Chronic Heart Failure (Chair: Matsuzaki), revised version | ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (Chair: Hunt)[4] | Guidelines for the diagnosis and treatment of chronic heart failure (Chair: Swedberg)[12] Guidelines on the diagnosis and treatment of acute heart failure (Chair: Nieminen)[13] |
| 2006 | Guidelines for Treatment of Acute Heart Failure (Chair: Maruyama), revised version | | |
| 2008 | | | Guidelines for the diagnosis and treatment of acute and chronic heart failure (Chair: Dickstein)[6] |
| 2009 | | A revised version that contains a new section "The Hospitalized Patient"[5] | |
| 2010 | Guidelines for Treatment of Chronic Heart Failure (Chair: Matsuzaki), revised version | | |
| 2011 | Guidelines for Treatment of Acute Heart Failure (Chair: Izumi), revised version | | |
| 2012 | | | ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 (Chair: McMurray),[1] as a revision of the previous version |
| 2013 | | 2013 ACCF/AHA Guideline for the Management of Heart Failure (Chair: Yancy)[7] | |
| 2016 | | | ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2016 (Chair: Ponikowski)[14] |
| 2017 | | 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure (Chair: Yancy)[8] | |
| 2018 | Guidelines for diagnosis and treatment of acute and chronic heart failure (Chair: Tsutsui), revised version | | |

ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; ESC, European Society of Cardiology.

# Preamble

In Japan, the Japanese Circulation Society (JCS) published the "Guidelines for Treatment of Chronic Heart Failure" and the "Guidelines for Treatment of Acute Severe Heart Failure" in 2000, and revised the guidelines for chronic heart failure in 2005 and 2010 to reflect new evidence. In 2011, the JCS published "Guidelines for Treatment of Acute Heart Failure" as a revision of the Guidelines for Treatment of Acute Severe Heart Failure. Similarly to the revised guidelines published by the European Society of Cardiology (ESC) in 2012[1] and the American Heart Association (AHA), the revised guideline covered all aspects of heart failure (**Table 1**). In the United States, the American College of Cardiology (ACC) and the AHA published the Guidelines for the Evaluation and Management of Heart Failure[2] in 1995, and revised them in 2001,[3] 2005,[4] and 2009.[5] The 2009 revision added a new section "the Hospitalized Patient" to align with the 2008 ESC Guideline[6] and covered acute heart failure. The ACC/AHA revised the guideline in 2013[7] and 2017.[8] In Europe, the ESC published the Guidelines for the Diagnosis of Heart Failure[9] in 1995, and the Treatment of Heart Failure[10] in 1997. In 2001, the ESG revised these documents to publish as one document, the Guidelines for the Diagnosis and Treatment of Chronic Heart Failure[11] and revised the document in 2005.[12] In 2005, the ESC published the Guidelines on the Diagnosis and Treatment of Acute Heart Failure,[13] and then published the Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure to cover both acute and chronic heart failure,[6] and revised them in 2012[1] and 2016.[14] The ESC's categorization in heart failure guidelines substantially affected guidelines on acute heart failure published by the AHA and JCS.

This revised version of "the Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure" was prepared as joint guidelines by the JCS and the Japanese Heart Failure Society (JHFS). The working committee for this project includes members and collaborators involved in the previous versions of the heart failure guidelines and members recommended from 11 societies (the JCS, the JHFS, the Japanese Association for Thoracic Surgery, the Japanese Society of Hypertension, the Japanese Society of Echocardiography, the Japanese Society for Cardiovascular Surgery, the Japanese College of Cardiology, the Japanese Association of Cardiac Rehabilitation, the Japan Society of Ultrasonics in Medicine, the Japan Diabetes Society, and the Japanese Heart Rhythm Society). Also, the working group includes members of "the Study Group on Idiopathic Cardiomyopathy" supported by the Health and Labor Sciences Research Grant on Intractable Diseases and those of "the Study Group on the Multi-center Observational Study of Dilated- phase Hypertrophic Cardiomyopathy", supported by the "Practical Research Project for Rare/ intractable Diseases by the Japan Agency for Medical Research and Development".

The working group started the process of fully revising the guideline from October 2016, and developed the first draft in January 2017. Members and collaborators reviewed the guideline according to a total of 885 comments based on blinded review, revised 5 times, and further revised according to a total of 141 comments from the independent assessment committee, before being finalized after detailed discussions at 3 study group meetings. The present guidelines intend to describe standard practice for acute and chronic heart failure according to latest information provided in Western guidelines and the evidence and clinical experience accumulated in Japan.

We hope that this document will help all healthcare professionals involved in the diagnosis and treatment of heart failure.

# I.  Introduction

## 1.  Classes of Recommendations and Levels of Evidence

Classification of recommendations and levels of evidence are described similarly to our previous heart failure guidelines using a style similar to those used in the ACC/AHA guidelines and the ECS guidelines (**Tables 2** and **3**). In Japan, guidelines for cardiovascular diseases have extensively used a common style that is highly consistent with Western guidelines. On the other hand, the Japan Council for Quality Health Care uses a different style in its Medical Information Network Distribution Service (MINDS) to show grades of recommendations and levels of evidence as described in the "Minds Handbook for Clinical Practice Guideline Development 2007" (**Tables 4** and **5**).[15] Accordingly, the present document shows classification of recommendations and level of evidence in the tables including both styles; class of recommendation, level of evidence, grade of recommendation (MINDS) and level of evidence (MINDS).

## 2.  Major Revisions of the Present Guidelines

The most important change is that the guidelines on acute heart failure and chronic heart failure are provided in one document, rather than the conventional two separate documents. This reflects our consensus that describing guidelines in two separate documents are not practical since many cases of acute heart failure represents acute worsening of chronic heart failure, and patients require seamless treatment from acute to chronic phase.

In the present guidelines, the following major revisions were made:
1) The definition of heart failure is further clarified, and an easy-to-understand definition is provided for general population. (Section "**1. Definition and Classification**" in Chapter "**II. General Principles**").
2) Stages of heart failure, its risk factors, and treatment goals are described (Section "**1. Definition and Classifi-**

**Table 2. Classes of Recommendations**

| | |
|---|---|
| Class I | Evidence and/or general agreement that a given procedure or treatment is useful and effective |
| Class II | Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given procedure or treatment |
| Class IIa | Weight of evidence/opinion is in favor of usefulness/efficacy |
| Class IIb | Usefulness/efficacy is less well established by evidence/opinion |
| Class III | Evidence or general agreement that the given procedure or treatment is not useful/effective, and in some cases may be harmful |

**Table 3. Level of Evidence**

| | |
|---|---|
| Level A | Data derived from multiple randomized clinical trials or meta-analyses |
| Level B | Data derived from a single randomized clinical trial or large-scale non-randomized studies |
| Level C | Consensus of opinion of the experts and/or small-size clinical studies, retrospective studies, and registries |

**Table 4. MINDS Grades of Recommendations**

| | |
|---|---|
| Grade A | Strongly recommended and supported by strong evidence |
| Grade B | Recommended with moderately strong supporting evidence |
| Grade C1 | Recommended despite no strong supporting evidence |
| Grade C2 | Not recommended because of the absence of strong supporting evidence |
| Grade D | Not recommended as evidence indicates that the treatment is ineffective or even harmful |

The grade of recommendation is determined based on a comprehensive assessment of the level and quantity of evidence, variation of conclusion, size of effectiveness, applicability to the clinical setting, and evidence on harms and costs. (Adapted from MINDS Treatment Guidelines Selection Committee. 2007[15])

**Table 5. MINDS Levels of Evidence (Levels of Evidence in Literature on Treatment)**

| | |
|---|---|
| I | Systematic review/meta-analysis of randomized controlled trials |
| II | One or more randomized controlled trials |
| III | Non-randomized controlled trials |
| IVa | Analytical epidemiological studies (cohort studies) |
| IVb | Analytical epidemiological studies (case-control studies and cross-sectional studies) |
| V | Descriptive studies (case reports and case series) |
| VI | Not based on patient data, or based on opinions from a specialist committee or individual specialists |

(Adapted from MINDS Treatment Guidelines Selection Committee. 2007[15])

cation" in Chapter "**II. General Principles**" and Chapter "**V. Basic Principles for the Treatment of Heart Failure**").

3) In the classification of heart failure based on left ventricular ejection fraction (LVEF), a new category of heart failure with mid-range ejection fraction (HFmrEF) defined as a LVEF of 40–49%, is added to the conventional two categories of heart failure with reduced ejection fraction (HFrEF), and heart failure with preserved ejection fraction (HFpEF). Another category of patients in whom LVEF recovered after treatment, described as "HFpEF, improved" or "HF with recovered EF", is added as well (Section "**1. Definition and Classification**" in Chapter "**II. General Principles**").

4) An algorithm for the diagnosis of heart failure is newly presented (Section "**1. Diagnosis**" in Chapter "**III. Diagnosis**").

5) A new chapter is added to describe how to prevent heart failure for each stage of heart failure (Chapter "**IV. Prevention of Heart Failure**").

6) An algorithm for the treatment of heart failure is newly presented (Chapter "**V. Basic Principles for the Treatment of Heart Failure**".

7) Pathophysiology and treatment of comorbidities are described in detail (Chapter "**IX. Pathophysiology and**

Treatment of Comorbidities").

8) A flowchart of the treatment and clinical course over time of acute heart failure is newly presented (Chapter "**X. Acute Heart Failure**").

9) A flowchart on the use of ventricular assist devices for patients with severe heart failure is newly presented (Chapter "**XI. Surgical Treatment**").

10) Palliative care is described in detail (Chapter "**XIII. Palliative Care**")

# II. General Principles

## 1. Definition and Classification

### ▌1.1 Definition of Heart Failure

Heart failure is defined as a clinical syndrome consisting of dyspnea, malaise, swelling and/or decreased exercise capacity due to the loss of compensation for cardiac pumping function due to structural and/or functional abnormalities of the heart (**Table 6**).

Heart failure is a disease condition where the heart is

**Table 6. Definition of Heart Failure (HF)**

| | |
|---|---|
| Definition of HF in the present guidelines | Clinical syndrome consisting of dyspnea, malaise, swelling and/or decreased exercise capacity due to the loss of compensation for cardiac pumping function due to structural and/or functional abnormalities of the heart |
| Definition of HF for the public (Patient-friendly version) | Heart failure is a heart disease that causes shortness of breath and swelling, gets worse with time, and shortens life expectancy. |

**Table 7.  Classification of Heart Failure by Left Ventricular Ejection Fraction (LVEF)**

| Definition | LVEF | Description |
|---|---|---|
| Heart failure with reduced ejection fraction (**HFrEF**) | <40% | The main feature is systolic dysfunction. In many clinical studies, patients with a low LVEF despite standard medical treatment for heart failure are enrolled as patients with HFrEF. |
| Heart failure with preserved ejection fraction (**HFpEF**) | ≥50% | The main feature is diastolic dysfunction. Other diseases that may cause similar symptoms should be ruled out. No effective treatments have been established. |
| Heart failure with mid-range ejection fraction (**HFmrEF**) | 40 to <50% | Borderline heart failure. Clinical features and prognosis have not yet been fully characterized. Treatment should be selected on an individual basis. |
| Heart failure with preserved ejection fraction, improved (**HFpEF improved**) or heart failure with recovered EF (**HFrecEF**) | ≥40% | Patients with an improvement of LVEF from <40% to ≥40% after treatment. It has been suggested that these patients may have a different prognosis from those with HFrEF, but further studies are required. |

(Source: Prepared based on Yancy CW, et al. 2013[7] and Ponikowski P, et al. 2016[16])
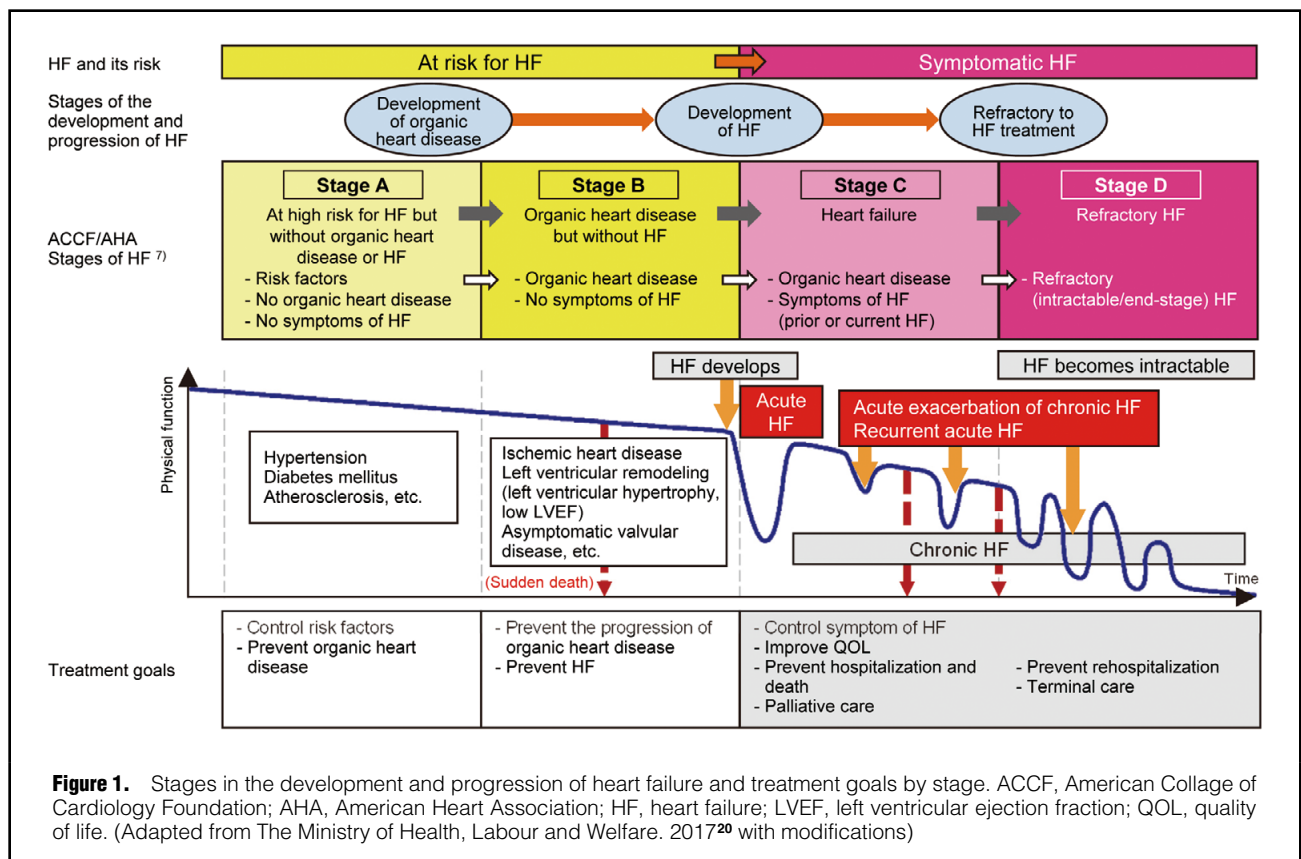


**Figure 1.**    Stages in the development and progression of heart failure and treatment goals by stage. ACCF, American Collage of Cardiology Foundation; AHA, American Heart Association; HF, heart failure; LVEF, left ventricular ejection fraction; QOL, quality of life. (Adapted from The Ministry of Health, Labour and Welfare. 2017[20] with modifications)

unable to fill with and eject enough blood for various reasons such as epicardial, myocardial or endocardial lesions, valvular disease, coronary arterial disease, aortic disease, arrhythmias, and endocrine disorders. However, in many cases left ventricular dysfunction is associated with heart failure, and is the most important factor in determining monitoring and treatment strategies. Heart failure should thus be defined and classified according to left ventricular function.

The Japanese Circulation Society has decided to classify heart failure mainly according to left ventricular ejection fraction in the present guidelines for the treatment of acute heart failure and chronic heart failure as the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) and the European Society of

Cardiology (ESC) do in their guideline documents.[7,16] Heart failure with reduced left ventricular ejection fraction (HFrEF) and heart failure with preserved left ventricular ejection fraction (HFpEF) are defined as follows (**Table 7**).[7,16]

### 1.1.1  HFrEF
In many large-scale clinical studies in heart failure, HFrEF was defined as heart failure with a left ventricular ejection fraction (LVEF) of ≤35% or <40. In the present guidelines, HFrEF is defined as heart failure with a LVEF of <40%.

HFrEF is characterized with the high prevalence of left ventricular enlargement, which is present in more than 50% of patients, and the relatively high prevalence of left ventricular diastolic dysfunction.

**Table 8.** Comparison Between the Stages of Heart Failure and the NHYA Functional Classification

| Stages of HF | NYHA Functional Classification[20a] |
|---|---|
| **A.** At high risk for HF but without organic heart disease | None |
| **B.** At high risk for HF and with organic heart disease | None |
| **C.** Symptomatic heart failure | **I.** No limitation of physical activity. Ordinary physical activity does not cause severe fatigue, palpitations, dyspnea or angina. |
| | **II.** Slight or moderate limitation of physical activity. Comfortable at rest, but ordinary physical activity causes fatigue, palpitations, dyspnea or angina. |
| | **III.** Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitations, dyspnea or angina. |
| | **IV.** Unable to carry on any physical activity without symptoms of HF, or symptoms of HF and angina at rest. Even slight activity worsens symptoms. |
| **D.** Refractory heart failure | **III.** Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitations, dyspnea or angina. |
| | **IV.** Unable to carry on any physical activity without symptoms of HF, or symptoms of HF and angina at rest. Even slight activity worsens symptoms. |

The NYHA functional classification was developed by the New York Heart Association as a system to classify patients with heart diseases according to the severity of symptoms resulting from physical activity, and has been used in the severity classification of heart failure. NYHA class II patients further classified into those with slight limitation of physical activity (IIs) and those with moderate limitation of physical activity (IIm). HF, heart failure; JCS, Japanese Circulation Society; NYHA, New York Heart Association. (Source: Prepared based on Yancy CW, et al. 2013[7])

## ▌1.1.2 HFpEF

It has been reported that about half of patients with symptomatic heart failure have normal or preserved LVEF.[17] In this guideline document, HFpEF is defined as heart failure with a LVEF of ≥50% to differentiate it clearly from HFrEF. HFpEF may be caused by arrhythmias such as atrial fibrillation, coronary heart disease, diabetes mellitus, and dyslipidemia, but the most common cause of HFpEF is hypertension.[18]

Patients with a mild reduction in LVEF may present some degree of systolic dysfunction, but their clinical manifestations are often similar to those of HFpEF. However, unlike patients with HFpEF, such patients with borderline LVEF may respond well to treatments that have been demonstrated to be effective in the treatment of systolic dysfunction in HFrEF. Accordingly, this condition is defined as heart failure with mid-range LVEF (HFmrEF) or HFpEF borderline. In the present guidelines, HFmrEF is defined as heart failure with a LVEF of 40 to 49%.

In some patients with heart failure initially presented with low LVEF, the LVEF may improve over time during treatment or follow-up. This type of heart failure is referred to as "HFpEF improved" or "HF with recovered EF"
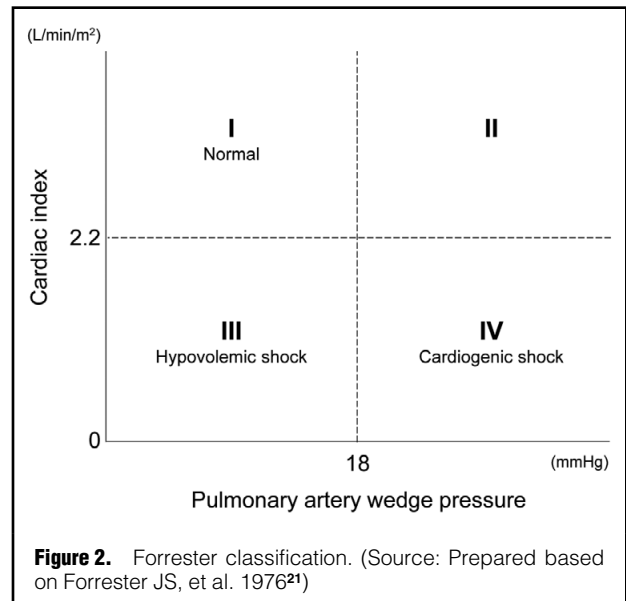


**Figure 2.** Forrester classification. (Source: Prepared based on Forrester JS, et al. 1976[21])

(HFrecEF).[19] This type of heart failure is often observed in patients with tachycardia-induced cardiomyopathy mainly due to tachycardiac atrial fibrillation, ischemic heart disease, or dilated cardiomyopathy whose cardiac function has improved with β-blockers. In these patients, left ventricular systolic and/or diastolic function, cardiothoracic ratio (CTR), and brain (B-type) natriuretic peptide (BNP) may return to normal levels.

## ▌1.2 Stages of Heart Failure

The ACCF/AHA Stages of Heart Failure[7] is widely used to determine the progression stage of heart failure. The ACCF/AHA created this staging system to help physicians make appropriate treatment intervention, and encourages to treat patients at high risk earlier even when they are asymptomatic. In this guidelines, four stages of heart failure are used according to the ACCF/AHA Stages of Heart Failure: Stage A, asymptomatic patients at high risk of developing heart failure without structural heart disease; Stage B, patients with asymptomatic heart failure who have structural heart disease; Stage C, patients with symptomatic heart failure and structural heart disease, including those with a history of heart failure; and Stage D, patients with refractory heart failure who have had New York Heart Association (NYHA) Class III or IV heart failure despite all available drug therapy or nonpharmacologic therapy with proven efficacy, and are hospitalized for heart failure at least twice a year (**Figure 1**).[20]

**Table 8** outlines a comparison between the JCS stages of heart failure and the NYHA functional classification.[7,20a]

## ▌1.3 Classification of Heart Failure

The Forrester classification is one of the most common used criteria to classify the severity of heart failure according to hemodynamic measures (**Figure 2**).[21] It was originally developed to predict the prognosis of patients with acute heart failure due to acute myocardial infarction, and the correlation between this severity classification and mortality rate has been demonstrated. The Forrester classification is

Profile A: No congestion or low perfusion (dry-warm)
Profile B: Congestion but no low perfusion (wet-warm)
Profile C: Congestion and low perfusion (wet-cold)
Profile L: Low perfusion but no congestion (dry-cold)
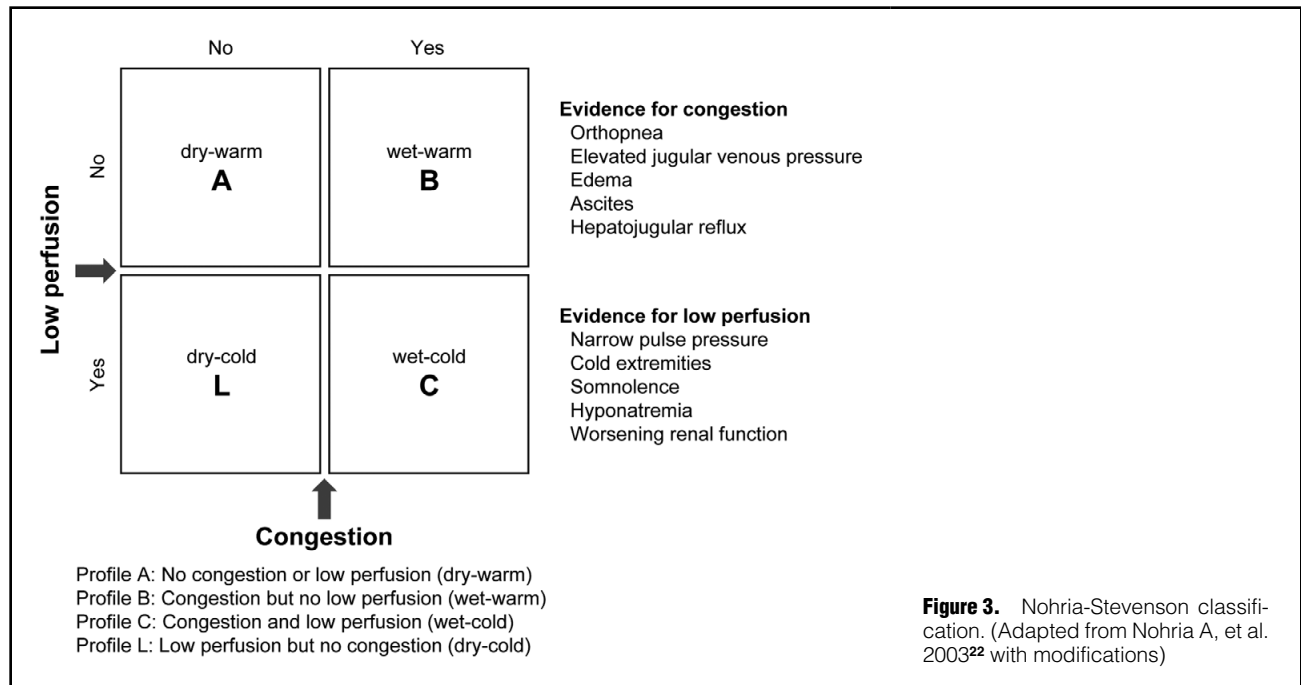
**Figure 3.** Nohria-Stevenson classification. (Adapted from Nohria A, et al. 2003[22] with modifications)

based on objective measures of organ perfusion and congestion and is thus useful in the assessment of pathophysiological condition of non-ischemic heart failure, but invasive measurements are necessary.

Alternatively, the Nohria-Stevenson classification that can assess the severity of heart failure more easily based only on physical findings is commonly used to assess the risk profile of patients with heart failure according to their peripheral hemodynamics and lung auscultation findings (**Figure 3**).[22]

## 2. Epidemiology, Etiology, and Prognosis

Heart diseases are the second leading cause of death in Japan, next to malignancy (cancer). Heart failure is the most common cause of death from heart disease.[23] According to a report of the Japanese registry of all cardiac and vascular diseases, the Japanese Registry of All cardiac and vascular Diseases (JROAD) 2015 study,[24] the total number of patients hospitalized for heart failure in medical and educational institutions was 238,840 patients in 2015, showing an increase by more than 10,000 each year. The ratio of patients with acute and chronic heart failure was about half and half. Although there are no accurate statistics on the total number of patients with heart failure in Japan, it has been estimated that the number was about 1 million in 2005 and will reach 1.2 million by 2020.[25] As the corresponding number in the United States was estimated to be about 5 million in 2005,[26,27] the prevalence of heart failure may be relatively lower in Japan than in the United States. However, it is highly likely that heart failure will increasingly become more common in Japan as the population ages.

In Japan, large-scale registry studies such as the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD; patients registered from 2004 to 2005),[28] Chronic Heart failure Analysis and Registry in Tohoku district-1

(CHART-1; 2000 to 2004),[29] and CHART-2 (2006 to 2010)[30,31] have been conducted. The average age of registered patients was 71 years in the JCARE-CARD study, 69 years in the CHART-1 study, and 69 years among Stage C or D heart failure in the CHART-2 study, indicating that elderly people account for large percentages of the registered patients.

An observational study in the United States has reported that LVEF was maintained at ≥50% in nearly half of patients with heart failure.[17] In Japan, patients with HFpEF account for more than 50% of all patients with heart failure, and this percentage tends to increase in recent years.[30] The prognosis of patients with HFpEF has been reported to be poor similarly, although not identically, to those with HFrEF.[32,33] Physicians should be aware that HFpEF will likely become even more common in the super-aged society.

A variety of diseases cause heart failure (**Table 9**). Almost all types of heart diseases may lead to heart failure. Heart failure may also result from systemic diseases and myocardial injury due to external causes. The most common cause of heart failure is ischemic heart disease, which is followed by hypertension, and valvular diseases.[28–30] Heart failure due to ischemic heart disease is becoming more common,[29] while hypertension is considered as the most common cause of HFpEF.[34]

In the assessment of prognosis in the JROAD 2015, in-hospital mortality in patients hospitalized for heart failure was about 8%.[24] One-year all-cause mortality in patients with heart failure was 7.3% in the JCARE-CARD and CHART-1 studies. The high rate of rehospitalization due to worsening heart failure is another problem.

According to the JROAD report that described the epidemiology of acute heart failure in Japan, the number of patients hospitalized for acute heart failure was 85,512 in 2013 and increased substantially to 107,049 in 2016.[24]

The epidemiology of acute heart failure in Japan has been extensively studied in the Heart Institute of Japan

| Table 9. Causes of Heart Failure |
|---|
| **Myocardial disease** |
| **Ischemic heart disease** |
|   Ischemic cardiomyopathy, stunning, hibernation, microcirculatory disorder |
| **Cardiomyopathy (including genetic forms)** |
|   Hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, noncompaction, takotsubo cardiomyopathy |
| **Cardiotoxic substances and other factors** |
|   • Addictive and abused substances |
|     Alcohol, cocaine, amphetamines, anabolic steroids |
|   • Heavy metals |
|     Copper, iron, lead, cobalt, mercury |
|   • Drugs |
|     Antitumor drugs (e.g., anthracycline), immunosuppressive drugs, antidepressant drugs, antiarrhythmic drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), anesthetic drugs |
|   • Radiation damage |
| **Infectious diseases** |
|   • Myocarditis |
|     e.g., viral, bacterial or rickettsial infections; Chagas' disease |
| **Immune disorders** |
|   e.g., rheumatoid arthritis, systemic lupus erythematosus, polymyositis, mixed connective tissue disease |
| **Pregnancy** |
|   • Peripartum cardiomyopathy |
|     Including puerperal cardiomyopathy |
| **Infiltrative diseases** |
|   Sarcoidosis, amyloidosis, hemochromatosis, invasive malignant tumors |

(**Table 9** continued the next column.)

| |
|---|
| **Endocrine disorders** |
|   e.g., hyperthyroidism, Cushing's disease, pheochromocytoma, adrenal insufficiency, abnormal growth hormone secretion |
| **Metabolic disorders** |
|   Diabetes mellitus |
| **Congenital enzyme abnormality** |
|   Fabry's disease, Pompe's disease, Hurler's syndrome, Hunter's syndrome |
| **Muscle disorders** |
|   Muscular dystrophy, laminopathy |
| **Abnormal hemodynamics** |
| **Hypertension** |
| **Valvular disease, cardiac structural abnormality** |
|   • Congenital conditions |
|     Congenital valvular disease, atrial septal defect, ventricular septal defect, other congenital heart diseases |
|   • Acquired conditions |
|     Aortic valve disease, mitral valve disease |
| **Epicardial abnormalities other related conditions** |
|   Constrictive pericarditis, cardiac tamponade |
| **Endocardial abnormalities** |
|   Eosinophilic endomyocardial disease, endocardial fibroelastosis |
| **High-output heart failure** |
|   Severe anemia, hyperthyroidism, Paget's disease, arteriovenous shunt, pregnancy, beriberi heart |
| **Increased fluid volume** |
|   Renal failure, excessive transfusion |
| **Arrhythmias** |
|   • Tachyarrhythmias |
|     e.g., atrial fibrillation, atrial tachycardia, ventricular tachycardia |
|   • Bradyarrhythmias |
|     e.g., sick sinus syndrome, atrioventricular block |

Department of Cardiology – Heart Failure (HIJC-HF) registry,[35] the JCARE-CARD study,[28] and the Acute Decompensated Heart Failure Syndromes (ATTEND) registry[36] in chronological order. The average age of registered patients was over 70 years in all these studies, and many patients had hypertension, diabetes mellitus, dyslipidemia and/or atrial fibrillation. The most common cause of acute heart failure was ischemic heart disease, which accounted for >30% in all studies. As compared with epidemiological findings in other countries, patients with acute heart failure in Japan do not differ substantially from those in other countries in terms of age, gender ratio, and prevalence of hypertension, diabetes, and dyslipidemia.[37,38] However, it should be noted that the prevalence of ischemic heart disease as an underlying cardiac condition is lower in Japanese patients than those in Western countries, while the prevalence of hypertensive heart disease is higher in Japanese patients than Western patients.

Gender differences should be considered in the diagnosis and treatment of heart failure. Both the results of registry studies in Japan and data in Western countries have indicated that women have a better prognosis than men when adjusted for background characteristics of patients.[39–42] In Japan where the population is aging rapidly, more women are expected to experience heart failure, but there are only limited data available on gender difference in the treatment of heart failure.

# III. Diagnosis

## 1. Diagnosis (Algorithms) (Figure 4)

In the diagnosis of heart failure, patients should be examined first for symptoms, medical history, their family history, physical findings, ECG, and chest X-ray findings.

Next, the concentration of brain (B-type) natriuretic peptide (BNP) or N-terminal pro-brain (B-type) natriuretic peptide (NT-proBNP) in the blood should be determined. **Figure 4** outlines the cut-off levels of BNP and NT-proBNP for the diagnosis of heart failure.[43] However, physicians should be aware that BNP and NT-proBNP levels may be lower than these cut-off levels in patients with mild heart failure or patients with severe obese and heart failure. Accordingly, echocardiography is a reasonable diagnostic method to examine for heart failure even in patients with a BNP of ≥35 or 40 pg/mL or a NT-proBNP of ≥125 pg/mL who are strongly suspected to have heart failure according to their symptoms, patient history or underlying conditions, physical findings, ECG or chest X-ray findings. Patients should be examined comprehensively to determine whether
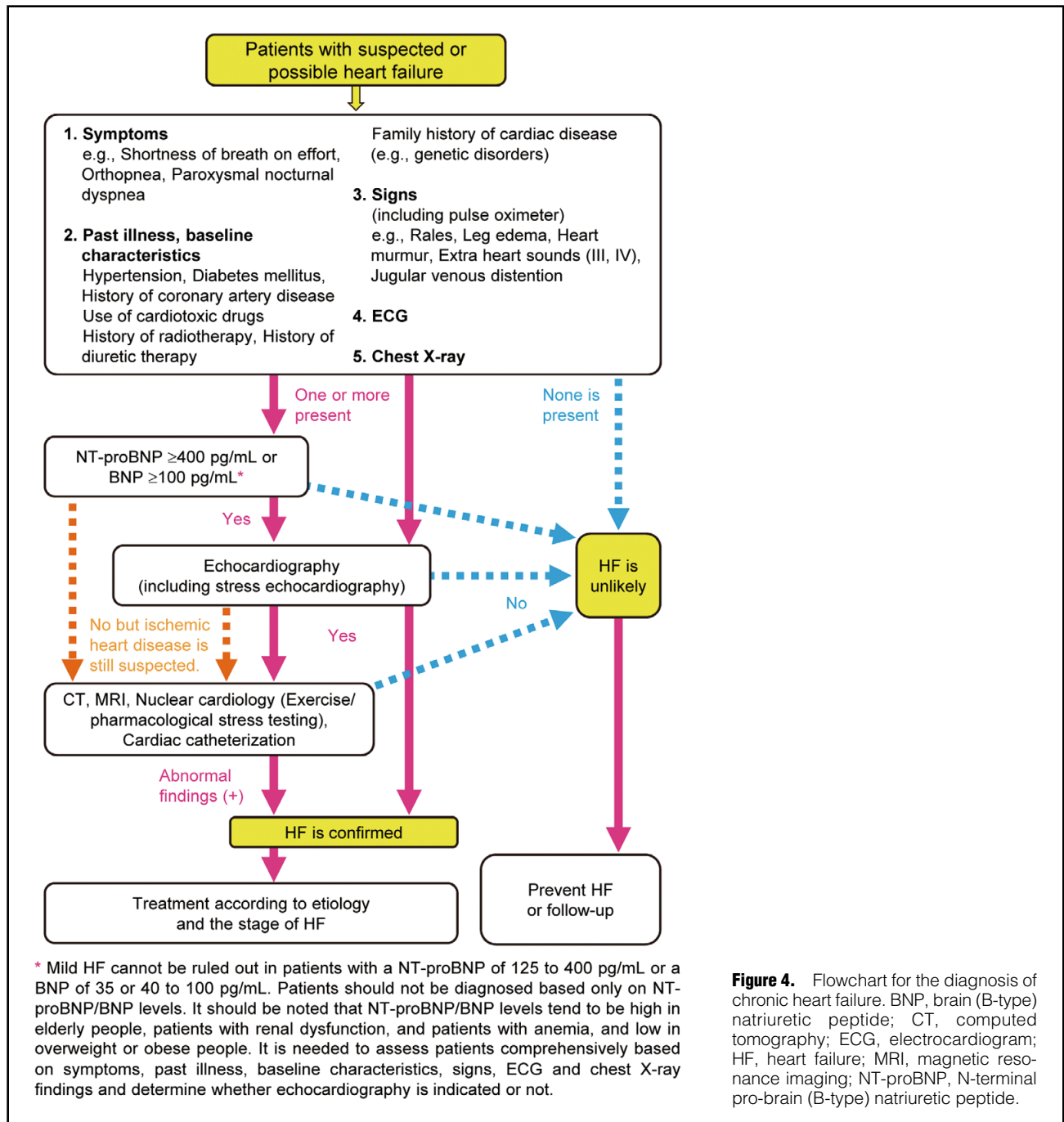
**Figure 4.** Flowchart for the diagnosis of chronic heart failure. BNP, brain (B-type) natriuretic peptide; CT, computed tomography; ECG, electrocardiogram; HF, heart failure; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-brain (B-type) natriuretic peptide.

additional examinations should be conducted or not. Echocardiography should be performed in patients who have heart murmur suggestive of valvular disease or abnormal ECG findings clearly indicative of the presence of old myocardial infarction regardless of the level of BNP or NT-proBNP.

Stress echocardiography should also be considered for patients who complain of symptoms inconsistent with echocardiographic findings at rest. When the causative disease cannot be identified with echocardiography, other modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and nuclear imaging should be used. Since some patients with ischemic heart disease may

present only with shortness of breath on effort, patients in whom ischemic heart disease cannot be ruled out should be examined for myocardial ischemia using exercise or pharmacological stress test.

Patients confirmed to have heart failure should receive appropriate treatment according to the causative disease and the stage of heart failure.

## 2. Symptoms and Signs

Patients with acute heart failure often show symptoms associated with pulmonary venous congestion due to

**Table 10.** Criteria for Diagnosis of Heart Failure: Framingham Criteria

| Major criteria | Major or minor criteria | Minor criteria |
|---|---|---|
| Paroxysmal nocturnal dyspnea | | Lower leg edema |
| Jugular venous distention | | Nocturnal cough |
| Pulmonary rale | Weight loss of 4.5 kg or more in 5 days in response to treatment. When the weight loss is attributable to the treatment of heart failure, it is considered 1 major criterion. Otherwise it is considered a minor criterion. | Dyspnea on ordinary exertion |
| Cardiomegaly on chest X-ray | | Hepatomegaly |
| Acute pulmonary edema | | Pleural effusion |
| Protodiastolic gallop (S3 gallop) | | Decrease in vital capacity by one third from maximum recorded |
| Increased central venous pressure (≥16 cm $H_2O$) | | Tachycardia (heart rate ≥120 bpm) |
| Increased circulation time (≥25 sec) | | |
| Hepatojugular reflux | | |
| (Pulmonary edema, visceral congestion of cardiomegaly on autopsy) | | |

Diagnosis of heart failure requires the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria. (Source: Prepared based on Mckee PA, et al. 1971[44])

**Table 11.** Symptoms and Signs of Heart Failure

| Congestion | | |
|---|---|---|
| Left-sided heart failure | Symptoms | Dyspnea, shortness of breath, tachypnea, orthopnea |
| | Signs | Bubbling rales, wheezing, pink foamy sputum, third or fourth heart sound |
| Right-sided heart failure | Symptoms | Right hypochondrium pain, anorexia, abdominal swelling, epigastric discomfort |
| | Signs | Hepatomegaly, increased hepatobiliary enzymes, jugular venous distention. Signs of pulmonary congestion are not apparent in patients with severe right heart failure. |
| **Low output** | | |
| Symptoms | | Disturbance of consciousness, restlessness, memory disorder |
| Signs | | Cold sweat, cold extremities, cyanosis, hypotension, oliguria, agitated or confused |



**Figure 5.** How to estimate jugular venous pressure.

increased left ventricular end-diastolic pressure or increased left atrial pressure, and/or systemic venous congestion due to increased right atrial pressure, as well as symptoms associated with decreased cardiac output. The Framingham criteria for the diagnosis of heart failure are based on symptoms and findings of left heart failure, right heart failure, and low cardiac output (**Table 10**).[44] Patients' symptoms and physical findings should be categorized accordingly to assess their pathophysiological condition (**Table 11**). Patients with bilateral cardiac failure show signs and symptoms of both left- and right-sided heart failure. The jugular venous pressure can be estimated based on the vertical distance between the horizontal lines drawn from the highest point of internal jugular venous pulse and the sternal angle when the patient is positioned at a 45° incline (**Figure 5**). The sternal angle is positioned about 5 cm above

the right atrium. A vertical distance between the sternal angle and the top of the jugular venous pulse of ≥3 cm indicates an increased central venous pressure.

The New York Heart Association (NYHA) Functional Classification provides a simple method of classifying the severity of heart failure based on the patient's symptoms and categorizes patients with heart failure into four groups from Class I to IV. The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines categorize patients with heart failure into four categories from Stage A (asymptomatic patients at risk for heart failure) to Stage D (patients with refractory heart failure and severe symptoms even at rest) (**Table 8**[7] in Section "**1. Definitions and Classification**" in "**II. General Principles**", and Section "**8.1. NYHA Functional Classification**" in this chapter). These two classifications are different in nature, but are generally well correlated as can be seen in**Table 8**.[7]

**Table 12.** Recommendations and Levels of Evidence for the Use of Biomarkers in Heart Failure

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| **Plasma BNP and serum NT-proBNP** | | | | |
| Diagnosis | I | A | A | I |
| Severity | I | A | A | I |
| Prognosis assessment | I | A | A | I |
| Efficacy evaluation | IIa | B | B | II |
| Screening | IIa | C | B | II |
| **Plasma atrial (A-type) natriuretic peptide (ANP)** | | | | |
| Diagnosis | I | A | A | I |
| Severity | IIa | B | B | II |
| Prognosis assessment | IIa | B | B | II |
| Efficacy evaluation | IIb | C | C1 | III |
| Screening | IIb | C | C1 | III |
| **Myocardial troponins (T, I)\* and plasma noradrenaline#** | | | | |
| Diagnosis | – | – | – | – |
| Severity | IIa | B | B | II |
| Prognosis assessment | IIa | B | B | II |
| Efficacy evaluation | – | – | – | – |
| Screening | – | – | – | – |
| **Aldosterone# and plasma renin activity#** | | | | |
| Diagnosis | – | – | – | – |
| Severity | IIa | C | B | III |
| Prognosis assessment | IIa | C | B | III |
| Efficacy evaluation | – | – | – | – |
| Screening | – | – | – | – |
| **Neurohumoral factors (other than above)#** | | | | |
| Diagnosis | – | – | – | – |
| Severity | IIb | C | C1 | V |
| Prognosis assessment | IIb | C | C1 | V |
| Efficacy evaluation | – | – | – | – |
| Screening | – | – | – | – |

*The use of cardiac troponins as biomarkers for heart failure is not covered by the National Health Insurance (NHI) in Japan. However, the guidelines for the management of heart failure proposed by the American College of Cardiology (ACC), the American Heart Association (AHA), and the Heart Failure Society of America (HFSA) suggest the measurement of cardiac troponins as a Class I recommendation with level of evidence A. The guidelines proposed by the European Society of Cardiology (ECS) suggest as a Class I recommendation with level of evidence C. #The use as a biomarker is not covered by the NHI in Japan.

## 3. Biomarkers (Table 12)

Among currently available biomarkers for heart failure, BNP and NT-proBNP are the most significant biomarkers for heart failure and have been used extensively for screening, diagnosis, and prognosis assessment of this condition.

### 3.1 Biomarkers Reflecting Sympathetic Activity

In patients with heart failure, the sympathetic nervous system is overactivated. Congestion and other conditions caused by heart failure reduce the clearance of noradrenaline, and thereby increase noradrenaline levels in the blood. Plasma noradrenaline levels are an indicator of sympathetic activity of the whole body and may be used to assess the prognosis of patients with heart failure.[45]

### 3.2 Biomarkers Reflecting the Renin-Angiotensin-Aldosterone System Activity

In patients with heart failure, the renin-angiotensin-aldosterone (RAA) system is overactivated, and angiotensin II is produced excessively. Plasma renin activity may be high in some patients with mild cardiac dysfunction, and may not be high even in patients with severe heart failure. This finding suggests that the tissue RAA system may be activated independently of the circulatory RAA system to play a role in cardiac remodeling.[46-48]

On the other hand, aldosterone levels in the blood are not necessarily high in patients with heart failure, and thus cannot be used as a sensitive marker of heart failure. However, there are many unclear points concerning the secretion and action of aldosterone in heart failure, and the significance of aldosterone/mineral corticoid receptor cascade, including the activation of mineral corticoid receptors, should not be underestimated.[49-51] Measurements of renin activity and aldosterone levels is strongly recommend in the diagnosis and treatment of hypertension, and is also expected to help physicians understand the cause and pathophysiology of heart failure.

**Table 13. Comparison of BNP and NT-proBNP**

| | BNP | NT-proBNP |
|---|---|---|
| Molecular weight | ca. 3,500 | ca. 8,500 |
| Hormonal activity | + | − |
| Cross-reactivity | proBNP | |
| Half-life | About 20 minutes | About 120 minutes |
| Clearance | NPR-C, NEP, renal | Renal |
| Blood samples | EDTA plasma | Serum/heparinized or EDTA plasma |
| Reference level | ≤18.4 pg/mL | ≤55 pg/mL |
| Factors that increase BNP and NT-proBNP levels* | Cardiac dysfunction, renal dysfunction, advanced age, systemic inflammation | |
| Factors that decrease BNP and NT-proBNP levels* | Obesity | |

*Indicating only typical factors that increase or decrease BNP and NT-proBNP levels. Some factors may affect BNP and NT-proBNP levels differently and further studies are needed to characterize the effects of these factors.
BNP, brain (B-type) natriuretic peptide; EDTA; ethylenediamine tetraacetic acid; NEP, neutral endopeptidase; NPR-C, natriuretic peptide receptor-C; NT-proBNP, N-terminal pro-brain (B-type) natriuretic peptide.
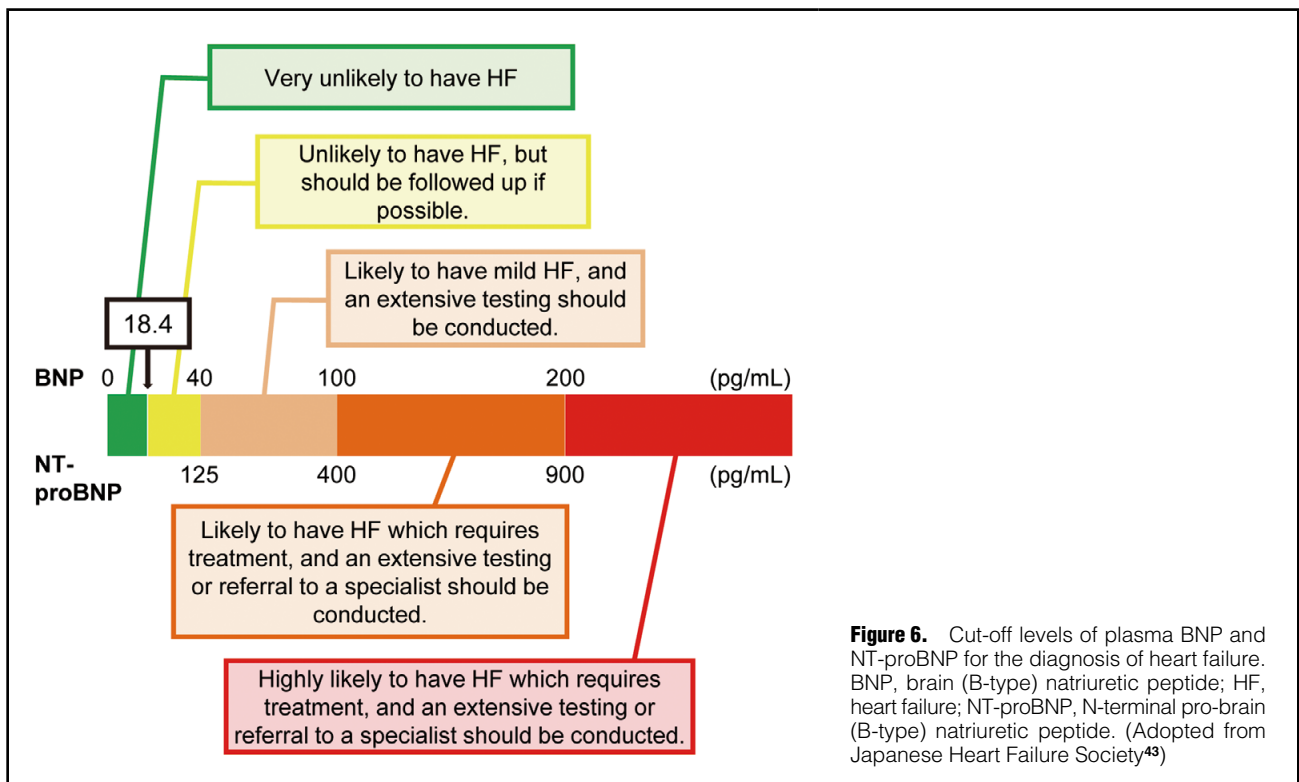


**Figure 6.** Cut-off levels of plasma BNP and NT-proBNP for the diagnosis of heart failure. BNP, brain (B-type) natriuretic peptide; HF, heart failure; NT-proBNP, N-terminal pro-brain (B-type) natriuretic peptide. (Adopted from Japanese Heart Failure Society[43])

## 3.3 Natriuretic Peptides

Natriuretic peptides include atrial (A-type) natriuretic peptide (ANP), BNP, and C-type natriuretic peptide (CNP). ANP and BNP are cardiac hormones that are synthesized mainly in the atrium and ventricle, respectively.[52–54] ANP secretion is stimulated by atrial stretch, while BNP secretion is stimulated mainly by ventricular load. Accordingly, BNP levels in the blood reflect the degree of ventricular burden, and thus can be used as a sensitive biochemical marker.[54–57]

Plasma levels of ANP and BNP are high in patients with heart failure because the production of these peptides is enhanced in the heart and their clearance from the blood is delayed. ANP and BNP are degraded through internalization after binding to the natriuretic peptide receptor C (NPR-C) or metabolized by neutral endopeptidase (NEP). No clear relationship has been shown between the metabolism of ANP and BNP and the pathophysiology of heart failure, but the clearance of these peptides is low in patients with renal dysfunction. When comparing BNP and its N-terminal fragment NT-ProBNP, a precursor of BNP with a larger molecular weight, the effect of renal dysfunction is more substantial on NT-proBNP than on BNP (**Table 13**).

BNP is superior to ANP in terms of the sensitivity and specificity as a supportive diagnostic marker for heart failure.[58] BNP (or NT-proBNP) is useful in confirming the presence and classifying the severity of heart failure, as well as in assessing the prognosis of patients with heart failure.[59–64] It also plays a substantial role as a marker to monitor the efficacy of treatment over time in individual patients who may not compare with others.

The Japanese Heart Failure Society has published a statement entitled "Points to consider when using BNP and NT-pro BNP levels in the blood for the diagnosis and treatment of heart failure" (**Figure 6**).[43] This publication set a cut-off point of 40 pg/mL for plasma BNP concentration (125 pg/mL for NT-proBNP[43]) to identify patients susceptible to heart failure according to the results of the J-ABS multicenter study, although the upper normal limit for plasma BNP is set at 18.4 pg/mL (55 pg/mL for NT-pro BNP).[65,66] Plasma BNP levels differ among individuals, and tend to remain low in obese patients in whom the severity of heart failure may be underestimated.

## 3.4 Markers for Myocardial Injury

Cardiac troponin I and T levels in the blood, which are used as biomarkers for myocardial infarction, have been pointed out to increase in patients with non-ischemic myocardial diseases. Continued increase in troponin levels in the blood indicate a poor prognosis.[67,68] High-sensitivity troponin assays are useful in the diagnosis of acute coronary syndrome,[69,70] and are expected also useful in risk assessment in patients with chronic heart failure.[71,72]

## 3.5 Inflammatory Markers

It has been pointed out that immune cells and their production of cytokines are involved in the development of heart failure. In fact, blood levels of tumor necrosis factor (TNF) $\alpha$ and interleukin (IL)-6 are elevated in patients with heart failure, and also are related to their prognosis.[73–75] A report has described that high-sensitivity C-reactive protein (CRP) levels is related to the prognosis of heart failure regardless of whether patients have underlying diseases or not.[76] In Western countries, a rapid test for ST2, a receptor for IL-33 that is a member of IL-1 family, has been used. Elevated blood levels of ST2 have been reported in patients with acute heart failure, and this is expected to be useful in prognostic assessment of heart failure.[77]

## 3.6 Oxidative Stress Markers

It is considered that oxidative stress is enhanced in patients with heart failure, and causes endothelial damage and cardiac dysfunction. Reports have described that low density lipoprotein (LDL) levels in the blood and levels of 8-isoprostagrandin F2$\alpha$ (also known as 8-iso-PGF2$\alpha$ or 8-isoprostane) and 8-hydroxy-2'-deoxyguanosine (8-OHdG) in the blood or urine are useful biomarkers of oxidative stress.[78–80]

## 3.7 Uric Acid

Although an association between high uric acid levels and heart failure has been indicated,[81–84] its sensitivity and specificity as a biomarker of heart failure are not high enough. Further studies are awaited to better clarify its benefits and usage in the diagnosis of or risk assessment for heart failure.

## 3.8 Vasopressin

Vasopressin, a hormone secreted by the posterior pituitary gland, induces vasoconstriction through $V_1$ receptors and affects fluid balance through $V_2$ receptors. Vasopressin secretion is stimulated in heart failure. It has been reported that levels of copeptin, a fragment of the vasopressin precursor, in the blood are related to the prognosis of heart failure.[85]

## 3.9 Others

Metabolic syndrome is a risk factor for ischemic heart disease and heart failure. Reports have described that levels of adiponectin, an adipocytokine related to metabolic syndrome, are high in patients with heart failure and are related to their prognosis.[86–88]

Endothelin (ET) is a potent vasoconstrictor.[89] Plasma levels of ET-1 and big-ET-1 correlate inversely with LVEF, and are determinants of mortality.[90,91]

Levels of adrenomedullin in the blood increase as the severity of heart failure progresses, and are related to the poor prognosis of heart failure.[92] Adrenomedullin is produced in the heart and the systemic vasculature, and has a role in cellular protection.

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## 4. Chest X-ray

Plain chest X-ray has remained as a useful technique to detect the presence of and assess the severity of heart failure (**Table 14**). Pulmonary congestion is an important X-ray finding of left heart failure, and is used to assess the severity of it (**Figure 7**). Patients with mild heart failure (pulmonary venous pressure: 15 to 20 mmHg) show redistribution of blood flow towards the apex (cephalization). Patients with interstitial pulmonary edema (pulmonary venous pressure: 20 to 30 mmHg) show peribronchial or perivascular edema

**Table 14.** Recommendations and Levels of Evidence on the Use of Chest X-ray in Heart Failure

|  | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| Chest X-ray to examine patients with a new-onset or an acute worsening of heart failure | I | C | B | V |

① **Cephalization**
Indicating a redistribution of pulmonary blood flow toward the apex (pulmonary venous pressure, 15 to 20 mmHg)

② **Perivascular cuffing**

③ **Kerley's B line**

④ **Kerley's A line**

⑤ **Kerley's C line**

⑥ **Peribronchial cuffing:**
② - ⑥ Indicating interstitial pulmonary edema (pulmonary venous pressure, 20 to 30 mmHg)

⑦ **Vanishing tumor**
Pleural effusion

⑧ **Butterfly shadow**
Indicating pulmonary alveolar edema (pulmonary venous pressure, ≥30 mmHg)

⑨⑩ **Dull costophrenic angle**
Pleural effusion

⑪ **Distention of the superior vena cava**

**Figure 7.** Chest X-ray findings of heart failure (schema).

(cuffing signs) or Kerley's A, B, and/or C lines. More advanced patients show alveolar pulmonary edema (pulmonary venous pressure: ≥30 mmHg) with butterfly shadow. Pleural fluid is often found in patients with bilateral cardiac failure, while it is rarely found in patients with right cardiac failure.[93] Pleural fluid and pulmonary edema are more commonly found in the right lungs.[94] Shadows in the mediastinum may be found in association with left atrial enlargement, right ventricular enlargement, or enlarged shadows of the pulmonary artery, but the diagnostic significance of these X-ray findings is not superior to echocardiographic findings.

## 5. Echocardiography

Echocardiography is used to assess cardiac function and hemodynamics, as well as the cause, pathophysiology, and severity of heart failure. Repetitive measurement is also useful in the assessment of treatment efficacy and prognosis (**Table 15**). **Table 16** lists normal values for transthoracic echocardiographic and Doppler parameters obtained in the Japanese population, which are essential in the assessment of cardiac function in patients with heart failure.[95,96]

### 5.1 Assessment of Cardiac Function

### 5.1.1 Assessment of Left Ventricular Systolic Function
Left ventricular systolic function is assessed with LVEF. Patients with heart failure are classified into those with preserved LVEF (HFpEF), and those with reduced LVEF

(HFrEF). LVEF is determined using the modified Simpson method (disc method).

In addition to the LVEF-based assessment of systolic function of the left ventricle as a whole, regional wall motion should also be assessed. Left ventricular global longitudinal strain (GLS) determined with speckle-tracking echocardiography is highly reproducible and useful in early diagnosis of heart failure.[97]

### 5.1.2 Assessment of Left Ventricular Diastolic Function
Left ventricular diastolic function consists of left ventricular relaxation that defines early diastolic inflow velocity and left ventricular stiffness that defines mid- and end-diastolic inflow velocity. Left ventricular dilation and inflow may be limited not only by diastolic dysfunction due to left ventricular myocardial damage but also by compression due to right ventricular enlargement, constrictive pericarditis, or cardiac tamponade.

Echocardiographic parameters for the assessment of left ventricular diastolic function are based on secondary changes such as an increase in left atrial pressure and morphological changes. As there is no single parameter that can assess left ventricular diastolic function by itself, multiple parameters as listed below should be assessed comprehensively.

#### a. Left Ventricular Inflow Velocity Pattern (E/A)
In patients with sinus rhythm, peak blood flow velocity in early diastole (the E wave) and peak flow velocity in late diastole caused by atrial contraction (the A wave) are observed. Patients with an initial phase of diastolic dysfunc-

**Table 15.** Recommendations and Levels of Evidence for the Use of Echocardiography in Heart Failure

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| Echocardiography to assess cardiac function, left ventricular wall motion, valvular disease, right ventricular function, and pulmonary hypertension in patients suspected of having heart failure | I | C | A | IVb |
| Echocardiography to assess cardiac function in patients with heart failure who are going to receive drug therapy or device therapy | I | C | A | IVb |
| Repeat echocardiography to assess patients with a change in their clinical condition of heart failure | I | C | A | IVb |
| Stress echocardiography to assess myocardial viability in patients with HFrEF | IIa | B | B | IVb |
| Echocardiography to assess whether the limitation of physical activity is attributable to cardiac dysfunction | IIa | B | B | IVb |
| Echocardiography as a routine follow-up procedure for patients with stable heart failure | III | B | D | IVb |
| Transthoracic echocardiography in patients who can be diagnosed and assessed with transesophageal echocardiography | III | B | D | IVb |

HFrEF, heart failure with reduced ejection fraction.

**Table 16.** Normal Range of Echocardiographic Indices of Cardiac Function in Japanese Male and Females

| | Male | Female |
|---|---|---|
| Left ventricular end-diastolic diameter (mm) | 48±4 | 44±3 |
| Left ventricular end-systolic diameter (mm) | 30±4 | 28±3 |
| Left ventricular end-diastolic volume index (mL/m²) | 53±11 | 49±11 |
| Left ventricular end-systolic volume index (mL/m²) | 19±5 | 17±5 |
| Left ventricular ejection fraction (%) | 64±5 | 66±5 |
| Left ventricular mass index (g/m²) | 76±16 | 70±14 |
| Left atrial dimension (mm) | 32±4 | 31±3 |
| Left atrial volume index (mL/m²) | 24±7 | 25±8 |
| Right ventricular end-diastolic diameter (apical four-chamber view at the base level) (mm) | 31±5 | 28±5 |
| Right ventricular area change (FAC, %) | 44±13 | 46±11 |
| Tricuspid annular plane systolic excursion (TAPSE, mm) | 24±3.5 | |
| Tricuspid annular peak systolic velocity (s′) (cm/sec) | 14.1±2.3 | |
| E/e′ (septum) | 7.4±2.2 | 7.9±2.2 |
| e′ (septum, cm/sec) | 10.0±2.8 | 10.8±3.2 |
| E/e′ (lateral wall) | 5.5±1.8 | 6.2±1.8 |
| e′ (lateral wall, cm/sec) | 13.5±3.9 | 13.7±4.1 |

FAC, fractional area change. (Source: Prepared based on Daimon M, et al. 2008[95] and Lang RM, et al. 2015[96])

tion show "relaxation abnormality patterns", which are characterized by a low E/A ratio and prolonged E-wave deceleration time (DT). Patients with advanced diastolic dysfunction and increased left atrial pressure show "pseudonormalized filling pattern" with a high E wave and a high E/A ratio. Patients with more advanced diastolic dysfunction with higher left atrial pressure show "restrictive pattern" characterized by an even higher E/A ratio.

#### b. Early Diastolic Mitral Annular Velocity (e′)
Patients with diastolic dysfunction show a reduction of early diastolic mitral annular velocity (e′). This should be determined at either the septal side or lateral wall side of the mitral valve annuls or the mean of the measurements at the two locations.

#### c. E/e′ Ratio
E/e′ ratio, the ratio of peak early diastolic left ventricular filling (E) to the peak mitral annular velocity (e′) is useful in the diagnosis of heart failure independent of LVEF, and positively correlates with left atrial pressure.[98] However, it is noted that the correlation between E/e′ and the severity of heart failure is poor in patients with hypertrophic cardiomyopathy in whom a high E/e′ ratio may not be associated with high left atrial pressure.[99]

#### d. Left Atrial Volume Index (LAVI)
Left atrial enlargement is considered to reflect long-term left atrial load due to diastolic dysfunction, and correlates with the severity of diastolic dysfunction.[100]

#### e. Tricuspid Regurgitant Velocity
High left atrial pressure causes secondary pulmonary hypertension and an increase in the right ventricular systolic pressure. Tricuspid regurgitation velocity (TRV) may indicate an increase in left atrial pressure in patients without pulmonary arterial hypertension.

#### f. Assessment of Diastolic Function in HFpEF
The presence/absence of diastolic dysfunction in patients with preserved LVEF may be assessed based on E/e′, e′, TRV, and LAVI (**Figure 8**).[101] Patients diagnosed as having diastolic dysfunction should be examined as instructed for patients with reduced LVEF to estimate left atrial pressure. Constrictive pericarditis is a condition that must be differentiated from diastolic dysfunction associated with myocardial disorder, and usually shows high E waves of left and right ventricular inflow with substantial respiratory changes.

**LVEF >50%**

1. Average E/e' >14 (Septal E/e' >15 or lateral E/e' >13)
2. Septal e' velocity <7 cm/sec or later e' velocity <10 cm/sec
3. Tricuspid regurgitation velocity (TRV) >2.8 m/sec
4. Left atrial volume index (LAVI) >34 mL/m²

| 3 or 4 items positive | 2 items positive | 3 or 4 items negative |
| --- | --- | --- |
| Normal diastolic function | Indeterminable | Diastolic dysfunction |
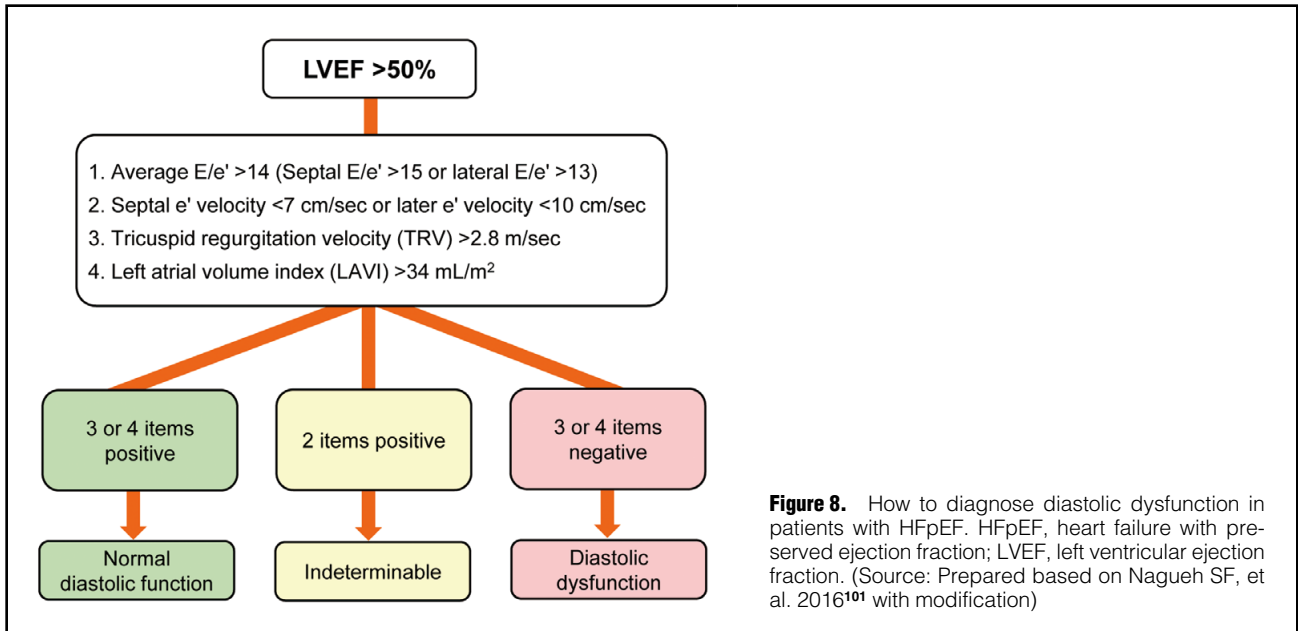
**Figure 8.** How to diagnose diastolic dysfunction in patients with HFpEF. HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction. (Source: Prepared based on Nagueh SF, et al. 2016[101] with modification)

**Mitral Inflow**

E/A ≤ 0.8 + E ≤ 50 cm/s

E/A ≤ 0.8 + E > 50 cm/s or E/A > 0.8 - <2

E/A ≥ 2

3 criteria to be evaluated*

**1**-Average E/e' > 14
**2**-TR velocity > 2.8 m/s
**3**-LA Vol. Index > 34 ml/m²

| 2 of 3 or 3 of 3 Negative | When only 2 criteria are available | 2 of 3 or 3 of 3 Positive |
| --- | --- | --- |

| 2 negative | 1 positive and 1 negative | 2 positive |
| --- | --- | --- |

Normal LAP Grade I Diastolic Dysfunction

Cannot determine LAP and Diastolic Dysfunction Grade*

↑ LAP Grade II Diastolic Dysfunction

↑ LAP Grade III Diastolic Dysfunction

*If Symptomatic*

Consider CAD, or proceed to diastolic stress test

(*LAP indeterminate if only 1 of 3 parameters available. Pulmonary vein S/D ratio <1 applicable to conclude elevated LAP in patients with depressed LV EF)

**Figure 9.** Algorithm for the diagnosis of elevated left atrial pressure by echocardiography. CAD, coronary artery disease; LA, left atrium; LAP, left atrial pressure; TR, tricuspid regurgitation. (Adapted from Nagueh SF, et al. 2016[101])

### g. Assessment of Diastolic Function in HFrEF

Diastolic dysfunction is considered present in all patients with low LVEF. E/A, E wave velocity, E/e′, TRV, LAVI, and other parameters are used to assess whether left atrial pressure is high or not (**Figure 9**).[102]

## 5.1.3 Assessment of Right Ventricular Function

Right ventricular function may be assessed with relatively simple parameters, such as fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), and tricuspid annular peak systolic velocity (s′). Right ventricular volume cannot be determined using two-dimensional echocardiography because of its complex morphology. Right ventricular volume and ejection fraction may be determined using three-dimensional echocardiography.

## 5.2 Assessment of Hemodynamics

### a. Right Ventricular Systolic Pressure (Pulmonary Artery Systolic Pressure)

Right ventricular systolic pressure (pulmonary artery systolic pressure) may be estimated based on the sum of systolic right ventricular-atrial pressure gradient, which can be calculated from tricuspid regurgitant velocity, and right atrial pressure. However, it cannot be estimated in patients with tricuspid valve separation causing laminar regurgitation flows. Also, it should be noted that patients with substantial right heart dysfunction might show moderately increased or normal pulmonary artery systolic pressure due to low cardiac output.

### b. Right Atrial Pressure

Right atrial pressure may be estimated on the basis of inferior vena cava diameter at a distance of 1 to 2 cm from the right atrium and whether or not the diameter changes with respiration.

### c. Cardiac Output

Cardiac output is calculated as a product of outflow tract area and velocity-time integral (VTI).

## 5.3 Stress Echocardiography

Contractile reserve and cardiac viability cannot be assessed solely with parameters at rest. Dobutamine-stress or exercise echocardiography may be useful in such cases. Exercise echocardiography is also beneficial in assessing the presence of diastolic dysfunction or pulmonary hypertension in patients with shortness of breath on effort.[103]

## 5.4 Assessment for Causative Conditions

It is important to assess the cause of heart failure and its severity in individual patients. Heart failure may develop in ischemic heart disease, hypertensive heart disease, cardiomyopathy, structural valvular disease, and infective endocarditis. Transesophageal echocardiography should be considered in patients who are suspected to have infective endocarditis but do not show abnormal findings on transthoracic echocardiograms and in patients after valvular surgery whenever necessary.

## 5.5 Assessment in Acute Heart Failure

Hemodynamics should be assessed in patients with acute heart failure. LVEF may be determined by visual estimation in these cases.

Patients with pericardial effusion should be suspected for cardiac tamponade. Myocarditis should be suspected in patients with pericardial effusion associated with transient ventricular wall thickening and diffuse wall hypokinesis as well as elevated levels of inflammatory markers and myocardial proteins in the blood.

Lung ultrasound assessment has been reported to be beneficial in the diagnosis of pulmonary edema. B-lines, that appears as 8 lines in the right and left lungs, are useful for differentiating dyspnea due to acute heart failure than that due to other causes with a 94% sensitivity and 92% specificity.[104]

---

## 6. Imaging (MRI, CT, Nuclear Imaging, and PET) (Table 17)

## 6.1 Cardiac Magnetic Resonance Imaging (MRI)
## 6.1.1 Assessment of Cardiac Morphology and Function

Cardiac MRI is the most reliable imaging technique for the assessment of the morphology and ejection fraction of the left and right ventricles, and left ventricular mass because of its accuracy and reproducibility.[105] Cardiac MRI is used to specify the cause of heart failure according to the results of morphologic assessment and ventricular wall motion based on cine images.[106,107] MRI is highly useful in the assessment of right ventricular and complex congenital heart diseases that are often difficult to be assessed correctly with echocardiography.[108] However, MRI should be used alternative to echocardiography only when necessary because of the latter is less time-consuming and inexpensive method that does not require substantial expertise in imaging analysis.

## 6.1.2 Assessment of Myocardial Tissues

The presence of myocardial fibrosis may be detected with late gadolinium enhancement MRI. The distribution of delayed enhancement is useful information in differentiating from ischemic and non-ischemic cardiomyopathy or in evaluating myocardial viability.[105,107] T1 mapping can be used for similar assessment without using contrast, and is becoming a more common technique.[109] As high signals in T2 weighed images are consistent with edema, this technique can be used in the assessment of inflammation associated with acute myocardial infarction, acute myocarditis, or cardiac sarcoidosis.[107]

## 6.2 Cardiac CT

Cardiac CT can be used to assess the morphology and function of the heart in addition to anatomical features of the coronary arteries. Considering its high specificity for the diagnosis of ischemic heart disease, cardiac CT should be considered for patients with heart failure whose pre-test probability of coronary artery disease is low or moderate or in whom diagnosis is difficult with other non-invasive stress tests to rule out coronary artery disease.[110,111]

## 6.3 Nuclear Imaging
## 6.3.1 Thallium or Technetium

Patients with ischemic cardiomyopathy should be assessed for myocardial ischemia and viability using thallium chlo-

| Table 17.  Recommendations and Levels of Evidence for the Use of Imaging Techniques in Heart Failure | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| **MRI** | | | | |
| **MRI to assess cardiac anatomy and function** Patients who cannot be assessed appropriately with echocardiography, patients with congenital heart disease, and patients who require right ventricular assessment | I | C | A | IVb |
| **Delayed-enhancement MRI** To differentiate between ischemic and non-ischemic cardiomyopathy in patients who cannot be assessed adequately with other procedures | I | C | A | IVb |
| **Delayed-enhancement MRI** To identify underlying heart disease in patients with non-ischemic myocardiopathy | IIa | C | B | IVb |
| **MRI T2-wighed images** To assess the severity of myocardial inflammation | IIa | C | B | V |
| **CT** | | | | |
| **Coronary artery CT** To rule out coronary artery disease in patients with heart failure whose pre-test probability of coronary artery disease is low or moderate | IIa | C | B | IVa |
| **Nuclear cardiology** | | | | |
| **SPECT using thallium chloride or technetium-labeled tracers** To assess myocardial ischemia and myocardial viability in patients with ischemic cardiomyopathy | I | B | A | II |
| **SPECT using thallium chloride or technetium-labeled tracers** To assess myocardial blood flow in patients with dilated cardiomyopathy | IIb | C | C1 | IVa |
| **ECG-gated SPECT** To assess left ventricular volume and LVEF in patients who cannot be assessed appropriately with echocardiography | IIa | C | B | IVb |
| **I-123-BMIPP scintigraphy** To differentiate between ischemic and non-ischemic cardiomyopathy based on a mismatch between I-123-BMIPP uptake and blood flow distribution | IIb | C | C1 | IVb |
| **I-123-MIBG scintigraphy** To assess the severity of heart failure | IIa | C | B | IVb |
| **I-123-MIBG scintigraphy** To predict tolerability/efficacy and assess efficacy of drug therapy in patients with dilated cardiomyopathy | I | A | A | II |
| **Cardiac pool scintigraphy** To assess LVEF in patients who cannot be assessed adequately with other procedures | I | B | B | III |
| **Cardiac pool scintigraphy** To assess right ventricular function and anatomy in patients who cannot be assessed adequately with other procedures | IIa | B | B | IVa |
| **FDG PET** To assess myocardial viability in patients who cannot be assessed adequately with other procedures | IIb | C | C1 | IVb |
| **FDG PET** To detect active lesions of cardiac sarcoidosis | I | C | A | IVb |

BMIPP, β-methyl-p-iodophenyl-pentadecanoic acid; CT, computed tomography; FDG PET, fluorodeoxyglucose positron emission tomography; LVEF, left ventricular ejection fraction; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography.

ride or technetium (Tc) labeled radiopharmaceuticals.[111–113] Single-photon emission computed tomography (SPECT) may also provide additional information on cardiac function such as left ventricular volume and LVEF.

### 6.3.2 I-123 BMIPP and I-123 MIBG
Iodine-123-β-methyl-p-iodophenyl-pentadecanoic acid (I-123

BMIPP), a marker for myocardial fatty acid metabolism, is used to detect myocardial damage associated with infarction, myocardial ischemia, or non-ischemic cardiomyopathy. As washout rate of I-123- metaiodobenzylguanidine (I-123 MIBG) increases and heart/superior mediastinum ratio (H/M) on delayed images decreases in patients with heart failure, this technique can be used in severity assessment.[114–118]

**Table 18.** Recommendations and Levels of Evidence for the Use of Invasive Approaches With Catheterization in Heart Failure

|  | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| **Coronary angiography**<br>Patients with heart failure refractory to drug therapy or complicated with angina pectoris, or those who experienced symptomatic ventricular arrhythmia or cardiac arrest | I | C | B | IVb |
| **Invasive pulmonary artery pressure monitoring**<br>Patients with ARDS or circulation failure in whom adequate clinical assessment cannot be made | I | C | B | IVb |
| **Coronary angiography**<br>Patients in whom heart failure is suspected to be caused by ischemia | IIa | C | B | V |
| **Invasive pulmonary artery pressure monitoring**<br>Patients with acute heart failure who have persistent symptoms or unstable hemodynamics | IIa | C | B | IVa |
| **Endomyocardial biopsy**<br>For confirmatory diagnosis of specific disease that affect the strategies to treat heart failure | IIa | C | B | V |
| **Invasive pulmonary artery pressure monitoring**<br>Normotensive patients with symptomatic acute heart failure who respond well to diuretics and vasodilators | III | B | D | II |
| **Coronary angiography or endomyocardial biopsy**<br>As routine procedures in patients with heart failure | III | C | D | VI |

ARDS, acute respiratory distress syndrome.

I-123 MIBG is useful in predicting the prognosis of heart failure due to dilated cardiomyopathy and hypertrophic cardiomyopathy,[119–121] assessing tolerability of and predicting the efficacy of β-blocker therapy in dilated cardiomyopathy, and evaluating the efficacy of drug therapy in heart failure.[122–124]

### 6.3.3 Tc-99m Pyrophosphate
Tc-99m pyrophosphate (PYP) is useful in the detection of myocardial necrosis and the diagnosis of mutant or wild-type transthyretin-related cardiac amyloidosis.[125]

### 6.3.4 Gallium Scintigraphy
Gallium scintigraphy is used to detect new lesions of cardiac sarcoidosis, but its diagnostic sensitivity is lower than fluorodeoxyglucose positron emission tomography (FDG PET).[123–125] Gallium scintigraphy is used to detect the presence of inflammatory diseases such as myocarditis and infective endocarditis and cardiac lesions of malignant lymphoma.[107,112]

### 6.3.5 Cardiac Blood Pool Scintigraphy
Cardiac blood pool scintigraphy is a technique to determine LVEF using Tc-labeled human serum albumin or Tc-labeled red blood cells,[112,126] and can be used to asses left ventricular diastolic function.[126] This technique is also useful in assessing the function of the right ventricle, which has a complex anatomy.[127,128] This is used for patients in whom assessment with echocardiography, MRI, CT, and ECG-gated SPECT is difficult.

## 6.4 PET
PET can be used in combination with N-13 ammonia to assess the severity of myocardial ischemia, and in combination with F-18 FGD to assess myocardial viability and detect active lesions of cardiac sarcoidosis.[129,130]

# 7. Cardiac Catheterization (Hemodynamics and Biopsy)

Common indications for right side heart catheterization, left side heart catheterization, and endomyocardial biopsy in patients with heart failure are summarized in **Table 18**.

# 8. Exercise Tolerance

Exercise tolerance is the most important determinant of functional status in patients with heart failure. Exercise intolerance is a major manifestation in patients with heart failure, which reflects the severity of heart failure, and is closely related to decreases in activities of daily living and quality of life (QOL) in patients. One of the main purposes of heart failure treatment is to improve exercise tolerance, which is a factor of better prognosis.

## 8.1 NYHA Functional Classification (Table 8)[7]
The New York Heart Association (NYHA) functional classification is used to assess the severity of heart failure based on the level of ADL,[131] and reflects the QOL of patients. However, this is not a quantitative or objective scaling system.

## 8.2 Specific Activity Scale
Specific activity scale (SAS) describes the amount of exercise to perform a given activity of daily living with the number of metabolic equivalent units (METs) (**Table 19**).[132,133] With this scale, the minimum amount of exercise that causes

| Table 19. Questionnaire on Physical Activity |
|---|
| In the Specific Activity Scale (SAS), patients are asked to answer the following questions with "yes," "hard to do" or "I don't know". The amount of exercise (in METs) described in the first question to which the patient answered "hard to do" indicates the minimum amount of physical activity to provoke symptoms, and is recorded as the SAS score. |
| 1. Can you have a comfortable sleep at night? (≤1 MET) |
| 2. Do you feel comfortable in the lying position? (≤1 MET) |
| 3. Can you take meals or wash your face by yourself? (1.6 METs) |
| 4. Can you go to the bathroom by yourself? (2 METs) |
| 5. Can you change your clothes by yourself? (2 METs) |
| 6. Can you do kitchen work or sweep the room with a broom? (2 to 3 METs) |
| 7. Can you make your bed by yourself? (2 to 3 METs) |
| 8. Can you swab the floor? (3 to 4 METs) |
| 9. Can you have a shower without trouble? (3 to 4 METs) |
| 10. Can you practice radio gymnastic exercises without any trouble? (3 to 4 METs) |
| 11. Can you walk 100–200 m of level ground at the same speed as healthy persons do (4 km/hr) without any trouble? (3 to 4 METs) |
| 12. Can you garden (weeding for a brief time, etc.) without any trouble? (4 METs) |
| 13. Can you take a bath by yourself? (4 to 5 METs) |
| 14. Can you go upstairs at the same speed as healthy persons do without any trouble? (5 to 6 METs) |
| 15. Can you do light farming (digging the garden, etc.)? (5 to 7 METs) |
| 16. Can you walk 200 m of level ground at a quick pace without any trouble? (6 to 7 METs) |
| 17. Can you remove snow? (6 to 7 METs) |
| 18. Can you practice tennis (or ping pong) without any trouble? (6 to 7 METs) |
| 19. Can you practice jogging (at about 8 km/hr) over a distance of 300 to 400 meters without any trouble? (7 to 8 METs) |
| 20. Can you practice swimming without any trouble? (7 to 8 METs) |
| 21. Can you practice rope skipping without any trouble? (≥8 METs) |
| Minimum amount of physical activity to provoke symptoms: _____ METs |

METs, metabolic equivalents. (Excerpted from Sasayama S, et al. 1992[132] and The Japanese Intractable Diseases Information Center[133])

| Table 20. A Comparison of Major Exercise Capacity Measures in Patients With Heart Failure | | |
|---|---|---|
| NYHA classification | Specific Activity Scale (SAS) | Percent peak oxygen uptake (% peak V̇O₂) |
| I | 6 METs or more | 80% or more of the reference level |
| II | 3.5 to 5.9 METs | 60 to 80% of the reference level |
| III | 2 to 3.4 METs | 40 to 60% of the reference level |
| IV | 1 to 1.9 METs or less | Impossible to determine or <40% of the reference level |

There is no established formula indicating exact correspondence between NYHA functional classes and SAS. In this table, according to a consensus among experts, the following assumption was used: the amount of exercise is 2 METs for walking inside a room, 3.5 METs for usual walking, 4 METs for light exercise or stretching exercise, 5 to 6 METs for fast walking, and 6 to 7 METs for walking upstairs.
METs, metabolic equivalents; NYHA, New York Heart Association. (Adapted from The Japanese Intractable Diseases Information Center[133])

reported that the six-minute walking distance well correlates with NYHA functional classification and peak oxygen uptake (peak V̇O₂),[135] and is useful in predicting the prognosis of patients with heart failure.[136]

## 8.4 Cardiopulmonary Exercise Testing

The most objective index of exercise tolerance is oxygen uptake during maximal exercise. Peak V̇O₂, which is measured during cardiopulmonary exercise testing (CPX),[137] is suitable parameter in assessing the prognosis of patients with heart failure,[138–141] selecting candidates for heart transplantation,[138,141–143] and classifying the severity of heart failure.[144] Patients with a Peak V̇O₂ of <14 mL/kg/min have a poor prognosis,[138] and those with <10 mL/kg/min have an extremely poor prognosis. When peak V̇O₂ is expressed as percentage of age-predicted peak V̇O₂ (% peak V̇O₂), patients with a % peak V̇O₂ of <50% are considered to have a poor prognosis.[145] **Table 20** shows the relationship between the NYHA classification, SAS, and % peak V̇O₂.[133]

The anaerobic threshold, that is defined as the point during exercise when anaerobic metabolism occurs in addition to aerobic metabolism, accounts for about 50 to 55% of the maximal exercise capacity. This threshold is used as an index of daily activity level,[137,146] on which allowable exercise level[147] and exercise prescriptions[148] are determined.

The V̇E/V̇CO₂ slope indicates the tidal volume needed to eliminate carbon dioxide produced during metabolism, and is considered as a factor related to dyspnea on exertion in patients with heart failure. Patients with a V̇E/V̇CO₂ slope of >35 are considered to have a poor prognosis.[149]

**Table 21** summarizes recommendations for exercise capacity evaluation in heart failure and their evidence levels.

symptoms of heart failure may be quantified using a unit of oxygen uptake.

## 8.3 Six-Minute Walking Test

The six-minute walking test is a maximal exercise test to measure the maximal distance an individual able to walk in 6 minutes. The reference value for the Japanese population is calculated by multiplying [454−0.87×age (years)−0.66×weight (kg)] ±82 (2SD) by height (m).[134] It has been

## IV. Prevention of Heart Failure

The development, progression (exacerbations), and recurrence of heart failure should be prevented through lifestyle management such as diet and exercise and treatment inter- ventions to control risk factors for heart failure and manage asymptomatic heart failure (**Table 22**). It is also important that patients are managed continuously in hospitals, local

| Table 21. Recommendations and Level of Evidence for Exercise Capacity Evaluation in Heart Failure | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| **Medical interview**<br>To survey the patient's exercise capacity, mental status, cognitive function, and social environment | I | B | B | IVa |
| **Cardiopulmonary exercise testing**<br>To consider the indication of heart transplantation and other advanced treatment | I | B | B | II |
| **Cardiopulmonary exercise testing**<br>To specify the cause in patients in whom dyspnea on exertion or easy fatigability limits their physical activities | I | B | B | IVb |
| **Measurement of peak oxygen uptake**<br>To assess prognosis | I | B | B | II |
| **Cardiopulmonary exercise testing**<br>To develop an exercise prescription | IIa | B | B | II |
| **Cardiopulmonary exercise testing**<br>In patients with atrial fibrillation or pacing, to assess heart rate response, to determine optimal exercise programs, to evaluate blood pressure, arrhythmia, strength of physical activities during exercise, to assess change in exercise capacity over time, and to assess treatment efficacy | IIa | B | B | II |
| **Cardiopulmonary exercise testing**<br>As a routine test procedure | III | C | C2 | VI |

communities, and their home by multidisciplinary approach involving diverse healthcare professionals, including physicians, nurses, pharmacists, dieticians, and physical therapists and hospital-clinic collaborations.

# 1. Hypertension

Antihypertensive treatment has been shown to prevent the development of heart failure and improve the prognosis of patients with hypertension.[150–153] In addition to lifestyle modifications such as low-salt diet and body weight management, patients should be treated with antihypertensive drugs (e.g., angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs]), diuretics and $\beta$-blockers.[154]

# 2. Coronary Heart Disease

Patients with coronary artery disease should be treated with ACE inhibitors to prevent cardiovascular events including heart failure and improve the ptognosis.[155] Patients after myocardial infarction should be treated with ACE inhibitors,[156–158] $\beta$-blockers,[159] statins,[160–162] and/or mineralocorticoid receptor antagonists (MRA)[163–165] as secondary prevention for cardiovascular events.[166] ARBs are indicated for patients who are intolerant to ACE inhibitors, especially those with left ventricular dysfunction.[167,168]

In the Occluded Artery Trial (OAT)[169] that investigated the efficacy of percutaneous coronary intervention (PCI) in the prevention of heart failure in patients after acute myocardial infarction with a LVEF of <50%, PCI to the culprit lesion of complete occlusion during the period between 3 and 28 days after the onset was not effective in preventing cardiac accidents including heart failure for four years after PCI.

# 3. Obesity and Diabetes Mellitus

As obesity and diabetes mellitus are associated with the development of heart failure,[170–173] and diabetes mellitus and metabolic syndromes, which are conditions caused by insulin resistance, are major risk factors for cardiovascular diseases, patients with these conditions should receive comprehensive risk management including lifestyle modifications for weight management and exercise therapy as well as drug therapy.[174]

In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), the sodium-glucose cotransporter 2 (SGLT2) inhibitor empagliflozin reduced the risk of hospitalization for and death from heart failure in patients with type 2 diabetes mellitus and a history of cardiovascular disease, and reduced the rate of hospitalization for heart failure in patients without a history of cardiovascular events.[175–177] Similarly, in the Canagliflozin Cardiovascular Assessment Study (CANVAS), canagliflozin reduced the risk of hospitalization for heart failure in patients with type 2 diabetes and a high cardiovascular risk (34% of the participants received treatment for the primary prevention of cardiovascular events and the remaining 64% had a history of cardiovascular disease).[178] These findings indicate that SGLT2 inhibitors are effective in preventing heart failure in patients with type 2 diabetes mellitus who have a history of cardiovascular disease, but further studies should be conducted to demonstrate their efficacy in primary prevention of cardiovascular events or in people aged 75 and over.

# 4. Smoking

Smokers are strongly advised to receive smoking cessation treatment.

**Table 22.** Recommendations and Level of Evidence for Interventions to Modify Risk Factors for Preventing Prevent Heart Failure

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| **Hypertension** | | | | |
| Treatment of hypertension including low-salt diet and weight reduction | I | A | A | I |
| Thiazide diuretics | I | A | A | I |
| **Coronary artery disease** | | | | |
| ACE inhibitors in patients with coronary artery disease* | I | A | A | I |
| Statins in patients with coronary artery disease | I | A | A | I |
| ACE inhibitors in patients with left ventricular contractile dysfunction | I | B | A | II |
| β-blockers in patients with myocardial infarction | I | B | A | II |
| MRAs in patients with myocardial infarction | I | B | A | II |
| PCI to the culprit lesion of complete occlusion during the period between 3 and 28 days after the onset of myocardial infarction | III | B | C2 | II |
| **Obesity and diabetes mellitus** | | | | |
| General lifestyle modifications through weight reduction and increased physical activity | I | A | A | I |
| Treatment with SGLT2 inhibitors (empagliflozin,** canagliflozin***) in patients with type 2 diabetes mellitus and a history of cardiovascular disease | I | A | B | II |
| Smoking cessation | I | C | B | IVb |
| Alcoholic control | IIa | C | C1 | VI |
| Physical activity and exercise habits | I | B | B | IVa |
| **Others** | | | | |
| Comprehensive multidisciplinary (educational) programs and team medical care | I | C | C1 | VI |
| Preventions of infectious disease including vaccinations | IIa | C | B | IVb |

*ARBs are recommended for patients intolerant of ACE inhibitors (especially those with left ventricular dysfunction).
**In the EMPA-REG OUTCOME study of empagliflozin,[175] all participants had a history of cardiovascular disease.
***In the CANVAS study of canagliflozin,[178] 34% of the participants were at high risk of cardiovascular events and received the treatment for primary prevention, and 66% of the participants had a history of cardiovascular disease. The dose range of canagliflozin in the CANVAS study was wider than the approved dose range in Japan. ARB, angiotensin II receptor blocker; ACE, angiotensin converting enzyme; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention; SGLT, sodium glucose cotransporter.

## 5. Alcohol

As there is a U-shaped curve between alcohol consumption and the incidence of heart failure,[179–181] people who have habitual drinking should be advised to drink moderately.

## 6. Physical Activity and Exercise

A dose-related inverse relation between physical activity and the risk of heart failure has been reported.

## 7. Others

Patients with stable, Stage C heart failure should be managed appropriately to prevent rehospitalizations due to worsening heart failure. In order to prevent rehospitalizations for heart failure, patients and their family members should be educated well on the nature of heart failure and the importance of keeping treatment adherence, and receive comprehensive programs (such as patient education) through social supports and multidisciplinary healthcare support.

<div style="border:1px solid black; text-align:center">

# V. Basic Principles for the Treatment of Heart Failure

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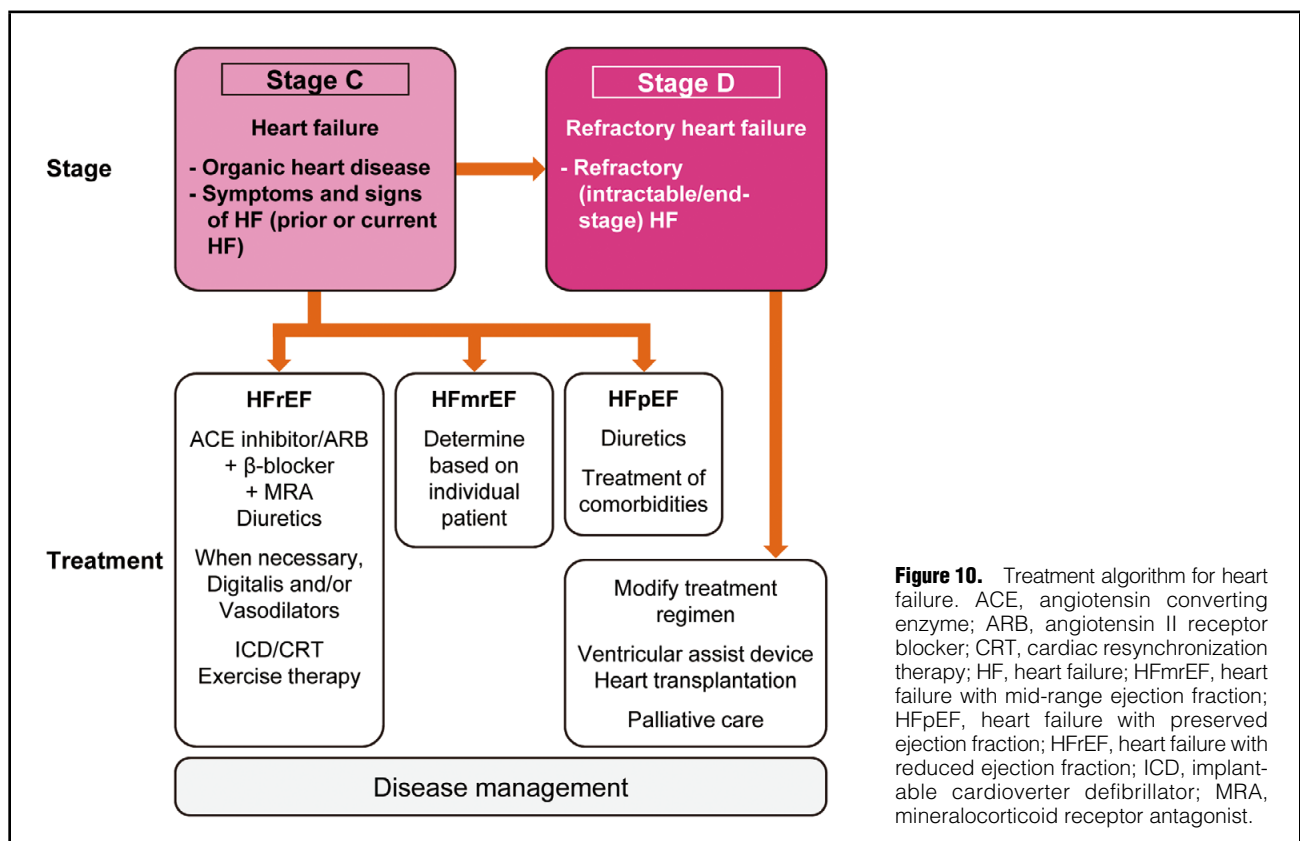## 1. Goals of Heart Failure Treatment (Figure 1)

The present guidelines classify the development and progression of heart failure into 4 stages. Stages A and B represent conditions at high risk of heart failure rather than the presence of heart failure. The guidelines include recommendations on treatment for patients at risk stages because it is critically important to prevent the onset of heart failure. This staging classification is based on the criteria that was first described in the ACC/AHA guidelines in 2005 and the concept of this classification has remained important for more than a decade also in Japan.

The primary goals of treatment for each stage of heart failure are to prevent the progression to the next stage. Specifically, the primary goals are to prevent structural heart disease that may cause heart failure in Stage A (patients at risk of heart failure); to prevent the progression of structural heart disease and prevent the onset of heart failure in Stage B (patients with structural heart disease); and to improve the prognosis and control symptoms of heart failure in Stage C (patients with established heart failure). The primary goals for patients with stage D heart failure (refractory heart failure) are essentially the same for those in Stage C, but controlling symptoms are the most important goal in patients with end-stage heart failure. Stage-based treatment is therefore important to achieve optimal treatment goals for different stages of patients (See

Figure 1[20] in Section "**1. Definition and Classification**" in Chapter "**II. General Principles**").

## 2. Treatment Algorithms for Heart Failure (Figure 10)

The clinical course of heart failure is generally chronic and progressive. Heart failure often manifests as acute heart failure, and then progresses to compensated, chronic heart failure (Stage C, the stage of heart failure). Patients with established heart failure show chronic progression, and may have repeated episodes of acute decompensated heart failure. Repeated acute exacerbations gradually lead to the development of more severe heart failure. Sudden death may occur during the progression of heart failure. Accordingly, heart failure does not progress linearly from Stage C to Stage D (refractory heart failure), and it is quite difficult to predict how the disease progresses (See **Figure 1[20]** in Section "**1. Definition and Classification**" in Chapter "**II. General Principles**"). Heart failure progresses in a way quite different from malignant tumors. Patients who do not respond to standard treatment and have exacerbations repeatedly progress to Stage D heart failure. The clinical course from Stage C to D differs substantially among patients depending on the severity of underlying heart disease and comorbidities. This makes it even difficult to predict the course of heart failure.



**Figure 10.** Treatment algorithm for heart failure. ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CRT, cardiac resynchronization therapy; 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; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid receptor antagonist.

Patients with Stage C heart failure need treatment both for chronic heart failure and for acute exacerbations of chronic heart failure. As many patients with heart failure are in Stage C and will stay in this stage even after symptomatic improvement, smooth transition from acute-phase to chronic-phase treatment is important. Treatment modalities for Stage C heart failure include those for heart failure with reduced LVEF (HFrEF) and those for heart failure with preserved LVEF (HFpEF) (**Figure 10**). As treatments for heart failure with mid-range LVEF (HFmrEF) have not been fully evaluated, physicians should select treatments for them according to the individual patient's condition. Although many patients require diuretics to control their symptoms of heart failure, no evidence has demonstrated that diuretics improve the prognosis of patients with heart failure. Dose adjustment of diuretics based on the severity of organ congestion is important. Patients who still have severe symptoms at rest despite sufficient Stage C treatment and are repeatedly hospitalized for worsening heart failure should receive Stage D treatment.

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# VI. Pharmacological Therapy

## 1. Heart Failure With Reduced Ejection Fraction (HFrEF) (Tables 23, 24, and 25)

### 1.1 Drugs for the Treatment of HFrEF

### 1.1.1 ACE Inhibitors
The results of large-scale clinical studies such as the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)[182] and the Studies of Left Ventricular Dysfunction (SOLVD) trial[183,184] have demonstrated that angiotensin converting enzyme (ACE) inhibitors improve the prognosis of patients with heart failure due to left heart dysfunction and a reduction of the risk of cardiovascular events. Long-term follow-up of patients who participated in these large-scale studies have demonstrated that ACE inhibitors are also effective in those with asymptomatic left ventricular systolic dysfunction in reducing hospitalizations for heart failure and improving prognosis.[185] ACE inhibitors should thus be given to all patients with left ventricular systolic dysfunction.

### 1.1.2 Angiotensin II Receptor Blockers (ARBs)
The results of large-scale clinical studies[186–188] have indicated that ARBs are as effective as ACE inhibitors in reducing cardiovascular events in patients with chronic heart failure due to left ventricular systolic dysfunction. Accordingly, ARBs should be used for patients who cannot receive ACE inhibitors because of intolerance or other reasons.

### 1.1.3 Mineralocorticoid Receptor Antagonists (MRAs)
In two large-scale clinical studies in patients with contractile dysfunction and clinical studies in Japan, the benefits of spironolactone and eplerenone have been confirmed.[163,164,189,190] Accordingly symptomatic patients with LVEF<35% should be treated with MRAs if not contraindicated. However, it has been reported that the use of spironolactone in combination with ACE inhibitors or ARBs may increase the risk of death and hospitalization through increasing serum potassium levels.[191] Spironolactone should not be used in combination with both ACE inhibitors and ARBs. Careful monitoring should be performed when patients with an estimated glomerular filtration rate (eGFR) of <30 mL/min or a serum potassium level of ≥5.0 mEq/L at the start of the treatment with MRAs.

### 1.1.4 β-Blockers
Large-scale clinical studies have demonstrated that bisoprolol, metoprolol succinate, and carvedilol, a nonselective β-blocker/α₁-blocker, improves prognosis in patients with heart failure.[192–195] Evidence has also been published on the efficacy of β-blockers in patients with left ventricular dysfunction without heart failure symptoms.

Treatment with β-blockers for patients with NYHA class III or IV heart failure should be started in the hospital setting to confirm improvement in fluid retention and until the patient is in a stable condition. The dose should then be gradually titrated upwards in intervals of a few days to 2 weeks. Before initiating β-blocker therapy, the absence of underlying conditions that are contraindicated for β-blockers should be confirmed. Dose escalation should be made according to symptoms, pulse rate, blood pressure, cardiothoracic ratio, and chamber size measured with echocardiography, and patients should be monitored carefully for any signs/symptoms of worsening heart failure, excessive hypotension, and bradycardia.

β-blocker therapy should be initiated in the hospital setting during the recovery phase of acute exacerbation of heart failure.[196] Patients should receive the initial doses in the hospital setting, and the dose should then be escalated in the ambulatory setting. When heart failure worsens during β-blocker therapy, the treatment should be continued whenever possible, but discontinuation may be unavoidable depending on the severity of heart failure. β-blocker therapy should be restarted whenever possible after the condition becomes stable.[197]

Large-scale clinical studies of β-blockers in chronic heart failure have demonstrated the efficacy of carvedilol, bisoprolol, and metoprolol succinate. In Japan, the use of carvedilol and bisoprolol in chronic heart failure is covered by the National Health Insurance.

### 1.1.5 Diuretics
Diuretics are the most effective drugs in the treatment of symptoms of congestion in heart failure, such as dyspnea on exertion and edema. Loop diuretics should be tried first, and thiazide diuretics may be added for patients who do not respond well to loop diuretics. However, these diuretics may cause hypokalemia and hypomagnesemia, increase the risk of digitalis intoxication, and induce serious ventricular arrhythmia. During diuretic therapy, serum levels of potassium and magnesium should be monitored to keep appropriate levels.

Loop diuretics have been used commonly to alleviate congestion during acute exacerbations of heart failure. Many patients with chronic heart failure have routinely received long-term treatment with loop diuretics. Retrospective analyses using data of large-scale clinical studies

| Table 23. Recommendations and Levels of Evidence for Medications for HFrEF | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| **ACE inhibitors** | | | | |
| Use in all patients (including asymptomatic patients) unless contraindicated | I | A | A | I |
| **ARBs** | | | | |
| Use in patients intolerable ACE inhibitors | I | A | A | I |
| Concomitant use with ACE inhibitors | IIb | B | C2 | II |
| **β-blockers** | | | | |
| Use in symptomatic patients to improve prognosis | I | A | A | I |
| Use in asymptomatic patients with left ventricular systolic dysfunction | IIa | B | A | II |
| Use for rate control in patients with atrial fibrillation with a rapid ventricular response | IIa | B | B | II |
| **MRAs** | | | | |
| Use in patients with NYHA Class II-IV, LVEF <35% who are receiving loop diuretics and ACE inhibitors | I | A | A | I |
| **Loop diuretics, thiazide diuretics** | | | | |
| Use in patients with symptoms of congestion | I | C | C1 | III |
| **Vasopressin V₂ receptor antagonists** | | | | |
| Start treatment during hospitalization to relieve symptoms of fluid retention due to heart failure in patients who do not respond well to other types of diuretics including loop diuretics | IIa | B | B | II |
| **Other diuretics such as carbonate dehydratase inhibitors and osmotic diuretics** | | | | |
| Diuretics other than loop diuretics, thiazide diuretics, and MRAs | IIb | C | C2 | III |
| **Digitalis** | | | | |
| Patients in sinus rhythm (maintain digoxin concentration in blood at ≤0.8 ng/mL) | IIa | B | C1 | II |
| Use for rate control in patients with atrial fibrillation with a rapid ventricular response | IIa | B | B | II |
| **Oral inotropic drugs** | | | | |
| Use short-term to improve QOL and discontinue intravenous inotropic drugs | IIa | B | C1 | II |
| Use when initiating β-blockers | IIb | B | C1 | II |
| Long-term use in asymptomatic patients | III | C | D | III |
| **Amiodarone** | | | | |
| Use in patients with a history of serious ventricular arrhythmia leading to cardiac arrest | IIa | B | C1 | II |
| **Concomitant use of isosorbide dinitrate and hydralazine** | | | | |
| Use as an alternative to ACE inhibitors or ARBs | IIb | B | C2 | II |
| **Others** | | | | |
| Treatment with calcium channel blockers in patients without angina pectoris or hypertension | III | B | C2 | II |
| Long-term oral treatment with Vaughan Williams Class I antiarrhythmic agents | III | B | D | III |
| Use of α-blockers | III | B | D | II |

ARB, angiotensin II receptor blocker; ACE, angiotensin converting enzyme; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; QOL, quality of life; SGLT, sodium glucose cotransporter.

**Table 24.** Medications for HFrEF According to Class of Recommendation

**Class of Recommendation I**

ACE inhibitors: Use in all patients (including asymptomatic patients) unless contraindicated

ARBs: Use in patients intolerable ACE inhibitors

β-blockers: Use in symptomatic patients to improve prognosis

MRAs: Use in patients with NYHA Class II-IV, LVEF <35% who are receiving loop diuretics and ACE inhibitors

Loop diuretics, thiazide diuretics: Use in patients with symptoms of congestion

**Class of Recommendation IIa**

β-blockers: Use in asymptomatic patients with left ventricular systolic dysfunction

β-blockers or digitalis: Use for rate control in patients with atrial fibrillation with a rapid ventricular response

Vasopressin receptor antagonists: Start treatment during hospitalization to relieve symptoms of fluid retention due to heart failure in patients who do not respond well to other types of diuretics including loop diuretics

Digitalis (maintain digoxin concentration in blood at ≤0.8 ng/mL): Use in patients in sinus rhythm

Oral inotropic drugs: Use short-term to improve QOL and discontinue intravenous inotropic drugs

Amiodarone: Use in patients with a history of serious ventricular arrhythmia leading to cardiac arrest

**Class of Recommendation IIb**

ARBs: Concomitant use with ACE inhibitors

Concomitant use of isosorbide dinitrate and hydralazine: Use as an alternative to ACE inhibitors or ARBs

Oral inotropic drugs: Concomitant use when initiating β-blockers

Other diuretics such as carbonate dehydratase inhibitors and osmotic diuretics: Diuretics other than loop diuretics, thiazide diuretics, and MRAs

**Class of Recommendation III**

Oral inotropic drugs: Use long term in asymptomatic patients

Calcium channel blockers: Use in patients without angina pectoris or hypertension

Long-term oral treatment with Vaughan Williams Class I antiarrhythmic agents

Use of α-blockers[210]

ARB, angiotensin II receptor blocker; ACE, angiotensin converting enzyme; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; QOL, quality of life; SGLT, sodium glucose cotransporter.

**Table 25.** Medications for HFrEF: Drugs and Dosing Regimens

| Drugs* | Dosing regimen |
|---|---|
| **ACE inhibitors** | |
| Enalapril | Start at 2.5 mg/day, and maintain at 5 to 10 mg/day once daily |
| Lisinopril | Start at 5 mg/day, and maintain at 5 to 10 mg/day once daily |
| **ARBs** | |
| Candesartan | Start at 4 mg/day (2 mg/day in severe cases or renal dysfunction), and maintain at 4 to 8 mg/day once daily (maximum daily dose: 12 mg/day) |
| **MRAs** | |
| Spironolactone | Start at 12.5 mg/day, and maintain at 25 to 50 mg/day once daily |
| Eplerenone | Start at 25 mg/day, and maintain at 50 mg/day once daily |
| **β-blockers** | |
| Carvedilol | Start at 2.5 mg/day,** and maintain at 5 to 20 mg/day twice daily |
| Bisoprolol | Start at 0.625 mg/day,** and maintain at 1.25 to 5 mg/day once daily |
| **Diuretics** | |
| Furosemide | 40 to 80 mg/day once daily |
| Azosemide | 60 mg/day once daily |
| Torasemide | 4 to 8 mg/day once daily |
| Tolvaptan | 7.5 to 15 mg/day once daily |
| Trichlormethiazide | 2 to 8 mg/day once daily |
| **Antiarrhythmic drugs** | |
| Amiodarone | Start at 400 mg/day, and maintain at 200 mg/day once or twice daily |
| **Digitalis** | |
| Digoxin | 0.125 to 0.25 mg/day once daily |
| **Oral inotropic drugs** | |
| Pimobendan | 2.5 to 5.0 mg/day once daily |

*National Health Insurance-covered medications. **Start at a half dose in severe cases. ARB, angiotensin II receptor blocker; ACE, angiotensin converting enzyme; MRA, mineralocorticoid receptor antagonist.

have concluded that furosemide and other loop diuretics may deteriorate prognosis in patients with heart failure.[198–201] The long-acting loop diuretic azosemide is considered not to affect neurohumoral factors substantially as it does not cause significant hemodynamic changes. In a study that compared azosemide and furosemide in Japan, the primary composite endpoint of cardiovascular death or hospitalization for worsening heart failure occurred less frequently in patients receiving azosemide than those receiving furosemide.[202]

Tolvaptan, a vasopressin V2 receptor antagonist, blocks vasopressin V2 receptors on renal medullary collecting duct cells, and thereby increases water excretion. In the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST), a randomized, placebo-controlled study of tolvaptan in patients with acute worsening heart failure, the vasopressin V2 receptor antagonist improved symptoms of congestion but did not improve

long-term outcome of patients with heart failure.[203,204]

### 1.1.6 Antiarrhythmic Drugs

Amiodarone is expected to prevent serious ventricular arrhythmias such as ventricular tachycardia and ventricular fibrillation, and reduce the risk of sudden death in patients with heart failure. Patients receiving amiodarone should periodically undergo thyroid function tests, pulmonary function tests, chest X-ray, determination of KL-6 concentration in the blood, and ophthalmological tests to detect adverse drug reactions to amiodarone (e.g., thyroid function disorder, interstitial pneumonia, corneal pigmentation, and abnormal liver function tests) promptly. As the use of amiodarone for the treatment of atrial fibrillation associated with heart failure is covered by the National Health Insurance in Japan, this drug is used also to maintain sinus rhythm or control heart rate.

### 1.1.7 Vasodilators

Western guidelines recommend combination therapy using hydralazine and isosorbide dinitrate to improve prognosis in patients who cannot receive ACE inhibitors for various

| Table 26. Recommendations and Levels of Evidence for Medications for HFpEF | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| **Diuretics** | | | | |
| Use of diuretics to relieve symptoms of congestion | I | C | C1 | VI |
| Preference of long-acting drugs when using loop diuretics | IIb | C | C1 | III |
| Out-patient use of tolvaptan introduced during hospitalization for acute heart failure to control congestion* | IIa | C | C1 | IVb |
| **ACE inhibitors/ARBs** | | | | |
| Increasing the dose of ACE inhibitors/ARBs to maximum tolerable level to reduce the risk of clinical events | IIb | C | C1 | III |
| **β-blockers** | | | | |
| Increasing the dose of β-blockers to maximum tolerable level to reduce the risk of clinical events | IIb | C | C1 | III |
| **MRAs** | | | | |
| Increasing the dose of MRAs to maximum tolerable level to reduce the risk of clinical events | IIb | C | C1 | III |
| **Nitrates** | | | | |
| Use of nitrates to improve prognosis and increase activities of daily living | III | B | D | II |

*Tolvaptan must be introduced during hospitalization. There are no data on the efficacy and safety of long-term treatment with tolvaptan. ARB, angiotensin II receptor blocker; ACE, angiotensin converting enzyme; MRA, mineralocorticoid receptor antagonist.

reasons.[205,206] In Japan, such combination therapy is not used proactively. Calcium channel blockers are not generally recommended as long-term treatment because calcium channel blockers may worsen heart failure.

### ▌1.1.8 Digitalis
In 1997, results from the Digitalis Investigation Group (DIG) trial were published and described that digoxin reduces the risk of hospitalization for worsening heart failure in patients with normal sinus rhythm, but does not improve their prognosis.[207] The risk of death related to arrhythmia rather tended to increase with the use of digoxin in this population. On the other hand, patients with heart failure and atrial fibrillation are often treated with digitalis to control heart rate and increase left ventricular filling period. Digitalis is used to relieve symptoms, but there is no evidence regarding whether it may improve the prognosis of patients with left ventricular systolic dysfunction and atrial fibrillation.

### ▌1.1.9 Oral Inotropic Drugs
Since 1980s, large clinical studies have failed to demonstrate the efficacy of oral inotropic drug in heart failure,[208,209] and experts in the United States do not recommend oral inotropic drugs for the treatment of heart failure. However, given the perspective that prolonging the survival is not the sole purpose of the treatment for patients with chronic heart failure, the possible clinical benefits of oral inotropic drugs in this patient population should be reconsidered.

### ▌1.2 Dug Therapy for Heart Failure With Mid-Range Ejection Fraction (HFmrEF)
Some data have indicated that β-blockers and other drugs used to treat HFrEF are also effective in the treatment of HFmrEF.[34] However, no conclusive evidence has been obtained in this patient population and further studies are awaited.

### ▌1.3 Heart Failure Treatment by Stage

### ▌1.3.1 Stage C (Symptomatic Heart Failure)
NYHA class II: Introduce β-blockers in addition to ACE inhibitors. Patients with symptoms of fluid retention such as pulmonary congestion and generalized edema should receive diuretics. MRAs should be added to patients with LVEF <35%.

NYHA class III: Similar to NYHA class II patients, ACE inhibitors, β-blockers, and diuretics should be used. MRAs should be added to patients with LVEF <35%.

NYHA class IV: Patients should be hospitalized and receive parenteral medications such as catecholamines, phosphodiesterase (PDE) III inhibitors, diuretics, and carperitide to stabilize the condition. After the condition is stabilized, these regimens should be switched to oral drugs such as ACE inhibitors, diuretics, MRAs, and digitalis. β-blockers should also be tried.

### ▌1.3.2 Stage D (Refractory Heart Failure)
Treatment regimens should be reviewed whether the patient is receiving appropriate fluid management and drug therapy. The indication of heart transplantation should be considered (See Section "**3. Heart Transplantation**" in Chapter "**XI. Surgical Treatment**" Tables 70, 71,[522] and 72). Patients who are not indicated for heart transplantation or ventricular assist devices should receive palliative care to alleviate symptoms based on a consent given by the patient and his or her family members (See Chapter "**XIII. Palliative Care**" for details).

## 2. Heart Failure With Preserved Ejection Fraction (HFpEF) (Table 26)

No prospective interventional studies on drugs for the treatment of HFpEF have demonstrated a clear reduction in the risk of death or clinical events. At present, patients with HFpEF should be treated to control the causative condition and thereby alleviate heart failure symptoms, and to treat comorbid conditions that may worsen heart failure.

### 2.1. Interventions to Reduce Disease Burden

### 2.1.1 Treatment for Congestion
Diuretics are beneficial in improving subjective symptoms caused by congestion. Loop diuretics are used commonly. In the Japanese Multicenter Evaluation of Long-versus short-acting Diuretics in Congestive heart failure (J-MELODIC) trial conducted in Japan, the long-acting loop diuretic azosemide was superior to the short-acting loop diuretic furosemide in improving prognosis, especially in preventing re-worsening heart failure.[202] In Japan, an increasing number of patients start tolvaptan therapy during hospitalization for acute heart failure, and continue the treatment after discharge.

### 2.1.2 Treatment for Hypertension
See Section "**6. Hypertension**" in Chapter "**IX. Pathophysiology and Treatment of Comorbidities**".

### 2.2 Interventions Not Directly Aiming at Reducing the Burden of Heart Failure

ACE inhibitors,[211] ARBs,[212,213] β-blockers,[214] MRA,[215] and digitalis[216] did not reduce the incidence of the primary endpoint in their prospective interventional studies in HFpEF. However, large-scale observational studies and meta-analyses have indicated that ACE inhibitors/ARBs,[217] and β-blockers,[218,219] improve the prognosis of patients with HFpEF. MRAs also significantly reduced hospitalizations for heart failure.[215]

In addition to the above-described common medications for HFrEF, the efficacy of nitrates in HFpEF has been evaluated. In the NEAT-HFpEF (Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction) trial, a prospective interventional study, nitrates did not improve exercise capacity of patients with HFpEF, and did reduce their physical activity.[220] In a large-scale observational study, the Swedish Heart Failure Registry, nitrates deteriorated the prognosis of patients with HFpEF.[221]

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# VII. Nonpharmacological Therapy

## 1. Implantable Cardioverter Defibrillator

### 1.1 Secondary Prevention of Sudden Death (Table 27)

Patients with sustained ventricular tachycardia or ventricular fibrillation associated with heart failure and patients resuscitated from sudden cardiac death are at a high risk of recurrent arrhythmias. Implantable cardioverter defibrillators (ICDs) are highly effective in secondary prevention of sudden cardiac death associated with coronary artery disease in these patients.[222–224] Especially, patients with heart failure and LVEF ≤35% are expected to benefit more from ICDs.[14,225,226] However, sustained ventricular tachy-

cardia or ventricular fibrillation developed during acute phase (within 48 hours after onset) of acute coronary syndrome are not necessarily indicated for ICDs as the risk of recurrent arrhythmias is low after ischemia is treated and arrhythmic substrates are stabilized.[227] As the risk of recurrent arrhythmias is high in patients in whom sustained ventricular tachycardia or ventricular fibrillation developed at least 48 hours after the onset of myocardial infarction, they are indicated for ICDs.[226,227]

Although data on ICDs in secondary prevention of sudden death in patients with heart failure associated with non-ischemic dilated cardiomyopathy are limited, these patients are considered to benefit from ICDs similarly as patients with coronary disease are.[222–224]

Catheter ablation is now available for hemodynamically

| Table 27. Recommendations and Levels of Evidence for the Use of ICD as Secondary Prevention of Sudden Death | | | | |
|---|---|---|---|---|
| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
| Patients who meet both of the following criteria:<br>(1) Have heart failure associated with structural heart disease<br>(2) Sustained ventricular tachycardia, ventricular fibrillation, or resuscitated from sudden cardiac death | I | A | A | I |
| Patients who meet either of the following criteria:<br>(1) Have limited physical activity due to chronic diseases<br>(2) Can neither express consent nor cooperate with treatment due to mental disorder or other reasons<br>(3) Suspected with a life expectancy of 1 year or less | III | C | C2 | VI |

| Table 28. Recommendations and Levels of Evidence for the Use of ICD and WCD as Primary Prevention of Sudden Death | | | | |
|---|---|---|---|---|
| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
| Use of ICDs in patients who meet all the following criteria:<br>(1) Have coronary artery disease (at least 40 days post myocardial infarction) or non-ischemic dilated cardiomyopathy<br>(2) Receiving optimal medical therapy<br>(3) Have NYHA Class II or greater symptoms<br>(4) LVEF ≤35%<br>(5) Have non-sustained ventricular tachycardia | I | A | B | II |
| Use of ICDs in patients who meet all the following criteria:<br>(1) Have coronary artery disease (at least 40 days post myocardial infarction) or non-ischemic dilated cardiomyopathy<br>(2) Receiving optimal medical therapy<br>(3) Have NYHA Class II or greater symptoms<br>(4) LVEF ≤35% | IIa | B | B | II |
| Use of ICDs in patients who meet either of the following criteria:<br>(1) Have limited physical activity due to chronic diseases<br>(2) Can neither express consent nor cooperate with treatment due to mental disorder or other reasons<br>(3) Suspected with a life expectancy of 1 year or less | III | C | C2 | VI |
| Use of wearable cardioverter defibrillators (during consideration of ICD implantation and before starting treatment with ICD, <40 days post myocardial infarction, <3 months post-revascularization, or <3 months after starting drug therapy for heart failure) in patients who meet all the following criteria:<br>(1) Have acute myocardial infarction or received coronary revascularization for the treatment of cardiac dysfunction, or stated drug therapy for heart failure<br>(2) Have a high risk of sudden death<br>(3) Expected to show changes in cardiac function during treatment | IIa | C | B | III |

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

unstable patients with ventricular tachycardia or ventricular fibrillation,[228] but ICD therapy should be considered for these patients even after successful ablation.

## ▌1.2 Primary Prevention of Sudden Death (Table 28)

The benefits of ICDs in patients with coronary artery disease and low LVEF have been demonstrated in clinical studies conducted mainly in North America,[14,226] including the Multicenter Automatic Defibrillator Implantation Trial (MADIT-I),[229] MADIT-II,[230] Multicenter Unsustained Tachycardia Trial (MUSTT),[231] and Defibrillator in Acute Myocardial Infarction Trial (DINAMIT)[232] in patients with coronary artery disease, the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial in patients with non-ischemic dilated cardiomyopathy,[233] and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) in patients with coronary artery disease or non-ischemic dilated cardiomyopathy.[234]

Cohort studies on the prognosis of patients with coronary artery disease in Japan have indicated that patients in Japan generally have a favorable prognosis, and ICDs may not be cost effective if ICD therapy is indicated according to the criteria used in the MADIT-II trial. It is recommended that appropriate evaluations such as electrophysi-

ological testing should be used to stratify the risk of patients with coronary artery disease.[229–231] The use of ICD for primary prevention after myocardial infarction should be considered for patients who survived for at least 40 days after the onset of myocardial infarction.

A meta-analysis of five clinical studies[233–237] in non-ischemic dilated cardiomyopathy (n=1,854) revealed that ICDs significantly reduced relative mortality risk. A recent meta-analysis including the data from the Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH) trial[238] indicated similar results.

There are only limited data on the incidence of sudden death among patients with non-ischemic heart failure in Japan. However, the results of a cohort study on the outcome of patients with chronic heart failure[35] and the Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART) trial[239] suggested that the prognosis of heart failure and incidence of sudden death in patients with non-ischemic dilated cardiomyopathy in Japan may be similar to those in Western countries, and thus such patients should be considered for ICD therapy.

## 2. Cardiac Resynchronization Therapy (Table 29)

### 2.1 Clinical Efficacy

Since 2001, several randomized prospective studies have been conducted to assess the efficacy of cardiac resynchronization therapy (CRT) in heart failure.[237,240–247] These studies have demonstrated that CRT improves exercise capacity and other QOL measures as well as left ventricular remodeling, and reduced all-cause mortality and hospitalizations for heart failure. A meta-analysis has indicated that CRT reduced all-cause mortality.[248] In addition, the RD-CHF trial[249] and the Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) trial[250] demonstrated the benefits of CRT in patients with heart failure who are indicated for pacemaker.

### 2.2 Points to Consider When Planning CRT

### 2.2.1 Use of Defibrillation Function

No studies have compared a CRT-pacemaker (CRT-P) and a combined CRT defibrillator (CRT-D) in Japan. The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPARISON) trial[237] and a prospective registry in four European medical institutions[251] demonstrated that CRT-D was superior to CRT-P in reducing the incidence of sudden cardiac death. CRT-D is recommended for many patients, but is more expensive than CRT-P. Cost-effectiveness should also be considered.

### 2.2.2 CRT in Patients With Atrial Fibrillation

The Multisite Stimulation in cardiomyopathy - Atrial Fibrillation (MUSTIC-AF) trial[242] demonstrates the benefits of CRT in patients with heart failure in whom pacing is indicated to treat chronic bradycardic atrial fibrillation. The percentage of ventricular pacing after rate control in atrial fibrillation is also important. The Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA)/Asia-Pacific Heart Rhythm Society (APHRS)/Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLAEC) expert consensus recommends to produce the highest achievable percentage of ventricular pacing, preferably ≥98% in ICD patients with biventricular pacing.[252] In patients with chronic atrial fibrillation in whom an adequate pacing percentage cannot be obtained in CRT, atrioventricular node ablation should be considered.[14]

### 2.2.3 Effects of CRT by QRS Configuration and Duration

It has been reported that about 30 to 40% of patients undergoing CRT implantation do not respond well to CRT therapy, that is non-responders. A meta-analysis of randomized controlled trials that assessed the influence of QRS configuration on the benefits of CRT therapy has revealed that only patients with a left bundle branch block (LBBB) benefit from CRT.[253] The results of the Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS (RethinQ) trial[254] and the Echocardiography Guided Cardiac Resynchronization Therapy (EchoCRT) trial[255] have suggested that CRT therapy is less effective in patients with a QRS duration of <130 msec.[14,226]

### 2.2.4 Indications for Patients With Mild Heart Failure

The Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial,[256] the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial,[257] and the Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) trial[258] have reported that CRT is beneficial in patients with mild heart failure (NYHA class II or greater), and that CRT is especially indicated for patients with a QRS duration of ≥150 msec.

### 2.2.5 Combination With Drug Therapy

Indication for CRT should be considered only for patients who are receiving optimal medical therapy. Other than exceptional cases, CRT is not indicated for patients who underwent revascularization within the past 3 months and patients who introduced new drugs for the treatment of heart failure within the past 3 months. As some patients can receive higher doses of β-blockers after CRT is introduced,[259] patients should be assessed regularly for whether their drug therapy is optimal.

### 2.3 Telemetry Monitoring (Table 30)

Current implantable devices such as ICD, CRT-P, and CRT-D have telemetry functions that can send data on arrhythmic events and device information to the data center. As telemetry monitoring can send highly accurate data, device malfunctions and arrhythmias can be detected promptly.[260–264] In the Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME) trial in patients with heart failure,[265] heart failure management through telemetry monitoring significantly reduced all-cause mortality, but these findings should be interpreted carefully with clear understanding on their methods of intervention. In Japan, only a limited number of medical institutions have introduced telemetry monitoring systems. Further studies are awaited to clarify how to utilize telemetry data in clinical practice.

## 3. Respiratory Support (Table 31)

Respiratory support for patients with acute decompensated heart failure and patients with sleep-disordered breathing is described in the relevant sections. This section describes respiratory support for patient with chronic heart failure.

In chronic severe heart failure, respiratory support especially positive pressure ventilation improves hemodynamics and symptoms of chronic heart failure independent of improvement of sleep-disordered breathing by 1) reducing pulmonary congestion and left ventricular preload, 2) reducing left ventricular afterload, and 3) reducing the activity of the sympathetic nerve system. Continuous positive airway pressure (CPAP) can promptly increase cardiac output in patients with severe congestion, but there is no evidence on its long-term efficacy in patients with chronic heart failure with no (or only mild) sleep-disordered breathing. As adaptive servo-ventilation (ASV) has an acute effect similar to that of CPAP,[266] and may maintain a stable tidal volume, it is considered to be more effective in reducing the activity of the sympathetic nerve system.[267,268] In fact, reports have described that ASV decreases the incidence of cardiac events in patients with heart failure with and without sleep-disordered breathing in Japan.[269] In the Confirmatory, Multicenter, Randomized, Controlled

**Table 29.** Recommendations and Levels of Evidence for CRT

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| **NYHA Class III/IV** | | | | |
| Patients who meet all the following criteria:<br>(1) Receiving optimal medical therapy<br>(2) LVEF ≤35%<br>(3) Left bundle branch block (LBBB) with QRS interval ≥120 msec<br>(4) Sinus rhythm | I | A | A | I |
| Patients who meet all the following criteria:<br>(1) Receiving optimal medical therapy<br>(2) LVEF ≤35%<br>(3) Non-LBBB with QRS interval ≥150 msec<br>(4) Sinus rhythm | IIa | B | B | II |
| Patients who meet all the following criteria:<br>(1) Receiving optimal medical therapy<br>(2) LVEF ≤35%<br>(3) Non-LBBB with QRS interval 120 to 149 msec<br>(4) Sinus rhythm | IIb | B | C1 | III |
| Patients who meet all the following criteria:<br>(1) Receiving optimal medical therapy<br>(2) LVEF <50%<br>(3) Indicated for pacing or ICD<br>(4) Expected to require ventricular pacing frequently | IIa | B | B | II |
| Patients who meet all the following criteria:<br>(1) Receiving optimal medical therapy<br>(2) LVEF ≤35%<br>(3) LBBB with QRS ≥120 msec, or non-LBBB with QRS interval ≥150 msec<br>(4) Have atrial fibrillation and can undergo biventricular pacing at a high pacing percentage | IIa | B | B | II |
| **NYHA Class II** | | | | |
| Patients who meet all the following criteria:<br>(1) Receiving optimal medical therapy<br>(2) LVEF ≤30%<br>(3) LBBB with QRS interval ≥150 msec<br>(4) Sinus rhythm | I | B | B | II |
| Patients who meet all the following criteria:<br>(1) Receiving optimal medical therapy<br>(2) LVEF ≤30%<br>(3) Non-LBBB with QRS interval ≥150 msec<br>(4) Sinus rhythm | IIa | B | B | II |
| Patients who meet all the following criteria:<br>(1) Receiving optimal medical therapy<br>(2) LVEF ≤30%<br>(3) QRS interval 120 to 149 msec<br>(4) Sinus rhythm | IIb | B | C1 | III |
| Patients who meet all the following criteria:<br>(1) Receiving optimal medical therapy<br>(2) LVEF <50%<br>(3) Indicated for pacing or ICD<br>(4) Expected to require ventricular pacing frequently | IIa | B | B | II |
| **NYHA Class I** | | | | |
| Patients who meet all the following criteria:<br>(1) Receiving optimal medical therapy<br>(2) LVEF <50%<br>(3) Indicated for pacing or ICD<br>(4) Expected to require ventricular pacing frequently | IIb | B | B | II |
| **NYHA Class I to IV** | | | | |
| Patients who meet either of the following criteria:<br>(1) Have limited physical activity due to chronic diseases<br>(2) Can neither express consent nor cooperate with treatment due to mental disorder or other reasons.<br>(3) Suspected with a life expectancy of 1 year or less | III | C | C2 | VI |

Different criteria are set for NYHA Class III/IV and II patients in sinus rhythm:
1) LVEF cutoff value is ≤35% for NYHA Class III/IV patients and, ≤30% for NYHA Class II patients.
2) In patients with a QRS interval of 120 to 149 msec, the use of CRT is a Class I and IIb recommendation for NYHA Class III/IV patients with LBBB and non-LBBB, respectively, and is a Class IIb recommendation for NYHA Class II patients regardless of whether LBBB or non-LBBB is present.

CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

**Table 30. Recommendations and Levels of Evidence for the Use of Telemetry Monitoring of Implantable Device Therapy**

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| Introduction and management of telemetry monitoring in patients with implantable cardiac devices | IIa | A | B | I |

**Table 31. Recommendations and Levels of Evidence for Adaptive Servo-Ventilation (ASV)**

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| Use of ASV in the hospital setting to relieve symptoms of congestion in patients receiving guideline-based, optimized treatment for heart failure | IIa | B | B | II |
| Continued use of ASV in patients satisfying the above criterion who respond well to the ASV and are expected to worsen by discontinuing ASV | IIa | C | B | VI |
| Continued use of ASV after improvement of heart failure without reviewing its necessity | III | C | C1 | VI |

**Table 32. Recommendations and Levels of Evidence for Exercise Therapy in Patients With Heart Failure**

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| **Patients with HFrEF** Combination with drug therapy to relieve symptoms and improve exercise capacity | I | A | A | I |
| **Patients with HFrEF** To improve QOL, reduce cardiac accidents, and improve life expectancy | IIa | B | B | II |
| **Patients with HFpEF with low exercise capacity** To improve exercise capacity | IIa | C | B | IVa |
| **Patients with heart failure after ICD or CRT-D implantation** To improve exercise capacity and QOL | IIa | C | B | IVa |
| **Patients with pulmonary hypertension whose symptoms are stable on drug therapy** Consider supervised exercise therapy at experienced institutions to improve exercise capacity and QOL | IIa | B | B | II |
| **Patients with advanced deconditioning and patients with reduced physical function** Resistance training to improve ADL and QOL by increasing muscle strength and endurance | IIa | C | B | IVb |

ADL, activities of daily living; CRT-D, cardiac resynchronization therapy defibrillator; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; QOL, quality of life.

Study of Adaptive Servo-Ventilation in Patients with Chronic Heart Failure (SAVIOR-C) trial that evaluated the efficacy of ASV in patients with chronic heart failure with and without sleep-disordered breathing in Japan, LVEF assessed as the primary endpoint did not differ significantly between the ASV and guideline-directed medical therapy, but a clinical composite response assessed as a secondary endpoint improved significantly in the ASV group as compared with the medical therapy group.[270] In 2016, the National Health Insurance started to cover the use of ASV for the treatment of congestion in patients with heart failure who meet particular conditions. The Japanese Circulation Society and the Japanese Heart Failure Society published the second statement on appropriate use of ASV to clarify who are indicated for ASV (See **Supplement 1**).[271]

As the Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure (SERVE-HF) trial[272] suggested that ASV may increase the risk of cardiovascular death, patients who meet the inclusion criteria for the SERVE-HF trial should be considered for discontinuing ASV or switching to CPAP when heart failure is stabilized after introducing ASV.

## 4. Exercise Therapy (Table 32)

### 4.1 Effects of Exercise Therapy (Supplement 2)[148]

Exercise therapy increases peak $\dot{V}O_2$ by 15 to 30% (mean of about 20%), and also improves anaerobic threshold

(AT).[273–283] It has been described that exercise therapy may elevate exercise capacity by increasing the muscular mass and volume density of mitochondria in skeletal muscle,[279] enhancing the metabolism and function of skeletal muscles,[278,284] improving the function of respiratory muscles,[285,286] and improving the endothelial function through increased nitric oxide (NO) production,[287,288] among other peripheral mechanisms.[275,279] Exercise therapy also exerts beneficial effects on neurohumoral factors such as the reduction of C reactive protein (CRP), an inflammatory substance,[289] and cytokines (e.g., TNF-$\alpha$ and IL-6[290]), and improves autonomic nervous system dysfunction, which is an important prognostic factor.[291–293] A considerable body of evidence has been accumulated on the beneficial effects of exercise therapy on patients with heart failure through relieving anxiety and depression, and improving QOL.[273,276,282,294]

The findings from the Exercise Training Meta Analysis of Trials in Chronic Heart Failure (ExTraMATCH) have indicated that exercise therapy improves the prognosis of patients with heart failure.[295] In the Participants in Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial, a large-scale randomized controlled study,[296] exercise therapy reduced the risk of all-cause death or hospitalization by 11% and the risk of cardiovascular death or hospitalization for heart failure by 15% after adjusting for confounding factors. A Cochrane systematic review of exercise-based cardiac rehabilitation for heart failure has indicated that exercise therapy significantly reduces the risk of all-cause and heart-failure-related hospitalizations in patients with heart failure.[297]

## 4.2 Heart Failure in Patients With Special Conditions

The findings of randomized controlled traials[298–300] and a meta-analysis[301] in patients with heart failure with preserved ejection fraction (HFpEF) have indicated that exercise training improves exercise capacity measured by peak oxygen uptake as well as QOL in this patient population.

Randomized controlled trials of exercise therapy in patients with implantable devices have reported that patients in the exercise therapy group showed significant improvement in peak oxygen uptake, NYHA functional class, and QOL score, among other measures.[302,303] A recent randomized controlled trial that evaluated effectiveness of exercise therapy in patients with pulmonary hypertension[304] reported that patients in the exercise therapy group showed better improvement in exercise capacity and QOL as compared with the control group. The 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension recommend supervised exercise rehabilitation as a Class IIa recommendation.[305]

## 4.3 Methodology of Exercise Training

In patients with deconditioning, elderly patients with low muscle strength, and patients with sarcopenia or frailty, resistance training may be highly effective.[306–310] A recent study addressed the efficacy of high-intensity interval training (HIT) in heart failure.[311] However, a randomized controlled study has concluded that HIT is not superior to continuous exercise training in terms of increasing exercise capacity and preventing left ventricular remodeling.[312]

## 4.4 Contraindications for Exercise Therapy

Supplement 3[148] lists contraindications for exercise therapy.

## 4.5 Exercise Prescription

Exercise therapy for patients with heart failure should be conducted according to appropriate exercise prescriptions (Supplement 4).[148] Supervised exercise therapy is required especially for elderly patients and patients with severe left ventricular dysfunction, high-risk arrhythmias, or a risk of ischemia. These patients may benefit from exercise therapy even with low or intermediate intensity (40 to 60% of peak $\dot{V}O_2$).[148,280,313]

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# VIII.  Treatment of Underlying Conditions

## 1.  Basic Treatment Strategies

Heart failure management consists of two strategies. The first strategy is to treat heart failure, and the second is to treat the cause of heart failure. When patients showed signs and symptoms of heart failure, heart failure is related directly to patients' complaints and sometimes risk of death, and treatment for heart failure should generally be prioritized over treatment for causative disease.

## 2.  Underlying Conditions That May Modify Treatment Strategies

Some underlying cardiac disorders causing heart failure may require special plan for treatment sequencing. Patients with such cardiac disorders show ever-changing conditions should be treated for the causative disease and the condi-

tions simultaneously. These conditions include acute coronary syndrome and pulmonary thromboembolism, for which revascularization is effective, arrhythmias which can be treated well by defibrillation and pacing, and acute myocarditis for which outcome cannot be readily predicted. Other cardiac disorders require careful decongestion because an abrupt change in intravascular volume may compromise hemodynamics. These disorders include structural heart diseases with significant pressure gradient such as aortic valve stenosis; severe right ventricular dysfunction and other right heart disease causing a significant increase in pulmonary vascular resistance; and severe cardiac diastolic dysfunction such as constrictive pericarditis and restrictive cardiomyopathy.

## 3.  Comorbid Conditions Causing Advanced Stage Heart Failure

Lifestyle-related diseases such as hypertension, diabetes

mellitus, and dyslipidemia are typical risk factors for Stage A heart failure, while there is little evidence on the management of these factors in Stage C or D heart failure. Conditions affecting non-cardiac organs such as chronic kidney disease and chronic obstructive pulmonary disease (COPD) also modify the risk of heart failure, but treatment strategies for these conditions in patients with heart failure have not been established yet.

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# IX. Pathophysiology and Treatment of Comorbidities

## 1. Atrial Fibrillation (Table 33)

### 1.1 Pathophysiology

Atrial fibrillation is one of the most common types of arrhythmias associated with heart failure, and is known to negatively affect cardiac function and hemodynamics, and worsen heart failure.[314] A meta-analysis[315] has revealed that $\beta$-blockers for the treatment of atrial fibrillation do not improve the prognosis of patients with severe chronic heart failure associated with atrial fibrillation. Moreover, $\beta$-blockers reduced mortality in patients with heart failure in sinus rhythm and achieving a lower heart rate, but it was not observed in patients with atrial fibrillation. However, atrial fibrillation in the patients with acute heart failure which causes or is expected to cause an abrupt disturbance of hemodynamics or worsening symptoms should receive appropriate treatments. Treatment strategies for atrial fibrillation are classified into "rate control" that accepts the presence of atrial fibrillation and controls heart rate, and "rhythm control" that aims to return to and maintain sinus rhythm. As the effect of atrial fibrillation on hemodynamics differs between patients with acute heart failure and patients with chronic heart failure, appropriate treatment strategies should be selected to address the relevant condition.

### 1.2 Treatment

### 1.2.1 Treatment for Atrial Fibrillation With a Rapid Ventricular Response Complicated With Acute Heart Failure

When atrial fibrillation develops during the treatment of acute heart failure and is considered highly likely to negatively affect hemodynamics, electrical cardioversion should be performed immediately. Patients who are not receiving appropriate anticoagulation therapy in whom the duration of atrial fibrillation is unknown should undergo transesophageal echocardiography to confirm the absence of thrombus in the left atrium before starting defibrillation.[316–318] Patients with symptoms of heart failure who need rate control therapy immediately may be treated with intravenous digitalis.[319] Landiolol has been reported to be beneficial effect for controlling the heart rate as compared with digoxin in the atrial fibrillation or atrial flatter with left ventricular dysfunction, and the use of this drug for this indication is covered with the National Health Insurance in Japan.[320] Non-dihydropyridine calcium channel blockers (e.g., verapamil and diltiazem) are contraindicated for patients with decompensated heart failure as they may worsen heart failure via their negative inotropic effects.[16]

### 1.2.2 Rate Control

A meta-analysis of clinical trials in Western countries has concluded that $\beta$-blockers do not improve the prognosis of patients with chronic heart failure and atrial fibrillation, but many studies included in the analysis were conducted in patients with severe heart failure such as NYHA Class III or IV and patients with LVEF <30%.[315] It is likely that atrial fibrillation rather than heart rate affects the prognosis of this patient population. On the other hand, a registry of patients with moderate or severe heart failure associated with atrial fibrillation has reported that $\beta$-blockers significantly reduced all-cause mortality, and mortality increased significantly in patients with a heart rate of >100 bpm.[321] Accordingly, physicians should be aware that the benefits of $\beta$-blockers on prognosis may differ depending on the severity of heart failure. Patients with atrial fibrillation who have severe symptom due to tachycardia, and those with elevated and sustained heart rate of >130 bpm are at high risk for developing heart failure, and thus should receive rate control.[322] In the Guidelines for Pharmacological of Atrial Fibrillation (JCS 2013) proposed by the Japanese Circulation Society, the target heart rate at rest is set at <110 bpm for patients without heart failure. When no improvement in symptoms or cardiac function is observed, the target should be set at <80 bpm at rest and <110 bpm during moderate exercise.[323]

Patients with chronic heart failure and atrial fibrillation with mild symptoms and stable hemodynamic should be considered for rate control in atrial fibrillation first. Carvedilol or bisoprolol is an oral $\beta$-blocker of choice, and should be started at a low dose considering the severity of heart failure. Oral digoxin exerts rate control and cardiotonic actions, but unlike $\beta$-blockers, may reduce heart rate at night.[324,325]

### 1.2.3 Rhythm Control

Rhythm control is selected for patients in whom rate control cannot be achieved with drug therapy and patients in whom maintaining sinus rhythm is beneficial in maintaining hemodynamics and managing heart failure. Amiodarone is the first-choice of oral drugs for rhythm control used in patients with cardiac dysfunction. In Japan, low-dose amiodarone therapy has been effective in maintaining sinus rhythm and reducing heart rate in patients with heart failure and atrial fibrillation,[326] and this use is covered by the National Health Insurance in Japan. Regardless of whether heart failure is acute or chronic, sodium channel blockers (with slow kinetic activation kinetics), which may exert negative inotropic action, must not be used to maintain sinus rhythm in patients with heart failure and atrial fibrillation.[327]

### 1.2.4 Anticoagulant Therapy

The CHADS$_2$ score has been used extensively to assess the risk of cerebral infarction and systemic embolism in patients with atrial fibrillation (Supplement 5),[328] and is used when initiating anticoagulant therapy in Japan. As the stroke rate without antithrombotic therapy is as high as 1.9 per 100 patient-years even in patients with a CHADS$_2$ score of 0,[328] Western countries use the CHA$_2$DS$_2$-VASc score to specify truly low-risk patients.[329,330] As patients with heart

**Table 33. Recommendations and Levels of Evidence for Treatment of Atrial Fibrillation in Patients With Heart Failure**

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| **Treatment of atrial fibrillation with a rapid ventricular response in patients with acute heart failure** | | | | |
| **Urgent electrical cardioversion** To restore to sinus rhythm in the patients with hemodynamically compromised atrial fibrillation in whom heart rate control is difficult with drug therapy | I | C | C1 | VI |
| **Landiolol** To control heart rate | IIa | B | B | II |
| **Digoxin** To control heart rate | IIa | C | B | II |
| **Oral or intravenous non-dihydropyridine calcium channel blockers** To control heart rate | III | C | D | II |
| **Sodium channel blockers (with slow activation kinetics)** To maintain sinus rhythm in patients who returned to sinus rhythm and those who received defibrillation | III | C | D | II |
| **Rhythm control** | | | | |
| **Oral amiodarone** To maintain sinus rhythm | IIa | B | B | II |
| **Elective electrical cardioversion** To treat persistent atrial fibrillation lasting for <1 year without substantial left atrial enlargement | IIa | C | C1 | VI |
| **Catheter ablation** To treat symptomatic atrial fibrillation in patients with heart failure who do not respond well to rate control therapy or drug therapy for heart failure | IIb | C | B | II |
| **Oral sodium channel blockers (with slow activation kinetics)** To maintain sinus rhythm in patients who returned to sinus rhythm and those who received defibrillation | III | A | D | II |
| **Rate control** | | | | |
| **Oral β-blockers and oral digoxin** To control heart rate | IIa | B | A | I |
| **Oral amiodarone** To control heart rate in patients in whom monotherapy with β-blockers or digoxin or combination of the two drugs are not effective in rate control | IIb | C | C1 | VI |
| **Oral non-dihydropyridine calcium channel blockers** To control heart rate | III | C | D | II |
| **Anticoagulant therapy** | | | | |
| Use of the CHADS2 score and the HAS-BLED score to predict the benefits of anticoagulant therapy | I | B | A | II |
| Oral anticoagulant therapy for the treatment of atrial fibrillation in patients with heart failure (unless contraindicated) | I | A | A | I |
| Anticoagulant therapy for 3 weeks before and 4 weeks after pharmacological or electrical cardioversion in patients with atrial fibrillation lasting ≥48 hours | I | B | A | II |
| Electrical cardioversion with heparin after ruling out intracardiac thrombi by transesophageal echocardiography in patients with atrial fibrillation who are not receiving anticoagulant therapy | I | C | A | II |
| Considering DOACs as first-line therapy | IIa | B | A | II |
| Concomitant use of DAPT and anticoagulation after coronary intervention in patients with heart failure and ischemic heart disease | IIb | C | C2 | II |
| Use of DOACs in patients using prosthetic valves (mechanical or bioprosthetic valves) and in patients with rheumatic mitral valve disease | III | B | D | II |

DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant.

failure and atrial fibrillation have a CHADS2 score of ≥1, anticoagulant therapy should be considered for them unless it is contraindicated.

Atrial fibrillation in patients with heart failure have been treated with anticoagulant therapy using warfarin. However, direct oral anticoagulants (DOACs), that have been launched recently, have changed anticoagulant strategies for atrial fibrillation in patients with heart failure.[331–334] DOACs are as effective as warfarin in patients with heart failure, and are safer than warfarin as the risk of major bleeding such as intracranial hemorrhage is lower in patients

treated with DOACs than those treated with warfarin.[335,336] However, DOACs are indicated only for patients with non-valvular atrial fibrillation, and warfarin should be used for patients with severe mitral valve stenosis and patients using valve prostheses (mechanical valves or bioprosthetic valves).[337] As renal function may change as heart failure advances or improves during treatment, the dose of anticoagulant drugs, especially DOACs, should be adjusted carefully according to the criteria for dose reduction or careful administration. The HAS-BLED score has been used to assess the risk of bleeding during anticoagulant

**Table 34.** Recommendations and Levels of Evidence for Treatment of Ventricular Arrhythmias in Patients With Heart Failure

|  | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| **Removal of factors leading to ventricular arrhythmia** Interventions to reduce mental/physical stress and pain, correct electrolyte imbalance, and reduce myocardial ischemia | I | A | C1 | VI |
| **Electrical defibrillation** To treat ventricular fibrillation and sustained ventricular tachycardia with decompensated hemodynamics | I | C | C1 | VI |
| **Intravenous nifekalant or amiodarone** To prevent recurrence of ventricular tachycardia and ventricular fibrillation | IIa | C | B | IVb |
| **Oral amiodarone** To avoid implantable cardioverter defibrillator (ICD) shocks for life-threatening arrhythmias in patients with heart failure after ICD implantation | IIa | B | B | I |
| **Catheter ablation** To avoid ICD shocks for repeated life-threatening arrhythmias in patients heart failure after ICD implantation | IIb | C | B | IVa |
| **Oral antiarrhythmic drugs** Use in patients with asymptomatic ventricular arrhythmia and low cardiac function | III | A | D | II |

therapy.[337a]

Patients with heart failure due to ischemic heart disease often receive dual antiplatelet therapy (DAPT) for percutaneous coronary intervention (PCI). When accompanied by atrial fibrillation, anticoagulant therapy is added and the risk of bleeding may further increase.[338] The European Society of Cardiology (ESC) guidelines for the management of atrial fibrillation provide recommendations on the contents and duration of anticoagulant and antiplatelet therapy according to the risk of stroke, the risk of bleeding, and patient characteristics.[339] In the What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting (WOEST) trial,[338] patients receiving warfarin for the treatment of stable angina underwent PCI were randomized to triple therapy (warfarin, aspirin, and clopidogrel) or duel therapy (warfarin, and clopidogrel). Comparisons between the two groups in terms of the incidence rates of bleeding events and thromboembolic events revealed that all-cause mortality and the incidence of bleeding events were significantly lower in the duel therapy group, and the incidence rates of myocardial infarction, stroke, and in-stent thrombosis did not differ between the two groups.

## 2. Ventricular Arrhythmias (Table 34)

Ventricular arrhythmias associated with heart failure includes premature ventricular contractions, non-sustained/sustained ventricular tachycardia and ventricular fibrillation. Especially hemodynamically intolerable ventricular tachycardia and ventricular fibrillation should be treated electrical defibrillation immediately. Intravenous amiodarone and nifekalant, as antiarrhythmic drugs, have a rapid onset of actions and are expected to be highly effective in preventing ventricular arrythmias.[340,341] Also, risk factors and predisposing factors for life-threatening ventricular arrhythmias, such as electrolyte imbalance and use of

proarrhythmic drugs, should be identified and treated accordingly. When myocardial ischemia is involved in the development of arrhythmia, revascularization to treat the ischemia is important. Polymorphic ventricular tachycardia with prolonged QT interval[342] and torsade de pointes in the patients with heart failure should be confirmed and treated for electrolyte imbalance such as hypokalemia and hypomagnesemia. Intravenous magnesium sulfate is also effective.[343]

In patients with an implantable cardioverter defibrillator (ICD), the experience of ICD shocks may cause physical and/or mental stress, leading to frequent ICD shocks. Patients who have three or more episodes of life-threatening ventricular arrhythmia within 24 hours, so-called "electrical storm", and in case of refractory to ICD therapy should receive percutaneous cardiopulmonary support (PCPS) to stabilize hemodynamics and treat arrhythmias. When sustained ventricular arrhythmia cannot be controlled with drug therapy, catheter ablation should also be considered.[344,345] Oral β-blockers are effective in preventing the recurrence of life-threatening ventricular arrhythmia and sudden death in patients with chronic heart failure.[192–194] Amiodarone is another treatment option,[346] but careful observation is required because of its serious adverse drug reactions. Nonpharmacologic therapy using ICDs is mainly used to prevent sudden death in patients with heart failure.[234] Antiarrhythmic drugs are used as adjunctive therapy to reduce the frequency of arrhythmic episodes.

## 3. Bradyarrhythmia (Table 35)

When patients have symptoms of cerebral ischemia associated with bradycardia caused by drug therapy, dose reduction should be considered first. The ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure recommend that when sinus arrest lasting for >3 seconds, bradycardia of <50 bpm in sinus rhythm or

**Table 35.** Recommendations and Levels of Evidence for Pacemaker Treatment for Bradyarrhythmia in Patients With Heart Failure

|  | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| Pacing for patients with symptomatic heart failure due to bradycardia caused by poor sinus function, sinoatrial block, sinus arrest, or poor rate response during exercise, or caused by second-degree, advanced, or third-degree atrioventricular block (including patients with bradycardia caused by long-term necessary drug therapy) | I | C | A | VI |
| Pacing for patients with symptomatic heart failure due to bradycardic atrial fibrillation (including patients with bradycardia caused by long-term necessary drug therapy) | I | C | A | VI |
| Pacing for patients with symptomatic heart failure which has not been confirmed to be caused by bradyarrhythmia | IIa | C | B | VI |

<60 bpm in atrial fibrillation is occurred, the dose of rate limiting medications should be reconsidered.[16] In patients with atrial fibrillation and heart failure, β-blockers and other drugs are effective in the treatment of heart failure. Patients in whom continuation or dose escalation of β-blocker therapy for heart failure is necessary may be considered for pacemaker implantation. Patients with heart failure and bradyarrhythmia who are indicated for pacemaker should receive atrioventricular synchronization pacing unless permanent atrial fibrillation is present. Some patients with heart failure may have a wide QRS complex as a result of ventricular pacing for the treatment of brady-arrhythmia, and need biventricular cardiac pacing (See Section "**2. Cardiac Resynchronization Therapy**" in Chapter "**VII. Nonpharmacologic Therapy**").

## 4. Coronary Artery Disease (Table 36)

### 4.1 Pathophysiology

In addition to hypertension and dilated cardiomyopathy, coronary artery disease is one of the most common conditions that underlies heart failure.[347] The prevalence of coronary heart disease among patients with heart failure was 23% in the Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART)-1 Study in which patients were registered from 2000 to 2004, but increased to 47% in the CHART-2 Study in which patients were registered from 2006 to 2010.[30,348] The prevalence of coronary heart disease among patients with acute heart failure was 31% in the Acute Decompensated Heart Failure Syndromes (ATTEND) registry[349] and 32% in the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD).[32] The prevalence of patients with ischemic heart failure with preserved LVEF is increasing. For example, in the CHART Studies, the prevalence of ischemic heart failure among patients with LVEF ≥50% was increased from 19% in the CHART-1 Study to 45% in the CHART-2 Study.[31]

In the CHART-1 Study, three-year mortality in patients with heart failure following myocardial infarction was 29%, which was higher than that in patients with non-ischemic heart failure (12%).[350] In the ATTEND study, the mortality in patients with acute heart failure due to ischemic heart disease was similar to those in patients with acute heart failure due to other diseases among patients with LVEF ≥40%, while it was as high as in patients with acute

heart failure due to valvular heart disease, both of which were higher that the mortality in those with acute heart failure due to other diseases among those with LVEF <40%.[351] Three-year mortality in patients with ischemic heart disease with a NYHA class of II or greater was 29% in the CHART-1 Study, and 15% in the CHART-2 Study, showing a decrease in mortality over time in the CHART Studies.[31]

Myocardial ischemia impairs systolic and dilative functions of the heart, and myocardial injury due to myocardial infection causes ventricular dysfunction. Myocardial ischemia and injury may cause fatal arrhythmias and compromise hemodynamics. Patients with coronary risk factors such as lifestyle-related diseases should be monitored carefully as they are susceptible to arteriosclerosis or cardiac dysfunction. Treatment of ischemic heart disease should aim at the management of 1) cardiac function, 2) myocardial ischemia, 3) arrhythmia, and 4) coronary risk factors.

### 4.2 Treatment

#### 4.2.1 Acute Heart Failure
#### a. Heart Failure Associated With Acute Myocardial Infarction

In patients with acute myocardial infarction, an abrupt loss of cardiac pump function may lead to acute heart failure. Accordingly, patients with acute myocardial infarction should also receive oxygen therapy and vasodilators to treat acute heart failure as well (See Section "**3. Treatment Strategies and Flowcharts**" in Chapter "**X. Acute Heart Failure**"). Whenever necessary, hemodynamics monitoring via Swan-Ganz catheterization should be conducted and PCI, coronary artery bypass grafting (CABG), thrombolysis or other appropriate reperfusion therapy should be conducted to treat myocardial ischemia. Additional treatment should be initiated in the acute phase to prevent left ventricular remodeling, and intra-aortic balloon pumping (IABP) or other circulatory assist devices should also be considered if necessary (See Section "**2.2. Percutaneous Circulatory Support for Patients With Acute Heart Failure**" in Chapter "**XI. Surgical Treatment**"). Moreover, angiotensin converting enzyme (ACE) inhibitors should be started in acute phase to prevent long-term cardiac remodeling,[352] and β-blockers should be started immediately after hemodynamics is stabilized.[353] Treatment of arrhythmias, and surgical treatment of mechanical complications and

**Table 36. Recommendations and Levels of Evidence for Drug Therapy for Heart Failure in Patients With Coronary Artery Disease**

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| **ACE inhibitors** | | | | |
| Use in patients with congestive heart failure or left ventricular systolic dysfunction | I | B | A | I |
| Use within 24 hours after onset of acute myocardial infarction in patients who are highly likely to have left ventricular dysfunction (LVEF <40%) or heart failure | I | A | A | I |
| Use in post-myocardial infarction patients with left heart dysfunction | I | A | A | I |
| Use in patients with myocardial infarction who have normal left heart function, but have hypertension, diabetes mellitus, or a moderate to high risk of developing cardiovascular accidents | I | A | A | I |
| Use in all patients with acute myocardial infarction within 24 hours after onset | IIa | B | B | II |
| Use in patients with normal cardiac function and low risk of cardiovascular accidents | IIa | B | B | II |
| **ARBs** | | | | |
| Starting treatment in the acute phase of myocardial infarction in patients intolerable to ACE inhibitors who have symptomatic heart failure or LVEF of ≤40% | I | A | A | I |
| Use in combination with ACE inhibitors for the treatment of myocardial infarction in patients with left ventricular systolic dysfunction in whom the risk of renal dysfunction is considered low | IIb | B | C2 | II |
| **β-blockers** | | | | |
| Use in patients other than low-risk patients* who are not contraindicated for β-blockers | I | A | A | I |
| Use with upward dose titration in patients with moderate or severe left heart dysfunction | I | B | A | II |
| Use in low-risk patients* | IIa | B | B | II |
| Monotherapy in patients in whom coronary spasm is involved | III | B | C2 | V |
| **MRAs** | | | | |
| Use at low doses for the treatment of moderate or severe heart failure in patients without renal dysfunction or hyperkalemia | IIa | B | B | II |

*Patients after successful revascularization of the culprit artery of myocardial infarction who have normal or nearly normal left heart function and do not have serious ventricular arrhythmia. ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist.

ischemic mitral valve insufficiency are described in other sections (From Section "**1. Atrial Fibrillation**" to "**3. Bradyarrhythmia**" in Chapter "**IX. Pathophysiology and Treatment of Comorbidities**", and "**5.5. Treatment of Mechanical Complications Associated With Acute Myocardial Infarction**" in Chapter "**X. Acute Heart Failure**").

### b. Acute Exacerbations of Ischemic Heart Failure

In patients with ischemic heart failure, progression of coronary artery lesions, coronary spasm, anemia due to gastrointestinal bleeding, tachycardia due to paroxysmal atrial fibrillation, and/or excessive daily activities may cause imbalance of oxygen supply and demand, and then myocardial (subendocardial) ischemia may occur, resulting in development of acute heart failure due to acute diastolic or systolic dysfunction.[354] Patients with diabetes mellitus or hypertension who have cardiac hypertrophy are susceptible to subendocardial ischaemia,[355] and may experience an abrupt onset of pulmonary edema due to acute diastolic dysfunction.[356] Such patients should be carefully observed,

and should undergo reperfusion therapy such as PCI and CABG whenever necessary. Patients with systolic dysfunction due to chronic myocardial ischemia (myocardial hibernation)[357] should also be considered for PCI or CABG.

### 4.2.2 Chronic Heart Failure

Treatment of chronic ischemic heart failure is basically same as other types of heart failure, and mainly consists of assessment of cardiac function (cardiac protection) and myocardial ischemia, prevention of arrhythmic events, and management of coronary risk factors.

For cardiac protection in patients with ischemic heart failure and reduced LVEF, β-blockers and renin-angiotensin inhibitors (e.g., ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists [MRAs]) are mainly used (**Table 36**).[192–194,215,358–360] These drugs should be started at low doses to avoid worsening heart failure. Nitrates have not been demonstrated to improve long-term prognosis,[205] but have been shown to improve symptoms of heart failure and hemodynamics[361] and are the first-line treatment for

**Table 37.** Recommendations and Levels of Evidence for the Treatment of Valvular Disease in Patients With Heart Failure

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| Valvular replacement/repair in patients with heart failure associated with severe, structural mitral or aortic valve disease (excluding patients at significantly high risk for surgery) | I | B | B | III |
| Conducting standard heart failure treatment (e.g., drug therapy and CRT) to reduce mitral regurgitation in patients with heart failure and secondary (functional) mitral valve insufficiency | I | C | C1 | IVb |
| Dobutamine-stress or exercise echocardiography to consider for aortic valve replacement in symptomatic patients with low-flow low-gradient aortic stenosis (aortic valve area <1.0 cm², aortic transvalvular pressure gradient <40 mmHg) and low LVEF | IIa | C | C1 | IVb |
| TAVI in patients with heart failure due to severe aortic stenosis who are determined at high risk for surgery by heart team, and are considered to have a life expectancy of more than 1 year | I | B | B | II |

CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; TAVI, transcatheter aortic valve implantation.

angina pectoris. Nicorandil and diuretics should also be considered as needed.

Patients with angina symptoms or proven to have ischemia due to cardiac dysfunction should be considered for PCI or CABG.[362,363] A cohort study in Japan have suggested that the CABG is superior to PCI in patients with heart failure associated with severe coronary artery disease.[364] According to the recommendations in the Guidelines for Non-Pharmacotherapy of Cardiac Arrhythmias (JCS 2011) issued by the Japanese Circulation Society, indications for ICD should be considered as a primary prevention therapy.[365]

For management of risk factors of coronary heart disease and details about exercise therapy, see Sections "**6. Hypertension**" to "**9. Hyperuricemia/Goat**" in Chapter "**IX. Pathophysiology and Treatment of Comorbidities**" and Section "**4. Exercise Therapy**" in Chapter "**VII. Nonpharmacologic Therapy**". Regarding management of dyslipidemia and smoking that are not described in the present guidelines, refer to other relevant guidelines.

## 5. Valvular Heart Disease (Table 37)

Patients with heart failure and valvular disease are at high risk for poor outcome. If the main cause of heart failure is valvular disease itself, following the treatment strategy for valvular disease are recommended (See the Guidelines for Surgical and Interventional Treatment of Valvular Heart Disease [JCS 2012]).[366] Patients with valvular disease secondary to dilated cardiomyopathy or other heart disease should be treated for the relevant underlying cardiac diseases.

### 5.1 Mitral Valve Insufficiency

In patients with dilated or ischemic cardiomyopathy, mitral valve insufficiency secondary to mitral valve tethering or mitral annular enlargement may lead to further worsening of hemodynamics. However, no consensus has been reached whether interventions for mitral insufficiency may improve

the prognosis of patients with moderate or severe secondary mitral valve insufficiency. In 2016, the Cardiothoracic Surgical Trials Network conducted an interventional study and reported that CABG plus mitral valve repair does not improve the outcome in patients with moderate secondary mitral valve insufficiency and ischemic heart disease.[367] On the basis of these findings, the ACC/AHA guideline for the management of patients with valvular heart disease, which was revised partially in 2017, describes that the usefulness of mitral valve repair in patients with moderate secondary mitral valve insufficiency and ischemic heart disease who are undergoing CABG is unclear.[368]

### 5.2 Tricuspid Valve Insufficiency

As a result of right ventricular overload due to left-sided heart failure or pulmonary hypertension, tricuspid valve insufficiency secondary to tricuspid annular enlargement and tricuspid valve tethering is often observed and is a factor of poor prognosis.[369] Patients with secondary tricuspid valve insufficiency should first be treated to correct underlying condition causing heart failure. During surgery for left-sided valve surgery, concomitant tricuspid valve repair is recommended.[366,370,371]

### 5.3 Aortic Valve Stenosis

When aortic stenosis develops in patients with left ventricular systolic dysfunction due to underlying cardiac condition, the severity of aortic stenosis should be examined carefully. Treatment strategies for patients with low-flow, low-gradient aortic stenosis and reduced LVEF should be based on changes in aortic valve area and aortic transvalvular pressure gradient before and after an increase of stroke volume during dobutamine stress echocardiography.

For details about transcatheter aortic valve implantation (TAVI) and transcatheter aortic valve replacement (TAVR), see Section "**1. Surgical Procedures and TAVI**" in Chapter "**XI. Surgical Treatment**".

**Table 38.** Recommendations and Levels of Evidence for Drug Therapy for HFrEF in Patients With Hypertension

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| ACE inhibitors | I | A | A | I |
| ARBs (use in patients intolerable to ACE inhibitors) | I | A | A | I |
| β-blockers | I | A | A | I |
| MRAs | I | A | A | II |
| Diuretics | I | B | A | I |
| Calcium channel blockers* | IIa | B | B | II |

*Calcium channel blockers other than long-acting dihydropyridines should not be used as they have negative inotropic effects. ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist.

**Table 39.** Recommendations and Levels of Evidence for Drug Therapy for HFpEF in Patients With Hypertension

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| Appropriate blood pressure management | I | B | B | II |
| Identification and treatment of underlying disease | I | C | B | VI |

# 6. Hypertension

## 6.1 Pathophysiology

Hypertension is a major risk factor on heart disease independent of age and left ventricular dysfunction.[172,372] Appropriate treatment for hypertension reduces the risk of the development of heart failure.[150–152]

## 6.2 Treatment

Patients with hypertension and cardiovascular disease are classified as high risk, and it is recommended to start antihypertensive treatment promptly, as well as lifestyle modifications (e.g., low-salt healthy diet, exercise, weight reduction in obesity patients, and reducing alcohol consumption).[154] However, no clear evidence has been accumulated on treatment goals of blood pressure in patients with heart failure and hypertension, as the etiology and pathophysiology of heart failure are diverse. Although, there have been controversies about optimal blood pressure targets for this patient population,[373,374] and it is difficult to establish common goals for diverse patients, target systolic blood pressure of 110 to 130 mmHg has been supported in the United States,[375] and is the same in Japan.

### 6.2.1 Patients With HFrEF and Hypertension (Table 38)
ACE inhibitors[182,184,376] and β-blockers[193–195,377,378] have been demonstrated to improve the long-term prognosis of patients with heart failure and hypertension, and monotherapy or combination therapy of these drug classes are first-line treatment. Patients intolerable to ACE inhibitors

may be treated with ARBs.[168,187,188] Treatment with β-blockers should be started at low doses, and the dose should be titrated gradually based on tolerability. In patients who do not respond well to antihypertensive drugs or patients with heart failure associated with organ congestion, diuretics should be added, and MRAs added to standard therapy is expected to improve prognosis in patients with severe conditions.[163,164,189] Among calcium channel blockers, long-acting dihydropyridines can be used safely without compromising the prognosis of patients with heart failure,[379] but other types of calcium channel blockers with negative inotropic effects should be avoided.

### 6.2.2 Patients With HFpEF and Hypertension (Table 39)
As heart failure with preserved ejection fraction (HFpEF) is generally caused by both cardiovascular diseases (e.g., atrial fibrillation, hypertension, coronary artery diseases, and pulmonary hypertension) and non-cardiovascular diseases (e.g., diabetes, chronic kidney disease, anemia, and COPD), patients should be examined for these underlying conditions and should be treated accordingly.[380,381]

As hypertension is one of the most common underlying conditions of HFpEF,[382] blood pressure control is considered essential. However, there is no sufficient evidence regarding optimal antihypertensive regimens or treatment targets for this patient population, and patients should be treated individually to control blood pressure.

### 6.2.3 Acute Heart Failure
Patients with acute heart failure except for those corresponding to the clinical scenario (CS) #3 are treated with vasodilators and diuretics according to their conditions.

**Table 40.** Recommendations and Levels of Evidence for the Treatment of Diabetes Mellitus in Patients With Heart Failure

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| Comprehensive approach including life style modification such as diet and exercise | I | A | A | I |
| SGLT2 inhibitors (empagliflozin,* canagliflozin**) | IIa | A | B | II |
| Thiazolidinediones | III | A | D | I |

*In the EMPA-REG OUTCOME trial of empagliflozin,[175] all participants had a history of cardiovascular disease.
**In the CANVAS trial of canagliflozin,[178] 34% of the participants were at high risk of cardiovascular events, and 66% of the participants had a history of cardiovascular disease. The dose range of canagliflozin in the CANVAS study was wider than the approved dose range in Japan. SGLT, sodium glucose cotransporter.

See Chapter "**X. Acute Heart Failure**" for detail.

# 7. Diabetes Mellitus

## 7.1 Pathophysiology

The prevalence of diabetes mellitus among patients with heart failure increased from 13% in 1989 to 47% in 1999.[383] Also, about half of patients with diabetes mellitus have been reported to have left ventricular diastolic dysfunction[384] and poor cardiovascular outcome including heart failure.[385]

As diabetes mellitus is an independent risk factor for heart failure,[386] interventions for diabetes mellitus are needed to prevent the development or progression of heart failure.

## 7.2 Treatment

### 7.2.1 Treatment of Heart Failure in Patients With Diabetes Mellitus

Although no clinical studies have evaluated the effectiveness of ACE inhibitors, ARBs, or β-blockers with proven efficacy in heart failure in patients with heart failure and diabetes mellitus, sub-analyses of large-scale clinical trials of ACE inhibitors and ARBs have demonstrated efficacy in patients with heart failure with or without diabetes mellitus.[187,387,388] β-blockers are expected to exert similar efficacy regardless of whether diabetes mellitus is present or not.[389,390] The efficacy of MRAs in the treatment of heart failure has also been demonstrated in patients with and without diabetes mellitus.[164,391]

These findings suggest that patients with heart failure and diabetes mellitus should be treated similarly to those without diabetes mellitus.

### 7.2.2 Treatment of Diabetes Mellitus in Patients With Heart Failure (Table 40)

Although no evidence has been obtained on the efficacy of specific treatment strategies to control diabetes mellitus in patients with heart failure, comprehensive approach depending on individual pathology using guidelines-based antidiabetic drugs, as well as lifestyle modifications such as diet and exercise, is important.

In cardiovascular outcome trials of most of the currently available incretin-based drugs, neither beneficial effects on heart failure nor increased the risk of poor outcome was observed in patients with heart failure. However, in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus - Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial,[392] the incidence of hospitalizations for heart failure increased significantly in patients receiving saxagliptin.[393]

Among currently available SGLT2 inhibitors, empagliflozin[175] and canagliflozin[178] have been demonstrated to reduce the composite endpoint of major adverse cardiovascular events including cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, and the number of hospitalizations for heart failure in patients with type 2 diabetes mellitus and high cardiovascular risk, and are expected to improve the cardiovascular prognosis of patients with type 2 diabetes mellitus and high cardiovascular risk regardless of the presence or absence of heart failure.[176,177] However, as patients complicated with heart failure account for only 10 to 15% of patients enrolled in these large-scale clinical studies of SGLT2 inhibitors, further studies are necessary to clarify the beneficial effects of these drugs on heart failure. Also, as there has been no evidence indicating that these results reflect class effects of SGLT2 inhibitors, the results of large-scale clinical studies of other SGLT2 inhibitors are awaited. In addition, further studies should be conducted to clarify the efficacy of SGLT2 inhibitors in patients aged 75 and over.

Accordingly, physicians should treat patients with diabetes mellitus and heart failure carefully considering pharmacological characteristics of antidiabetic agents and results of clinical trials while avoiding hypoglycemia.

# 8. CKD and Cardiorenal Syndrome

## 8.1 Pathophysiology

As patients with heart failure often have renal dysfunction, treatment strategies should be developed based on the patient's estimated glomerular filtration rate (eGFR), a clinical indicator of renal function.

The present guidelines describe the benefits of drugs according to chronic kidney disease (CKD) stages that are based on eGFR. Patients with an eGFR of <60mL/min/1.73m² are classified into CKD stage 3 (eGFR: 30 to 59mL/min/1.73m²), stage 4 (15 to 29mL/min/1.73m²) and stage 5 (<15mL/min/1.73m²).

## 8.2 Treatment (Table 41)

Many large-scale clinical studies in acute or chronic heart diseases excluded patients with renal dysfunction. In

**Table 41.** Recommendations and Levels of Evidence for Drug Therapy for Patients With Chronic Kidney Disease (CKD) and Heart Failure

|  | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| **CKD Stage 3 (eGFR 30 to 59 mL/min/1.73 m²)** | | | | |
| β-blockers | I | A | A | I |
| ACE inhibitors | I | A | A | I |
| ARBs | I | B | A | II |
| MRAs | I | A | A | I |
| Loop diuretics | I | C | C1 | VI |
| **CKD Stage 4 to 5 (eGFR <30 mL/min/1.73 m²)** | | | | |
| β-blockers | IIa | B | B | II |
| ACE inhibitors | IIb | B | C1 | III |
| ARBs | IIb | C | C1 | IVb |
| MRAs | IIb | C | C2 | V |
| Loop diuretics | IIa | C | C1 | VI |

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; MRA, mineralocorticoid receptor antagonist.

general, patients with CKD stage 3 can be treated almost similarly to patients without CKD. However, little evidence has been obtained in terms of treatment of heart failure in patients with CKD stage 4 or 5, and such patients are treated at the discretion of the attending physicians and/or consulting specialists.

### 8.2.1 β-Blockers

The efficacy of β-blockers in the treatment of heart failure has been established. A meta-analysis of the data from the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial[394] and Carvedilol Post-infarct Survival Controlled Evaluation (CAPRICORN) trial[159] that assessed the efficacy of carvedilol in patients with heart failure revealed that carvedilol significantly improved the prognosis of patients with CKD stage 3 with an eGFR of 45 to 60 mL/min/1.73 m².[395] In a sub-analysis of the Cardiac Insufficiency Bisoprolol Study II (CIBIS II) trial that assessed the efficacy of bisoprolol, the drug improved the prognosis of patients with an eGFR of <45 mL/min/1.73 m² or 45 to 60 mL/min/1.73 m².[396] In a cohort study investigating the efficacy of β-blockers in patients with heart failure who are undergoing hemodialysis, oral β-blockers significantly improved the prognosis of this patient population.[397]

### 8.2.2 ACE Inhibitors and ARBs

The efficacy of angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) in patients with heart failure has been established. In the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial[182] in which patients with a serum creatinine level of ≥3.4 mg/dL were excluded, participants had a mean serum creatinine level of 1.4 mg/dL and an eGFR of about 45 mL/min/1.73 m², which indicate that

CKD was prevalent among the participants. In a sub-analysis that dichotomized patients according to mean serum creatinine level, the efficacy of enalapril was comparable between patients with higher and lower serum creatinine levels. In a study in patients with heart failure with a serum creatinine level of ≥2.4 mg/dL or a creatinine clearance of <30 mL/min (CKD stage 4 or 5), renin-angiotensin (RA) system inhibitors significantly improved the prognosis of these patients.[398] It has also been reported that addition of oral RAS inhibitors improved the prognosis of hemodialysis patients receiving oral β-blockers as compared with no addition of RAS inhibitors.[397] As ACE inhibitors and ARBs may rarely reduce renal function or cause hypokalemia in patients with CKD stage 4 or 5 and elderly patients with CKD, these drugs should be started at low doses.[399]

### 8.2.3 MRAs

The Randomized Aldactone Evaluation Study (RALES) trial[189] and the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS-HF) trial[163] have reported the benefits of mineralocorticoid receptor antagonists (MRAs) in patients with heart failure, but patients with a serum creatinine level of ≥2.5 mg/dL and patients with an eGFR of <30 mL/min/1.73 m² were excluded respectively and almost no evidence is available on the benefits of MRAs in patients with CKD stage 4 or 5. However, in patients with CKD stage 3 (eGFR <60 mL/min/1.73 m²), who accounted for 48% and 33% of the participants in the RALES and EPHESUS-HF trials, MRAs improved prognosis in a similar degree to patients with an eGFR ≥60 mL/min/1.73 m².[400,401] MRAs should be used carefully in patients receiving ACE inhibitors or ARBs because of concern about hyperkalemia or renal dysfunction.

**Table 42.** Recommendations and Levels of Evidence for the Management of Hyperuricemia in Patients With Heart Failure

|  | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| Use of serum uric acid level as a prognostic marker for heart failure | IIa | B | B | IVa |
| Treatment intervention to hyperuricemia in patients with heart failure | IIb | B | C1 | II |

### 8.2.4 Diuretics

Diuretics are often prescribed to patients with heart failure, and loop diuretics are essential for treatment of patients with congestive heart failure. However, as overuse of loop diuretics may reduce renal function and worsen the prognosis of patients,[200,402] loop diuretics should be limited to the minimum required for treatment.

### 8.2.5 Other Drugs

No evidence is available on the efficacy of digitalis in patients with a serum creatinine level of ≥3.0mg/dL. When digitalis is administered to patients with renal dysfunction, they should be carefully observed for signs of digitalis intoxication.[403] In the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) trial,[404] aliskiren, a direct renin inhibitor, reduced renal function.

### 8.2.6 Drugs Mainly Used for the Treatment of Acute Heart Failure

In Japan, carperitide is often used for the treatment of acute heart failure, but no conclusion has been reached on whether carperitide has a renal protective effect.[405] Tolvaptan, a vasopressin $V_2$ receptor antagonist, has been reported to reduce the dose of furosemide in patients with CKD stage 3/4 with an eGFR of 15 to 60mL/min/1.73m$^2$ in a small study.[406] Hemofiltration should be considered for patients with acute heart failure in whom drug therapy do not lead sufficient diuresis, or do not improve hemodynamics or symptoms.

## 9. Hyperuricemia/Gout

### 9.1 Pathophysiology

Hyperuricemia is a common comorbid condition in patients with heart failure. Hyperuricemia is defined as a serum uric acid level of >7.0mg/dL regardless of gender or age.[407] Patients with heart failure have serum uric acid levels higher than healthy individuals in genral.[84] It has been suggested that hyperuricemia in heart failure may be explained by excessive production and reduced excretion of uric acid. Xanthine oxidase (XO), the enzyme involved in the final process of uric acid production, is present in a small amount in the myocardium. In patients with myocardial ischemia or heart failure, XO activity is elevated, and uric acid production is enhanced, while uric acid excretion is reduced by decrease in renal blood flow and glomerular filtration rate. Moreover, furosemide and other diuretics that are commonly used for the treatment of heart failure may suppress the uric acid excretion and elevate serum uric acid level even further.

Although a relationship between serum uric acid level and prognosis has been suggested in patients with heart failure and the pathophysiological significance of uric acid in heart failure has gained attention, the details have not been revealed yet. Anker et al[81] conducted a prospective study to investigate a possible relationship between uric acid level and life expectance in 112 patients with heart failure and concluded that a serum uric acid level of ≥9.5mg/dL may predict poor prognosis. In a subsequent interventional trial of allopurinol in patients with heart failure, the treatment reduced uric acid levels but did not result in an improvement of cardiovascular outcomes.[408] Studies on novel drugs that decrease uric acid production such as febuxostat and topiroxostat have been conducted to investigate their effects in patients with heart failure, but no conclusive evidence has been found on whether high uric acid levels and the use of these drugs to reduce uric acid levels may affect the pathophysiology and prognosis of heart failure (**Table 42**).

### 9.2 Treatment

Many patients with heart failure also have underlying diseases such as hypertension, ischemic heart disease, diabetes mellitus, and chronic kidney disease. In Japan, an intervention to control hyperuricemia, consisting of lifestyle modification followed by pharmacotherapy if needed, is recommended for patients with gouty arthritis or gouty tophus with a serum uric acid level of >7.0mg/dL and patients with underlying disease such as renal dysfunction, hypertension, ischemic heart disease and diabetes mellitus with a serum uric acid level of ≥8.0mg/dL.[407] Although no evidence has been found regarding the optimal goal of serum uric acid level in patients with chronic heart disease, it would be appropriate to set a goal of ≤7.0mg/dL considering the above findings.

## 10. COPD and Asthma (Table 43)

### 10.1 Pathophysiology

In patients with bronchial asthma, chest X-ray findings are usually normal, and severe symptoms develop during asthma attack.[409]

Chronic obstructive pulmonary disease (COPD) is observed in about 20 to 30% of patients with left-sided heart failure,[410–412] and is an independent risk factor for the development of left-sided heart failure and cardiovascular death associated with heart failure.[413,414] BNP or NT-proBNP is a useful tool to differentiate heart failure from exacerbation of COPD in patients with respiratory failure.[412,415]

**Table 43.** Recommendations and Levels of Evidence for Examinations and Treatment for Patients With Heart Failure and COPD or Bronchial Asthma

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| **Examinations** | | | | |
| Measurement of BNP levels for the diagnosis of HFrEF in patients who also have COPD or bronchial asthma | I | A | A | I |
| **Treatments** | | | | |
| Use of ACE inhibitors or ARBs for the treatment of HFrEF in patients who also have COPD or bronchial asthma | I | A | A | I |
| Use of β-blockers for the treatment of HFrEF in patients who also have COPD | I | A | A | I |
| Careful administration of $\beta_1$ selective blockers for the treatment of HFrEF in patients who also have bronchial asthma | IIa | B | B | II |
| Continuing treatment of COPD or bronchial asthma during treatment of HFrEF | IIa | B | B | III |

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; HFrEF, heart failure with reduced ejection fraction.

**Table 44.** Recommendations and Levels of Evidence for the Treatment of Anemia in Patients With Heart Failure

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| **Red blood cell transfusion** in patients in whom anemia worsens heart failure and blood transfusion is expected to improve the condition | IIb | C | C1 | V |
| Oral iron supplementation | III | B | D | II |
| Erythropoiesis stimulating agent | III | B | D | II |

## 10.2 Treatment

### 10.2.1 Treatment of Heart Failure in Patients With Heart Failure and COPD

Treatment with ACE inhibitors, ARBs, β-blockers and/or diuretics are also recommended for patients with heart failure and COPD.[410,412] β-blockers can be used safely in most patients with heart failure and COPD.[192,412,415–417] β-blocker therapy should be initiated using $\beta_1$ selective blockers at low doses, and the dose should be titrated upward slowly. β-blockers should be used carefully in patients with COPD and uncontrolled asthma.[418]

### 10.2.2 Treatment of Heart Failure in Patients With Bronchial Asthma

Treatment with ACE inhibitors, ARBs, and/or diuretics are also recommended for patients with heart failure and bronchial asthma.[409,419]

### 10.2.3 Treatment of COPD in Patients With Heart Failure

Monotherapy or combination therapy using long-acting $\beta_2$ agonists and long-acting anticholinergics for the treatment of COPD should be continued in combination with treatment for heart failure.[410]

### 10.2.4 Treatment of Bronchial Asthma in Patients With Heart Failure

Inhaled corticosteroids for the treatment of bronchial asthma are safe and recommended for patients with asthma and heart failure.[409]

## 11. Anemia (Table 44)

Patients with heart failure often have anemia, defined as hemoglobin levels of <13.0 g/dL in men and <12.0 g/dL in women by World Health Organization (WHO). Anemia is an independent prognostic factor in heart failure.[420,421]

Anemia in patients with heart failure is treated with red blood cell transfusion, iron supplementation, and/or erythropoiesis stimulating agents (ESAs). **Table 44** lists recommendations and levels of evidence for the treatment of anemia in patients with heart failure.

## 12. Sleep-Disordered Breathing

The most common pathology of sleep-disordered breathing (SDB) is sleep apnea, which is classified into obstructive sleep apnea (OSA) caused by the obstruction of the upper airway and central sleep apnea (CSA) caused by the loss of respiratory drive. Patients with CSA and heart failure often have Cheyne-Stokes respiration (CSR), which is referred to as central sleep apnea with Cheyne-Stokes respiration (CSR-CSA).

**Table 45.** Recommendations and Levels of Evidence for the Treatment of OSA in Patients With Heart Failure

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| **Guideline-based CPAP treatment** in patients with symptomatic OSA | I | A | A | I |
| **CPAP treatment** in patients with HFrEF and moderate* or severe OSA to improve left ventricular function | IIa | A | B | I |
| **CPAP treatment** in patients with heart failure and moderate* or severe OSA to improve prognosis | IIb | C | C2 | III |

*Moderate OSA is commonly defined as AHI ≥15, but the National Health Insurance in Japan covers OSA treatment for patients with AHI ≥20. CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea.

## 12.1 Pathophysiology
### 12.1.1 Prevalence of SDB in Patients With Heart Failure
The prevalence of OSA is high among patients with cardio-vascular diseases including heart failure. In addition to OSA, CSR-CSA is frequently found in patients with heart failure (about 50%).[422–426] A considerable percentage of patients with heart failure have both OSA and CSR-CSA.

### 12.1.2 Effects of SDB on the Onset and Progression of Heart Failure
OSA increases the risk of the onset or exacerbation of cardiovascular diseases through different mechanisms such as hypoxemia associated with apnea, sympathetic hyperactivity, increased left ventricular afterload due to intratho-racic negative pressure, endothelial dysfunction, oxidative stress, inflammation, hypercoagulability, obesity, and insulin resistance,[427–429] and is involved in the development of heart failure.[430] CSR-CSA is caused by the occurrence of low arterial partial pressure of carbon dioxide ($PaCO_2$) due to pulmonary congestion and excessive response to low $PaCO_2$,[427,431] as well as prolonged circulation time. Nocturnal rostral leg fluid displacement[432] worsen OSA by causing upper airway edema that narrows the airways and CSA by pulmonary congestion.

### 12.1.3 Effects of SDB on the Prognosis of Patients With Heart Failure
Moderate or severe OSA is associated with a poor prognosis in patients with heart failure,[433] and the presence of even mild or severer CSR-CSA is a prognostic factor in patients with heart failure.[434]

## 12.2 Treatment

### 12.2.1 Screening for SDB in Patients With Heart Failure
As SDB is often asymptomatic in patients with heart failure,[435] screening for SDB is recommended for patients with heart failure who do not respond well to standard treatment to identify underlying conditions. See the Guide-lines for Diagnosis and Treatment of Sleep Disordered Breathing in Cardiovascular Disease (JCS 2010)[427] for detail.

### 12.2.2 Treatment of Heart Failure
Modifications of lifestyle as risk factors or worsening factors of OSA should be tried first as they are beneficial for the treatment of heart failure. As CSR-CSA is caused by heart failure, optimization of treatment for heart failure is most important.

### 12.2.3 Positive Pressure Ventilation for the Treatment of SDB in Patients With Heart Failure
#### a. Positive Pressure Ventilation for OSA (Table 45)
In randomized controlled trials and meta-analyses of continuous positive airway pressure (CPAP) in patients with OSA and reduced LVEF, CPAP improved LVEF.[436,437] Observational studies have reported that positive pressure ventilation improves the prognosis of patients with heart failure,[438,439] no large-scale clinical studies have been conducted to date.

At present, OSA should be treated according to the guidelines for the treatment of SDB even in patients with heart failure. CPAP should be considered in patients with heart failure with reduced LVEF and moderate or severe OSA to improve LVEF.

#### b. Positive Pressure Ventilation for Patients With Heart Failure and CSR-CSA (Table 46)
Positive pressure ventilation is generally considered for patients who still have CSR-CSA even after optimal treat-ment for heart failure. In the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP) study that investigated the effects of CPAP on the prognosis of patients with CSR-CSA and HFrEF (LVEF ≤45%),[440] the severity of CSR-CSA decreased by about 50% and LVEF increased in patients receiving CPAP, but no improvement in prognosis was observed. However, patients in whom CPAP suppressed CSA at 3 months showed better prognosis than in patients in the control group.[441]

Adaptive servo-ventilation (ASV) has been reported to be more effective in suppression of CSR-CSA, and random-ized controlled trials and meta-analyses have indicated that ASV improves LVEF in patients with CSR-CSA and HFrEF (LVEF ≤45%) and decreases BNP.[442–445] A prospec-tive observational study has reported that ASV may improve the prognosis of patients with heart failure and CSR-CSA,[446] while in the Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure (SERVE-HF) trial,[272] a randomized clinical trial of ASV in patients with heart failure with LVEF ≤45% and predominant CSA, ASV did not improve long-term prognosis, and did significantly increased all-cause deaths and cardiovascular deaths. Accordingly, the 2016 ESC guidelines and the 2017 ACC/AHA/HFSA guidelines descried that ASV is not recommended for patients with chronic heart disease with LVEF ≤45% and predominant CSA.[8,14] However, in Japan, the use of ASV in this patient population is covered with the National Health Insurance even with certain

**Table 46.** Recommendations and Levels of Evidence for Treatment for Patients With CSR-CSA and Heart Failure

|  | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| Optimization of heart failure treatment according to the heart failure guideline | I | A | A | I |
| **CPAP treatment** in patients with heart failure and moderate or severe CSR-CSA to improve symptoms, exercise capacity, and left ventricular function | IIa | B | B | II |
| **ASV treatment** in patients with HFpEF and moderate or severe CSR-CSA who are intolerable or refractory to CPAP to improve symptoms and exercise capacity | IIa | B | B | II |
| **ASV treatment** Use in patients with HFrEF (LVEF ≤45%) and moderate or severe CSR-CSA who are intolerable or refractory to CPAP to improve symptoms and exercise capacity | IIb | B | B | II |
| **Aimless continuation of ASV treatment** in patients with HFrEF (LVEF ≤45%) and CSR-CSA to aimlessly continue ASV as CSR-CSA treatment even after improvement or stabilization of heart failure | III | A | C1 | II |

ASV, adaptive servo-ventilation; CSR-CSA, central sleep apnea with Cheyne-Stokes respiration; CPAP, continuous positive airway pressure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; OSA, obstructive sleep apnea.

**Table 47.** Recommendations and Levels of Evidence for Home Oxygen Therapy for Patients With Sleep-Disordered Breathing (SDB) and Heart Failure

|  | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| **Home oxygen therapy** in patients with moderate* or severe CSR-CSA and NYHA Class III or VI HFrEF (LVEF ≤45%) to improve cardiac function and symptoms | IIa | B | B | II |

*Moderate OSA is commonly defined as apnea hypopnea index (AHI) ≥15, but the National Health Insurance in Japan covers OSA treatment for patients with AHI ≥20. CSR-CSA, central sleep apnea with Cheyne-Stokes respiration; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

limitations, and the Japanese Circulation Society and the Japanese Heart Failure Society have published a statement (second report) for appropriate use of ASV with a consideration of the requirement for NHI coverage (**Supplement 1**).[271]

### 12.2.4 Oxygen Therapy (Table 47)
Oxygen therapy increases arterial partial pressure of oxygen ($PaO_2$), which reduces central carbon dioxide ($CO_2$) sensitivity and hyperventilation and slightly increases $PaCO_2$,[447] and thereby suppresses CSR-CSA. Short-term studies have reported that nocturnal oxygen therapy is effective in suppressing CSR-CSA, reducing sympathetic nerve activity, improving exercise capacity, and reducing BNP levels in patients with chronic heart failure.[448,449] In a multicenter clinical study of oxygen therapy in patients with CSR-CSA and HFrEF (LVEF ≤45%) in Japan, three-month oxygen therapy reduced the severity of CSR-CSA and improved the Specific Activity Scale score, and the efficacy of treatment was maintained in patients who continued oxygen therapy for one year.[450,451] In Japan, oxygen therapy for patients with NYHA class III or IV chronic heart failure and CSR with an apnea hypopnea index (AHI) of ≥20 is covered with the National Health Insurance.

## X.  Acute Heart Failure

### 1.  Definition and Classification

#### 1.1 Definition
Acute heart failure is defined as the rapid onset or exacer-bation of signs and symptoms caused by acute disturbance of pump function that leads to insufficient or inadequate blood filling and poor blood delivery to peripheral tissues due to structural and/or functional abnormalities of the heart.

## 1.2. Classification

### 1.2.1 Clinical Classification of Acute Heart Failure in Initial Management: CS Classification

The clinical scenario (CS) classification is a tool to classify patients with acute heart failure according to pathophysiological condition with reference on systolic blood pressure, and provide appropriate initial management for each type of patients.[452]

**Table 48. Killip Classification**

| Class I | No clinical signs of heart failure |
|---|---|
| Class II | Mild to moderate heart failure. Rales up to 50% of lung fields or S3 heart sound |
| Class III | Severe heart failure. Frank pulmonary edema with rales more than 50% of lung fields |
| Class IV | Cardiogenic shock. Signs include hypotension (systolic blood pressure <90mmHg), oliguria, cyanosis, cold and wet skin, and loss of consciousness |

(Source: Prepared based on Killip T, et al. 1967[453])

**Table 49. Precipitating Factors of Heart Failure**

- Acute coronary syndrome
- Tachyarrhythmia (e.g., atrial fibrillation, atrial flutter, and ventricular tachycardia)
- Bradyarrhythmia (e.g., complete atrioventricular block, and sick sinus syndrome)
- Infections (e.g., pneumonia, infective endocarditis, and sepsis)
- Poor adherence (e.g., insufficient salt/water restriction and noncompliance)
- Acute pulmonary thromboembolism
- Acute exacerbation of chronic obstructive pulmonary disease
- Drugs (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], negative inotropes, and cancer chemotherapy)
- Excessive stress or overwork
- Excessive blood pressure elevation
- Endocrine or metabolism disorders (e.g., hyperthyroidism/hypothyroidism, adrenal dysfunction, and peripartum cardiomyopathy)
- Mechanical complications (e.g., cardiac rupture, acute mitral valve insufficiency, chest trauma, and acute aortic dissection)

### 1.2.2 Pathophysiological Classification of Acute Heart Failure

1) Acute pulmonary edema
2) Systemic fluid retention (congestion)
3) Low cardiac output/hypoperfusion (including cardiogenic shock)

### 1.2.3 Classification by History of Hospitalization for Heart Failure

1) De novo heart failure (patients with no history of hospitalization for heart failure)
2) Rehospitalization for heart failure (patients with history of hospitalization for heart failure)

### 1.2.4 Killip Classification (Table 48)[453]

Killip classification is a tool to classify patients after acute myocardial infarction according to their objective findings. It is also important to identify factors predicting prognosis of heart failure (**Table 49**).

## 2. Diagnosis

### 2.1 Diagnosis (Table 50)

The diagnosis of acute heart failure is based on signs and symptoms and the levels of natriuretic peptides (BNP or NT-proBNP). Biomarkers such as BNP and NT-proBNP are important indicators for diagnosis, treatment, and prognosis of patients with acute heart failure. Acute heart failure is unlikely in patients with BNP of ≤100 pg/mL or NT-proBNP of ≤400 pg/mL.[43]

### 2.2 Signs and Symptoms

### 2.2.1 Congestion

Almost all patients with acute heart failure are hospitalized with congestion such as pulmonary edema and systemic fluid retention. Symptoms of congestion develop when intracardiac pressure abruptly increases from the baseline level.

### 2.2.2 Low Cardiac Output/Hypoperfusion

Symptoms of low cardiac output include fatigue, feeling of weakness, oliguria, cyanosis, cold extremities, and/or anorexia.

**Table 50. Recommendations and Levels of Evidence for the Diagnosis of Acute Heart Failure**

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| Measurement of BNP or NT-proBNP levels at a clinic visit for differential diagnosis | I | A | A | I |
| Evaluation of ECG, chest X-ray, troponin, blood urea nitrogen, creatinine, electrolytes, blood glucose, blood cell count, liver function test, and thyroid function test at a clinic visit | I | C | B | VI |
| Evaluation of cardiac function using echocardiography | I | C | B | VI |
| Evaluation of pulmonary edema and pleural fluid using lung ultrasound | IIa | B | B | III |

BNP, brain (B-type) natriuretic peptide; ECG, electrocardiogram; NT-proBNP, N-terminal pro-brain (B-type) natriuretic peptide.

# 3. Treatment Strategies and Flowcharts

During initial management including diagnosis of acute heart failure, patients should be evaluated carefully to clarify pathological characteristics and communicate the findings with healthcare professionals involved in acute phase treatment and ensure the earliest possible intervention. Clinical evaluation should be repeated whenever necessary to facilitate early improvement.

## 3.1 Initial Management

**Table 51** lists the purpose of initial management for patients arriving at hospital. Arterial blood gas analysis should be performed whenever necessary, and appropriate oxygen therapy should be initiated promptly (**Table 52**).

Monitoring of vital signs, hemodynamics and respiratory function should be initiated immediately after hospitalization to examine whether peripheral circulation and organ perfusion are maintained (**Figure 11**).[454] Oxygen saturation, blood pressure, body temperature, respiratory rate, and ECG must be monitored. Urine volume should be monitored whenever possible. In initial management, presence of cardiogenic shock and respiratory failure should be examined and treated appropriately. It is important to rule out specific conditions such as acute coronary syndrome (ACS) and acute thromboembolism. **Table 53** lists patients indicated for CCU/ICU care.

Management strategies for the specific conditions are as follows:
1) **M**yocarditis: With the possibility of fulminant myocarditis in mind, patients should be monitored with ECG and echocardiography. Even in fulminant cases, prompt treatment may help improve the prognosis for many patients. Mechanical circulatory support including ventricular assist devices should be used when necessary. See the Guidelines for Diagnosis and Treatment of Myocarditis (JCS 2009) for detail.[455]
2) **R**ight-sided heart failure: It is important to identify the cause of right-sided heart failure, and select appropriate

treatment strategies accordingly. Patients diagnosed as having severe pulmonary arterial hypertension should be treated mainly with intravenous prostacyclin analogs, and the introduction or dose-escalation of the remaining two types of anti-pulmonary hypertension drugs should be considered. Other drugs such as dobutamine should be used whenever necessary to maintain or improve cardiac output. Right-sided heart failure due to constrictive pericarditis or other heart diseases should be differentiated from that due to pulmonary arterial hypertension.
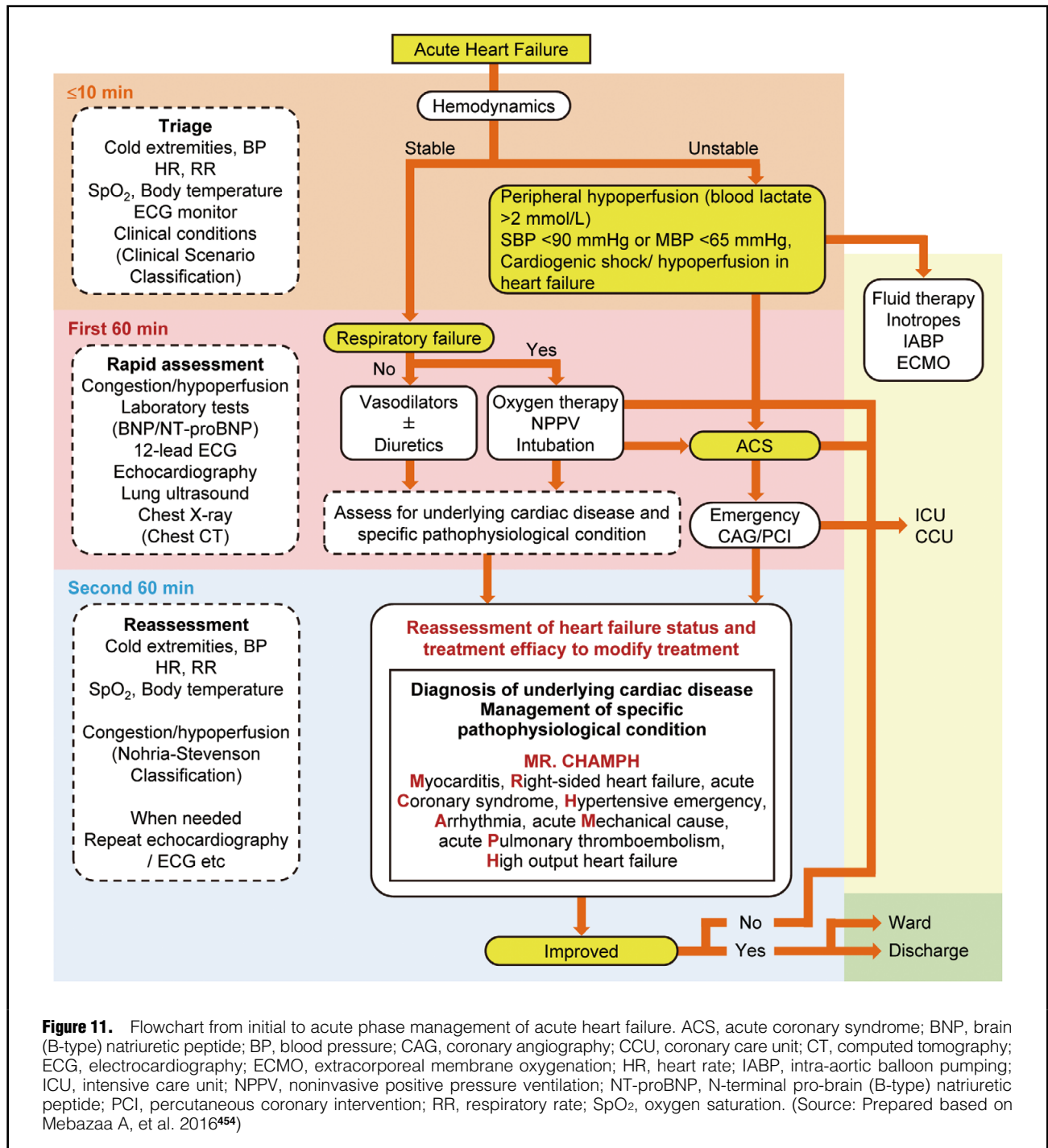3) **A**cute **C**oronary syndrome: Acute heart failure due to acute coronary syndrome should be diagnosed and treated according to the guidelines for the management of patients with ST-elevation acute myocardial infarction (JCS 2013)[456] and the Guidelines for Management of Acute Coronary Syndrome without Persistent ST Segment Elevation (JCS 2012).[457]
4) **H**ypertensive emergency: Vasodilators should be administered intravenously to reduce blood pressure promptly. Diuretics should be added to patients with systemic fluid retention.
5) **A**rrhythmias: Patients with acute heart failure due to ventricular tachycardia and other types of tachyarrhythmias should be treated with intravenous amiodarone or direct current defibrillation. Patients with acute heart

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**Table 51. Purpose of Initial Management for Patients With Acute Heart Failure**

1. Rescue and stabilize vital signs
2. Improve hemodynamics and maintain oxygenation
3. Relieve dyspnea and other signs and symptoms of congestion
4. Diagnose acute heart failure and rule out acute coronary syndrome or pulmonary thromboembolism
5. Prevent the progression of cardiac disorder and other organ disorders
6. Shorten the duration of ICU/CCU treatment through early intervention to achieve early improvement

CCU, coronary care unit; ICU, intensive care unit.

---

**Table 52. Recommendations and Levels of Evidence for Oxygen Therapy and Respiratory Management in Patients With Acute Heart Failure**

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| Measurement of pH, $CO_2$, and lactic acid levels in venous blood in patients who also have pulmonary edema or COPD. Measurement of pH, $CO_2$, and lactic acid levels in arterial blood in patients with cardiogenic shock | IIa | C | B | IVb |
| Oxygen therapy for patients with $SpO_2$ <90% or $PaO_2$ <60 mmHg to treat hypoxemia | I | C | B | VI |
| Prompt introduction of noninvasive positive pressure ventilation (NPPV) in patients with dyspnea (respiratory rate >25 breaths per minute, $SpO_2$ <90%) to alleviate difficult breathing and avoid tracheal intubation | I | A | A | I |
| Tracheal intubation for patients who cannot control the following conditions despite above-described treatment:<br>• Hypoxemia ($PaO_2$ <60 mmHg)<br>• $CO_2$ retention ($PaCO_2$ >50 mmHg)<br>• Respiratory acidosis (pH <7.35) | I | C | B | VI |

COPD, chronic obstructive pulmonary disease; $PaCO_2$, arterial partial pressure of carbon dioxide; $PaO_2$, arterial partial pressure of oxygen; $SpO_2$, oxygen saturation.

**Figure 11.** Flowchart from initial to acute phase management of acute heart failure. ACS, acute coronary syndrome; BNP, brain (B-type) natriuretic peptide; BP, blood pressure; CAG, coronary angiography; CCU, coronary care unit; CT, computed tomography; ECG, electrocardiography; ECMO, extracorporeal membrane oxygenation; HR, heart rate; IABP, intra-aortic balloon pumping; ICU, intensive care unit; NPPV, noninvasive positive pressure ventilation; NT-proBNP, N-terminal pro-brain (B-type) natriuretic peptide; PCI, percutaneous coronary intervention; RR, respiratory rate; SpO2, oxygen saturation. (Source: Prepared based on Mebazaa A, et al. 2016[454])

| Table 53. Indications for CCU/ICU Treatment for Acute Heart Failure |
|---|
| 1. Patients who require or have already received tracheal intubation |
| 2. Patients with hypotension (systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg) or shock |
| 3. Patients with oxygen saturation <90% despite oxygen therapy |
| 4. Patients with forced breathing and respiratory rate >25/min |
| 5. Patients with uncontrolled dangerous arrhythmias |

failure due to severe bradycardia should be treated with external pacing.

6) **Acute Mechanical causes**: Acute mechanical causes include free wall rupture, ventricular septal perforation, or papillary muscle rupture associated with ACS, PCI complications such as coronary artery obstruction or perforation, acute aortic dissection, infective endocarditis, malfunctioning mechanical valves, and chest injuries. Echocardiography is essential for the diagnosis of these complications and emergency surgery is often needed.

**Table 54.** Recommendations and Levels of Evidence for Monitoring in Patients With Acute Heart Failure

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| Measurement of body weight and volume balance on the day of hospitalization and daily during the hospital stay | I | C | B | VI |
| Daily assessment for signs/symptoms of heart failure (dyspnea, moist rales, peripheral edema, body weight) on daily basis | I | B | B | IVb |
| Measurement of renal function (blood urea nitrogen and creatinine), electrolytes (Na and Cl) (especially in patients receiving diuretics or renin-angiotensin-aldosterone system inhibitors) | I | B | B | IVb |
| Echocardiography to estimate hemodynamics and causative disease | I | C | B | VI |
| Arterial pressure monitoring in patients with unstable hemodynamics | IIa | C | C1 | VI |
| **Swan-Ganz catheterization to determine hemodynamics** 1) In patients with cardiogenic shock not responding promptly to appropriate fluid therapy 2) In patients with pulmonary edema associated with shock/near shock that does not respond to appropriate treatment measures 3) Use as a diagnostic measure to confirm whether the cause of pulmonary edema is cardiogenic or noncardiogenic | I | C | B | IVb |
| **Swan-Ganz catheterization to determine hemodynamics** in patients with repeated hypotension and hypoperfusion despite drug therapy | IIa | C | B | IVa |
| **Swan-Ganz catheterization to determine hemodynamics** As routine procedure | III | B | D | II |

7) **Acute Pulmonary thromboembolism**: Acute pulmonary thromboembolism should be diagnosed and treated according to the Guidelines for Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis (JCS 2009).[458]

8) **High output heart failure**: High output heart failure may be caused by sepsis, thyrotoxicosis, anemia, cardiac shunts, beriberi heart, or Paget's disease. Pathological assessment should be performed, and causative disease should be diagnosed and treated promptly.

## ▌ 3.2 Basic Principle for Acute Phase Treatment (Table 54, Figure 12)[452,459]

Patients who received initial management in the ICU/CCU should be reassessed for changes in pathological conditions including symptoms of heart failure and body weight, and their treatments should be modified whenever necessary.

## ▌ 3.3 Pathological Conditions and Treatment Strategies in Acute Heart Failure (Figure 12)[452,459]

Although there are various diseases that can cause acute heart failure, the conditions of acute heart failure may be generally classified into three categories: acute cardiogenic pulmonary edema, systemic fluid retention, and hypoperfusion due to low cardiac output.

## ▌ 3.3.1 Acute Cardiogenic Pulmonary Edema
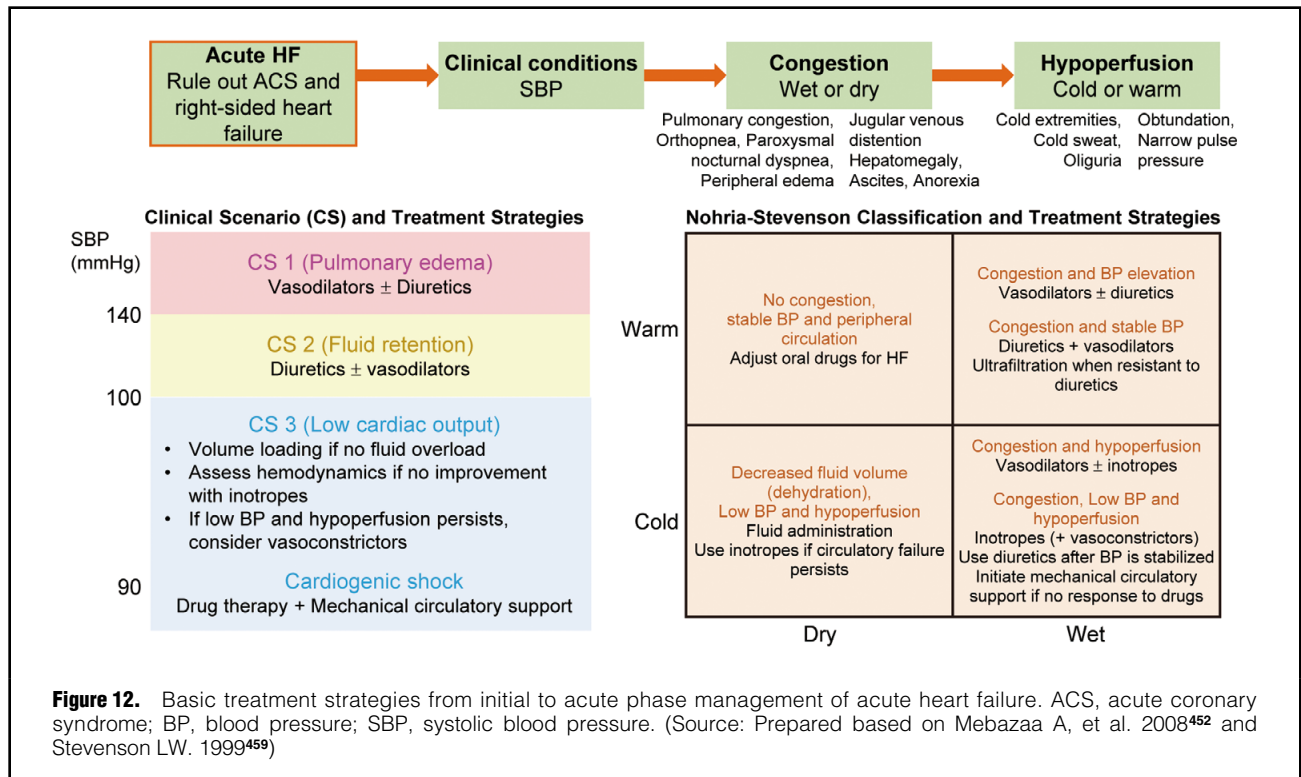Acute cardiogenic pulmonary edema is a CS 1 condition.

Patients often have orthopnea and an oxygen saturation ($SpO_2$) of <90%. Noninvasive positive pressure ventilation (NPPV) is effective in alleviating symptoms, increasing arterial blood oxygenation, and improving hemodynamics (**Table 52**). Before intravenous access is established, NPPV, sublingual nitrates, or nitrate spray should be used to treat dyspnea and improve oxygenation promptly. If pulmonary edema persists, vasodilators should be infused intravenously while avoiding an abrupt lowering in blood pressure. Physicians should keep in mind that about 50% of patients with CS 1 have low LVEF,[460] and are at risk of low cardiac output during treatment.

## ▌ 3.3.2 Systemic Fluid Retention
Systemic fluid retention is a CS 2 condition. Patients have excessive systemic fluid overload with peripheral edema. Their treatment should be mainly performed by diuretics.

## ▌ 3.3.3 Low Cardiac Output/Hypoperfusion
Low cardiac output or hypoperfusion is a CS 3 condition. The main symptoms are cold extremities, general fatigue, anorexia and reduced physical activity, but some patents may not complain of severe dyspnea or edema and thus treatment should be initiated carefully to avoid abrupt change in hemodynamics. Patients receiving β-blockers should continue treatment unless they present with shock. The use of phosphodiesterase (PDE) III inhibitors[461] and dobutamine should be considered for such patients as needed.

**Figure 12.** Basic treatment strategies from initial to acute phase management of acute heart failure. ACS, acute coronary syndrome; BP, blood pressure; SBP, systolic blood pressure. (Source: Prepared based on Mebazaa A, et al. 2008[452] and Stevenson LW. 1999[459])

### 3.3.4 Cardiogenic Shock (Table 55)

Cardiogenic shock is defined as a systolic blood pressure of <90mmHg or a mean arterial blood pressure of <65mmHg with signs of tissue hypoperfusion in the absence of decrease in circulatory plasma volume or lack of preload due to bleeding or dehydration. In addition to physical findings, an increase in blood lactate levels (>2mmol/L, 18mg/dL) suggests hypoperfusion. All patients with cardiogenic shock must undergo emergency 12-lead ECG and echocardiography to identify the causative condition and treat it accordingly. Rehydration should be attempted in patients without fluid retention. Dobutamine is a first-line drug for this patient population. Addition of PDE III inhibitors can be considered for patients with biventricular cardiac failure. Mechanical circulatory support should be considered in patients who do not respond well to these drugs. The prognosis of patients often depends on the cause and conditions of cardiogenic shock rather than the treatment itself.

### 3.4 Management During Transition Period From Acute Heart Failure to Chronic Phase

In patients transferred from the CCU/ICU to the general ward with stable condition, treatment for the causative conditions should be continued.

**Table 56** summarizes the goal of in-hospital treatment for heart failure during transition from acute heart failure to chronic phase. Management to avoid worsening heart failure is important, and patients should be assessed accurately for symptomatic improvement in orthopnea, jugular venous distinction, coarse crackles in the lung fields, peripheral edema, and general fatigue at discharge.

### 3.5 From Discharge to Ambulatory Care

As rehospitalization due to worsening heart failure often occurs during early period after discharge from hospital, early clinic visit should be scheduled after discharge whenever the patient's conditions permit. It is desirable to continue multidisciplinary heart failure team care after discharge.

Treatment goals after discharge are as follows:
1) To prevent worsening symptoms and decline in QOL, and improve prognosis.
2) To prevent rehospitalization early phase after discharge.
3) To develop a comprehensive clinical path to help the hospital and clinics collaborate to provide lifestyle modification intervention for each patient.
4) To try increasing the doses of standard treatments such as β-blockers to target levels, even after hospital discharge.
5) To consider for the indication of device therapy, whenever necessary.

## 4. Pharmacological Therapy

**Tables 57** and **58** list the indications and recommended dosage regimens of drugs used for the treatment of acute heart failure in Japan.

### 4.1 Sedation

### 4.1.1 Morphine Hydrochloride

Through its central actions, morphine diminishes excessive sympathetic tone and thereby decreases myocardial oxygen demand. It reduces afterload by dilating arterioles, and

**Table 55.** Recommendations and Levels of Evidence for the Treatment of Patients With Cardiogenic Shock

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| Transfer to ICU/CCU where mechanical circulatory support is available | I | C | B | VI |
| Continuous monitoring of ECG and arterial blood pressure | I | C | B | VI |
| Rapid intravenous infusion of physiological saline or Ringer solution (≥200 mL over 15 to 30 min) in patients without fluid retention | I | C | B | V |
| Treatment with inotropic drugs (dobutamine) to increase cardiac output | IIa | B | B | III |
| Treatment of vasoconstrictors (norepinephrine) to maintain systolic blood pressure in patients with persistent peripheral hypoperfusion | IIa | B | B | III |
| Routine use of IABP | III | B | D | II |
| Short-term use of mechanical circulatory support considering the age, higher brain function, complications and social factors | IIb | C | C1 | VI |

See the Guidelines for the Management of Patients with ST-Elevation Acute Myocardial Infarction (JCS 2013)[456] and the Guidelines for Management of Acute Coronary Syndrome without Persistent ST Segment Elevation (JCS 2012)[457] for management of ACS.
ACS, acute coronary syndrome; CCU, coronary care unit; IABP, intra-aortic balloon pump; ICU, intensive care unit.

improves pulmonary congestion by dilating veins and thereby reducing venous return.[462] Morphine should be administered carefully in patients with hypotension, bradycardia or high-grade atrioventricular block. In patients with intracerebral hemorrhage, decreased consciousness, bronchial asthma, or COPD, morphine should generally be avoided. Based on the reported effects of morphine on prognosis,[463,464] morphine should not be used as a routine treatment.

## 4.2 Diuretics

### 4.2.1 Loop Diuretics
#### a. Furosemide
Loop diuretics alleviate symptoms of heart failure such as pulmonary congestion and edema, and decreases left ventricular end-diastolic pressure by reducing preload. Furosemide has a rapid onset of action in patients with acute heart failure.[465] Western guidelines[7,16] recommend diuretics for patients with symptomatic left ventricular systolic heart failure. Findings from an observational study in Japan have indicated the importance of early treatment of congestion to shorten the duration of congestion.[466]

Patients with severe heart failure and renal dysfunction should receive diuretics at higher doses.[467] A study has suggested that patients in whom adequate diuresis was not obtained with a single bolus dose of furosemide may respond well to continuous intravenous infusion of the drug.[468]

The dose of loop diuretics should be limited to minimum necessary. The method of administration, i.e., bolus injection vs. continuous infusion, should be selected based on the individual patient's condition. The dose should be adjusted based on LVEF or other pathological features.

Loop diuretics are less effective in patients with hypotension (systolic blood pressure: <90 mmHg), hyponatremia, hypoalbuminemia, or acidosis. Patients who do not respond well to loop diuretics may respond to diuretics which have different site of action. However, non-loop diuretics should

**Table 56.** Treatment Goals for Hospitalized Patients During Transition From Acute to Chronic Heart Failure

1. Identify the cause of heart failure and complications and treat them accordingly
2. Treat the patient to alleviate signs/symptoms of heart failure and improve cardiac function (e.g., treatment with diuretics or vasodilators)
3. For patients with HFrEF, start treatment with RAAS inhibitors and β-blockers and then increase the doses to the target levels. For patients with HFpEF, standard drug therapy has not been established and focus on the management of risk factors such as hypertension.
4. Consider device treatment such as ICD and CRT/CRT-D, if indicated.

ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy defibrillator; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; RAAS, renin-angiotensin-aldosterone system.

be used carefully as they may cause electrolyte imbalance and an increase in blood urea nitrogen more frequently than loop diuretics.

### 4.2.2 Vasopressin V2 Receptor Antagonists (AVP Antagonists)
Tolvaptan is an oral drug that inhibits arginine vasopressin (AVP) type 2 receptors. In Japan, it is indicated for patients with heart failure who are resistant to other diuretics. AVP antagonists suppress hyponatremia and are beneficial in the treatment of patients with intractable heart failure, especially those with heart failure and hyponatremia. Although AVP antagonists are considered effective in fluid management in patients with diuretic-resistant heart failure and severe congestion, the dose should be limited to the minimum necessary. Patients should be observed carefully for adverse reactions such as thirst and hypernatremia.

**Table 57. Recommendations and Levels of Evidence for Drug Therapy for Patients With Acute Heart Failure**

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| **Diuretics** | | | | |
| **Loop diuretics** | | | | |
| Intravenous and oral administration to alleviate fluid retention in patients with acute heart failure | I | C | B | II |
| Continuous intravenous infusion to patients not responding to bolus injections | IIa | B | B | IVb |
| **Vasopressin V₂ receptor antagonists (tolvaptan)** | | | | |
| Use for the treatment of fluid retention in patients not responding well to other diuretics including loop diuretics (Excluding patients with hypernatremia) | IIa | A | B | II |
| Use for the treatment of fluid retention in patients with hyponatremia | IIa | C | C1 | II |
| **MRAs** | | | | |
| Use in combination with loop diuretics in patients in whom loop diuretics become less effective | IIb | C | C1 | III |
| Use in patients with hypokalemia and normal renal function | IIa | B | B | II |
| Use in patients with renal dysfunction and hyperkalemia | III | C | D | VI |
| **Thiazide diuretics** | | | | |
| Use in combination with furosemide in patients in whom furosemide becomes less effective | IIb | C | C1 | III |
| **Vasodilators** | | | | |
| **Nitrates** | | | | |
| Use for the treatment of pulmonary congestion in patients with acute heart failure or acute worsening chronic heart failure | I | B | A | II |
| **Nicorandil** | | | | |
| Use for the treatment of pulmonary congestion in patients with acute heart failure or acute worsening chronic heart failure | IIb | C | C1 | II |
| **Carperitide** | | | | |
| Use for the treatment of pulmonary congestion in patients with decompensated heart failure | IIa | B | B | II |
| Use in combination with inotropes in patients with intractable heart failure | IIa | B | C1 | II |
| Use in patients with serious hypotension, cardiogenic shock, acute right ventricular infarction, or dehydration | III | C | C2 | VI |
| **Calcium channel blockers** | | | | |
| Sublingual administration of nifedipine to patients with hypertensive emergency | III | C | D | IVb |
| **Inotropes/vasopressors** | | | | |
| **Dobutamine** | | | | |
| Use in patients with pump dysfunction and pulmonary congestion | IIa | C | B | II |
| **Dopamine** | | | | |
| Use in expectation of increase in urine volume and renal protective effect | IIb | A | C2 | II |
| **Norepinephrine** | | | | |
| Use in combination with catecholamines in patients with pulmonary congestion and hypotension | IIa | B | B | III |
| **PDE III inhibitors** | | | | |
| Use in patients with non-ischemic pump dysfunction and pulmonary congestion | IIa | A | B | II |
| Use in patients with ischemic pump dysfunction and pulmonary congestion | IIb | A | B | II |
| Use in combination with dobutamine in patients with a severe reduction in cardiac output | IIb | C | C1 | IVb |
| **Rate controllers** | | | | |
| **Digitalis** | | | | |
| Use for rate control of atrial fibrillation in patients with tachycardia-induced heart failure | I | A | B | II |
| **Landiolol** | | | | |
| Use for rate control of atrial fibrillation in patients with tachycardia-induced heart failure | I | C | B | II |

MRA, mineralocorticoid receptor antagonist; PDE, phosphodiesterase.

## 4.3 Vasodilators

Vasodilators, like diuretics, are effective in the treatment of acute cardiogenic pulmonary edema. In general, vasodilators are the first choice, but diuretics should mainly be used in patients with severe congestion due to fluid retention such as those with acute exacerbation of chronic heart failure. On the other hand, vasodilators may be preferred for patients with high blood pressure, those with myocardial ischemia, and those with mitral valve regurgitation, among others. Vasodilators should not be used for patients with cardiogenic shock with a systolic blood pressure of <90 mmHg. Since excessive hypotension may worsen renal function, the dose of vasodilators should be titrated carefully, and careful monitoring after dosing is crucial. Especially, patients with renal dysfunction, elderly patients, and patients with aortic valve stenosis should be carefully observed for hypotension.

### 4.3.1 Nitrates

Sublingual, spray or intravenous administration of nitroglycerin or isosorbide dinitrate are effective in alleviating pulmonary congestion in patients with acute heart failure and patients with acute exacerbation of chronic heart failure (**Table 57**). Nitrates dilate venous capacitance vessels at low doses and arterial resistance vessels at high doses, reducing preload (pulmonary capillary pressure) and afterload (a slight increase in cardiac output associated with reduced peripheral vascular resistance). As nitrates dilate coronary arteries, they are often used for the treatment of acute heart failure due to ischemic heart disease.

Adverse drug reactions to nitrates include hypotension, and decrease in arterial oxygen saturation due to increased intrapulmonary shunting. Physicians should be aware that nitrate tolerance may develop rapidly when administered intravenously.

### 4.3.2 Nicorandil

Nicorandil dilates both veins and arteries, and, like nitrates, reduces pulmonary artery wedge pressure. Nicorandil is less likely to develop tolerance[469,470] and cause excessive hypotension than nitrates.[471]

### 4.3.3 Carperitide

Carperitide, a recombinant human atrial natriuretic peptide (hANP), reduce cardiac load by vasodilation, sodium diuresis, and inhibition of renin and aldosterone synthesis. The drug is indicated for the treatment of pulmonary congestion and is also used in combination of catecholamines or other inotropic drugs for the treatment of refractory heart failure. As with other vasodilators, carperitide have not been demonstrated to improve the prognosis of patients with acute heart failure and further studies are needed to identify patients in whom the drug may improve prognosis.

Carperitide may cause hypotension at the beginning of treatment, carperitide should be administered by continuous intravenous infusion at a low dose, i.e., 0.025 to 0.05 μg/kg/min, and 0.0125 μg/kg/min for some cases. A prospective study in Japan has reported that carperitide is often administered at a dose of 0.05 to 0.1 μg/kg/min (maximum recommended dose is 0.2 μg/kg/min), and improves clinical conditions in 82% of patients.[472] The efficacy is especially high in patients with decompensated heart failure due to cardiomyopathy, hypertensive heart disease, or valvular diseases. Carperitide is contraindicated for patients with

| Table 58. Intravenous Drugs and Dosage Regimens for Patients in the Acute Phase of Acute Heart Failure ||
|---|---|
| **Drugs** | **Dosage regimens** |
| Morphine | Dilute an ampule of 5 to 10 mg, and administer 2 to 5 mg intravenously over 3 minutes. |
| Furosemide | Start treatment with a bolus dose of 10 to 120 mg or an infusion at 1 to 2 mg/hr, then infuse continuously at 1 to 5 mg/hr. |
| Potassium canrenoate | Dissolve 100 to 200 mg in 10 to 20 mL solution to administer by slow intravenous injection. Do not continue treatment unnecessarily. Limit the daily dose to 600 mg. |
| Digoxin | Administer 0.125 to 0.25 mg by slow intravenous injection. |
| Dopamine | Start infusion at 0.5 to 5 μg/kg/min and maintain at 0.5 to 20 μg/kg/min. When discontinuing the infusion, reduce the dose gradually. Limit the dose and treatment duration to minimum necessary. |
| Dobutamine | Start infusion at 0.5 to 5 μg/kg/min and maintain at 0.5 to 20 μg/kg/min. When discontinuing the infusion, reduce the dose gradually. Limit the dose and treatment duration to minimum necessary. |
| Norepinephrine | Start and continue infusion at 0.03 to 0.3 μg/kg/min. |
| Milrinone | Start infusion at 0.05 to 0.25 μg/kg/min and maintain at 0.05 to 0.75 μg/kg/min. |
| Olprinone | Start infusion at 0.05 to 0.2 μg/kg/min and maintain at 0.05 to 0.5 μg/kg/min. |
| Colforsin daropate | Start and continue infusion at 0.1 to 0.25 μg/kg/min. |
| Nitroglycerin | Start and continue infusion at 0.5 to 10 μg/kg/min. |
| Isosorbide dinitrate | Start and continue infusion at 1 to 8 mg/hr. |
| Nicorandil | Start and continue infusion at 0.05 to 0.2 mg/kg/min. |
| Nitroprusside | Start and continue infusion at 0.5 to 3 μg/kg/min. |
| Carperitide | Start infusion at 0.0125 to 0.05 μg/kg/min and maintain at ≤0.2 μg/kg/min. |
| Landiolol | Start infusion at 1 μg/kg/min, adjust the dose according to heart rate and blood pressure, and maintain at 1 to 10 μg/kg/min. |

serious hypotension, cardiogenic shock, acute right ventricular infarction, or dehydration.

## 4.4 Inotropes and Vasopressors

Drugs with inotropic action are indicated for patients with hypotension, patients with peripheral circulatory failure, and patients not responding to treatment to optimize circulating volume. Inotropes are effective in improving hemodynamics and clinical conditions in the short term, and are often administered to patients with left ventricular enlargement and reduced LVEF. However, these drugs increase myocardial oxygen demand and cause myocardial calcium loading, which may result in arrhythmias, myocardial ischemia or myocardial injury and poor prognosis. Accordingly, it is desirable that dose and duration of inotropic treatment should be limited to minimum necessity.

### 4.4.1 Catecholamine Inotropes

Catecholamines bind to adrenergic receptors (e.g., $\alpha_1$, $\alpha_2$,

$\beta_1$, and $\beta_2$) and exerts various physiological effects. $\beta$-receptors on myocytes are mainly $\beta_1$ receptors, and catecholamines enhance myocardial contraction, accelerate myocardial relaxation, increase heart rate, and increase myocardial conduction velocity via $\beta_1$ receptors. On the other hand, catecholamines dilate peripheral vessels by stimulating $\beta_2$ receptors on vascular smooth muscle cells, exert vasoconstriction through $\alpha_1$ receptors mainly located in the vascular smooth muscle, and enhance cardiac contraction mildly through the $\alpha_1$ receptors on myocytes.

### a. Dobutamine

Dobutamine is a synthetic catecholamine that stimulates $\beta_1$, $\beta_2$, and $\alpha_1$ receptors. As a $\beta_2$ receptor stimulant, dobutamine at 5 μg/kg/min or lower doses acts as a mild vasodilator to decrease systemic peripheral vascular resistance and pulmonary capillary pressure. As dobutamine does not increase heart rate or myocardial oxygen demand substantially at 10 μg/kg/min or lower doses, the drug can be used for the treatment of ischemic heart disease. Dobutamine reduces pulmonary artery diastolic pressure more substantially than dopamine does, and is effective in the treatment of pulmonary congestion.[473] In patients with unstable blood pressure, consideration for addition of dopamine or noradrenaline is necessary. Dobutamine may increase the number of eosinophils in the myocardium and blood.[474] When dobutamine therapy is discontinued, the dose should be tapered gradually. A study evaluated the effect of dobutamine on long-term prognosis have suggested that dobutamine may increase the risk of cardiac accidents.[475] The dose and duration of dobutamine therapy should be limited to minimum necessity.

### b. Dopamine

Dopamine is an endogenous catecholamine and a precursor of noradrenaline. Studies with animal model and healthy subjects show that at low doses (≤2 μg/kg/min), dopamine induces diuresis through its vasodilative effects on renal arteries and direct action to renal tubules. At intermediate doses (2 to 10 μg/kg/min), dopamine exerts positive inotropic effects, increases heart rate, and constricts vessels and at high doses (10 to 20 μg/kg/min), increase vascular resistance.

It is unclear whether low-dose dopamine is beneficial in patients with heart failure in terms of increasing urine volume or protecting renal function.[476–479]

### c. Norepinephrine

Norepinephrine is an endogenous catecholamine, and enhances myocardial contraction and increases heart rate by stimulating $\beta_1$ receptors and also acts as a potential vasoconstrictor by $\alpha$ receptors located on peripheral veins. Patients in refractory cardiogenic shock should be treated with continuous intravenous infusion of noradrenaline starting at a dose of 0.03 to 0.3 μg/kg/min. Norepinephrine is well indicated for patients with septic shock. As the drug increases afterload and myocardial oxygen consumption and reduces blood flow to the kidneys, brain and other organs, monotherapy with norepinephrine as an inotrope should be avoided, and the dose and duration of noradrenaline therapy should be limited to minimum necessity. In patients who require large doses of noradrenaline, mechanical support such as intra-aortic balloon pump (IABP) and percutaneous cardiopulmonary support (PCPS) should be introduced to decrease the dose of noradrenaline.

### 4.4.2 Digitalis

Digoxin is beneficial in improving hemodynamics in a short period of time.[480] Digoxin is not expected to improve long term prognosis, but will reduce the frequency of rehospitalizations in keeping attentions to blood concentration.[207] In patients with acute heart failure, digitalis is indicated for the treatment of heart failure induced by tachycardias such as atrial fibrillation. Treatment with digitalis is not recommended for patients with acute heart failure due to acute myocardial infarction or myocarditis.

In general, digoxin is administered slowly intravenously to control heart rate in patients with atrial fibrillation or other conditions at a dose of 0.125 to 0.25 mg while avoiding digitalis toxicity.

Digitalis is contraindicated for patients with bradycardia, second or third degree atrioventricular block, sick sinus syndrome, Wolff-Parkinson-White (WPW) syndrome, hypertrophic obstructive cardiomyopathy, hypokalemia, or hypercalcemia.

### 4.4.3 PDE III Inhibitors

Strengths of PDE III inhibitors include: 1) they are effective even in patients not responding to catecholamines; 2) they possess both vasodilative and positive inotropic effects and are associated with a smaller increase in myocardial oxygen consumption as compared with catecholamines; 3) and they are less likely to develop tolerance than nitrates. PDE III inhibitors exert rapid onset of action after the initiation of intravenous administration and improve hemodynamics almost in a dose-dependent manner.[481]

For acute worsening heart failure in patients who are receiving $\beta$-blockers, PDE inhibitors and adenylate cyclase activators favorably increase cardiac output and decrease pulmonary capillary pressure because their actions are not mediated by $\beta$-receptors.[482]

As with the catecholamine inotropes, PDE III inhibitors should be carefully used for the treatment of appropriate conditions, and the dose and duration of treatment should be limited to minimum necessity. In general, treatment with PDE III should be initiated with continuous intravenous infusion, and patients should be observed carefully for hypotension and arrhythmias.

### 4.4.4 Adenylate Cyclase Activators (Colforsin Daropate)

Adenylate cyclase activators are inotropes available only in Japan. They act as inodilators, but have slower onset of action and induce a larger increase in heart rate as compared with PDE inhibitors. Physicians should be aware that they may induce arrhythmias.

### 4.4.5 Calcium Sensitizers (Pimobendan)

Although pimobendan increases the myocardial contractility and dilates vessels to increase cardiac output and decrease pulmonary capillary pressure, no clear evidence has been obtained about the efficacy of this drug in the treatment of acute heart failure.

### 4.5 Myocardial Protective Agents

Survival should be prioritized in the treatment of acute heart failure. Once survival is ensured, then improvement of long-term prognosis and QOL should be aimed. Considering the fact that many cases of acute heart failure are acute worsening of chronic heart failure, physicians should try to protect the myocardium while taking into account

**Table 59. Indications and Contraindications of Noninvasive Positive Pressure Ventilation (NPPV) in Patients With Acute Heart Failure and the Criteria for Conversion to Tracheal Intubation**

| General indications of NPPV |
| --- |
| (1) Patient is alert and cooperative |
| (2) The airway is patent |
| (3) Patient can expectorate |
| (4) Patient has no facial injuries |
| (5) Patient can wear a mask |
| **Contraindications of NPPV** |
| (1) Patient has undrained pneumothorax |
| (2) Patient has vomiting, intestinal occlusion, or active gastrointestinal bleeding |
| (3) Patient has a large amount of airway secretions |
| (4) Patient is at a high risk of aspiration |
| **Criteria for conversion to tracheal intubation** |
| (1) Patient's condition worsened |
| (2) Patient shows no improvement or even worsening of arterial blood gas levels |
| (3) New symptoms/signs (e.g., pneumothorax, sputum retention, and nose erosion) or complications developed |
| (4) Symptoms do not disappear |
| (5) Patient's level of consciousness has declined |

**Table 60. Criteria for Weaning From Ventilatory Support to Patients With Acute Heart Failure**

| |
| --- |
| 1. Resolution of acute phase disease |
| 2. Adequate cough |
| 3. Adequate oxygenation ($FiO_2$ <0.5 and $PaO_2$ ≥60 mmHg) |
| 4. Stable hemodynamics (heart rate <140 bpm, stable blood pressure, and no or minimal treatment with vasopressors) |
| 5. Afebrile (temperature ≤38°C) |
| 6. No respiratory acidosis |
| 7. Adequate hemoglobin (8 to 10 mg/dL or higher) |
| 8. Adequate mentation |
| 9. Acceptable electrolytes |

$FiO_2$, fraction of inspiratory oxygen; $PaO_2$, arterial partial pressure of oxygen. (Source: Prepared based on MacIntyre NR, et al. 2001[486])

the management during transition period from the acute to chronic phases.

For details, see Chapter "**VI. Drug Therapy**".

# 5. Nonpharmacological Therapy

## 5.1 Mechanical Ventilation

### 5.1.1 Pathophysiology of Pulmonary Edema and Oxygen Therapy

Patients with acute left-sided heart failure have high pulmonary capillary pressure, severe pulmonary congestion or pulmonary edema. In patients with normal plasma protein levels, an increase in pulmonary capillary pressure to ≥24 mmHg causes leakage of plasma components into alveoli. As pulmonary capillary pressure increases the severity of pulmonary edema increases in a linear manner. In patients in whom plasma protein levels decrease to half of the lower normal limit, pulmonary edema develops when pulmonary capillary pressure is 11 mmHg or higher.[483] Treatment of pulmonary edema should prioritize the management of dyspnea and hypoxemia to improve oxygen supply to peripheral tissues.

### 5.1.2 Oxygen Therapy and Non-Invasive Positive-Pressure Ventilation (NPPV)

In patients with acute heart failure, oxygen administration should be started with a nasal cannula or face mask at 2 to 6 L/min. In patients with a $PaO_2$ of less than 80 mmHg (oxygen saturation [$SpO_2$] of less than 95%) or an arterial partial pressure of carbon dioxide ($PaCO_2$) of 50 mmHg or more, or patients in whom symptoms such as tachypnea, forced respiration, and orthopnea are not improved or are worsening, NPPV should be initiated promptly using a mask or bag-mask device (**Table 59**).

Continuous positive airway pressure (CPAP) is the first-choice treatment for patients with acute heart failure, but patients who still have high $CO_2$ levels or dyspnea during CPAP should receive bi-level PAP. Patients who do not respond well to NPPV should be intubated promptly to receive artificial respiration. **Table 59** summarize how switch from NPPV to endotracheal intubation. In order to ensure the success of ventilation in patients with acute cardiogenic pulmonary edema, oxygen therapy should not be continued aimlessly. Patients who still have hypoxemia and dyspnea despite oxygen therapy should start receiving NPPV without delay.[484,485]

### 5.1.3 Mechanical Ventilation With Endotracheal Intubation

In patients with no improvement of respiratory condition or arterial blood gasses during NPPV, or patients who have a consciousness disorder, loss of cough reflex, or difficulty in expectoration, artificial respiration under endotracheal intubation is indicated (**Table 59**).

Patients with acute decompensated heart failure associated with pulmonary congestion or pulmonary edema should receive positive end-expiratory pressure (PEEP) at around 2 to 10 cmH2O to maximize oxygen delivery to peripheral tissues unless contraindicated. Typical ventilation conditions include a tidal volume of 10 to 15 mL/kg, a respiratory rate of 10 to 20 breaths per minute (target $PaCO_2$: 30 to 40 mmHg), and an inhale: exhale ratio of 1 to 1.5:2. These settings should be individualized based on the results of arterial blood gas analysis. Immediately after intubation, the fraction of inspiratory oxygen ($FiO_2$) should be set at 1.0, and then should be adjusted to maintain a $PaO_2$ of ≥80 mmHg. It is desirable that $FiO_2$ be set at ≤0.5 to prevent oxygen toxicity.

### 5.1.4 Weaning From Artificial Respiration and Extubation

When the condition required artificial respiration has been corrected with a $FiO_2$ of <0.5, a PEEP of <5 to 10 cmH2O, and a $PaO_2$ of ≥60 mmHg, weaning from artificial ventilation should be considered (**Table 60**).[486] Recently, high-flow nasal cannula oxygen therapy has been tried after extubation.[487]

## 5.2 Management With Pacing (Cardiac Resynchronization Therapy and Other Types of Pacing)

### 5.2.1 Cardiac Resynchronization Therapy (CRT)

No studies have investigated the effects of CRT during the acute phase of acute heart failure. Patients with acute heart

**Table 61.** Recommendations and Levels of Evidence for Pacing (Cardiac Resynchronization Therapy and Other Techniques) in Patients With Acute Heart Failure

|  | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| Prompt initiation of emergency temporary pacing in patients with bradycardia that worsens hemodynamics and causes transient cerebral ischemia, and who do not respond well to atropine | I | C | C1 | VI |
| Cardiac resynchronization therapy in the very early phase of acute heart failure | IIb | C | C2 | VI |

**Table 62.** Recommendations and Levels of Evidence for Hemofiltration in Patients With Acute Heart Failure

|  | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| **Hemofiltration** | | | | |
| Extracorporeal ultrafiltration method (ECUM) | IIb | B | C2 | II |
| Continuous venovenous hemofiltration (CVVH) for patients with volume overload and stable hemodynamics | IIb | B | C2 | II |
| **Hemodialysis** | | | | |
| Hemodialysis | IIb | B | C2 | II |
| Peritoneal dialysis | IIb | B | C2 | II |
| **Hemodiafiltration** | | | | |
| Continuous hemodiafiltration (CHDF) | IIb | B | C2 | II |

failure should receive pharmacotherapy first, and should then be considered for the indication of CRT during the chronic phase of heart failure (See Section "**2. Cardiac Resynchronization Therapy**" in Chapter "**VII. Nonpharmacologic Therapy**").

### 5.2.2 Emergency Temporary Pacing

Emergency temporary pacing should be performed promptly in patients with bradycardia leading to compromised hemodynamics or transient cerebral ischemia who do not respond to atropine regardless of type of causative conditions (**Table 61**).

### 5.3 Acute Hemofiltration

In patients with acute decompensated congestive heart failure, hepatic congestion and edema may develop in association with pulmonary congestion and excessive fluid retention. During the acute phase treatment, excessive fluid should be rapidly corrected. Patients with renal dysfunction in whom diuresis cannot be achieved require acute hemofiltration (**Table 62**).

At present, ultrafiltration should be reserved for patients in whom fluid removal is difficult or impossible with any drug therapies.

### 5.4 Indications and Methods of Surgical Treatment in Patients With Acute Heart Failure (Cardiac Tamponade and Acute Valvular Disease)

### 5.4.1 Cardiac Tamponade

Cardiac tamponade is a condition of elevated pericardial pressure caused by pericardial effusion, resulting in decreased venous return during the diastolic phase and impaired ventricular filling.

In cases of urgency, echocardiography-guided pericardiocentesis and drainage are conducted. Inotropes are not effective in urgent situations. In patients with hemorrhagic cardiac tamponade with hypovolemia, drainage is effective in maintaining hemodynamics on a temporary basis. In patients with unsuccessful pericardiocentesis or patients with recurrent pericardial effusion due to hemorrhagic cardiac tamponade, surgical drainage by pericardiotomy through a subxiphoid approach or pericardiotomy should be performed.

### 5.4.2 Acute Valvular Disease
#### a. Acute Aortic Regurgitation[488]
Acute aortic regurgitation is an emergent condition that may lead to cardiogenic shock unless prompt surgical intervention is undertaken. Causes of acute aortic regurgitation include aortic dissection, infective endocarditis, injuries, and iatrogenic aortic valve injury. Indication for surgery should be considered promptly for patients with acute aortic regurgitation. Echocardiography is essential for confirmatory diagnosis and severity assessment, and provides information that helps physicians specify the cause and assess the severity of pulmonary hypertension. IABP is contraindicated for patients with acute aortic regurgitation.

#### b. Acute Mitral Valve Insufficiency[488]
Acute mitral valve insufficiency (mitral valve regurgitation) causes acute volume overload of the left ventricle and left

**Table 63.** Recommendations and Levels of Evidence for Invasive Treatment of Acute Mitral Regurgitation in Patients With Acute Myocardial Infarction

|  | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
| --- | --- | --- | --- | --- |
| Surgical repair through prompt IABP insertion | I | B | C1 | IVa |
| Addition of CABG | I | B | C1 | IVa |

CABG, coronary artery bypass grafting; IABP, intra-aortic balloon pump.

atrium, which results in pulmonary edema and cardiogenic shock. Patients with no improvement in hemodynamics after treatment with vasodilators and catecholamines are indicated for emergency surgery. IABP is used to maintain hemodynamics in patients who are waiting for surgery. Accurate color Doppler examination can be performed with transesophageal echocardiography. IABP may stabilize the hemodynamics of patients in preparation for surgery.

## 5.5 Treatment of Mechanical Complications Associated With Acute Myocardial Infarction

### 5.5.1 Left Ventricular Free Wall Rupture

Left ventricular free wall rupture develops in 4 to 24% of patients with acute myocardial infarction. Treatment often fails, and deaths due to this condition account for 20% of early deaths from acute myocardial infarction.[489] Left ventricular free wall rupture often develops in 1 to 7 days after the onset of acute myocardial infarction. It is classified by mode of onset into oozing (slow rupture) type, which develops as cardiac tamponade caused by gradual accumulation of bloody pericardial effusion, and blow-out type, which develops as an abrupt rupture of the myocardial wall. Oozing cases can be diagnosed before shock develops, and should be treated with pericardial drainage followed by surgery. However, in blow-out cases, pulseless electrical activity develops rapidly, and leads to death. Patients should be diagnosed immediately after onset, receive percutaneous cardiopulmonary support (PCPS) promptly to maintain systemic circulation before undergoing emergency surgery.

### 5.5.2 Ventricular Septal Perforation

The incidence of ventricular septal perforation has been reported about half the incidence of free wall rupture. Ventricular septal perforation often develops on the third to fifth day after the onset of acute myocardial infarction. Patients with ventricular septal perforation often experience abrupt hemodynamic decompensation, hypotension, bilateral cardiac failure (right-sided heart failure is prominent in some cases), and newly developed holosystolic murmur. Patients with cardiogenic shock should undergo emergency surgery.

### 5.5.3 Mitral Papillary Muscle Dysfunction[490] (Table 63)

Acute mitral regurgitation in patients with acute myocardial infarction is mainly caused by rupture of papillary muscle or chordae. Mitral regurgitation develops in about 14% of patients after acute myocardial infarction as mild to moderate in severity in almost all cases. Severe mitral regurgitation develops in 3% of patients after acute myocardial infarction, and the mortality is high. The prognosis

depends on whether patients are diagnosed, and start receiving medical treatment without delay and promptly undergo emergency surgery. Effective medical treatment includes afterload reduction through intense vasodilation and diuresis. IABP is effective as well. Patients should receive medical treatment to stabilize hemodynamics, and undergo surgical treatment as soon as it is ready.

## 5.6. Cardiac Rehabilitation in Patients With Acute Heart Failure

### 5.6.1 Significance of Cardiac Rehabilitation in Patients With Acute Heart Failure

The goals of cardiac rehabilitation in patients with acute heart failure are
(1) facilitating early ambulation to prevent consequences of prolonged bed rest (e.g., physical/mental deconditioning, bedsores, and pulmonary embolism);
(2) establishing/sharing plans for prompt and safe discharge from hospital and return to society;
(3) improving QOL by increasing exercise capacity; and
(4) preventing recurrent heart failure and rehospitalization through comprehensive patient education and disease management.

As patients with heart failure are prone to have physical/mental deconditioning or disuse syndrome due to prolonged bed rest, and skeletal muscle atrophy due to malnutrition or increased proinflammatory cytokine levels ("cardiac cachexia"), it is important to start cardiac rehabilitation, consisting of physical therapy, exercise therapy and education/counseling, in the early phase of acute heart failure.

After the disease is stabilized, a comprehensive cardiac rehabilitation program should be initiated. The program should be shifted to an ambulatory cardiac rehabilitation program to continue disease management.[148]

Cardiac rehabilitation only during hospitalization has not been demonstrated to improve long-term prognosis in patients with acute heart failure. However, comprehensive ambulatory cardiac rehabilitation programs have been reported to be effective in preventing rehospitalizations of patients with heart failure. In-hospital cardiac rehabilitation programs should aim for not only early ambulation and early discharge but also encouraging patients to participate and continue ambulatory cardiac rehabilitation after discharge.

Patients hospitalized in the ICU for the treatment of acute heart failure tend to have strong anxiety and unstable mental state because they are often overwhelmed with the abrupt onset of the disease, emergency hospitalization, invasive treatment procedures, fear of death, anxiety about the future, and unfamiliar environment apart from the family. They also have physical stress caused by invasive

**Table 64.** Recommendations and Levels of Evidence on Rehabilitation for Patients With Acute Heart Failure

|  | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| Educational programs on the prevention of recurrence and self-management for all patients | I | C | C1 | VI |
| Rehabilitation for patients with heart failure who are treated with intravenous inotropic drugs and have stable hemodynamics, including low-intensity resistance training under strict supervision | IIb | C | C1 | V |
| Comprehensive cardiac rehabilitation programs for all patients with heart failure after stabilization | IIa | C | C1 | VI |

procedures and prolonged bed rest as well as mental stress and shame of receiving nursing care. Therefore, mental support for patients in the early stage of acute heart failure is important to alleviate patients' mental stress and improve the QOL of patients during hospital stay. Healthcare professionals should try to detect mental health problems early, provide appropriate mental counseling, prescribe drug therapy, and consider for cognitive behavioral therapy, if necessary.[148]

### 5.6.2 Early-Phase Cardiac Rehabilitation in Patients With Severe Heart Failure in the ICU (Table 64)

Exercise therapy is not recommended for patients with unstable hemodynamics due to acute heart failure or severe heart failure and patients with dyspnea at rest due to pulmonary congestion or fever. However, it has been reported that even patients with severe heart failure on mechanical ventilation, IABP or CHDF or those who are receiving continuous infusion of cardiovascular drugs can safely receive early-phase cardiac rehabilitation including low-strength physical or exercise therapy when they have stable hemodynamics and no symptoms at rest.[491] For example, rhythmic low-strength resistance training using a rubber tube or ball can be conducted under the monitoring by ECG and vital signs in the bed or at the bedside. When unsupported sitting becomes possible, patients should prolong sitting time gradually, and then should try to stand. When standing at the bedside becomes possible, patients should try to stand on their tiptoes, among other training.

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# XI.  Surgical Treatment

## 1.  Surgical Procedures and TAVI

### 1.1  Left Ventricular Reconstruction

Left ventricular reconstruction was initially introduced as a surgical procedure for the treatment of left ventricular aneurysm in 1980s. As the resection of left ventricular aneurysm, which increases in size during cardiac constriction, increases cardiac output by increasing the effective left ventricular volume and thereby improves cardiac function and symptoms. On the other hand, as prompt reperfusion therapy for the treatment of myocardial infarction has become a common procedure, cases of left ventricular aneurysm due to transmural infarction have become less common, while cases of ischemic cardiomyopathy with akinesis due to post-reperfusion extensive subendocardial infarction have become more common. Since Dor et al[492] have reported that left ventricular reconstruction may improve the long-term prognosis of patients with ischemic myocardiopathy and akinesis, diverse procedures have been developed. In 2009, the results of the Surgical Treatment for Ischemic Heart Failure (STICH) trial, a randomized controlled trial to assess the effects of adding left ventricular reconstruction to coronary-artery bypass grafting (CABG), were published.[493] This study had unexpected results that adding left ventricular restoration to CABG are not effective in exercise capacity, symptoms, or prognosis in patients with ischemic cardiomyopathy and LVEF ≤35%. A considerable number of objections have been published, but it is still unclear how surgical left ventricular resizing decreases wall tension against the remodeling myocardium, and thereby reverse the remodeling process. In a study in Japan, adding left ventricular reconstruction to mitral annuloplasty was beneficial in patients with ischemic cardiomyopathy with a left ventricular end-systolic volume index (LVESVI) of 105 to 150 mL/m². [494] While in the J-STICH registry in patients undergoing left ventricular reconstruction, the one-year survival of patients with ischemic cardiomyopathy and severe mitral regurgitation was 60%.[495] Myocardial viability should be considered to determine whether surgery is indicated or not. The efficacy of Batista procedure and other left ventricular reconstructive procedures for the treatment of non-ischemic cardiomyopathy has not been established. In 2005, the ACC/AHA guidelines for the diagnosis and treatment of chronic heart failure dropped the use of left ventricular reconstruction for this patient population to a Class III recommendation.[4] In Japan, these procedures are conducted only in limited cases.

### 1.2  Transcatheter Aortic Valve Implantation (TAVI)

At present, transcatheter aortic valve implantation (TAVI) or transcatheter aortic valve replacement (TAVR) are indicated for the treatment of severe aortic stenosis. The indications and timing of these procedures are in accordance of those of aortic valve replacement (**Table 65**). For details, refer to latest guidelines for the treatment of valvular heart diseases.[370,371,496]

TAVI is recommended for patients with severe aortic stenosis who are not indicated for surgery and are expected

**Table 65.** Recommendations and Levels of Evidence for Transcatheter Aortic Valve Implantation (TAVI) as a Treatment of Aortic Valve Stenosis

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| TAVI conducted by the multidisciplinary heart team | I | C | C1 | VI |
| TAVI conducted only at medical institutions which have a department of cardiovascular surgery | I | C | C1 | VI |
| TAVI for patients with aortic valve stenosis who cannot undergo cardiotomy and are expected to survive for at least 12 months after the procedure | I | A | A | II |
| TAVI as an alternative procedure for patients who are indicated for aortic valve replacement but in whom surgery risk is high | IIa | A | B | II |
| TAVI for patients with aortic valve stenosis in whom treatment is not expected to improve QOL or prognosis | III | A | D | II |
| TIVI for patients with aortic valve stenosis and low LVEF | III | C | C2 | IVa |

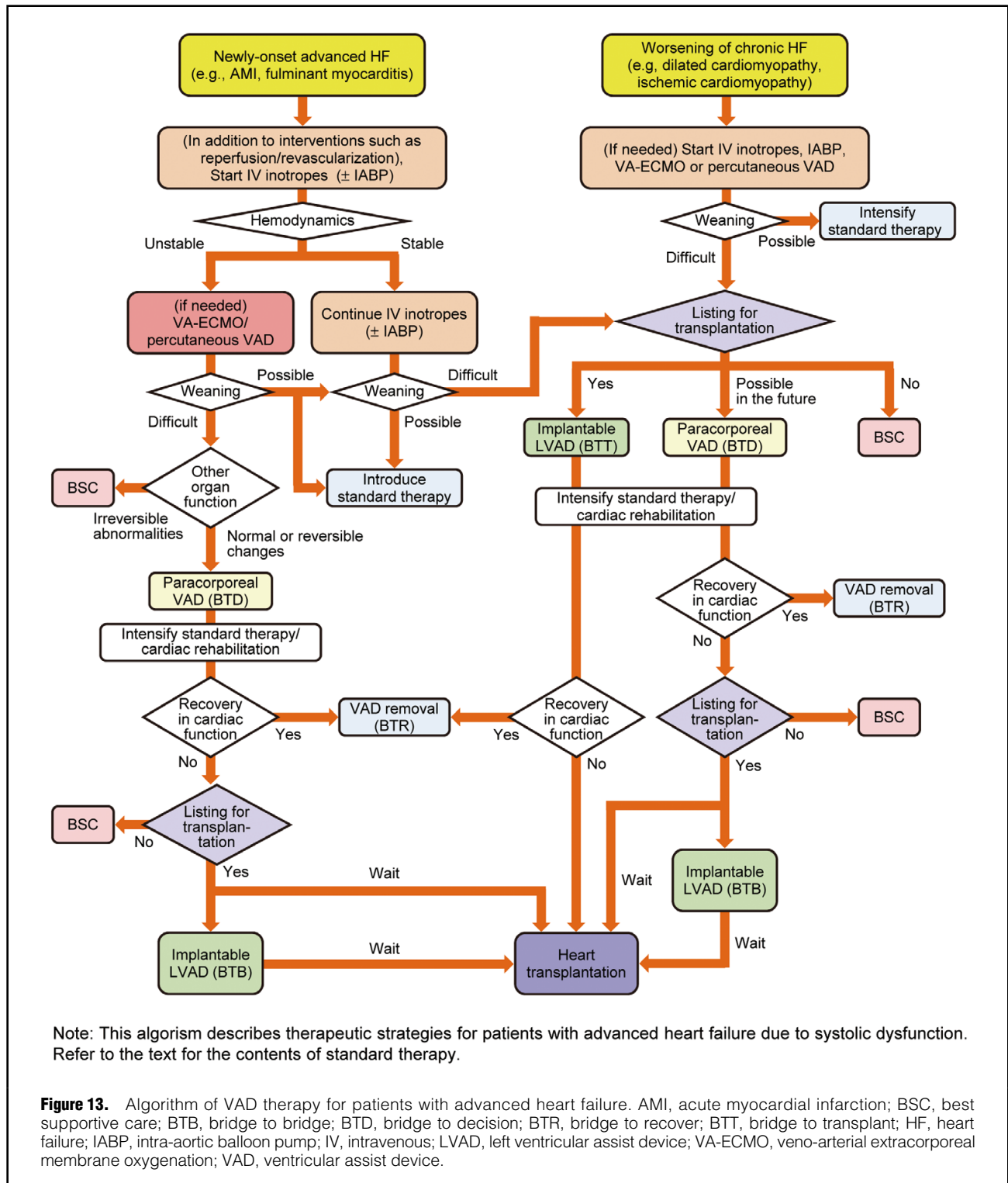LVEF, left ventricular ejection fraction; QOL, quality of life; TAVI, transcatheter aortic valve implantation.

**Table 66.** The INTERMACS and J-MACS Classifications and Options of Device Therapy

| Profile | INTERMACS / J-MACS | Status | Options of device therapy |
|---|---|---|---|
| 1 | Critical cardiogenic shock "Crash and burn" | Patients with compromised hemodynamics and peripheral hypoperfusion despite rapid escalation of intravenous inotropes and/or introduction of mechanical circulatory support | IABP, peripheral VA-ECMO, percutaneous VAD, centrifugal pumps for extracorporeal circulation, and paracorporeal VADs |
| 2 | Progressive decline despite inotropic support "Sliding on inotropes" | Patients with declining renal function, nutritional status, and signs of congestion despite intravenous inotropes and required incremental doses of them | IABP, peripheral VA-ECMO, percutaneous VAD, centrifugal pumps for extracorporeal circulation, paracorporeal VADs, implantable LVADs |
| 3 | Stable but inotrope-dependent "Dependent stability" | Patients with stable hemodynamics on intravenous inotropes at relatively low doses, but physicians are not able to discontinue the intravenous treatment because of the risk of hypotension, worsening symptoms of heart failure, or worsening renal function | Implantable LVADs |
| 4 | Resting symptoms "Frequent flyer" | Patients who can be weaned from intravenous inotropic support temporarily and be discharged from hospital, but may soon repeat hospitalizations for worsening heart failure | Consider implantable LVADs (especially patients with modifier A*) |
| 5 | Exertion intolerant "House-bound" | Patients who can do daily routines in the house, but have significant limitations in activities of daily livings, and hardly go out | Consider implantable LVADs for patients with modifier A* |
| 6 | Exertion limited "Walking wounded" | Patients who can go out, but are difficult in doing anything other than light activities, and have symptoms during walk less than 100-meter | Consider implantable LVADs for patients with modifier A* |
| 7 | Advanced NYHA III "Placeholder" | Patients can walk more than 100 meters without fatigue, and have had no hospitalizations in the recent 6 months | Consider implantable LVADs for patients with modifier A* |

*Recurrent appropriate ICD shocks due to life-threatening ventricular arrhythmias. IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; PCPS, percutaneous cardiopulmonary support; VAD, ventricular assist device; VA-ECMO, veno-arterial extracorporeal membrane oxygenation. (Source: Prepared based on Stevenson LW, et al. 2009[511] and the Japanese Association for Thoracic Surgery[512])

to live more than 1 year after surgery by the heart team.[497–500] TAVI should also be considered for high-risk patients who are indicated for surgery when the heart team considers that TAVI is a more preferable treatment option according to the patient's risk factors and anatomical conditions.[499–502]

Patients in whom TAVI is not expected to improve symptoms and QOL are not indicated for the procedure.[497,500–503]

Among patients with severe aortic stenosis and left ventricular dysfunction, those with low-flow/low-gradient aortic stenosis (defined as a valve area of <1 cm², LVEF

**Figure 13.** Algorithm of VAD therapy for patients with advanced heart failure. AMI, acute myocardial infarction; BSC, best supportive care; BTB, bridge to bridge; BTD, bridge to decision; BTR, bridge to recover; BTT, bridge to transplant; HF, heart failure; IABP, intra-aortic balloon pump; IV, intravenous; LVAD, left ventricular assist device; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VAD, ventricular assist device.

<40%, and a mean aortic transvalvular gradient of <40 mmHg) are known to be associated with worse outcomes, and dobutamine stress echocardiography is useful in identifying such patients.[504,505] When the cause of left ventricular dysfunction cannot be determined to be excessive afterload, TAVI may not substantially improve left ventricular function or clinical symptoms, but does improve life expectancy.[506] In patients with low cardiac function, some studies have reported favorable early postoperative results,[507,508] while other studies have pointed out that low cardiac function predicts poor prognosis after TAVI.[509,510] No consensus has been achieved regarding the efficacy of TAVI in patients with cardiac dysfunction. Careful consideration should be given to determine whether TAVI should be conducted or not in patients with cardiac dysfunction.

**Table 67.** Various Strategies for VAD Therapy

| Abbreviation | Strategy | Definition |
|---|---|---|
| BTD | Bridge to decision | Temporal use of VADs for the treatment of acute-onset cardiogenic shock before deciding the next treatment options |
| BTR | Bridge to recovery | Use of VADs to support circulation and thereby promote the recovery of cardiac function aiming for removal of VADs |
| BTB | Bridge to bridge | Conversion from a paracorporeal LVAD to an implantable LVAD |
| BTC | Bridge to candidacy | LVAD therapy to reverse organ dysfunction to obtain the eligibility for heart transplantation |
| BTT | Bridge to transplant | LVAD therapy as a bridge to transplant in patients who have been listed for heart transplantation but cannot maintain hemodynamics with medical treatment |
| DT | Destination therapy | Permanent LVAD therapy as an alternative to heart transplantation in patients who are ineligible for transplantation |

LVAD, left ventricular assist device; VAD, ventricular assist device.

## 2. Mechanical Circulatory Support

### 2.1 Classification of Advanced Heart Failure

Advanced heart failure is classified by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles[511] or the Japanese registry for Mechanically Assisted Circulatory Support (J-MACS) profiles[512] (**Table 66**). In the INTERMACS profile, modifier A (arrhythmia) is defined as recurrent appropriate ICD shocks due to life-threatening ventricular arrhythmias.

### 2.2 Percutaneous Circulatory Support for Patients With Acute Heart Failure

### 2.2.1 Intra-Aortic Balloon Pump (IABP)
IABP has been traditionally indicated for patients with acute myocardial infarction/complex coronary lesions who need hemodynamic support during reperfusion/revascularization or until surgical repair of mechanical complications, although its routine use is not recommended. IABP also has become indicated for patients with advanced heart failure who are categorized as INTERMACS profile 1 or 2. IABP is contraindicated for patients with moderate or severe aortic regurgitation or patients with aortic dissection.

### 2.2.2 Peripheral Veno-Arterial Extracorporeal Membrane Oxygenation (VA-ECMO)
The use of peripheral VA-ECMO (also called percutaneous cardiopulmonary support [PCPS] in Japan) is considered for patients with INTERMACS profile 1 or 2 often in combination with IABP. VA-ECMO is used as a temporal flow support system aiming for hemodynamic stabilization or bailing out of multiple organ failure, which sometimes works as a bridging device towards listing for heart transplant or converting to durable ventricular assist devices (VADs). Since it does not unload left ventricle in itself, an improvement in pulmonary congestion may not be expected.

**Table 68.** Criteria for Implantable LVAD Under the Bridge-to-Transplant Policy

| | | |
|---|---|---|
| Selection criteria | Patient status | Patient has advanced heart failure with progressive symptoms (generally NYHA class IV) despite standard therapy recommended in the relevant guidelines (stage D), who is listed or being listed for heart transplantation |
| | Age | <65 years |
| | Body surface area | Refer to the criterion specified for each device |
| | Severity | Patient depending on intravenous inotropes (INTERMACS profile 2 or 3), IABP or paracorporeal LVAD, or with modifier A (especially for patients with INTERMACS profile 4) |
| | Social indications | Patient and his/her caregivers understand the characteristics of VAD therapy in Japan as a long-term home-based treatment, and the patient is highly expected to return to society |
| Exclusion criteria | Systemic diseases | Patient has malignancy, collagen disease or other refractory systemic diseases that have poor prognosis |
| | Respiratory diseases | Severe respiratory failure, irreversible pulmonary hypertension |
| | End-organ dysfunction | Irreversible hepatic or renal dysfunction, insulin-dependent diabetes mellitus |
| | Cardiovascular disorders | Difficult-to-treat aortic aneurysm, untreatable moderate or severe aortic valve insufficiency, mechanical aortic valve that cannot be replaced by a bioprosthetic valve, severe peripheral vascular disease |
| | Pregnancy | Women being pregnant or planning to become pregnant |
| | Others | Severe obesity |

IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; NYHA, New York Heart Association.

### 2.2.3 Percutaneous VAD
In Japan, catheter-based transaortic microaxial pumps (Impella® 2.5 and 5.0) have been approved as percutaneous VADs for the treatment of cardiogenic shock. These devices are expected to improve pulmonary congestion through unloading left ventricle.

### 2.3 Mechanical Circulatory Support Requiring Thoracotomy

### 2.3.1 Centrifugal Pumps for Extracorporeal Circulation
VA-ECMO with central cannulation using centrifugal pumps for extracorporeal circulation can be used for patients who do not respond well to peripheral VA-ECMO and require stronger circulatory support, or who cannot continue peripheral VA-ECMO due to complications such as bleeding from the access site.

The reimbursement of these pumps as VADs is not covered by the Japanese National Health Insurance, and these pumps are often switched to durable VADs approved

**Table 69.** Recommendations and Levels of Evidence on the Use of Implantable Left Ventricular Assist Devices (LVADs)

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| Treatment with implantable LVADs in patients with stage D HFrEF who are eligible for heart transplantation in order to reduce the risk of death and hospitalizations for heart failure and improve QOL | IIa | C | B | IVa |

HFrEF, heart failure with reduced ejection fraction; LVAD, left ventricular assist device; QOL, quality of life.

**Table 70.** Indications for Heart Transplantation

**1. Indications**

Heart transplantation is indicated for patients with the following severe heart diseases in whom conventional treatment is not expected to save or prolong life:
1) Dilated cardiomyopathy, and dilated phase hypertrophic cardiomyopathy
2) Ischemic myocardial disease
3) Others (Conditions approved by the Heart Transplantation Indication Review Committee of the Japanese Circulation Society and the Japanese Society of Pediatric Cardiology and Cardiac Surgery)

**2. Eligibility Criteria**

1) Patients with an intractable end-stage heart disease that meet at least one of the following conditions:
   a) Heart failure requiring long-term or repeated hospitalization
   b) Patients with heart failure that remains in NYHA Class III or IV despite conventional treatment including β-blockers and ACE inhibitors
   c) Patients with life-threatening severe arrythmias not responding to any currently available treatments
2) It is desirable that patients be <65 years of age
3) Patients and their family members should fully understand heart transplantation and can cooperate to the treatment

**3. Exclusion criteria**

A) Absolute exclusion criteria
   1) Irreversible renal or hepatic dysfunction
   2) Active infection (including cytomegalovirus infection)
   3) Pulmonary hypertension (with pulmonary vascular resistance of ≥6 Wood units despite treatment with vasodilators)
   4) Drug and substance abuse (including alcoholic myocardial disease)
   5) Malignant tumor
   6) Human immunodeficiency virus (HIV) antibody positive
B) Relative exclusion criteria
   1) Renal or hepatic dysfunction
   2) Active peptic ulcer
   3) Insulin-dependent diabetes mellitus
   4) Mental disorders/neurosis (may be listed as exclusion criterion if no improvement is seen despite efforts to eliminate anxiety about the patient's own disease or condition)
   5) History of pulmonary infarction, pulmonary vascular obstructive disease
   6) Collagen disorder or other systemic diseases

**4. Determination of eligibility for heart transplantation**

- For the time being, the institutional review committee and the Heart Transplantation Indication Review Subcommittee of the Japanese Circulation Society will review patients in two stages to determine who are indicated for heart transplantation. After the selection of patients indicated for heart transplantation, the patients and family members provide informed consent and are included in the waiting list. Transplantation is conducted for patients on the list.
- The indications and the eligibility criteria listed above will be revised according to the advancement of medical/surgical treatment.
- Other organ disorders should be considered carefully to determine medical urgency.

ACE, angiotensin converting enzyme; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; NYHA, New York Heart Association. (Excerpted from the Heart Transplantation Committee of the Japanese Circulation Society. 2013[522])

in patients who require longer circulatory support (see below).

### 2.3.2 Types and Features of VADs

Among VADs currently available in Japan, paracorporeal VADs are pulsatile pumps, while implantable VADs are non-pulsatile (continuous flow) pumps. As these devices support the left ventricle in most cases, they are called left ventricular assist devices (LVADs). Paracorporeal VADs that support the right ventricle are called right ventricular assist devices (RVADs). Implantable RVADs are not approved in Japan.

In Japan, paracorporeal VADs are available only for in-hospital setting. The use of paracorporeal VADs may increase the risk of serious complications such as cerebrovascular disorder and infections, and pump exchanges due to pump thrombosis or device malfunctions are common. Although implantable LVADs are superior to paracorporeal ones in terms of QOL improvement and the risk of complications, the implantable LVADs are reimbursed only in patients listed (or being listed) for heart transplantation.

### 2.3.3 Therapeutic Strategies With VADs

As indicated in the algorithms (**Figure 13**) and strategies (**Table 67**) in the VAD therapy, indications should be carefully evaluated to achieve the goal of an individual patient.[513]

### 2.3.4 Indications and Outcomes of Paracorporeal VADs

Paracorporeal VADs are used as "bridge to decision" (BTD) in patients with INTERMACS profile 1 who cannot maintain hemodynamics even under mechanical circulatory support such as peripheral VA-ECMO, and as "bridge to candidacy" (BTC) in patients with INTERMACS profile 2 who are not immediate candidates for heart transplantation. Studies have reported that one-year survival rate in patients who received paracorporeal VADs implantation at high volume centers in Japan ranged between about 50 to 80%.[514–516]

### 2.3.5 Indications and Outcomes of Implantable LVADs

**Table 68** outlines the indication/exclusion criteria for implantable LVADs in Japan.[517] According to the J-MACS registry, one-year and two-year survival rates of patients with implantable LVADs were 93.6% and 89.8%, respectively, which were higher than the corresponding rates in patients with paracorporeal LVADs.[518] Complications requiring re-hospitalizations reported in patients with implantable LVADs include cerebrovascular disorder, device thrombosis, and drive-line infection.[519] Several complications such as gastrointestinal arteriovenous malformation, gastrointestinal bleeding, late-onset right-sided heart failure, and aortic regurgitation are rare among

| Table 71.  Recommendations and Levels of Evidence for Heart Transplantation | | | | |
|---|---|---|---|---|
| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
| Heart transplantation for patients with severe HFrEF resistant to appropriate drug therapies and device treatments | IIa | C | B | IVa |

HFrEF, heart failure with reduced ejection fraction.

patients using pulsatile LVADs but have been known to be more common in patients using continuous-flow LVADs.

### ▌2.3.6  Recommendations for and Evidence of LVADs (Table 69)

No controlled clinical studies of paracorporeal LVADs have been conducted. The use of implantable LVADs for bridge to transplant (BTT) is recommended, although their benefits have not been proven in randomized clinical trials. For the purpose of destination therapy (DT), the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, a randomized controlled trial of a pulsatile implantable LVAD vs. medical therapy has concluded that the device has a survival benefit.[520] Combined with the result of another randomized clinical trial that reported the superiority of continuous-flow device over the pulsatile device,[521] continuous-flow implantable LVADs are most effective to improve prognosis and is widely recommended.

## 3.  Heart Transplantation

Heart transplantation is performed for patients with underlying cardiovascular disease such as dilated cardiomyopathy or dilated-phase hypertrophic cardiomyopathy, ischemic myocardial disease, and congenital heart disease. Criteria for indication of heart transplantation include lack of effective treatment other than heart transplantation; understanding of heart transplantation by patients and family; and ability to continue lifelong treatment such as immunosuppressive therapy and examinations such as myocardial biopsy (**Table 70**).[522] Additional conditions for application are patients with heart failure who require long-term or frequent hospitalizations and remain in NYHA Class III or IV despite conventional drug therapy including β-blockers and ACE inhibitors, and those with potentially fatal severe arrhythmia that does not respond to conventional treatment. Both types of patients are preferably under 65 years of age. Absolute exclusion criteria include severe irreversible organ failure, active infection, severe pulmonary hypertension, drug and substance abuse, including tobacco and alcohol, malignant tumor and positive results of human immunodeficiency virus (HIV) antibody test. Patients with irreversible pulmonary hypertension with pulmonary vessel resistance of >6 Wood units despite available treatments are not indicated for heart transplantation, and should be considered for heart-lung transplantation. When heart failure progresses during the waiting period, VAD implantation should be considered before other organ dysfunctions occur. By June 2016, a total of 284 patients underwent heart transplantation,[523] and the survival rates at 5 and 10 years after the transplantation were 92.7% and 89.6%, respectively, which are among the highest in the world. According to an annual report of the heart and lung registries by the International Society for Heart and Lung Transplantation,[524] heart transplantation is proved to be the most favorable for treatment of advanced heart failure compared to other treatment modalities. **Table 71** summarizes recommendations and levels of evidence for heart transplantation in patients with heart failure.

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# XII.  Disease Management

## 1.  Disease Management Programs (e.g., Educational Programs) and Team Medical Care

### ▌1.1  Disease Management Programs by Multidisciplinary Teams

**Table 72** summarizes features and components of disease management for patients with heart failure. It is desirable that disease management for each patient should be operated by a multidisciplinary team of diverse healthcare professionals, including physicians, nurses, pharmacists and dieticians, and the team should contain two or more members who have expertise in the treatment, management and care of heart failure. In order to operate the disease management team efficiently, comprehensive cardiac rehabilitation programs should be utilized proactively. Disease management for patients with heart failure include guideline-based standard drug therapy, nonpharmacologic therapy and exercise therapy, patient education and counseling emphasizing the importance of treatment adherence and selfcare, symptom monitoring, preparation for and support of hospital discharge, appropriate use of social resources, follow-up examinations of patients, periodic assessment of physical, mental, and social functions, and mental support.

### ▌1.2  Contents of Disease Management Programs for Patients With Heart Failure (Tables 73 and 74)

### ▌1.2.1  Patient Education Emphasizing the Importance of Adherence and Self-Care

Appropriate self-care behaviors play an important role in preventing worsening heart failure, and patient education to prove their self-care capabilities is expected to improve prognosis and QOL.[525–527] Healthcare professionals should

| Table 72. | Features and Components of Disease Management Programs for Patients With Heart Failure |
|---|---|
| Features | • Multidisciplinary team approaches by cardiologists, cardiovascular surgeons, nurses, pharmacists, physical therapists, nutritionists, social workers, and psychologists, etc.<br>• Patient education, consultation and support by specially trained healthcare professionals<br>• Implementation of comprehensive cardiac rehabilitation programs |
| Components | • Drug and nonpharmacologic therapy<br>• Exercise therapy<br>• Patient education focused on adherence and self-care<br>• Symptoms monitoring by patients, family members, caregivers, or healthcare professionals<br>• Discharge planning and support and utilization of social resources<br>• Post-discharge follow-up<br>• Continuous assessment of patients' physical, mental and social functions (e.g., body weight, nutritional status, laboratory findings, ADL, mental status, and QOL changes)<br>• Provide mental support to patients, family members, and caregivers |

ADL, activities of daily living; QOL, quality of life.

evaluate appropriateness of patients' self-care, and educate and consult patients and their family members to improve the quality of self-care behaviors.[528,529] In patient education, healthcare professionals should consider their health literacy, the ability to access, understand, and utilize appropriate information on the disease,[530] and should provide materials suitable for individual patients according to the level of health literacy.[531] For patients with limited self-care capabilities such as elderly, people living alone, and patients also suffering from cognitive disorder, healthcare professionals should educate and support their family members, and utilize social resources such as sending home visiting physicians, nurses or caregivers in a more proactive way.

## 2. Comprehensive Cardiac Rehabilitation

### 2.1 Significance of Ambulatory Cardiac Rehabilitation in Disease Management Programs

The most common reasons for rehospitalization in patients with heart failure are 1) worsening congestion (fluid retention), 2) non-cardiac comorbidities, 3) poor adherence.[532] It has also been pointed out that sarcopenia and frailty predict the long-term prognosis of elderly patients with heart failure.[14] Accordingly, out-patient and home-based interventions are essential for elderly patients with heart failure and noncardiac comorbidities with a high risk of rehospitalization to improve QOL and exercise capacity and prevent rehospitalization and conditions requiring nursing care. These interventions should include systemic disease management covering both heat failure and non-cardiac comorbidities and exercise interventions to prevent sarcopenia and frailty.[533]

Although many studies have reported the efficacy of multidisciplinary intervention/disease management programs in patients with heart failure,[534] and a systematic review[535] has concluded that multidisciplinary interventions significantly reduce rehospitalization rates and all-cause mortality in patients with heart failure, there are many unsolved issues, such that the program contents have not been standardized.[536–539] In contrast, comprehensive ambulatory cardiac rehabilitation programs, which include lifestyle interventions to prevent recurrent heart failure and clinical monitoring of heart failure, are expected to serve as disease management programs for heart failure, and their benefits have been demonstrated.[540,541]

### 2.2 Practical Examples of Ambulatory Cardiac Rehabilitation as a Disease Management Program (Table 75)

**Figure 14** outlines a typical flowchart of exercise therapy and heart failure monitoring in an ambulatory cardiac rehabilitation program.[542] Every time when a patient visits the clinic for a rehabilitation session, he/she is checked for physical condition before, during and after the session, and periodically for improvement in exercise capacity (**Table 76**). When findings suggestive of worsening heart failure are observed, the patient is referred to his or her physician, who may modify the exercise prescription, limit water intake or increase the dose of diuretics, among other measures, to prevent worsening heart failure.[543] Comprehensive ambulatory cardiac rehabilitation sessions as a disease management program for patients with heart failure is superior to medical consultations at clinic in terms of identifying early signs of worsening heart failure through symptoms, signs and ECG changes during exercise.

## XIII. Palliative Care

The World Health Organization (WHO) describes palliative care as services that must be considered for all patients with life-threatening conditions such as cardiovascular diseases and respiratory diseases. Many patients with heart failure are suffering from total pain and healthcare professionals should support patients with heart failure and their family members from early stages of the disease in a multidisciplinary setting to improve their QOL. In 2014, WHO has reported that nearly 40% of adults who need palliative care has cardiovascular diseases.[544]

## 1. Advance Care Planning and Decision-Making Support

Although the number of elderly patients with heart failure, are increasing year by year, their recognition about prognosis is substantially more optimistic than the real situation.[545] Also, it is often difficult to introduce palliative care in a timely manner. Advance care planning (ACP) is an important step to help individual patients prepare for future changes in their disease condition. ACP is a process

| Table 73. Contents of Treatment/Lifestyle Education and Support for Patients With Heart Failure, Family Members, and Caregivers | |
| --- | --- |
| **Contents of education** | **Specific education/support methods** |
| Knowledge on heart failure | |
| • Definition, causes, symptoms, and clinical course<br>• Severity assessment (laboratory findings)<br>• Factors of worsening heart failure<br>• Comorbidities<br>• Drug and nonpharmacologic therapy | • Provide information using appropriate materials suitable for individual patient's comprehension and health literacy |
| Self-monitoring | |
| • Necessity and importance of symptom monitoring by patients themselves<br>• Self-monitoring skills<br>• Utilizing patient diaries | • Encourage patients to recording in their diaries and utilize recorded information for better practice and patient education |
| Management of disease worsening | |
| • Symptoms of worsening heart failure and assessment<br>• How to contact healthcare professionals when disease worsens | • Instruct patients to visit clinic when symptoms of worsening heart failure (e.g., dyspnea, swelling, body weight gain by >2 kg in 3 days) develop, and explain how to contact the clinic |
| Adherence to treatment | |
| • Name of drugs, expected effects, how to take drugs, adverse drug reactions<br>• Importance of taking drugs as directed<br>• Purpose of device therapy, and how to handle devices during daily life | • Provide information using appropriate materials suitable for individual patient's comprehension and health literacy<br>• Evaluate adherence to treatment periodically<br>• Patients with poor adherence should be educated and supported by healthcare professionals |
| Infection control and vaccination | |
| • Infections as factors worsening heart failure<br>• Necessity of vaccinations against influenza and pneumonia | • Provide knowledge on how to prevent infections during daily life<br>• Provide information on the timing of vaccinations |
| Salt and water management | |
| • Risk of excessive water intake<br>• Limit water intake in patients with severe heart failure<br>• Appropriate salt intake (<6 g/day)<br>• Importance of maintaining an appropriate body weight | • Explain how to measure water intake in detail<br>• Explain how to reduce salt intake efficacy using educational materials<br>• Observe patients for symptoms of decreased appetite due to salt restriction |
| Nutritional management | |
| • Importance of well-balanced diet<br>• Menus considering the nature of complications | • Observe patients periodically for nutritional status<br>• Provide nutritional guidance based on the individual patient's physical status (e.g. swallowing function) and life style<br>• Explain that reduced meal size and appetite may be signs of worsening heart failure |

(**Table 73** continued the next column.)

| Contents of education | Specific education/support methods |
| --- | --- |
| Alcohol | |
| • Risk of excessive alcohol consumption | • Suggest appropriate alcohol consumption based on the individual patient's causes of heart failure |
| Smoking cessation | |
| • Importance of quit smoking | • See the "Guidelines for Smoking Cessation (JCS 2010)" |
| Physical activity | |
| • Importance of appropriate physical activity during stable conditions<br>• Importance of bed rest and activity restrictions during worsening heart failure<br>• Negative effects of excessive bed rest (e.g. decreased exercise capacity) | • Evaluate exercise capacity and skeletal muscles<br>• Evaluate activities of daily living regularly<br>• Considering the individual patient's physical function and living environment, assess the risk of fall and provide detailed guidance on physical activities during daily life |
| Bath | |
| • How to take a bath appropriately | • Instruct appropriate methods according to the severity of heart failure and living environment |
| Travel | |
| • Precautions during travel (drug therapy, water intake, meals, and physical activity)<br>• Risk of worsening heart failure during travel<br>• How to manage worsening heart failure during travel | • Explain possible effects of changes in contents and timing of meals, weather and climates, and physical activities, etc. during travel on the condition of heart failure<br>• Provide information on pre-travel preparation |
| Sex life | |
| • Effects on sexual activity on heart failure<br>• Relationship between heart failure mediations and sexual function<br>• Precautions for using erectile dysfunction medications | • Explain that sexual activity may worsen heart failure<br>• Refer to specialist physicians whenever necessary |
| Mental support | |
| • Heart failure and mental/psychological changes<br>• Stress management during daily life | • Evaluate psychiatric symptoms periodically<br>• Explain the importance and methods of stress management during daily life<br>• When worsening psychiatric symptoms are suspected, consult the patient to psychiatrists, psychosomatic medicine specialists, and clinical psychotherapists |
| Periodic hospital visits | |
| • Importance of periodical clinic visits | • Before discharge, confirm appoints for out-patient clinic visits after discharge<br>• Instruct patients to contact medical institutions promptly when symptoms worsen regardless of visit schedule<br>• Ensure easy access to healthcare professionals (e.g., Telephone consultation, and utilization of social resources) |

**Table 74.** Recommendations and Levels of Evidence for Disease Management in Heart Failure

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| Multidisciplinary team-based education and support to improve treatment adherence and self-care for patients, family members, and caregivers | I | A | A | I |
| Discharge support and continuous follow-up | I | A | B | I |
| Smoking cessation | I | C | B | IVb |
| Symptom monitoring | I | C | C1 | VI |
| Monitoring and specialists' treatment for psychiatric symptoms | I | B | B | II |
| Educational support for patients at a high risk of worsening heart failure and use of social resources for people living alone, elderly patients, and people who also have dementia | I | A | A | I |
| Low-salt diet (ca. 6 g/day) | IIa | C | C1 | VI |
| Restriction of alcohol | IIa | C | C1 | VI |
| Vaccinations to prevent infections | IIa | C | B | IVb |

**Table 75.** Recommendations and Levels of Evidence for Comprehensive Ambulatory Cardiac Rehabilitation for Patients with Heart Failure

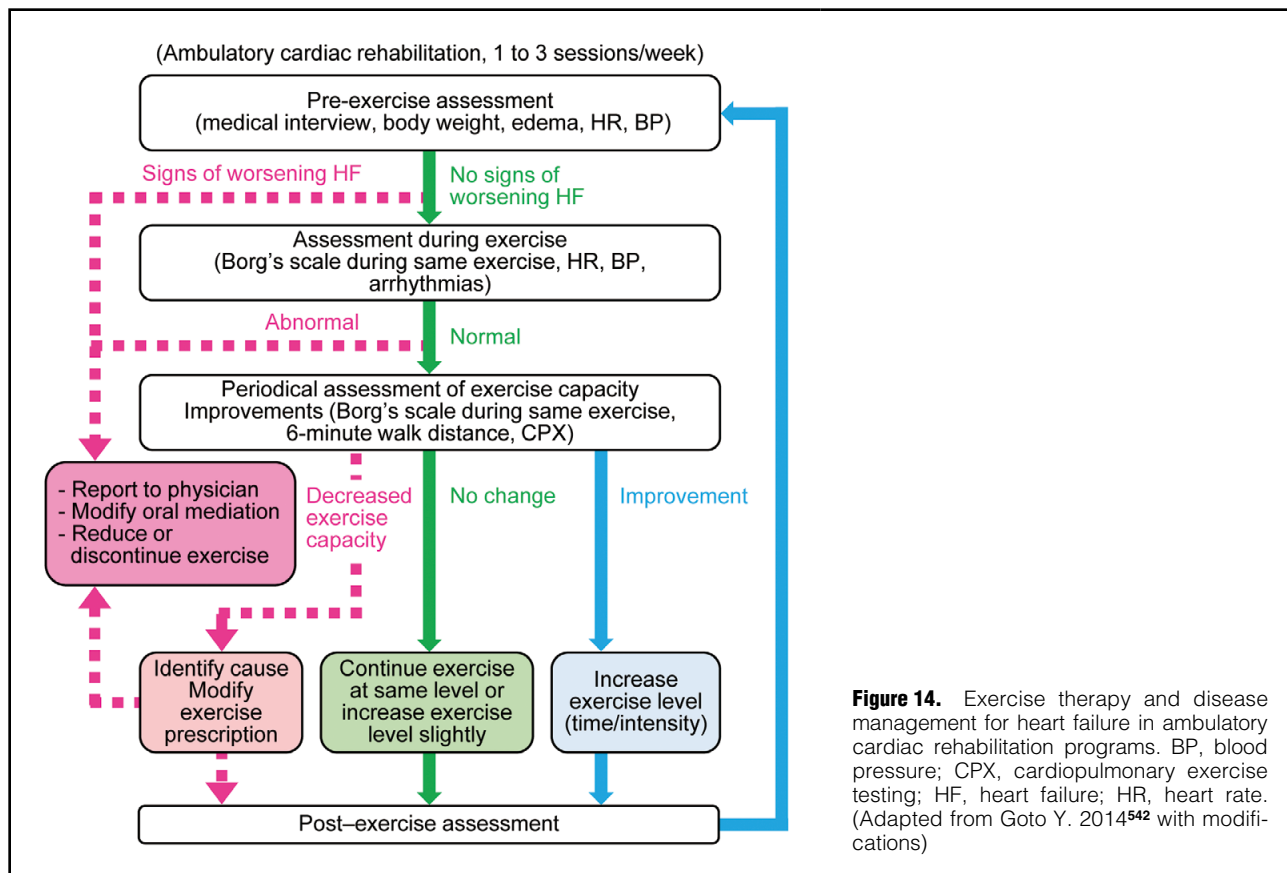| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| For patients with HFrEF, conduct exercise therapy as ambulatory cardiac rehabilitation sessions to improve symptoms and exercise capacity | I | A | A | I |
| For patients with HFrEF, conduct exercise therapy as ambulatory cardiac rehabilitation sessions to improve QOL and prevent rehospitalization | IIa | B | B | II |
| For patients hospitalized for heart failure, conduct multidisciplinary disease management to facilitate ambulatory cardiac rehabilitation sessions to improve QOL and exercise capacity and prevent rehospitalization after discharge | IIa | B | B | II |

HFrEF, heart failure with reduced ejection fraction; QOL, quality of life.

to share decisions what the patient and his or her family members decided about what treatment they want and what way of life they want to lead in advance, before the patient becomes difficult to make his or her own decisions. It has been recommended that ACP should be conducted at an annual heart failure review and at the end of hospitalization during which clinical milestones that trigger review of treatment strategies occurred (**Table 77**).[546] The aim of ACP is to avoid unwanted, invasive treatments near death and improve the quality of death. A randomized controlled in ACP in non-cancer patients has reported its benefits.[547]

ACP may include completion of an advance directive, a document that describes the patient's preferences about end-of-life care. Specifically, the patient may make shared decision making, with support from a multidisciplinary team, about Do Not Attempt Resuscitation (DNAR) orders and policies on whether or not to discontinue device therapy such as implantable cardioverter defibrillators (ICDs), cardiac resynchronization therapy (CRT), and left ventricular assist device (LVADs), and prepare an advance

directive. At this time, the patient should be informed that he or she can change the contents of the advance directive at any time. When necessary, the patient may designate another person to make health care decisions for him or her when the patient becomes unable to make health care decisions. In the guidelines for decision making with end-of-life care published by the Ministry of Health, Labor and Welfare in 2007, a flow process to determine medical and care policies at the end of life is described (**Figure 15**).[548]

"The statement on the treatment of elderly patients with heart failure" published by the Japanese Heart Failure Society in 2016 describes the importance of pain-relieving treatment in end-of-life care for elderly patients and the roles of multidisciplinary conferences and ACP.[549] In 2016, the Japanese Society of Intensive Care Medicine published "Advice on Do Not Attempt Resuscitation (DNAR) Order"[550] to describe that ACR is not a procedure just to determine DNAR policies but is an important process to share the patient's values and philosophy on life and death with healthcare professionals.

**Figure 14.** Exercise therapy and disease management for heart failure in ambulatory cardiac rehabilitation programs. BP, blood pressure; CPX, cardiopulmonary exercise testing; HF, heart failure; HR, heart rate. (Adapted from Goto Y. 2014[542] with modifications)

## 2. End-Stage Heart Failure and Indication for Palliative Care

End-stage heart failure is defined as a heart condition that doesn't respond to maximal medical or on-pharmaceutical treatments. End of life is defined as the period in which death is imminent due to repeated or rapid worsening of an illness and there is little likelihood of cure.[551] However, patients with advanced chronic heart failure show a clinical course different from that of patients with cancer. If is often difficult to know the end of life is approaching in patients with advanced heart failure (**Figure 16**).[552] The 2013 ACCF/AHA guideline for the management of heart failure described end-stage heart failure as Stage D heart failure, defined as "patients with truly refractory heart failure who might be eligible for specialized, advanced treatment strategies, such as mechanical circulatory support, procedures to facilitate fluid removal, continuous inotropic infusions, or cardiac transplantation or other innovative or experimental surgical procedures, or for end-of-life care, such as hospice".[553] The 2016 ESC guidelines for the diagnosis of treatment of acute and chronic heart failure defined heart failure requiring end-of-life care as the conditions, including:
- progressive functional decline (physical and mental) and dependence in most activities of daily living
- severe heart failure symptoms with poor quality of life despite optimal pharmacological and nonpharmacologic therapies
- frequent admissions to hospital or other serious episodes of decompensation despite optimal treatment

- heart transplantation and mechanical circulatory support ruled out
- cardiac cachexia
- clinically judged to be close to end of life.[14]

In Japan, the Japanese Circulation Society published the "Statement for End-stage Cardiovascular Care" in 2010.[554] All of these guidelines assume that patients with heart failure receive appropriate treatment throughout the disease course, which clearly differs from the situation of cancer treatment where end-stage patients often do not receive aggressive treatment. To alleviate their signs and symptoms, patients should be treated for heart failure and its complications throughout the life. Moreover, palliative care is not the same as end-of-life care, and is not indicated only for patients nearing the end of life (**Figure 17**).[555] Palliative care should be initiated in the early phase of heart failure where symptoms begin. ACP should be conducted in the early phase as well, and a multidisciplinary team should repeatedly assess the physical, psychological, and mental needs of patients (**Table 78**).

## 3. Importance of Multidisciplinary Approaches

In order to prevent and remove total pain in patients with heart failure, a multidisciplinary approach is essential. A team of physicians, nurses, pharmacists, clinical psycho-therapists, physical therapists, registered dieticians, medical social workers, clinical engineers and other health care experts should address this issue.

**Table 76.** Points to Be Examined During Ambulatory Cardiac Rehabilitation Sessions for Patients With Heart Failure, and Signs of Worsening Heart Failure or Excessive Exercise

| | Items | Signs of worsening heart failure/excessive exercise |
|---|---|---|
| Before exercise | Symptoms | Persistent malaise, residual fatigue from previous day |
| | Body weight | Tendency of body weight gain (by ≥2 kg in 1 week) |
| | Heart rate | High heart rate at rest (≥100 bpm), increase by ≥10 bpm from last week |
| | Blood pressure | Systolic blood pressure increased or decreased by ≥20 mmHg from last week |
| | ECG monitor | Occurrence of arrhythmias (paroxysmal atrial fibrillation, complete atrioventricular block, frequent premature ventricular contractions, and ventricular tachycardia), abnormal ST segment, or new left bundle branch block |
| | BNP levels in the blood | Increase by ≥100 pg/mL from the preceding value (measure once a month) |
| During exercise | Symptoms | Borg's scale during exercise of ≥14 or an increase in Borg's scale by ≥2 from last week. Respiratory symptoms (shortness of breath and dyspnea), anginal symptoms (chest compression and chest pain), low-cardiac-output symptoms (dizziness and malaise), and/or orthopedic symptoms (myalgia and arthralgia) |
| | Heart rate | High heart rate (≥130 bpm) during exercise, or an increase in heart rate by ≥10 bpm during same exercise load from last week |
| | Blood pressure | Increased or decreased systolic blood pressure during exercise by ≥20 mmHg from last week |
| | ECG monitor | Occurrence of arrhythmias (paroxysmal atrial fibrillation, complete atrioventricular block, frequent premature ventricular contractions, and ventricular tachycardia), abnormal ST segment, or new left bundle branch block |
| | Respiration, SpO₂ monitor | Substantial increase in respiratory rate during exercise, low SpO₂ (<90%) |
| After exercise | Symptoms | Persistent symptoms after exercise |
| | ECG monitor | Arrhythmia at rest after exercise (paroxysmal atrial fibrillation, frequent premature ventricular contractions, and ventricular tachycardia) |
| | Exercise capacity | Decreased exercise capacity (peak oxygen uptake, 6-minute walk distance), and reduced ventilation efficiency ($\dot{V}E/\dot{V}CO_2$ slope) from the last session |

ECG, electrocardiogram; SpO₂, oxygen saturation

# 4. Symptoms and Treatment of End-Stage Heart Failure

Typical symptoms of end-stage heart failure include dyspnea, generalized malaise, pain, anorexia, and depression.

**Table 77.** Triggers for Formally Assessing Prognosis and Having Conversations About Goals of Care and Voluntary Advance Care Planning (ACP)

Routine
- "Annual Heart Failure Review" with a scheduled clinic visit

Event-driven "milestones" that should prompt reassessment
- Increased symptom burden and/or decreased quality of life
- Significant decrease in functional capacity
  - Loss of ADLs
  - Falls
  - Transition in living situation (independent to assisted or LTC)
- Worsening heart failure prompting hospitalization, particularly if recurrent
- Serial increases of maintenance diuretic dose
- Symptomatic hypotension, azotemia, or refractory fluid retention necessitating neurohormonal medication underdosing or withdrawal
  - Circulatory-renal limitations to ACEI/ARB
  - Decrease or discontinuation of β-blockers because of hypotension
- First or recurrent ICD shock for VT/VF
- Initiation of intravenous inotropic support
- Consideration of renal replacement therapy
- Other important comorbidities: new cancer, etc
- Major "life events": death of a spouse

ADL indicates activities of daily living; LTC, long-term care; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ICD, implantable cardioverter-defibrillator; VT, ventricular tachycardia; and VF, ventricular fibrillation. (Adapted from Allen LA, et al. 2012[546])

It has been reported that 60 to 88% of patients with end-stage heart failure have dyspnea, 69 to 92% have generalized malaise, and 35 to 68% have pain.[556–558] It has also been reported that 70% of patients hospitalized for end-stage heart failure have depression.[559] As heart failure itself is considered to lease these problems through causing fluid retention and low cardiac output, heart failure treatment in Stage D should be continued in combination with the following treatments to control these symptoms.

## 4.1 Dyspnea

It has been reported that low-dose morphine and other opioids are safe and effective in releasing intractable dyspnea.[560,561] However, opioids may cause adverse drug reactions such as nausea, vomiting and constipation. Careful dose adjustment is required especially in elderly patients and patients with renal dysfunction to prevent overdosage, which may lead to respiratory depression in some patients.

## 4.2 Pain

A study has reported that the prevalence of pain increases as NYHA functional class worsens.[562] Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided whenever possible as they may worsen renal dysfunction and fluid retention in patients with end-stage heart failure. It is recommended that acetaminophen, a non-opioid analgesic, should be tried first and then opioids should be added if pain in difficult to control.
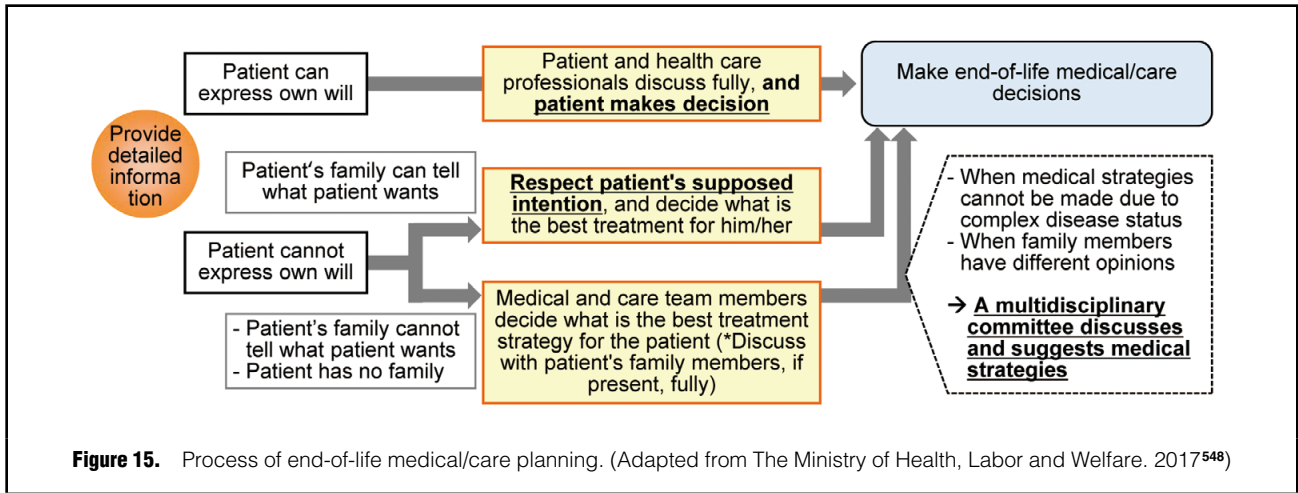
**Figure 15.** Process of end-of-life medical/care planning. (Adapted from The Ministry of Health, Labor and Welfare. 2017[548])



Patients with chronic heart failure show a clinical course different from that of patients with cancer. As patients repeat hospitalizations for worsening heart failure and experience an abrupt worsening of symptoms before death, it is often difficult to determine when the end of life is approaching.
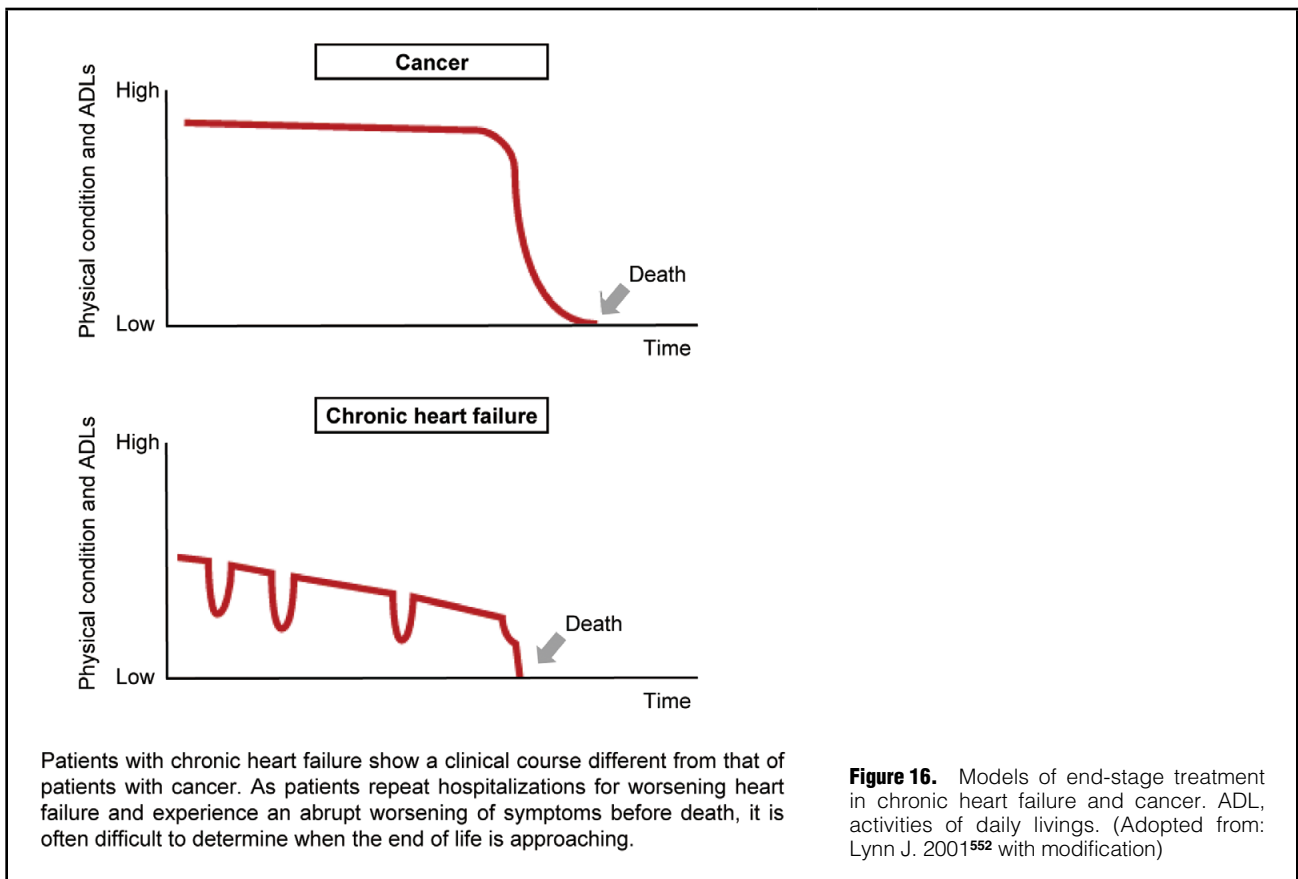
**Figure 16.** Models of end-stage treatment in chronic heart failure and cancer. ADL, activities of daily livings. (Adopted from: Lynn J. 2001[552] with modification)

## 4.3 Generalized Malaise

Patients should be examined not only for low cardiac output but also for depression, hypothyroidism, anemia, overuse of diuretics, electrolyte imbalance, sleep apnea, and occult infections, and should be treated accordingly. As pharmacotherapy is often ineffective in alleviating this condition, and nonpharmacologic therapy such as energy-conservation techniques may work in some patients.[563]

## 4.4 Depression and Anxiety

In patients with heart failure, depression predicts poor prognosis and is also associated with poor QOL.[564] Depression is commonly treated with selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors, and noradrenergic and specific serotonergic antidepressants, but it has been recently reported that concomitant use of $\beta$-blockers and SSRIs may increase the risk of death,[565] and antidepressants may not always improve the prognosis of patients with heart failure.[566–568]
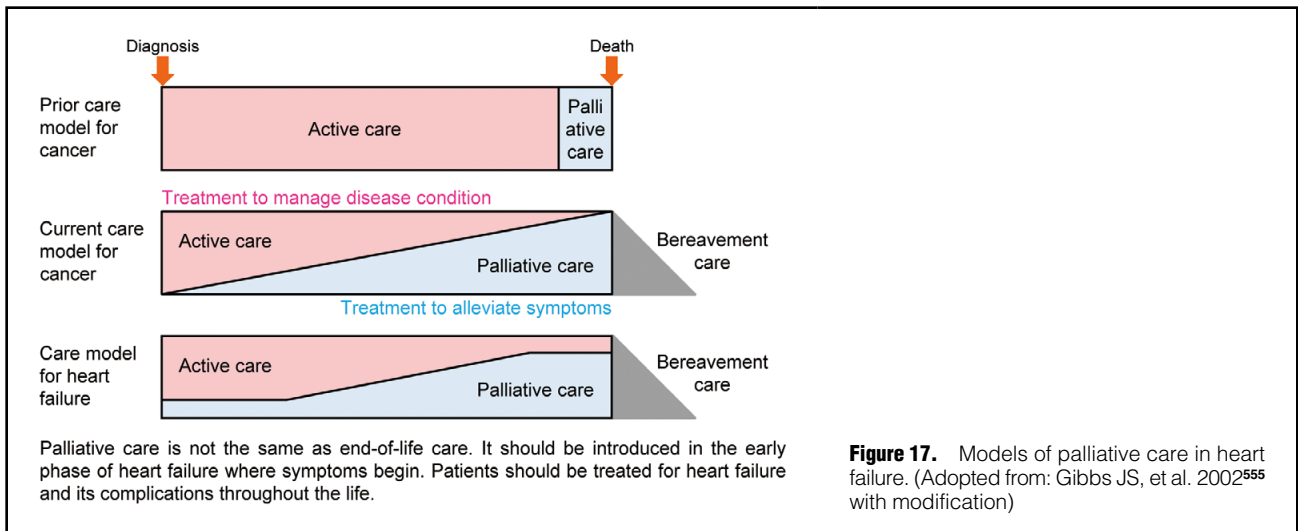
**Figure 17.** Models of palliative care in heart failure. (Adopted from: Gibbs JS, et al. 2002[555] with modification)

Palliative care is not the same as end-of-life care. It should be introduced in the early phase of heart failure where symptoms begin. Patients should be treated for heart failure and its complications throughout the life.

**Table 78.** Recommendations and Levels of Evidence for Palliative Care for Patients With End-Stage Heart Failure

| | Class of Recommendation | Level of Evidence | Grade of Recommendation (MINDS) | Level of Evidence (MINDS) |
|---|---|---|---|---|
| Conduct advance care planning (ACP) in which physicians share decisions with the patient and his/her family members about treatment and care before the patient becomes difficult to make his or her own decisions | I | B | B | II |
| Continued treatment to manage heart failure and complications and relieve symptoms | I | C | B | II |
| Multidisciplinary team-based frequent assessment for the patient's physical, mental and spiritual needs | II | C | C1 | VI |

Tricyclic antidepressants should be used with caution as they may prolong QT intervals and cause anticholinergic effects. Benzodiazepines are the first-line treatment for anxiety. Nonpharmacologic therapy such as cardiac rehabilitation and expert counseling are beneficial as well.[569,570]

## 4.5 Delirium

Delirium often develops in patients with end-stage heart failure, especially in elderly. Delirium should be differentiated from dementia and depression, and early intervention should be offered to prevent severe delirium. When delirium develops in a patient with heart failure, the physician should review his/her treatment and environment for whether or not he/she uses drugs that may induce or worsen delirium (e.g. antihypertensives, $\beta$-blockers, antiarrhythmics, sympathomimetics, anticholinergics, hypnotics, and antianxiety drugs), take appropriate safety measures, and, if the condition is severe, consult him/her to a psychiatrist and consider for antipsychotic therapy.

## 4.6 End-of-Life Pain

As the final measure for patients suffering from uncontrollable pain, an appropriate amount of midazolam, a benzodiazepine drug, may be administered.

## 4.7 Deactivation of Medical Devices

When the patient's clinical status reaches the end-of-life stage, the patient, his/her family members and the palliative care team should discuss fully to determine whether to deactivate his/her ICD, pacemaker or CRT.[571] In the "Concept of optimizing the indications for ventricular assist devices in Japan: Destination therapy (DT),"[572] the Japan VAD Council has recommended that the physician should explain about end-stage cardiovascular care to the patient and his or her family members before implanting cardiac devices, inform that he/she has an option to deactivate his/her implantable LVAD at the end-of-life stage, and recommend him/her to describe his/her preferences in an advance directive. Healthcare professionals should explain to patients about potential problems of DT (e.g., device malfunction, serious LVAD-related complications, status of comorbidities, and poor QOL after LVAD implantation) fully in advance, and help them plan how to address such problems in future according to the patients' own life philosophy and values. This process is called "preparedness planning."[573] The guidelines on the use of implantable LVADs proposed by the Japanese Circulation Society and the Japanese Society for Cardiovascular Surgery in 2013,[517] and the guidelines on end-stage care for patients in emergency room or ICU proposed by the Japanese Association for Acute Medicine, the Japanese Society of Intensive Care

Medicine, and the Japanese Circulation Society in 2014[574] recommend multidisciplinary process-oriented approaches based on the advance directives and family's wishes.

## 5. Early Introduction of Palliative Care for Heart Failure

The introduction of palliative care for heart failure does not mean abandoning hope for cure. Palliative care is conducted to improve the QOL of the patient and his or her family members, and is continued together with standard heart failure treatment. Accordingly, palliative care should be initiated in the early phase of the disease rather than considering near the end of life.

# XIV.  Future Treatment

## 1.  Ivabradine (If-Channel Blocker)

Ivabradine decreases heart rate by blocking If channels of sinus node cells. It is indicated only for patients with sinus rhythm. In a randomized, double-blind, placebo-controlled trial of ivabradine in patients who had HFrEF (LVEF <35%), were in sinus rhythm with a heart rate ≥70 bpm, had been admitted to hospital for heart failure within the previous year, and were receiving a $\beta$-blocker at the recommended or maximum tolerated dose, an angiotensin converting enzyme (ACE) inhibitor (or an ARB), and/or a mineralocorticoid receptor antagonist, ivabradine significantly reduced the composite of cardiovascular death or hospital admission for worsening heart failure.[575] This study revealed that increased heart rate is a risk factor in patients with HFrEF in sinus rhythm, and lowering heart rate is an important target for treatment of heart failure.[576]

## 2.  Sacubitril/Valsartan (ARNI)

Sacubitril/valsartan (LCZ696) is a new class of drug named as an angiotensin receptor neprilysin inhibitor (ARNI), and consists of valsartan, an ARB, and sacubitril (AHU-377), a prodrug of a neprilysin inhibitor, in a 1:1 mixture. Sacubitril is converted to the active form LBQ657, which exerts an inhibitory effect on neprilysin 3 to 4 hours after absorption. LBQ657 mainly inhibits the degradation of endogenous natriuretic peptide but does not inhibit ACE or aminopeptidase P. Therefore, it does not enhance the degradation of bradykinin, and the risk of angioedema is expected to be low. The half-life of LBQ657 is 12 hours and that of valsartan is 14 hours. Sacubitril/valsartan is administered twice daily.

The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial has revealed that sacubitril/valsartan is superior to ACE inhibitor enalapril in improving prognosis.[577] ESC and ACC/AHA Guidelines recommended the replacement from ACE inhibitor to ARNI for HFrEF and the inhibition of the renin-angiotensin system with ACE inhibitors, ARBs, or ARNI in patients with HFrEF as Class I recommendations with Level of Evidence B.[14,578]

In Japan, the Prospective comparison of ARNI with ACE inhibitor to determine the novel beneficial treatment value in Japanese Heart Failure patients (PARALLEL-HF), a phase III randomized double-blind trial to obtain the approval from the government, is underway.[579] Sacu-bitril/valsartan reduced plasma NT-proBNP levels to a greater extent than did valsartan at 12 weeks in heart failure with preserved ejection fraction (HFpEF) in the Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction (PARAMOUNT) trial.[580] The Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction (PARAGON-HF) trial, a large-scale clinical trial to investigate the effects of sacubitril/valsartan on clinical outcomes is underway in countries including Japan. These large-scale clinical trials are expected to provide further evidence on the benefits of ARNI in patients with heart failure.

## 3.  Vericiguat (cGS Activator)

In patients with heart failure, endothelial dysfunction and increased production of reactive oxygen species (ROS) reduce the production and bioavailability of nitric oxide (NO) and activity of the NO receptor, soluble guanylate cyclase (sGC), resulting in decreased activation of cyclic guanosine monophosphate (cGMP), as well as conversion to the NO-insensitive (inactive) sGC by ROS. Accordingly, cGMP-mediated intracellular signaling has attracted attention as a potential treatment target in HFrEF and HFpEF.[581–583]

Vericiguat is a novel sGC stimulator that directly stimulates sGC to promote NO production in a NO-independent manner via a site other than the NO binding site and also synergizes with NO.[581,583]

In a dose-finding phase II randomized controlled study of vericiguat in patients with HFrEF with a LVEF of <45% (the SOCRATES-REDUCED trial in the Soluble guanylate Cyclase stimulator in heart failure Study [SOCRATES] program),[584] patients who were clinically stable with LVEF <45% within 4 weeks of a worsening chronic heart failure event received placebo (n=92) or 1 of 4 daily target doses of oral vericiguat (1.25 mg, 2.5 mg, 5 mg, or 10 mg; n=91 for each dose) for 12 weeks. The primary endpoint, change from baseline to week 12 in log-transformed NT-proBNP level, was not significantly different between the pooled 3-highest-dose vericiguat group and placebo group, but a secondary analysis revealed that higher vericiguat doses were significantly associated with greater reductions in NT-proBNP level.[585]

As vericiguat was shown to tolerable in patients with HFrEF in phase II studies, the drug is currently being evaluated in a global phase III placebo-controlled randomized clinical trial called the Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction (VICTRIA) trial.[586] The VICTRIA trial plans to

The tip of MitraClip® device

MitraClip® grasping the anterior and posterior mitral leaflets

A view from the left atrium of mitral valves after a clip procedure



**Figure 18.** Treatment of mitral valve insufficiency with MitraClip®. (Figures courtesy of Abbott Vascular Japan Co., Ltd.)

enroll a total of 4,872 patients with NYHA class II to IV heart failure and LVEF >45% by the end of 2020, and will follow them for approximately 3.5 years. The primary endpoint is time to first occurrence of composite endpoint of cardiovascular death or heart failure hospitalization. The trial is conducted in many countries including Japan.

Phase III trials of vericiguat are expected to generate evidence that help position this drug in the treatment of heart failure, which will be described in the relevant guidelines including Western guidelines in the future.

## 4. Omecamtiv Mecarbil (Cardiac Myosin Activator)

As omecamtiv mecarbil increase the transition rate of myosin from weakly to strongly actin-bound force-generating state and thereby increase myocardial contractility,[587] this drug is expected to increase cardiac function without increasing intracellular calcium concentration and worsening prognosis.

In phase II clinical trial of intravenous omecamtiv mecarbil in patients with HFrEF,[588] left ventricular ejection time and stroke volume increased proportionally with plasma concentration of omecamtiv mecarbil, and higher plasma concentrations were also associated with reductions in left ventricular end-systolic and end-diastolic volumes. Heart rate decreased slightly but significantly. Cardiac ischemia developed in some patients receiving higher doses

of the drug.

In a following large-scale randomized controlled trial, the Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure (ATOMIC-AHF),[589] 606 patients with acute heart failure who had LVEF ≤40%, elevated natriuretic peptide level, and persistent dyspnea received omecamtiv mecarbil at 3 escalating intravenous doses. Omecamtiv mecarbil resulted in significantly greater dyspnea relief in the higher-dose group as compared with the control group, but plasma troponin levels were significantly higher in patients treated with omecamtiv mecarbil compared with placebo.

In the Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF) trial,[590] a clinical study of oral omecamtiv mecarbil in 448 patients with HFrEF, patients receiving the drug at 25 mg twice daily titrated to 50 mg twice daily guided by pharmacokinetics had longer systolic ejection time, larger cardiac output, smaller left ventricular end-systolic diameter, and lower heart rate than the control group.

A phase III study in about 8,000 patients with HFrEF to evaluate the effect of omecamtiv mecarbil on the risk of cardiovascular death or heart failure events, the Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure (GALACTIC-HF) trial, is currently ongoing.[591]

## 5. Percutaneous Mitral Valve Repair System (MitraClip®)

Percutaneous mitral valve repair should be considered for patients with mitral valve insufficiency for whom mitral repair is expected to reduce symptoms and improve QOL but surgical risk is high. In Japan, MitraClip® has become available recently (**Figure 18**). This system facilitates early ambulation after surgery. Symptomatic improvement reported by patients receiving this procedure on day 30 after the procedure is better than those undergoing thoracotomy.

## 6. Human (Autologous) Skeletal Muscle-Derived Cell Sheet (HeartSheet®)

Myoblast sheet is a cell therapy technology for severe heart failure, and five sheets, each contains $6 \times 10^7$ myoblasts, are applied on the epicardium to cover the anterior and lateral walls of the left ventricle through a left lateral thoracotomy. The implanted myoblast sheets secrete cytokines such as hepatocyte growth factor, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and stromal derived factor-1 that are considered to promote neovascularization, induce stem cells, and inhibit fibrosis, and thereby improve cardiac function.[592] In animal models of heart failure, the sheet improved cardiac function and prolonged survival.

It has been reported that among 4 patients with dilated cardiomyopathy supported by a LVAD who received the autologous myoblast sheet implantation, two patients showed an improvement in cardiac function and could remove the LVAD.[593] Safety and efficacy of the myoblast sheet technology for treatment of ischemic cardiomyopathy were demonstrated in clinical research[594] and a multi-center

company-sponsored study,[595] and the sheet was approved as the world's first tissue-engineered medical product, HeartSheet®, under the fast-track designation and reimbursed by the National health Insurance.

Investigator-initiated studies are now underway to assess the efficacy and safety of the product in the treatment of children and adults with dilated cardiomyopathy.

## 7. Waon Therapy

In Waon therapy,[596] a thermal therapy developed in Japan, patients stay in a far-infrared dry sauna at 60°C for 15 minutes, and then maintain body temperature for 30 minutes after sauna bath.

It has been reported that Waon therapy is beneficial in improving hemodynamics,[597] left ventricular function,[598–601] heart failure symptoms,[598,600,602] QOL and exercise capacity,[600] and peripheral vascular endothelial function,[600, 602] and reducing heart rate variability in patients with heart failure.[603,604] A retrospective study has revealed that Waon therapy significantly reduced the risk of death and rehospitalization for worsening heart failure, and improved the prognosis of patients with chronic heart failure.[605] In the WAON-CHF trial, a multicenter prospective randomized trial in 149 patients treated in 19 medical institutions,[606] patients receiving Waon therapy once daily for 10 days showed improvement in BNP levels, NYHA functional class, 6-minute walk distance, and cardiothoracic ratio and a favorable safety profile. However, no significant difference between the Waon therapy group and the control group was found in the change in BNP from before and after treatment, which was the primary endpoint of the study.

At present, Waon therapy in the treatment of heart failure is not covered by the National Health Insurance in Japan.

| Supplement 1. A Statement on Appropriate Use of Adaptive Servo-Ventilation (ASV) by the Japanese Circulation Society and the Japanese Heart Failure Society (the Second Statement) |
|---|
| 1) Adaptive Servo-Ventilation (ASV) for patients whose conditions are similar to the participants in the SERVE-HF trial (patients with heart failure who have predominant central sleep apnea and stable left ventricular systolic dysfunction with left ventricular ejection fraction [LVEF] ≤45%) |
| The introduction and continuation of ASV in these patients are not contraindicated, but careful consideration is required. In the clinical practice, it is desirable that, as described in the relevant guidelines in Japan,[1,2] patients should be first considered for continuous positive airway pressure (CPAP) and then ASV should be considered only for patients who still have sleep apnea despite CPAP or are intolerable to CPAP. After initiating ASV, patients should be observed carefully for clinical conditions, and should be considered for switching to CPAP whenever possible. Healthcare professional should fully inform patients and their family members of the advantages and disadvantages of ASV on the basis not only the relevant guidelines in Japan but also the results of small-scale clinical studies,[3] the SERVE-HF study,[4] and SAVIOR-C trial,[5] Western guidelines, and regulations for use of ASV by regulatory authorities to obtain informed consent from patients to introduce and continue taking ASV. |
| 2) ASV for patients who do not meet the above criteria 1 but have heart failure and sleep apnea (e.g. those with predominant obstructive sleep apnea, and those with sleep apnea and heart failure with preserved ejection fraction [LVEF >45%]) |
| At present, there are no reasons to limit the introduction and continuation of ASV in these patients. However, patients should be observed carefully for their clinical course during the introduction and continuation of ASV to ensure safety of treatment. Patients should first be considered for CPAP, and receive ASV only when it is necessary (the coverage with the National Health Insurance should be reviewed individually). |
| 3) ASV for patients with or without sleep apnea in whom ASV has been effective in the treatment of severe congestion |
| ASV may be continued in patients with heart failure in whom severe congestion was not alleviated with conventional medical treatment but was successfully treated with ASV when physicians consider that discontinuing ASV would worsen heart failure, regardless of whether sleep apnea is present or not. However, it should be considered whether patients can withdraw from ASV or switch from ASV to other procedures when they become clinically stable or when 6 months has passed since the introduction of ASV. At this time, patients should be assessed for sleep apnea and those with sleep apnea should be treated according to the criteria 1 and 2 above. |
| 4) ASV for patients who do not meet any of the criteria 1 to 3 |
| This statement does not describe the use or appropriateness of ASV for patients who do not meet any of the criteria 1 to 3. |
| 5) ASV in clinical research |
| No restrictions are placed on the use of ASV in clinical research that is conducted according to the ethical standard at the medical institution even when participating patients have conditions similar to those in the SERVE-HF trial. However, investigators must fully explain to participants and their family members the usage of ASV in non-research settings, as well as the results of small-scale studies, the SERVE-HF trial, and the SAVIOR-C trial before obtaining informed consent. Investigators of ongoing clinical research of ASV must share the results of the SERVE-HF trial as new safety guidelines with all relevant healthcare professionals at participating medical institutions. |
| 6) Other remarks |
| The above criteria 1 to 5 will be revised and updated when new information is available in the SERVE-HF trial or other studies. |

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2) Guidelines on Positive Pressure Ventilation (NPPV), Second Revision Nankodo 2015.
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(Adapted from The Japanese Circulation Society[271])

| Supplement 2. Effects of Exercise Therapy in Heart Failure |
|---|
| **1) Exercise capacity:** Improvement |
| **2) Effects on the heart** |
| a) Left ventricular function: No change or slight improvement in LVEF at rest, increase in the increment of cardiac output during exercise, and improvement in left ventricular early diastolic function |
| b) Coronary circulation: Improvement in coronary endothelial function, improvement in myocardial perfusion during exercise, and increase in coronary collateral flow |
| c) Left ventricular remodeling: Prevention (or inhibition) of progression, decrease in BNP |
| **3) Peripheral effects** |
| a) Skeletal muscle: Increase in muscle mass/strength, improvement in aerobic metabolism, and increase in expression of antioxidant enzymes |
| b) Respiratory muscles: Improvement in respiratory muscle function |
| c) Vascular endothelium: Improvement in endothelium-dependent vasodilation responses, and increase in expression of eNOS |
| **4) Neurohumoral factors** |
| a) Autonomic nervous system function: Suppression of sympathetic nervous activity, increase in parasympathetic activity, and improvement in heart rate variability |
| b) Ventilatory response: Improvement in ventilatory response and $CO_2$ sensitivity of the respiratory center |
| c) Inflammatory markers: Decreases in inflammatory cytokines (e.g., TNF-$\alpha$) and CRP |
| **5) QOL:** Improvement in health-related QOL |
| **6) Long-term prognosis:** Decrease in hospitalizations due to heart failure |

BNP: brain (B-type) natriuretic peptide; CRP, C-reactive protein; eNOS, endothelial nitric oxide synthase; LVEF, left ventricular ejection fraction; QOL, quality of life; TNF, tumor necrosis factor. (Adapted from The Japanese Circulation Society[148] with modification)

| **Supplement 3.  Contraindications in Exercise Therapy for Patients With Heart Failure** |
|---|
| **I.  Absolute contraindications** |
|   1)  Exacerbation of heart failure symptoms (e.g., dyspnea, easy fatigability) during the last 3 days |
|   2)  Unstable angina or low-threshold myocardial ischemia that is induced by slow walking on a flat surface (2 METs) |
|   3)  Severe valvular disease indicated for surgery, especially aortic stenosis |
|   4)  Severe left ventricular outflow tract stenosis (hypertrophic obstructive cardiomyopathy) |
|   5)  Untreated severe exercise-induced arrhythmia (ventricular fibrillation, sustained ventricular tachycardia) |
|   6)  Active myocarditis/pericarditis |
|   7)  Acute systemic disease or fever |
|   8)  Other diseases in which exercise therapy is contraindicated (moderate or severe aortic aneurysm, severe hypertension, thrombophlebitis, embolism within past 2 weeks, and serious organ diseases) |
| **II.  Relative contraindications** |
|   1)  NYHA Class IV or hemodynamically unstable heart failure |
|   2)  Heart failure with an increase in body weight by ≥2 kg during the last week |
|   3)  Exercise-induced decrease in systolic blood pressure |
|   4)  Moderate left ventricular outflow tract stenosis |
|   5)  Exercise-induced moderate arrhythmia (e.g., nonsustained ventricular tachycardia, tachycardiac atrial fibrillation) |
|   6)  Advanced atrioventricular block, exercise-induced Mobitz type II atrioventricular block |
|   7)  Occurrence or exacerbation of exercise-induced symptoms (e.g., fatigue, dizziness, excessive sweating, dyspnea) |
| **III.  Not contraindicated** |
|   1)  Elderly patients |
|   2)  Decreased LVEF |
|   3)  Use of ventricular assist devices (LVADs) |
|   4)  Use of implantable cardiac devices (e.g., ICDs, CRT-D) |

CRT-D, cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; LVAD, left ventricular assist device; METs, metabolic equivalents; NYHA, New York Heart Association. (Adapted from The Japanese Circulation Society[148] with modification)

| **Supplement 4.  Exercise Prescriptions for Patients With Heart Failure** | |
|---|---|
| Type of exercise | • Walking (begin with supervised indoor walking), cycle ergometer, light aerobics, low-intensity resistance training (for patients with muscle weakness)<br>• Jogging, swimming, and vigorous aerobics are not recommended |
| Exercise intensity | [Early phase]<br>• Indoor walking at 50 to 80 m/min for 5 to 10 min or a cycle ergometer at 10 to 20 W for 5 to 10 min<br>• The duration and intensity of exercise should be increased gradually over 1 month as guided by signs/symptoms during exercise |
| | [Goal in the stable phase]<br>• The target heart rate (HR) is set at 40 to 60% of the peak $\dot{V}O_2$ or at anaerobic threshold level<br>• The target HR is set at 30 to 50% of HR reserve, or 50 to 70% of the maximum HR<br>• Target rating of perceived exertion (RPE) is set at Borg scale 11 (fairly light) to 13 (somewhat hard) |
| Duration | • Start with 5 to 10 min/session, 2 sessions a day, and then increase gradually from 30 to 60 min/day |
| Frequency | • 3 to 5 days/week (3 days/week for patients with severe heart failure, and may be increased up to 5 days/week for those with stable condition)<br>• Low-intensity resistance training may be added at a frequency of 2 to 3 days/week |
| Precautions | • Exercise during the first month should be light in intensity and careful monitoring for worsening heart failure should be made<br>• Start with supervised training and then combine with non-supervised (home-based) exercise training during the stable phase<br>• Changes in subjective symptoms, physical findings, body weight, and blood BNP or NT-proBNP levels should be observed carefully |

BNP, brain (B-type) natriuretic peptide; NT-proBNP, N-terminal pro-brain (B-type) natriuretic peptide. (Adapted from The Japanese Circulation Society[148] with modification)

| Supplement 5: CHADS₂ Score | | |
|---|---|---|
| | **Clinical characteristics** | **Score** |
| C | Heart Failure | 1 |
| H | Hypertension | 1 |
| A | Age ≥75 years | 1 |
| D | Diabetes mellitus | 1 |
| S | History of cerebral infarction or transient ischemic attack | 2 |

| CHADS₂ Score | Stroke rate per 100 patient-years |
|---|---|
| 0 | 1.9 |
| 1 | 2.8 |
| 2 | 4.0 |
| 3 | 5.9 |
| 4 | 8.5 |
| 5 | 12.5 |
| 6 | 18.2 |

(Source: Prepared based on Gage BF, et al. 2001[328])

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## Appendix 1. JCS Joint Working Group

**Chair:**
• Hiroyuki Tsutsui, Department of Cardiovascular Medicine, Kyushu University Graduate School of Medical Sciences

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