



JCS/JHFS 2021 Statement on Palliative Care in Cardiovascular Diseases

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Abbreviations

ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACHD	adult congenital heart disease
ACP	advance care planning
ACS	acute coronary syndrome
AD	advance directive
ADL	activities of daily living

AHA	American Heart Association
ARB	angiotensin-receptor blocker
ATTR	transthyretin
BADL	basic ADL
BPS	Behavioral Pain Scale
BZD	benzodiazepine
CAM	Confusion Assessment Method

J-STAGE Advance Publication released online March 26, 2021

This document is an English version of JCS/JHFS 2021 Statement on Palliative Care in Cardiovascular Diseases reported at the 85th Annual Scientific Meeting of Japanese Circulation Society performed in 2021 (Website: https://www.j-circ.or.jp/cms/wp-content/uploads/2021/03/JCS2021_Anzai.pdf).

Refer to **Appendix 1** for the details of members.

JCS Joint Working Groups (consists of 4 groups): The Japanese Circulation Society, The Japanese Heart Failure Society, The Japan Stroke Society, Japanese Society for Palliative Medicine

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ISSN-1346-9843



CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CBT	cognitive behavioral therapy
CIED	cardiovascular implantable electronic device
CLI	critical limb ischemia
COPD	chronic obstructive pulmonary disease
CPOT	critical-care pain observation
CRT	cardiac resynchronization therapy
CVD	cardiovascular disease
DST	Delirium Screening Tool
DT	destination therapy
DNAR	Do Not Attempt Resuscitation
ECMO	extracorporeal membrane oxygenation
EOLC	end-of-life care
ESAS-r	Edmonton Symptom Assessment System revised
ESC	European Society of Cardiology
EQ-5D	EuroQol 5 Dimensions
FACIT	Functional Assessment of Chronic Illness Therapy measurement system
FICA	Faith, Importance and Influence, Community, and Address
GNRI	Geriatric Nutritional Risk Index
GRACE	The Global Registry of Acute Coronary Events
HADS	Hospital Anxiety and Depression Scale
HF	heart failure
HOPE	H: sources of hope, strength, comfort, meaning, peace, love and connection; O: role of organized religion for the patient; P: personal spirituality and practices; E: effects on medical care and end-of-life decisions
HRQOL	health-related quality of life
IADL	instrumental ADL
ICD	implantable cardioverter defibrillator
ICU	intensive care unit
IPOS	Integrated Palliative Care Outcome Scale
JROAD	Japanese Registry of All Cardiac and Vascular Diseases
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVAD	left ventricular assist device
MAGGIC	Meta-Analysis Global Group in Chronic Heart Failure
MCI	mild cognitive impairment
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
NAT: PD-HF	Needs Assessment Tool: Progressive Disease-Heart Failure
NaSSA	noradrenergic and specific serotonergic antidepressant
NHS	National Health Service

NICE	National Institute for Health and Care Excellence
NPPV	noninvasive positive-pressure ventilation
NRS	Numerical Rating Scale
NSAIDs	nonsteroidal anti-inflammatory drugs
NSTEMI	non-ST-elevation myocardial infarction
NT-proBNP	N-terminal pro-B-type natriuretic peptide
Nu-DESC	Nursing Delirium Screening Score
NYHA	New York Heart Association
OPTIMIZE-HF	Organization Program To Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure
PAH	pulmonary arterial hypertension
PAH-SYMPACT	pulmonary arterial hypertension-symptoms and impact
PAP score	Palliative Prognostic Score
PCI	percutaneous coronary intervention
PH	pulmonary hypertension
PHQ	Patient Health Questionnaire
PiPS	Prognosis in Palliative Care Study
PPI	Palliative Prognostic Index
PROMs	Patient-Reported Outcome Measures
PTSD	post-traumatic stress disorder
QALY	quality-adjusted life year
QOL	quality of life
RASS	Richmond Agitation-Sedation Scale
RCT	randomized clinical trial
SADHART-CHF	Sertraline Against Depression and Heart Disease in Chronic Heart Failure
SAS	Sedation-Agitation Scale
SF-36	MOS 36-Item Short-Form Health Survey
SHFM	Seattle Heart Failure Model
SNRI	serotonin noradrenalin reuptake inhibitor
SPICT	Supportive and Palliative Care Indicator Tool
SpiPas	Spiritual Pain Assessment Sheet
SSRI	selective serotonin reuptake inhibitor
STAS	Support Team Assessment Schedule
STEMI	ST-elevation myocardial infarction
SVI	stroke volume index
SVS	Society for Vascular Surgery
SQ	Surprise Question
TASC	TransAtlantic inter-Society Consensus
TAPSE	tricuspid annular plane systolic excursion
TAVI	transcatheter aortic valve implantation
TAVR	transcatheter aortic valve replacement
TCA	tricyclic antidepressant
TeamSTEPPS	Team Strategies and Tools to Enhance Performance and Patient Safety
VAS	Visual Analog Scale
WHO	World Health Organization

Preamble

Because cardiovascular diseases (CVDs) account for the largest proportion of deaths in advanced countries, numerous medical drugs and devices have been developed to improve the mortality rates of CVDs. Although their effect and safety have been vigorously assessed by randomized clinical trials (RCTs), the major purpose of these trials is improving

the survival rate, but not the quality of life (QOL). Therefore, it is still unsatisfactory how to improve QOL in patients with CVDs, especially in endstage CVD. Furthermore, among CVDs, the number of heart failure (HF) patients is markedly increasing with a super-aging society. Because elderly patients with HF have been almost always

excluded as subjects of clinical trials and are not uncommonly resistant to such evidence-based therapies, unresolved problems are expanding year by year as the aging population increases.

Now the time has come to consider how to improve patients' QOL, rather than mortality. In 2014, World Health Organization (WHO) reported that CVDs account for the largest proportion of diseases requiring palliative care in their end stage (38%), which was more than that of cancer (34%).¹

Although the prognosis of HF is as poor as that of cancer, HF is generally recognized as a benign disease. In addition, patients and their families tend to be optimistic about prognosis, because the symptoms of worsening HF usually resolve rapidly by temporalizing treatment. In fact, a previous report demonstrated that the subjective life expectancy of patients with HF is much longer than the objective one predicted by the HF model.²

Meanwhile, medical staff, especially cardiologists in advanced treatment hospitals, are obliged to choose aggressive treatment until the end of life unless there is clear refusal for such treatments by the patient and their family, because intensive care using mechanical circulatory support, implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) is potentially effective and improves survival rates even in patients with advanced HF. In addition, minimally invasive treatment, such as transcatheter aortic valve implantation/replacement (TAVI/TAVR) and percutaneous mitral valve repair (MitraClip®), are effective at improving survival rates in patients with severe valvular diseases. These procedures are widely performed in frail patients who cannot tolerate open chest surgery due to advanced age or several comorbidities. Moreover, left ventricular assist devices (LVADs) are now used as destination therapy (DT) for patients who are not indicated for cardiac transplantation.³ However, frequent activation of ICDs and complications such as infection and stroke after LVAD implantation can seriously worsen the QOL of these patients.

Rightfully, preceding device implantation, medical staff should thoroughly explain to patients and their family the possibility of future discontinuation of these devices' operation when transitioning to end-of-life stage. For the palliative care team, it is important to support their decision making about device discontinuation based on the patient's value and view of life.⁴

Although the introduction of palliative care in the field

of CVD has been recognized as a critical issue, it has been hard to merge palliative care and CVD treatment, because of the differences in recognition of prognosis and understanding of palliative care among patients, their families and other medical staff. To resolve this issue, advance care planning (ACP), which is the process of preparing for future events, including death, is required and is recommended for endstage HF as Class I by the Japanese Circulation Society (JCS) 2017 Guideline on diagnosis and treatment of acute and chronic HF.⁵ In terminal care, especially for elderly patients, supportive care to relief pain, rather than invasive procedures, should be considered based on ACP with a multidisciplinary team approach. Conversely, abandoning life-sustaining treatment should be avoided when based on a superficial advance directive suggesting Do Not Attempt Resuscitation.

In the field of cardiovascular medicine, the resource of palliative care is underused. A recent multicenter cohort study in the USA showed that the proportion of patients with CVD was only 15.0% among 12,914 patients referred to palliative care. Although 70% of all patients with CVD have a primary diagnosis of HF, the non-HF CVD diagnoses are various, such as coronary artery disease, valvular heart disease and peripheral artery diseases.⁶ HF patients suffer from total pain, consisting of physical, social, psychological and spiritual pain, so an early multidisciplinary approach by a palliative care team is necessary to improve their QOL.

In the palliative care of patients with CVD, treatment of CVD itself is also required until the end of life for relief of symptoms, which is essential to improve the patient's QOL. Therefore, cardiologists should work together with the palliative care team and be advised by the palliative care doctors how to use opioids or other treatments to resolve dyspnea, general fatigue, pain, depression, and anxiety that are resistant to CVD treatments. Therefore, collaboration is crucial for improvement of QOL in patients with CVD.

Because there is little evidence of the effectiveness of palliative care in patients with CVD, it is difficult to precisely describe the class of recommendation and the level of evidence in this Statement. However, it is hoped that this Statement will contribute to establishing both CVD treatment, including invasive and device-based therapies, and palliative care to improve QOL for CVD patients and their families.

I. General Principles

1. Importance of Palliative Care and Assessment of Total Pain

1.1 Introduction

Palliative care has developed mainly in the field of oncology in Japan. However, it is primarily intended to provide all patients and families facing life-threatening illnesses regardless of the type of disease. As of 2016, there are approximately 1.3 million deaths annually in Japan, with 70% of those deaths occurring at the age of 75 years. The

causes of death, in order of frequency was: cancer (21%), heart disease (15%), pneumonia (9%), and cerebrovascular disease (9%). Cardiac disease accounts for a very large proportion. Besides, in 2018 the World Health Organization (WHO) also included palliative care in its Universal Health Coverage (medical care that must be made available to all people), which includes serious illness.

In Japan, palliative care for cardiovascular disease (CVD) began in 2018 for endstage heart failure (HF), but at present, patients are often faced with a choice between 2 treatment options: active treatment or palliative care. Palliative care needs to be promoted as medical care that

Table 1. WHO Definition of Palliative Care⁷

Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.

Palliative care

- Provides relief from pain and other distressing symptoms
- Affirms life and regards dying as a normal process
- Intends neither to hasten or postpone death
- Integrates the psychological and spiritual aspects of patient care
- Offers a support system to help patients live as actively as possible until death
- Offers a support system to help the family cope during the patient's illness and in their own bereavement
- Uses a team approach to address the needs of patients and their families, including bereavement counseling, if indicated
- Will enhance quality of life, and may also positively influence the course of illness
- Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications

(Adapted from World Health Organization. 2002.⁷)

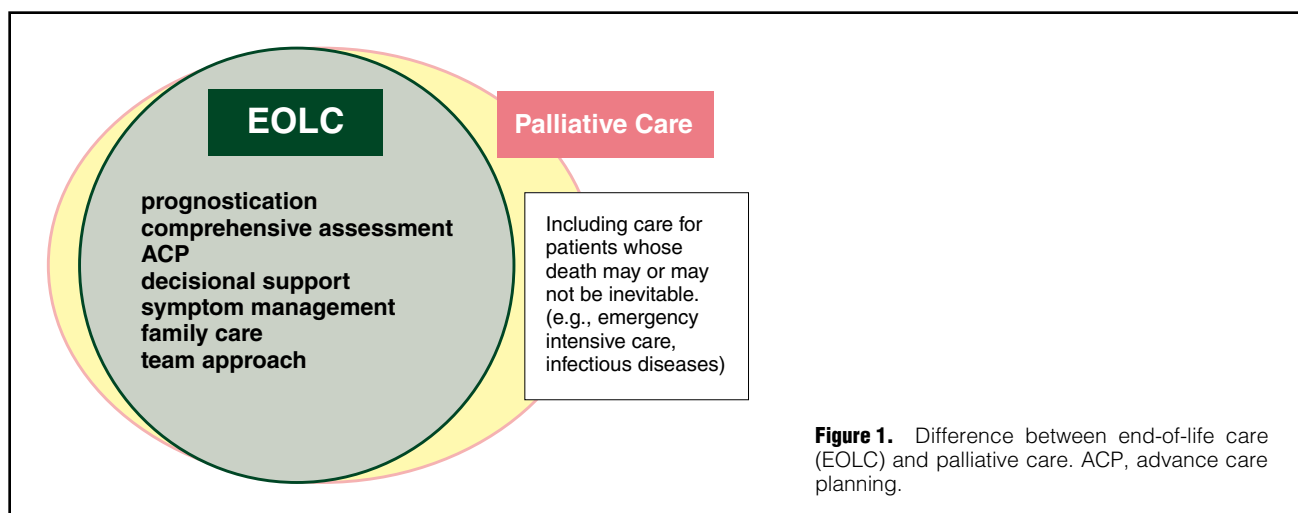


Figure 1. Difference between end-of-life care (EOLC) and palliative care. ACP, advance care planning.

is tailor-made for the patient, taking into account their prognosis and medical condition, and consistent with the patient's values and best interest for the patient.

Patients with advanced HF often have associated distressing symptoms, including fatigue and dyspnea. To implement palliative care for patients with HF, there is a comprehensive range of factors that need to be assessed, including physical, psychosocial, and spiritual distress, and the patient's values. Also, prognostic considerations are necessary to determine the course of treatment and care. Although it is difficult to apply palliative care, which has been developed mainly for cancer, directly to HF, many aspects of the comprehensive assessment can be used as a reference.

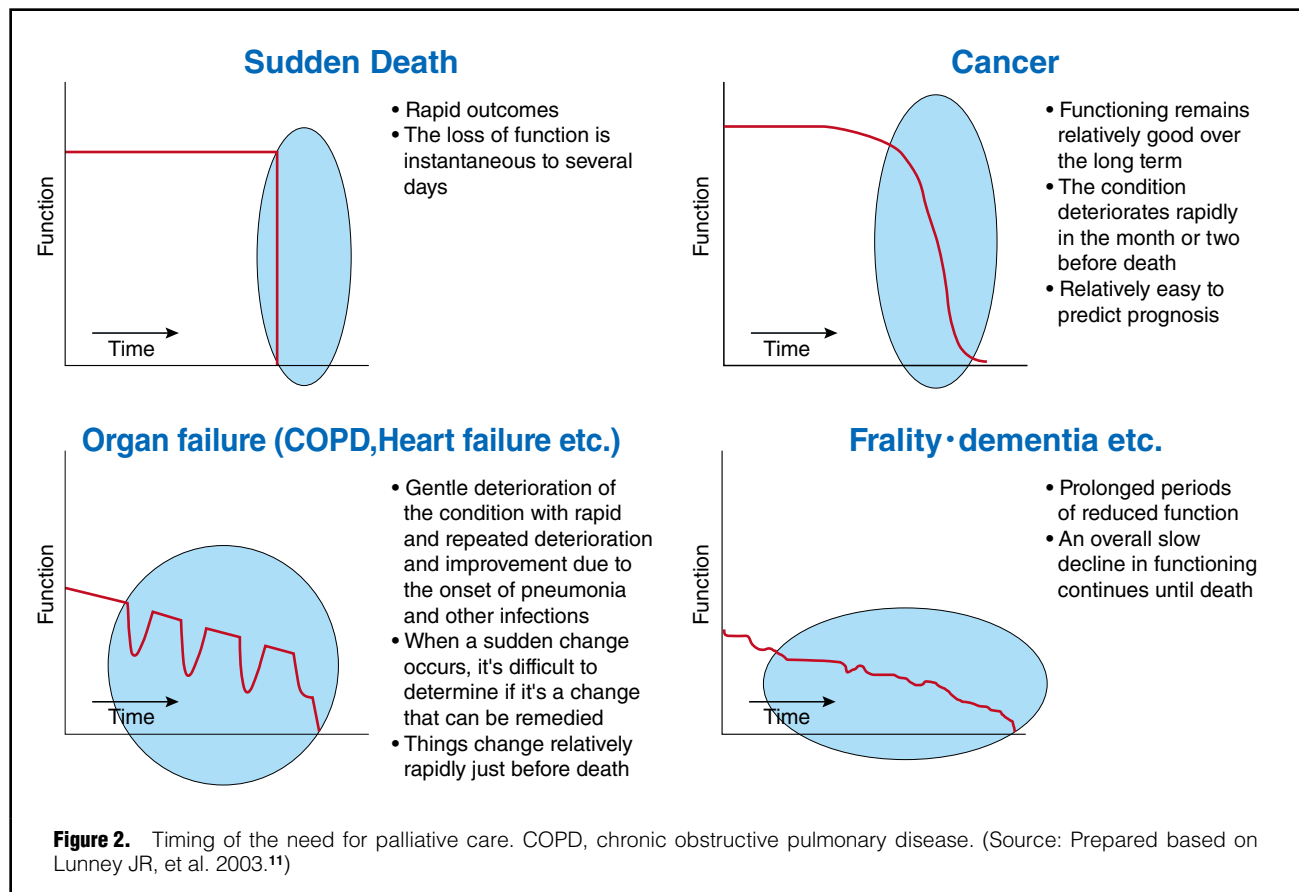
In this chapter, we will discuss the importance of holistic assessment of distress and palliative care in cardiovascular medicine.

1.2 Definition of Palliative Care

According to the 2002 WHO definition, palliative care is an approach that improves the quality of life (QOL) of patients and their families facing the problem associated with life-threatening illness, through the prevention and

relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual (Table 1).⁷ However, in 2018, the WHO identified palliative care as part of Universal Health Coverage, to further expand the coverage of palliative care. It recommends that palliative care should cover "serious illnesses" to include patients with "conditions that are very likely to cause death, but which can be cured with treatment".⁸

So how should we think about the difference between 'end-of-life care' or 'medical care in the final stages of life' and palliative care? The Japan Medical Association's XVth Bioethics Conference Report, "Super-aging Society and End-of-Life Care," issued in November 2018, states the following. "The Ministry of Health, Labour and Welfare (MHLW) has been changing the term 'end-of-life care' to 'medical care in the final stages of life' since 2015. Accordingly, "care in the final stages of life in Japan" is the equivalent of what the NHS calls "end-of-life care", which focuses on an individual's life as they approach the end of their 'life', as opposed to the medically determined 'terminal phase' where physical life is nearing the end.^{9,10} When defined in this way, the relationship between palliative care and end-of-life care (EOLC) is shown in Figure 1, based on



the thinking in the UK and USA. Simply put, palliative care is viewed as encompassing EOLC. Palliative care and EOLC have many common aspects, but the main difference is that palliative care is provided without regard to whether death is inevitable (i.e., it is also provided to patients in situations where they may recover). This is a situation that is often encountered in the field of cardiovascular medicine. It is important to remember that palliative care should be provided to these patients and their families.

1.3 When to Provide Palliative Care

So, when and at what point should we provide palliative care to the patient in chronic HF? In considering this clinical question, the illness trajectory proposed by Lunney and colleagues¹¹ categorizes the time course of functional decline in the final stages of life into 4 categories, which they present as illness trajectories. In **Figure 2**, The blue circles show the timing when palliative care should be provided in illness trajectories. The first pattern is in the case of sudden death, and specific examples include CVD, cerebrovascular disease, and death from accidents and disasters. In such cases, the final stage of life is often a lapse of hours to days, and emergency intensive care is applied during the same time. The second pattern is cancer, in which the final stage of life often proceeds on a monthly basis, during which the patient can go about normal daily life during the course of treatment, but there is often a sharp decline in functioning in the last several months. The third category is “organ failure”, and examples include

irreversible liver cirrhosis and chronic obstructive pulmonary disease (COPD), as well as chronic HF. The final stages of life are often years in length, with gradual remission and exacerbation, accompanying a gradual decline in function, and often a rapid decline in function just before death. Fourthly, there is frailty, with dementia being the most common disease. The final stage of life is an even longer process, ranging from a few years to more than 10 years, making it difficult to determine when the final stage of life occurs. Patients with HF are often included in the third category. Based on the premise of repeated remission and exacerbation, it is important to share the future course of the disease with the patient and family, and to understand the patient’s life and values, the expected future course of the disease, and the family’s thoughts and understanding of the disease’s condition before undertaking current treatment and care. This is because there are cases in which it is difficult to judge whether or not a patient is really receiving the best care from a long-term perspective, even if it appears to be the best treatment and care at the present time.

Thus, without awareness of the trajectory of illness in each disease, healthcare providers may be “missing” opportunities to provide palliative care when patients/families are actually in situations where palliative care should be provided. In order to provide palliative care at the right time, all patients/families need to be screened for distress and their palliative care needs to be assessed.

Table 2. Items and Tools for Comprehensive Assessment of the Heart Failure Patient	
Items	Tools
General condition and physical function	Daily living: BADL, IADL Heart failure: NYHA classification
Physical and psychological symptoms	Patient-reported outcome • NRS, VAS, ESAS-r, IPOS Proxy evaluation • STAS-J, IPOS Disease-specific evaluation • Anxiety/depression: HADS, PHQ-2, PHQ-9 • Delirium: CAM, DST, Nu-DESC
QOL	Health-related QOL (General) • SF-36, EQ-5D Disease-specific QOL • Malignancy: EORTC QLQ-C30 / -C15-PAL, FACIT • Heart failure: KCCQ, MLHFQ
Psychosocial aspects	Screening for cognitive function • Mini-Cog Comprehensive geriatric assessment • G8 screening tool
Spiritual aspects	Spiritual needs • FICA, SPIRITual History, HOPE, SpiPas
Prognostication	General • Palliative performance status Disease specific • Malignancy: PPI, PAPscore, PiPS, e-prognosis • Heart failure: SHFM, MAGGIC

BADL, Basic Activity of Daily Living; CAM, Confusion Assessment Method; DST, Delirium Screening Tool; EORTC, European Organization for Research and Treatment of Cancer; EQ-5D, EuroQol 5 Dimension; ESAS-r, Edmonton Symptom Assessment System revised, ; FACIT, Functional Assessment of Chronic Illness Therapy Measurement System; HADS, Hospital Anxiety and Depression Scale; IADL, Instrumental Activity of Daily Living; IPOS, Integrated Palliative Care Outcome Scale; KCCQ, Kansas City Cardiomyopathy Questionnaire; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NRS, Numerical Rating Scale; Nu-DESC, Nursing Delirium Screening Scale; NYHA, New York Heart Association classification; PAPscore, Palliative Prognostic Score; PHQ-2, Patient Health Questionnaire-2; PHQ-9, Patient Health Questionnaire-9; PiPS, Prognosis in Palliative care Study; PPI, Palliative Prognostic Index; SF-36, MOS 36-Item Short-Form Health Survey; SHFM, Seattle Heart Failure Model; SPICIT, Supportive and Palliative Care Indicator Tool; SpiPas, Spiritual Pain Assessment Sheet; STAS-J, Support Team Assessment Schedule-Japanese; VAS, Visual Analog Scale.

1.4 Comprehensive Assessment

In order to provide palliative care, we must first be aware of the patient's distress and suffering, and a comprehensive assessment of the patient is critical to the delivery of palliative care. In a busy clinical setting, there is a need for a comprehensive and efficient assessment of patient distress at the first visit. However, we believe that the current challenge is that healthcare professionals are unable to properly assess patients' palliative care needs and so palliative care is not being provided appropriately. Therefore, there is a future need to establish a system in which the attending physician and nurse in charge can identify patients with palliative care needs at an early stage, provide appropriate palliative care led by the attending physician, and refer patients to specialized palliative care services when necessary.

So, what items should be assessed in a comprehensive assessment? The recommended assessment items and tools are introduced below (Table 2). For assessment methods and tools specific to each symptom, please refer to "Evaluation and Care of Physical Symptoms" and "Evaluation and Care of Psychiatric Symptoms" in separate chapters.

1.4.1 Systemic Condition and Physical Function

Patients have varying degrees of impaired activities of daily living (ADL) and of psychological and social distress. Assessment of physical function is an important part of providing appropriate care. For patients with HF, the New York Heart Association (NYHA) classification is a good place to start. It is also important to assess both basic ADLs (BADLs) and instrumental ADLs (IADLs) in order to understand the patient's living situation.

1.4.2 Physical and Psychological Symptoms

Multiple concurrent physical and psychological symptoms are common in patients with CVD, and appropriate symptom palliation is an important part of palliative care. Appropriate symptom palliation requires that the patient's distressing symptoms be captured, so it is important to continue with a comprehensive symptom assessment. Representative tools are listed below, but it is important to note that these tools only screen for each symptom. After screening for symptoms using the tools introduced here, it is important to add multifaceted assessments specific to each symptom when it needs to be addressed.

a. Comprehensive Symptom Assessment: Patient-Reported Outcome Measures

Symptoms are subjective in nature, and patient-reported outcome measures (PROMs) are the gold standard in symptom assessment. The Numerical Rating Scale (NRS) and the Visual Analog Scale (VAS) are often used to assess the intensity of each symptom. Typical tools that can assess multiple symptoms simultaneously include the Edmonton Symptom Assessment System revised (ESAS-r), and the Integrated Palliative Care Outcome Scale (IPOS).

The ESAS-r is a tool that uses the NRS to assess 8 physical and mental symptoms and overall well-being. It is a screening tool designed for cancer patients, but has also been used for symptom screening in noncancer diseases, including HF.¹²

The IPOS consists of the following main items: physical symptoms, anxiety, worry, and depression, spirituality, communication between patient and family, the sufficiency of explanation of the condition, and response to financial and personal concerns, and is characterized by its inclusion of social and spiritual aspects as well as symptoms. It is widely used in the evaluation of noncancer patients, including patients with HF.¹³

b. Comprehensive Symptom Assessment: Proxy Assessment

Although PROMs are the gold standard for symptom assessment, subjective assessment can be difficult to perform if there is deterioration in the patient's general condition or cognitive impairment as the disease progresses. In such cases, a "patient-centered outcome assessment" with proxy reporting can be useful. A typical proxy assessment tool for comprehensive symptom assessment is the Support Team Assessment Schedule (STAS), which includes patient symptoms and anxiety/illness perceptions, family anxiety/

illness perceptions, patient–family–medical staff interaction. It consists of 9 items, such as communication between healthcare professionals. In addition, the Japanese version (STAS-J) which is specialized in symptom assessment are validated and clinically available.¹⁴ However, the IPOS was developed as a successor to the STAS, and because the IPOS also includes assessments for family and care providers and for healthcare workers, the use of the IPOS as a proxy assessment tool is expected to increase in the future.

c. Symptom-Specific Assessment

We will leave the details of assessment for each separate section, but we would like to present some tools that we believe are necessary for a comprehensive assessment.

i. Anxiety and Depression

Typical screening tools for psychiatric symptoms in cancer patients include the Hospital Anxiety and Depression Scale (HADS), the Patient Health Questionnaire (PHQ)-2 and the PHQ-9. We believe that all of these questionnaires can be administered in a short period of time and can be used in patients with CVD.

ii. Delirium

Screening for delirium is important for early detection and intervention, and appropriate screening tools should be used. Typical examples include the Confusion Assessment Method (CAM), the Delirium Screening Tool (DST), and the Nursing Delirium Screening Scale (Nu-DESC). The CAM is a simple tool that can be used to assess 4 items: an acute onset and symptom variability, attentional disturbance, disorganized thinking, and changes in the level of consciousness.

1.4.3 QOL

The goal of palliative care is to achieve the best possible QOL for the patient and family. QOL is therefore essential for assessing the effectiveness of current care and interventions, which are multifaceted and comprise physical, mental, cognitive, functional, and social factors. Therefore, QOL assessment scales are designed to assess these multifaceted elements and are essentially PROMs. Tools that measure overall health-related quality of life regardless of disease type include the MOS 36-Item Short-Form Health Survey (SF-36),¹⁵ and the EuroQol 5 Dimensions (EQ-5D),¹⁶ which are comprehensive, nondiscriminatory, and condition-independent. The EQ-5D is a simple 5-question tool that is the most widely used internationally to calculate quality-adjusted life-years (QALYs). Another cancer-specific health-related QOL measure developed by the European Organization for Research and Treatment of Cancer (EORTC), the QLQ-C30, includes 30 items to account for the burden on patients in palliative care. There is the EORTC QLQ-C15-PAL, which has been reduced to 15 items.¹⁷ Similarly, the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system has been developed as a chronic disease-specific QOL measure based on a cancer-specific health-related QOL scale.¹⁸

HF-specific assessment tools include the Kansas City Cardiomyopathy Questionnaire (KCCQ),¹⁹ and the Minnesota Living with Heart Failure Questionnaire (MLHFQ).²⁰ The KCCQ is a 23-item validated self-administered questionnaire that quantifies physical limitations, symptoms, self-efficacy, social contacts, and QOL. The MLHFQ is a 21-item self-administered

questionnaire consisting of physical and emotional domains. It is a questionnaire that provides a quantitative measure of the QOL for patients with HF.

1.4.4 Psychological and Social Aspects

Although it is always included in the assessment of the health-related QOL, we would like to mention the psychological and social aspects of the patient and their family. In making decisions with the patient and family about future medical care, and recuperation goals, it is first necessary to confirm the patient's and the family's understanding of the patient's medical condition. It is also important to assess the life history of the patient in terms of the home situation (home/facility), employment status, role in the community, hobbies, religion, personality, and stress coping (coping with stress, which can be classified into problem-focused and emotion-focused coping). When discussing future treatment and care with patients, it is important to assess the extent to which they want to be informed, the extent to which they want to be involved in decision making (wanting to make decisions on their own/in consultation with family and healthcare professionals/preferring family and healthcare professionals to make decisions for them), and their wishes regarding their health care and treatment (what they want/do not want to do), views of life and values, views of life and death, and images of death (whether the patient has experienced bereavement of a close relative) should also be assessed. Additionally, the patient should know who he or she trusts, surrogate decision-makers, the patient's caregivers, and those who bear the cost of medical care. In addition to the patient, family issues such as caregiving capacity, family fatigue, and family anxiety need to be assessed.

Because the number of elderly patients will be increasing in the future, it will be necessary to assess the overall functioning of the elderly. Mini-Cog²¹ is a simple screening tool, and the G8 screening tool,²² which is used in oncology, may be helpful.

1.4.5 Spiritual Aspects

Spirituality is usually unconscious, but is awakened in sickness and difficult situations. Through illness, we become aware of death, and when we are placed in a situation where death is imminent, we become aware of various spiritual needs (love, belonging, self-esteem, self-expression, etc.) that support our life as human beings. In Europe and the USA, assessment tools have been developed to enable medical professionals to easily listen to patients' spiritual needs in their daily clinical practice, including FICA, SPIRITual History, and HOPE. In Japan, the Spiritual Pain Assessment Sheet (SpiPas) has been developed to screen patients for their spirituality and to deepen the assessment of spiritual pain in specific dimensions. Using SpiPas in daily practice, we can identify and provide care for the spiritual pain of individual patients.^{23,24}

1.4.6 Prognostication

Predicting the amount of time a patient has left is essential for healthcare providers to consider the indication of medical interventions such as new investigations and medical care. Also, for patients and families, information about the future course of the disease, together with previous and current treatment progress, is important for setting goals and making appropriate decisions about future care. It is desirable to make decisions while combining objective

methods, such as prognostic tools, to complement the clinical prognostication of healthcare professionals and improve the estimation. This chapter only introduces prognostic tools; for details, please refer to **Chapter I.3: Prognostic Models**.

First, irrespective of disease, there are simple case-finding instruments such as the Surprise Question, and the Supportive and Palliative Care Indicator Tool (SPICT) that can be used by primary care physicians and others to identify patients who require palliative care at a more appropriate time.

Further prognostic measures include the Palliative Prognostic Index (PPI), Palliative Prognostic Score (PAP score), Prognosis in Palliative Care Study (PiPS), and e-prognosis. Typical prognostic tools specific to HF include the Seattle Heart Failure Model and MAGGIC heart failure risk. See **Chapter I.3: Prognostic Models** for more information.

Finally, screening for palliative care needs has been pioneered in the USA and the UK, but its implementation is now controversial because of its poor effectiveness for the effort involved. However, awareness of patient distress is necessary and continued assessment of palliative care needs is important. Future work needs to be done on what screening tools are appropriate and how to screen patients' palliative care needs in a minimally invasive and efficient manner.

1.5 Decision Making in Palliative Care

Decision-making support has an important role to play in palliative care for cardiovascular disease. How to facilitate discussion of decision-making in patients with inadequate decision-making capacity is particularly important, especially as patients are ageing and increasingly cognitively impaired. The Guidelines for the Health and Care Decision Making Process in the Final Stage of Life, revised in March 2018 An overview of the process of guideline-based decision-making is shown in the guideline^{25,26} and outlined. The decision-making process based on the Guidelines can be categorized into five major steps. Specifically, Step 1: Determine the person's decision-making capacity; Step 2 (when the person's intentions can be confirmed): based on the person's decision-making based on sufficient discussion with the person and the health and care team to reach a consensus; Step 3 (when the person's intentions cannot be confirmed and the family or others can presume the person's intentions): Respect his or her presumed will and take the best possible care for him or her; Step 4 (If the person's presumed will is not confirmed and no family members or others can presume the person's wish, or if there are no family members or others): the medical and care team will carefully determine the best interest for the person; Step 5 (depending on the person's mental and physical condition, etc.) (e.g., when it is difficult to decide on the nature of medical care or when the family and others cannot agree on the content of medical care): Establish a multi-professional discussion group to discuss and advise on policy. Each of these steps is outlined below.

Step 1: Determine the person's decision-making capacity: This step assesses the patient's decision-making capacity. The decision-making capacity of the person should be carefully assessed when the discussion is complex or has potentially serious consequences for the patient, if the

decisions expressed by the patient vary from person to person, if the assessment of the patient's decision-making capacity differs between healthcare providers, if the assessment of the patient's decision-making capacity differs between the patient and the assessor, and if the assessment of the patient's decision-making capacity differs between the person and the assessor, or there is a conflict of interest between a person and his or her family. Also, when assessing the decision-making capacity, it is important to note that the lack of decision-making capacity should not be judged solely based on age, disease name, appearance, social background, or history of cognitive decline or psychiatric disorders and that efforts to increase the person's decision-making capacity at the time of the assessment (empowerment: an explanation using pamphlets and other materials that include diagrams and other materials, and later (e.g., to be able to look back or to choose a time of day when the person's level of arousal is highest for discussion). Although several specific methods of decision-making ability have been proposed, it is standard to use the method of Grisso, Appelbaum et al.^{27,28} Specifically, the individual's decision-making ability is assessed through information provided and questions in discussions, through understanding (the individual understands what is needed to make a decision), perceptions (the individual sees the illness, treatment, and decision-making as their problem), logical thinking (decisions are based on a comparison of alternatives and their value judgments), and (i.e., the ability to communicate one's thoughts and conclusions) and "express" (i.e., the ability to communicate one's thoughts and conclusions) should be carefully observed and evaluated overall.

Step 2: When the person's will can be confirmed: The decision-making process is based on sufficient discussion between the person and the health and care team to reach a consensus:

If the person's decision-making capacity is deemed sufficient, he or she and his or her health care providers should have a sufficient discussion to reach a consensus and ensure that he or she receives the health and care he or she wishes to receive. In this process, the so-called informed consent process is necessary. Particularly in the medical field, everything tends to be done with the best of medical science in mind, since health care professionals have more knowledge and experience than patients. However, in the final stages of life, medical best and longevity may not always be the best interest for the patient. Conversely, the emphasis on self-determination has led to a tendency to delegate all decision-making to the patient, which places a significant burden on the patient and his or her family. After fully understanding the patient's sense of values, such as what is important to them and how they want to live their life, health care workers need to propose the best medical care and treatment for the patient that matches their sense of values and make decisions with mutual consent. It is important for medical and welfare professionals to take the stance that they are laymen in their affairs, and this decision-making process is also called Shared Decision Making.

Step 3: When the person's will cannot be confirmed and his or her family members can presume his or her will: Respect his or her presumed will and take the best policy for him or her:

If the patient's decision-making capacity is not sufficient and family members can presume the patient's intentions, the patient's presumed intentions as presumed by family members should be respected and the best policy for the patient should be adopted. The term "family members," in this case, is intended to mean those whom the patient trusts and who support the patient in the final stages of his or her life, and does not refer only to family members in the legal sense. We always ask family members and others, "If you were a patient, what kind of treatment and care would you like to receive?" It is necessary to estimate the person's intentions based on his or her values, past behaviour, and words and actions. In this step 3, Advance Care Planning (ACP) is a process to improve the quality of the person's presumed will by the person who presumes the person's will, such as a family member, is called Advance Care Planning (hereinafter referred to as ACP).

Step 4: When the person's will cannot be confirmed and the person's family or others cannot estimate the person's intentions, or there are no family or others present: the health and care team will carefully determine the best interest for the person:

If the patient does not have sufficient capacity to make decisions, and the family members or others are unable to estimate the patient's intentions, or if there are no family members or others, the health and care team will carefully determine the best interest for the patient. At this point, the physician must not make a self-righteous decision on his own, but rather a multidisciplinary team including the family members should make the decision.

Step 5: In case it is difficult to decide on the content of medical care due to physical and mental condition or if the family members cannot agree on the policy): A meeting consisting of multi-professional experts is set up to discuss the policy and give advice:

The above process is used to make decisions about treatment and care in the final stages of life; however, if health care professionals, family members, and others cannot agree on a decision, it is recommended that the decision-making process be further advanced by using clinical ethics consultation and other methods to obtain advice from multiple experts.

1.6 Challenges of Palliative Care in CVD

As noted in the previous section, palliative care is provided as needed whether or not the patient is in the final stages of life and whether or not the condition is amenable to improvement, and its primary providers are the primary team staff, including cardiologists, emergency and intensive care physicians. Palliative care is not provided only in the so-called terminal setting. The current challenges of palliative care and EOLC for CVD, particularly in the area of emergency intensive care,²⁹ are shown in **Table 3**.

Palliative care to be practiced in cardiovascular, emergency, and intensive care settings can be summarized in 6 areas: (1) palliative care screening and needs assessment; (2) relief of physical, psychosocial, and spiritual distress; (3) setting goals of care discussion, taking into account the patient's values, current medical condition and estimated prognosis; (4) implementation of treatment and care tailored to the patient's wishes; (5) transition care and discharge support from the hospital; and (6) self-care of

Table 3. Challenges for ICU Palliative Care Improvement

1. The necessary symptom relief is not being provided despite the high frequency of distressing symptoms
2. Communication with patients and families is not properly implemented (fragmented and slow)
3. Insufficient time for physicians and patients/families to discuss goals of care and for families to resolve their concerns
4. The family's painful feelings are left behind because there is no place for medical staff to show empathy for the family, and as a result, the family is unable to integrate and digest the information needed to make proxy decisions
5. Failure to provide appropriate symptom relief and communication after discontinuation of life-sustaining treatment
6. Patients/families are not adequately supported during discharge/transfer support
7. Unnecessary ICU stays and ICU deaths
8. There is no system for identifying palliative care needs for ICU survivors and subsequent ongoing follow-up
9. Failure to address burnout and depression among medical staff

ICU, intensive care unit. (Source: Prepared based on Aslakson RA, et al. 2014.²⁹)

healthcare providers. There is a need to be aware of these and to improve the basic palliative care knowledge and skills practiced by healthcare workers involved in CVD in each of these areas. In particular, improving communication skills is one of the most important issues. On the other hand, pain that is difficult to alleviate and complex psychological, social and ethical issues can be more effectively addressed by obtaining support from palliative care professionals. Therefore, the criteria by which patients should be consulted by palliative care professionals are also important³⁰ (**Figure 3**). In other countries, the NAT: PD-HF has been developed as a tool to assess the palliative care needs of patients with advanced HF and to indicate how palliative care should be provided.³¹ In Japan, an urgent issue is how to implement integrated cardiovascular treatment and palliative care in clinical settings.

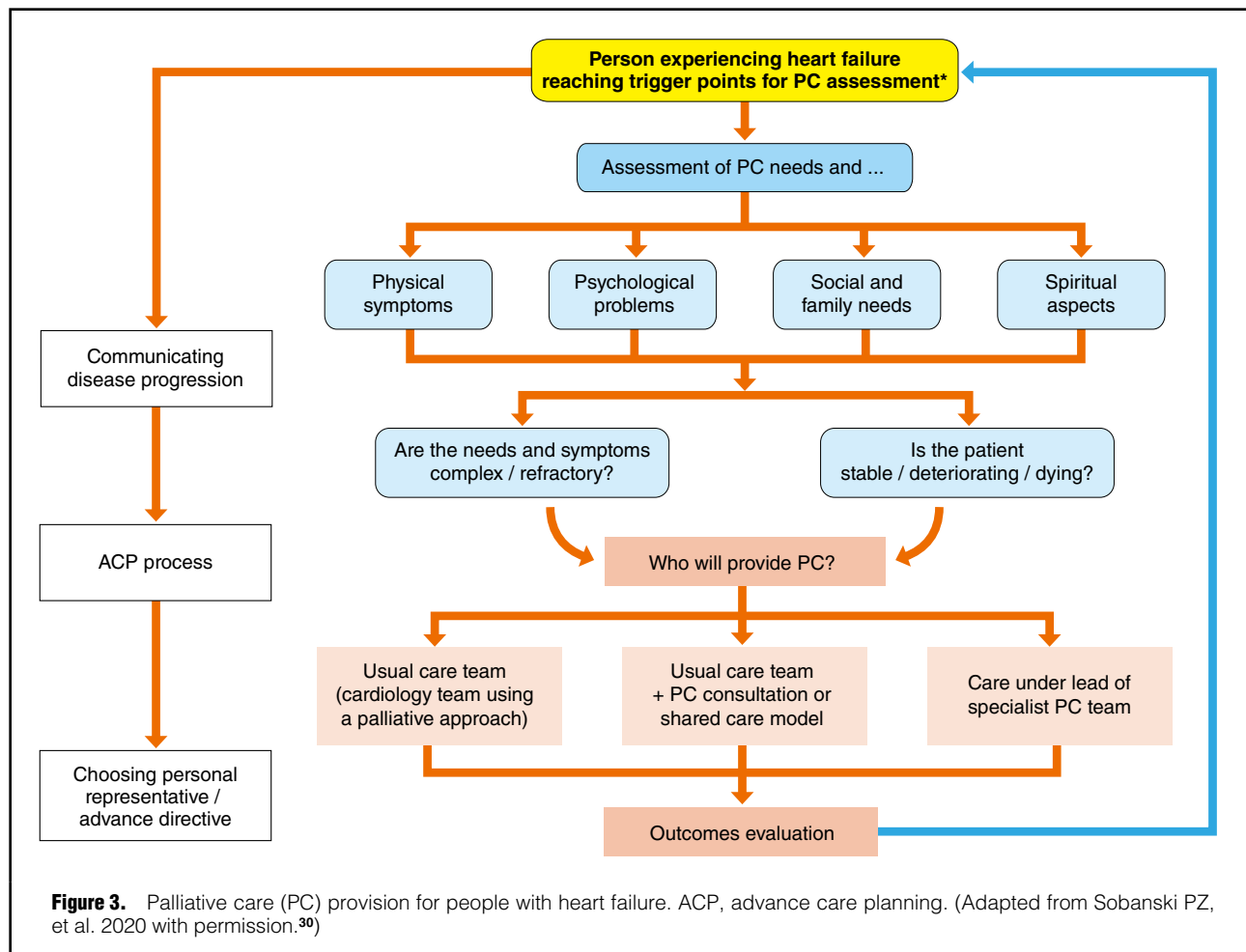
1.7 Conclusion

Palliative care must be provided in anticipation of the future course of the disease and in accordance with the patient's values and wishes. In the field of CVD, depending on the condition and course of the disease, intensive care or surgical treatment can make a significant contribution to the patient's QOL. For this reason, the choice of treatment should not be between active treatment and palliative care. Palliative care can be introduced with active cardiovascular treatment that is in the patient's best interest and in line with the patient's values, taking into account prognosis and disease status. We hope that palliative care will continue to make great success in the field of cardiovascular medicine.

2. Advance Care Planning and Advance Directive

2.1 Summary of the Concept of Advance Care Planning

While providing high-quality palliative care to patients with a serious illness, such as heart failure (HF), medical



care that honors their wishes and values is necessary. To provide this kind of medical care, it is considered essential to first share the patient's current medical condition, prognosis, and future course of the disease with both the medical care providers and the patient, and then discuss the goals of future treatment and care. However, as death approaches, the decision-making ability may decline, and it may be difficult for patients to communicate their wishes.³² To provide end-of-life care that respects the patient's will, even when the patient's decision-making capacity is impaired, initiatives such as an advance directive (AD), advance care planning (ACP), and end-of-life discussions (EOLDs) have been developed. First, the various terms and concepts that have been used to respect patients' wishes at the end of life, including AD, ACP, and EOLD, will be explained and operationally defined.

- AD allow patients or healthy individuals to indicate in advance their wishes regarding future medical treatment if they have lost their decision-making capacity. There are 2 types of AD. One is a "living will," which indicates what types of treatment/care, especially life-sustaining treatment, the patient would want or not want to receive. The other type of AD appoints a surrogate decision-maker for the patient in the event that the patient lacks decision-making ability.³³ The major difference between AD and ACP is that the latter refers to the decision-

making process itself and focuses on the sharing of that process among patient-surrogate decision-makers-healthcare providers of the patient's values and preferences.

Generally, there are 2 ways of describing ACP. ACP in the narrow sense is "to be prepared in anticipation of a time when the patient lacks decision-making capacity," whereas in the broad sense it is a discussion focusing not only on the time when the decision-making capacity is lost but also on the type of treatment and care the patient desires now and in the near future.

- ACP in the narrow sense refers to a voluntary process between the patient and care providers, in which the medical/care team and the patient, his/her family or the surrogate decision-maker discuss, on an on-going basis, future medical care in the event that the patient loses the capacity to make his/her own decisions.³⁴
- ACP in the broad sense refers to discussions among the patient, family, surrogate decision-maker, and medical care provider about the patient's future treatment/care plans while considering the patient's values, priorities, desires, goals, and preferences for future medical care.³⁵⁻³⁷
- The latest guidelines for HF in the USA and Europe, and the international Delphi study on ACP have adopted the broad sense of ACP as the definition. **Figure 4** shows these relationships.

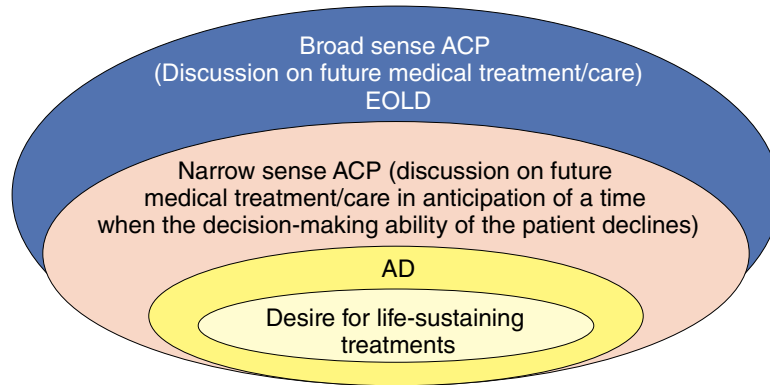


Figure 4. Conceptual diagram of advance care planning (ACP). AD, advance directive; EOLD, end-of-life discussion.

- EOLD refers to discussions that clarify the medical care that the patient wants to receive when death approaches, the goals for care, and specific preferences.^{38,39}
- In addition, AD and Do Not Attempt Resuscitation (DNAR) are occasionally confuse, but they are conceptually different. DNAR is a doctor's order not to perform cardiopulmonary resuscitation when cardiac arrest occurs, and this order is valid only in the event of a cardiac arrest.⁴⁰ DNAR orders should be issued by a doctor with the consent of the patient and the family based on comprehensive judgment of the patient's condition, medical indication, ACP discussion, AD, presumed wishes of the patient, and the family's wishes. Withholding and withdrawing oxygen administration, nutrition/infusion, analgesics/sedatives, antiarrhythmic drugs, vasopressor drugs, mechanical ventilation, and blood purification in situations other than cardiac arrest should be discussed separately based on the guidelines for decision making regarding medical treatment and care in the final stage of life, and on the guidelines for end-of-life medical care in emergency and intensive care.

2.2 Purpose and Necessary Elements of ACP in Palliative Care

The purpose of ACP in palliative care is to provide medical treatment and care that complies with the patient's wishes. To this end, it is desirable to first have discussions about disease prognosis and goals of care with all patients who need palliative care. Specifically, it is necessary to first share with the patient (1) the disease name and its condition, and (2) the expected future course and prognosis. That should be followed by a discussion of (3) the patient's values, priorities, wishes, living conditions, and family relationships, and (4) the goals of future treatment and care. These are important processes in the practice of palliative care that is in line with the patient's wishes.

Subsequently, if we feel fully prepared to talk to the patient and the patient agrees, we proceed to discussions of narrow-sense ACP. Specifically, we discuss the following: (5) what kind of treatment, care, and life the patient wants (including life-sustaining treatment) when it becomes difficult to make his/her own decisions as medical condition deteriorates; and (6) who will be the surrogate decision-

maker with the role of discussing treatment and care with medical providers on the patient's behalf. The results of the discussion of narrow-sense ACP are summarized as the AD.

Discussing narrow-sense ACP without EOLD is not desirable because it results in making choices regarding end-of-life treatment and care without the patient's understanding of his/her medical condition or sharing the same outlook with the medical providers. It is also said that generating an AD without EOLD or narrow-sense ACP may not reflect the patient's true wishes.

2.3 Benefits and Harm of ACP

The benefits of ACP include an increase in the patient's sense of self-control,⁴¹ and a decrease in the proportion of patients with depression and anxiety.⁴² It has also been demonstrated that ACP increases the level of satisfaction of both the patients and their families, and decreases anxiety and depression of the bereaved family, because care that respects the patient's wishes is provided.⁴³ According to a recent systematic review on the effects of ACP in HF patients, ACP increased discussions between medical staff and patients/families and may suppress depression in patients. However, it concluded that it was unable to evaluate whether ACP could achieve "care that respects patient's wishes" because the quality of the study was poor and the ACP interventions and measured outcomes varied.³⁷

It has become clear that ACP can be more harmful than beneficial if the patient is not ready to think concretely about his/her end of life, and can cause the patient to lose hope.⁴⁴ ACP is also time- and labor-consuming for medical care providers.

2.3.1 With Whom and When ACP Should Be Conducted

There are no high-quality studies validating which patients should have ACP initiated. In a life-threatening situation, all patients are eligible for ACP and the principle is to start based on the patient's state of readiness. The Surprise Question (SQ) is the most commonly used method to screen patients and ensure that patients in need of ACP are not missed.⁴⁵⁻⁴⁷ The SQ asks medical care providers whether they would be surprised if the patient were to pass away within a year. If the answer is "not surprised", it is a positive screening result.

Table 4. Method of Performing Advance Care Planning (ACP)**Carrying out goals of care discussion**

1. Introduce discussion
2. Ask about the patient's understanding of the medical condition
3. Discuss to what extent and in what way the patient wants to know medical information
4. Discuss prognosis
5. Discuss goals
6. Discuss fear and anxiety
7. Discuss sources of strength for the patient
8. Discuss essential abilities
9. Discuss the scope of treatment (trade-off)
10. Discuss the understanding of the family

Carrying out narrow-sense ACP (surrogate decision-makers should be involved)

1. Discuss (confirm) a surrogate decision-maker
2. Discuss what kind of treatment and care the patient does/does not want to receive when he/she lacks decision-making ability and the reason for it
3. Discuss where the patient wants to be treated when he/she lacks decision-making ability
4. Document the contents of discussions (if possible) (create advance directive)

(Source: Prepared based on Bernacki RE, et al. 2014,⁴⁸ and Ariadne Labs.⁵⁰)

Optimal timing of ACP has not been established either. As it is difficult to have ACP discussions with a patient if the medical condition is too acute, one way to conduct ACP is at outpatient clinics or at the time of discharge if the SQ is positive and the patient's medical condition is stable.

While attempting to improve patient outcomes, it is necessary to systematically identify patients needing ACP. Medical care providers, including doctors, should be educated in communication skills for introducing discussions without having a negative effect on patients. The results of these discussions should be recorded in a way that allows everyone to access them.⁴⁸

2.4 Method of Practicing ACP

There is no established method of practicing ACP to date. These guidelines only propose a method that suits the actual situation in Japan, assuming a diagnosis of HF, with reference to 2 programs, Respecting Choices⁴⁹ and the Serious Illness Care Program.⁵⁰ Both of these programs were first used in the USA and Europe and have since spread worldwide. **Table 4** is a summary of the practical method of ACP.

To practice ACP, first consider conducting a "goals of care" discussion, and then narrow-sense ACP, if possible. As described above, ACP leads to thinking about the future and scenarios that patients and families may not want to imagine. Therefore, it is important to proceed with discussions while maintaining the patient's hopes. To do this, it is essential to listen to the patient talk about their goals and support them as much as possible, while at the same time, maintaining the stance of "hope for the best and prepare for the worst," and, thus prepare for the worst possible outcome.⁵¹

2.4.1 EOLD

a. Introduction of Goals of Care Discussion

Discussions should be introduced with a focus on listening to what is important to the patient; for example, "I would like to tell you about what the illness will be like in the future. Then, I would like to ask you what is important to you so that we can provide medical treatment and care in the future that is in accordance with your wishes. Would that be OK with you?"

b. Ask About the Patient's Understanding of the Medical Condition

It is a good idea to verify the patient's understanding of the medical condition and prognosis to confirm his/her recognition of the diagnosis, the disease course, and readiness to have the discussion. This will allow the doctor to adjust the content of the discussion based on the level of the patient's understanding; for example, "What is your understanding of your medical condition? Would you please let me know in your own words, Mr./Ms. X?"

c. Discuss How and to What Degree Patients Want to Know Medical Information

Understanding the patient's preferences for his/her participation and involvement in decision making allows the doctor to tailor future discussions according to the patient's wishes. We should also bear in mind that there are patients who prefer being unaware of their medical condition. In such cases, we must typically enquire about the reason behind such a decision; we may need to discontinue the discussion at that point in some cases (e.g., "How much do you want to know about what your disease will be like in the future?")

d. Discuss Prognosis

Unless you share the future course of the disease, ACP discussions become extremely difficult. When talking about prognosis, proceed with the conversation with a pause when using expressions such as "Although I hope..., I am afraid that...", and "Although I wish..., I anticipate that ...", according to the patient's wishes regarding the degree of detail of the information being shared. During the conversation, it is necessary to pay attention to the patient's reactions and emotions that are being expressed and respond to them; for example, "I would like to tell you about your medical condition as far as I understand it..."; or "I am afraid it is difficult to predict how your illness will progress in the future. I am hoping you will stay well without progression of the disease for as long as possible. However, at the same time, there is a possibility that your condition could suddenly get worse, and I am very worried about that. I think it is important that we are prepared for such an event"; or "I deeply regret having to tell you that, unfortunately, you may only have X amount of time left", expressed as a number of days, weeks, months, or months to years; and "It is hard to have to tell you this, but the situation may be more imminent than you are thinking, and I am worried that the situation may become even more difficult in the future."

e. Discuss Goals

Enquiring about the patient's goals and daily living enables us to identify what the patient prioritizes, which leads to more personalized plans for medical treatment and care (e.g., "Let us think about the case where your medical

condition may progress further. What is the most important thing for you when your medical condition progresses?”)

f. Discuss Fears and Anxiety

Patients are often afraid and anxious about how their disease will progress and how it will affect their life in the future. It is very important to provide concrete support focusing on these fears and anxieties (e.g., “What are you most scared of regarding your future medical condition? What worries you?”)

g. Discuss Sources of Strength for the Patient

If patients mention fear and anxiety, enquire about their sources of strength while living with the disease. It is good to place importance on what gives the patient strength in the care that you provide or to propose such sources of support (e.g., “What is going to be a source of strength for you while you deal with your disease?”)

h. Discuss Essential Abilities

What patients think of as an essential physical function varies depending on the environment and life of each patient. When considering future treatment and care, ask the patient about important physical functions. This question will help you think specifically about the treatments that are and are not tolerable to the patient; for example, “What is so important to you that you cannot think of living without if you are unable to do it?” These abilities may include being able to consume food orally, perform self-care tasks, and communicate with family.

i. Discuss the Scope of Treatment (Trade-Off)

Patients with HF may be restricted in their daily life in several ways, as they require various devices for treatment and could be hospitalized. When making decisions, it is important to know what ideas the patient has about how to balance the quality of life and the length of life (e.g., “When your disease progresses, what extent of treatment would you be willing to receive to extend your life, regardless of the challenges?”)

j. Discuss the Understanding of the Family

Sharing the outlook of the medical condition with the patient’s family members and their understanding of the patient’s desires regarding treatment and care lead to an improvement in the health outcomes of both the patient and the family.^{42,43} You should ascertain the patient’s relationship with his/her family and explore the extent to which the patient discusses his/her thoughts about the disease and treatment with them (e.g., “How much does your family know about your desires and what you value?”)

Based on what you have discussed so far, summarize what the patient values and their wishes for treatment and care, and make a concrete policy for future treatment and care.

2.4.2 Narrow-Sense ACP

If the patient seems ready for EOLD, inform the patient what will be discussed regarding the types of treatment, care, and life the patient wants “when he/she loses decision-making capacity (as the condition further progresses).” Proceed in the following order.

a. Discuss (Confirm) the Surrogate Decision-Maker

It is important to consult the patient and identify the person

who will discuss and make treatment and care decisions with medical providers on their behalf when they lack decision-making capacity. Furthermore, it is necessary to inform the surrogate decision-maker in advance and obtain their consent. Narrow-sense ACP aims to improve the quality of surrogate decision-making, and it is necessary to share the content and process of EOLD and ACP with the surrogate decision-maker. For example, “Depending on the medical condition, it may become difficult for you to make decisions about care and treatment for the disease on your own. In such a case, who is the person who knows well what you value and can make judgments on things such as treatment on your behalf, Mr. X?” or “If it is OK with you, would you please let your wife know about it and come with her next time?”

If a surrogate decision-maker has been appointed in advance, you may wish to confirm this at this point and invite him or her to join the discussion.

b. Discuss What Type of Treatment and Care the Patient Does/Does Not Want to Receive When They Lacks Decision-Making Ability and the Reasons for This Decision

Talk about the types of treatment and care the patient wants to receive when their physical condition deteriorates to the extent that they have lost decision-making ability. The content of the discussion should not be limited to resuscitation and life sustaining treatments. Based on the conversations on the essential abilities and trade-off in EOLD, specific treatments and care the patient wants should be discussed.

Example 1: “When the disease advances, you may lose consciousness and it may become difficult to communicate your wishes. Just in case, I would like to discuss the time when you become unable to do basic self-care. Have you ever thought about where and how you want to receive treatment and care at such a time?” “Do you have any specific wishes in such a case?” “What are you most worried about in such a case?” “In such a case, if there is anything that you would not want, please tell me specifically about it.” “Would you please let me know why you feel that way?”

Example 2: “What kind of treatment would you like to receive when your condition gets worse and you can no longer express your thoughts, and improvement is not anticipated?” Give the following examples if you do not get an answer in the patient’s own words: (1) focus on prolonging life — opt for admission to the intensive care unit (ICU), tracheal intubation, and mechanical ventilation; (2) basic/general nonsurgical treatment — no admission to ICU, tracheal intubation, or mechanical ventilation; (3) focus on being comfortable, not on prolonging life. “What is your reason for choosing that?”

c. Discuss Where the Patient Wants to Be Treated When He/She Loses Decision-Making Ability

As described above, it is desirable to have a concrete discussion about where the patient wants to be treated; for example, “As the disease advances, your level of consciousness may decrease and it may become difficult for you to express your wishes. Where do you want to spend time in such a case?”

d. Document the Content of the Discussions (Create AD If Possible)

It is important to document who the surrogate decision-

maker will be and the contents of EOLD and ACP. Although there is no format for an AD with legal force in Japan, it is important to save the discussion contents in the electronic medical record to keep them accessible for referencing at any time and to share them with people involved in the patient's care. In addition, it is important to regularly check the content of the AD and make revisions as needed because the patient's preferences for treatment and care may change over time.

2.5 Clinical Ethics in Palliative Care

In palliative care, there are often discrepancies between the judgments made by the medical providers and the wishes of the patients and families during discussions about withholding and withdrawing life-sustaining treatment, such as the assisted artificial heart, and at the time that proxy decisions are being made these discrepancies can cause conflict. When a conflict arises, it is advisable to have the case examined by multidisciplinary professionals with the family, incorporating a clinical ethics viewpoint. The aim of clinical ethics is to improve the quality of patient care by recognizing, analyzing, and attempting to solve ethical issues that arise in medical care.⁵² The "Four-Quadrant Approach in Clinical Ethics" as shown by Jonsen et al⁵³ is a method with clinical application. Patient information is classified into 4 categories to organize the situation: (1) Indications for medical intervention, (2) preferences of patient, (2) quality of life, and (4) contextual features. Based on this classification, a multidisciplinary team discusses the case and seeks appropriate solutions with the common view of "what is best for the patient". This method is useful for making policy decisions when an ethical dilemma arises. It is difficult to identify countermeasures that fully satisfy everyone involved, because clinical medicine is an academic field with uncertainty. However, identifying the best solution for the patient of which everyone approves, by considering clinical ethics, organizing the problems, and conducting discussions, will lead to the provision of good medical treatment and care for the patient.

3. Prognostic Models

3.1 Introduction

In the management for patients with cardiovascular disease (CVD), understanding their prognosis is of significant importance. Notably, the physician's understanding of risks and sharing the trajectory of the disease with the patient and their family constitute important aspects of building the physician-patient relationship. Knowledge of future risks will also help to decide on optimal treatment strategies, particularly in high-risk patients who have a higher incidence of adverse events, and will be essential for determining when to introduce treatments such as pharmacotherapy, devices such as cardiac resynchronization therapy and implantable cardioverter-defibrillators, more detailed monitoring, or advanced care planning (ACP) in palliative care. Conversely, the identification of low-risk patients helps in reducing patient anxiety and curbing unnecessary use of high-cost healthcare resources, which is also important from a health economics perspective.

However, accurate prognostication for CVD is often difficult because of the relatively slow terminal course, compared with that of cancer, and the occasional abrupt

changes in the disease trajectory. Although many studies on outcome prediction in CVD have been published to date, outcome prediction using single factors such as biomarkers is insufficient, which has led to the development of statistical prognostic models.

This chapter provides an overview of the prognostic models for acute coronary syndrome (ACS) and heart failure (HF) patients who are at a high-risk of future cardiovascular events.

3.2 Prognostic Models for ACS

The Global Registry of Acute Coronary Events (GRACE) score is the most accurate score for comprehensive risk assessments of ACS patients (both ST-segment elevation myocardial infarction [STEMI] and non-ST-segment elevation acute coronary syndromes [NSTE-ACS]), and it can be calculated on the web (<https://www.mdcalc.com/grace-acs-risk-mortalitycalculator>).

The GRACE score is based on 8 factors: (1) age, (2) heart rate, (3) systolic blood pressure, (4) serum creatinine, (5) Killip classification, (6) hospitalization due to cardiac arrest, (7) increase in myocardial biomarkers, and (8) ST-segment deviations. These factors are weighted to produce projected rates of death or the incidence of myocardial infarction during hospitalization and 6 months after hospitalization.^{54,55} Moreover, this score allows for future risk stratification (low, intermediate, and high risk) for ACS, as well as prediction of in-hospital death and 6-month death after discharge.

3.3 Prognostic Models for HF

Compared with cancer and dementia, outcome prediction is extremely difficult in HF for the following reasons: (1) repeated functional deterioration due to acute exacerbation, which partially recovers with treatment, (2) the possibility of death at the time of exacerbation, and (3) the possibility of sudden death during a chronic phase.¹¹

Various prognostic models for HF have been reported to date. It is important to comprehensively evaluate the risks derived from multiple models by using 4 representative models, based on the purpose (prediction of short-term prognosis of acute exacerbation or chronic long-term prognosis after temporary recovery).

3.3.1 Acute HF

a. Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) Risk Score

OPTIMIZE-HF⁵⁶ is a model derived from a large real-world registry that enrolled approximately 50,000 patients with acute HF in the USA. Risk scores are calculated using 7 factors: age, systolic blood pressure, heart rate, serum creatinine, sodium, cause of hospitalization, and left ventricular ejection fraction (LVEF).

b. Get With The Guidelines-HF (GWTG-HF) Risk Score

Multiple in-hospital mortality risk factors were evaluated in approximately 40,000 patients with acute HF in the USA, and an ultimate risk scoring system was derived.⁵⁷ It is calculated using 7 variables: race, age, systolic blood pressure, heart rate, serum urea nitrogen, sodium, and the presence or absence of chronic obstructive pulmonary disease.

3.3.2 Chronic HF

a. Seattle Heart Failure Model (SHFM)

Based on data from approximately 10,000 patients with chronic HF and reduced LVEF enrolled in 6 randomized controlled trials or large registry cohorts, the SHFM⁵⁸ calculates mortality up to 5 years from basic clinical information, medications, cardiac devices, and laboratory data, and creates a comprehensive model capable of predicting outcomes following newly initiated medications and cardiac devices. Although this model can be used on the web (<http://depts.washington.edu/shfm/?width=1422&height=889>) and has been widely used in Europe and the USA, data on its validity in HF patients with preserved EF are scarce.

b. Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) Prognostic Model

This model⁵⁹ was developed by utilizing meta-analyses of data from approximately 40,000 patients with chronic HF enrolled in 30 randomized controlled trials or large registries. Outcome prediction for up to 3 years is feasible, and this model can also be used on the web (<http://www.HFrisk.org/>).

Compared with the SHFM, this is a relatively simpler model; however, the calculated mortality rate is slightly higher. There should be a margin in the interpretation of long-term prognostic models because the variability between models is somewhat greater than that in acute-phase models.

c. Surprise Question

The Surprise Question (SQ) was originally proposed as a case-finding instrument and not a prognostic model, but it is a unique technique by which physicians who treat patients ask themselves, “If this patient dies after a year, would I be surprised?” The answer aids in verbalizing a holistic impression of the patient and to determine the timing of when emphasis should be placed on palliative care. The SQ does not consider patient factors, such as prognostic factors applied in the prognostic models that have been mainly reported to date, including clinical findings and laboratory data, but instead refers to the physician’s subjectivity. However, as physicians can imagine the course of a patient’s death based on their clinical experience, they may be able to sense that the patient is dying by integrating small, subjective features, such as their impression of the patient rather than objective laboratory findings.

In a systematic review and meta-analysis of 16 studies on the SQ in patients with HF and cancer and those undergoing hemodialysis, it showed a positive predictive value of 37.1% and a negative predictive value of 93.1% for death between 6 and 18 months, which meant that 37.1% would actually die if physicians thought “I would not be surprised if this patient died”, while 93.1% would actually survive if physicians thought “I would be surprised if this patient died”.⁶⁰ Nevertheless, it should be noted that the number of deaths in the studies was small, and the predictive ability was inferior in noncancer patients, such as patients with HF (C statistic: 0.77) compared with patients with cancer (C statistic: 0.83). Straw et al⁴⁷ recently investigated the 1-year prognostic value of the SQ in 129 consecutive patients with decompensated HF and found that the sensitivity was 85% and the negative predictive value was 88% among cardiologists. However, as the specificity remained at ≈59%, significant differences were weakened to marginal after adjusting for important prognostic factors

such as age, renal function, and serum albumin. As the predictive ability among nonspecialists was lower, the SQ alone does not provide sufficient data to trigger the introduction of palliative care.

Given that special tests and equipment are not required, and that indicators of sensitivity and negative predictive value are high, the SQ may be helpful in identifying patients for whom shared decision making and earlier ACP should be introduced.⁶¹ In fact, the guidance issued by the National Institute for Health and Care Excellence (NICE) recommends initial use of the SQ, along with NYHA classification and the number of HF readmissions, to identify patients who require palliative care, rather than the statistically derived outcome prediction models.⁶²

3.4 Timing of Applying the Prognostic Models

Although there are few reports evaluating the appropriate timing of prognostication, the NICE guidance states that, “repeated prognostic evaluations are recommended”. Thus, for ACS and decompensated HF, there seems to be a need to perform reevaluations at the time of hospitalization, at discharge, and every 6 months to 1 year after discharge depending on the clinical situation of each patient.

Nevertheless, all of the prognostic models introduced in this chapter are insufficient in terms of their ability to predict clinical outcomes, and therefore it seems necessary to perform a comprehensive evaluation with repeated use of multiple models to share information with patients, family members, and multidisciplinary healthcare professionals.

4. Communication

4.1 Communication With Patients and Families

4.1.1 Communication With Patients

A physician’s good communication skills are known to improve patient satisfaction and treatment adherence.^{63,64} A trusting relationship towards a common treatment goal creates a beneficial collaboration between healthcare providers and patients. However, many healthcare providers find it difficult to communicate with patients suffering from life-threatening diseases. A systematic review of “end-of-life care conversations with heart failure patients” found that the focus of conversations between heart failure (HF) patients and their healthcare providers was mostly on disease management, with little discussion of goals or intentions of care.⁶⁵ Honest and compassionate communication promotes realistic goal setting and autonomy for patients and families, and strengthens the relationship between healthcare providers and patients.⁶⁶ Many patients want their healthcare providers to tell them the truth and not limit the information so that they do not lose hope.⁶⁷⁻⁶⁹ It is also important to note that patients’ communication preferences are highly diverse and can be influenced by their medical condition, mental state, and surroundings.

4.1.2 Communication With Families

The family supports the patient and shares in the suffering of the disease. To provide the best medical care for the patient, it is important to have a good relationship with the family and a good understanding of the patient’s social environment. Families often ask healthcare professionals not to share the “bad news” with patients. Instead of trying to convince the family, it is important to be empathetic

Table 5. Ask-Tell-Ask	
Ask	Ask the patient to describe his/her current understanding of the issue <i>“What have your other doctors been telling you about your illness since the last time we spoke?”</i> <i>“To make sure we are on the same page, can you tell me what your understanding of your disease is?”</i> <i>“What is the most important issue for us to talk about today?”</i>
Tell	Tell the patient in straightforward language what you need to communicate – the bad news, treatment options, or other information. Information should be provided in short, digestible chunks. Do not give more than 3 pieces of information at a time. Avoid medical jargon.
Ask	Ask the patient if he/she understood what you just said. Consider asking the patient to restate what was said in his/her own words. <i>“To make sure I did a good job of explaining this to you, can you tell me what you are going to say?”</i>

(Source: Prepared based on Back AL, et al. 2005.⁷¹)

Table 6. NURSE	
Naming	Naming a patient's emotion for yourself
Understanding	Understand difficult situations and emotions
Respecting	Acknowledging and respecting a patient's emotions
Supporting	Express willingness to support
Exploring	Explore the patient's emotion

(Source: Prepared based on Back AL, et al. 2005.⁷¹)

and ask why the family is concerned. Then discuss the advantages and disadvantages of telling your patient the bad news. These discussions also provide an opportunity to create open communication between patients, families and healthcare professionals. Patients can also be asked about their health and concerns in the presence of family members.

In contrast, as a right to information in the World Medical Association Declaration of Lisbon, the patient has the right to choose who, if anyone, should be informed on his/her behalf.⁷⁰

The patient has the right to leave the bad news to the family, so depending on the discussion with the patient, the diagnosis and prognosis may be discussed with the healthcare provider and the family alone. However, if the patient has not expressed such a wish, then not telling the patient the truth may raise an ethical issue.

4.2 Basic Communication Skills

It is important for physicians to not only give their patients accurate and honest information, but also to consider their patients' wishes and always act in the patients' best interest. Effective communication involves nonverbal as well as verbal communication. Examples include matching the line of sight, making proper eye contact, and incorporating positive gestures. It is also important to talk slowly and not to interrupt the conversation on the phone or otherwise. Empathic and supportive listening is just as important in communication as talking. One of the basic skills of

communication is called the “Ask-Tell-Ask” approach (Table 5).⁷¹ First, ask the patient to describe his/her current understanding of information. This will help you craft your message to consider the patient's level of knowledge, any misconceptions or concerns, emotional state, and degree of education. Ask the patient to explain his or her current level of understanding of the information (Ask). Second, provide new information to the patient and help them understand correctly if they have any misconceptions (Tell). Avoid medical jargon, speak honestly and clearly, and try not to give more than 3 new pieces of information at the same time to avoid “indigestion”. Finally, ask the patient if he/she understood what you just said. This allows you to check his/her understanding and to confirm a common understanding between the patient and the healthcare professional, as well as to clarify any concerns the patient may have by checking the patient's understanding and questions (Ask). “Ask-Tell-Ask” also facilitates discussions of emotionally charged information.

If the discussion does not go well, listen to what the patient says without criticism or interpretation, and treat the patient positively while asking the following questions: “Can you tell me what kind of information you need?”, “Can you tell us how you feel about it now?” (Tell me more). Some patients do not express their emotions, but this does not necessarily mean that they do not have strong emotions. NURSE⁷¹ (Table 6) is known as a communication point that encourages patients and their families to express their emotions and creates opportunities for patients to talk about their feelings.

4.3 How to Tell the Bad News

Bad news is defined as “any information likely to alter drastically a patient's view of his or her future”.⁷² Whether or not the information is “bad” news depends largely on the patient's beliefs, perceptions, and communication preferences from different cultural backgrounds. Compared with Western countries, where many patients are willing to talk about their diagnosis and prognosis, few patients in Japan and other Asian countries are willing to talk about their prognosis.⁷³ However, as time goes on, more and more patients in Japan are reporting that they want to have a realistic discussion about the future.⁷⁴ Both patients and their families need time to sort out their emotions and surroundings in the face of death, and not communicating information about their prospects can undermine their autonomy and trust. Patients and their families often want information about the prognosis; some may want to know what the future holds for planning their lives, while others may ask to be reassured that things are not so serious. When a discussion about prognostic information arises, think carefully about what it would mean for the patient and family to know that information and ask why they want to know it, especially when asked spontaneously by the patient. Considering the highly uncertain disease trajectory of cardiovascular disease (CVD), avoid stating definitive periods, such as “your life expectancy is about 6 months”. Healthcare providers might consider responding to questions of prognoses by giving a range of time that encompasses an average life expectancy and reflects both medical knowledge and uncertainty, such as “hours to days,” “days to weeks,” “weeks to months,” and “months to years”.⁷⁰ Patients with HF tend to overestimate their prognosis,² so it is important to take care of their disap-

pointment and anger when the prognosis is worse than expected. It is also essential to reassure patients that there are limits to prognosis and to make it clear to them that they should “hope for the best, prepared for the worst”.

SPIKES, developed in the United States, is a widely known communication tool in cancer care.⁷⁵ Similarly, SHARE is a framework for communicating bad news, developed within the cultural background of the Japanese people (Table 7).⁷⁶ SHARE was developed as a communication tool for oncology, but it can also be useful for CVD communication. There is also training in communication skills, such as the Serious Illness Care Program, which is not only for cancer but for incurable diseases in general.

4.4 Difficult Communication

It is difficult to deal with patients when they are highly anxious, in denial and expressing intense emotions. In this situation, it is important for healthcare professionals to first step back calmly and not get caught up in the emotions of the patient. Listen to the patient’s complaints to the end without interruption, show empathy, and clarify the underlying issues. It is also crucial to show a willingness to work with the patient to solve the underlying problem. It can be difficult to solve problems, but emotional issues can be resolved. If you are still having difficulty coping, consider talking to specialists such as the palliative care team or a psychiatrist.

4.5 Communication Among Healthcare Professionals

Multidisciplinary teams are an integral part of modern healthcare, but simply bringing together multiple healthcare providers does not automatically lead to improved outcomes. Good communication between team members is required to ensure a consistent message to patients and their families. Effective team activity requires an awareness of the team’s strengths and weaknesses. Particularly in large teams, individual members may tend to be silent for fear of saying the wrong thing, and when some members dominate the discussion, the others are silent again, and eventually, everyone tends to be swayed by the leader’s wishes. It is important to encourage the participation of all constituents, especially staff members who do not express their views, and to create an atmosphere that welcomes debate, even if the ideas are inadequate. Besides, humility is especially important in team activities and requires a willingness to acknowledge one’s weaknesses, respect the strengths and expertise of other professional staff members, and put team performance ahead of personal gain.⁷⁷

5. Decision Support for Patients in Cardiac Intensive Care

5.1 Introduction

This section outlines decision support for patients with advanced cardiovascular disease (CVD) receiving cardiac intensive care.

5.2 Characteristics of Patients With Endstage CVD

Patients with CVD at the end of life can follow a chronic course with slow exacerbation as in heart failure (HF), or

Supportive environment	Setting up supportive environment for interview (e.g., greeting patient cordially, looking at patient directly)
How to deliver the bad news	Considering how to deliver bad news (e.g., not delivering bad news without a preamble, checking to see whether talk is fast paced)
Additional Information	Discussing additional information that patient would like to know (e.g., answering patient’s questions fully, explaining second opinion)
Reassurance and Emotional support	Providing reassurance and addressing patient’s emotions with empathic responses (e.g., remaining silent out of concern for patient’s feelings, accepting patient’s expression of emotions)

(Source: Prepared based on Fujimori M, et al. 2014.⁷⁶)

can progress rapidly as in acute myocardial infarction, acute aortic dissection and stroke. In Japan, many patients, even those with endstage HF, do not usually die at home or in a palliative care unit. Instead, many are transferred to the emergency room for cardiac intensive care when symptoms deteriorate. One feature of CVD is that even patients with endstage HF can be saved by the introduction of cardiac intensive care and/or heart transplantation, representing the ultimate treatment. Saving patients with endstage CVD using maximum intensive treatment thus seems reasonable in the absence of clear wishes from the patient to withhold treatment for events in a terminal condition. Obtaining sufficient background information on the patient before cardiac intensive care is difficult in cases of acute-onset disease such as acute myocardial infarction. Many patients respond well to treatment, but others experience unfortunate results. Some patients may become dependent on mechanical circulatory support (MCS) and get to an end-of-life situation without making decisions about life-sustaining treatment. As mentioned above, the background of the patient is often unclear in the field of cardiac intensive care, so we often face cases in which it is difficult to reach a consensus with the patient and their family regarding treatment strategies. We need to promote decision support for patients with endstage CVD with a good understanding of the characteristics of cardiac intensive care.

5.3 “Endstage” and “End of Life” in Cardiac Intensive Care

5.3.1 Definitions of Endstage and End of Life

The “endstage” in CVD is defined as the presence of progressive and/or persistent severe signs and symptoms of CVD despite optimized medical, surgical, and device therapies.⁷⁸ In addition to the use of inotropic drugs, even to save the lives of endstage CVD patients, mechanical treatments such as artificial respiration, intra-aortic balloon pump, extracorporeal membrane oxygenation (ECMO), ventricular assist device (VAD), percutaneous VAD (pVAD) and continuous hemodiafiltration are used in intensive cardiac care.

“End-of-life” in CVD is defined as “a condition in which the patient in endstage is not expected to survive despite the best medical care available to save his or her life” or “a condition which results in the patient’s dependence on

inotropes and/or mechanical treatments, although these treatments are effective for the patient even in endstage". Indications for heart transplantation should be considered in patients with CVD before performing treatment based on end-of-life decisions.

5.3.2 Determining the End of Life

For critically ill patients in the acute phase, appropriate cardiac intensive care should be performed to save their lives regardless of their background. Whether a patient is at the end of life under current circumstances should be determined. The decision that a patient is at the end of life should be made by an interdisciplinary team comprising not only the attending physician, but also physicians from multiple departments, nurses and others.

Various conditions indicating the end of life include the following

- (1) A condition diagnosed as irreversible whole-brain dysfunction (e.g., brain death, severe hypoxic encephalopathy).
- (2) A condition in which the patient is dependent on mechanical treatment with irreversible dysfunction of multiple organs, and does not meet the indications for alternative treatments such as heart transplantation.
- (3) A condition in which no further treatment is available beyond the current treatment, and death is expected to occur in the near future even if the current treatment is continued, or when continuation of the current treatment is difficult due to complications.
- (4) A condition in which the patient is found to be in the end stages of an irreversible disease such as malignancy after the start of active treatment for CVD.

Some facilities have introduced initiatives such as a multidisciplinary rounds system with staff from the medical

safety office and doctors and nurses from multiple departments to make the final decision on whether a patient is at the end of life.

5.4 Response According to the Situation of the Patient and Their Family After Deciding a Patients at the End of Life

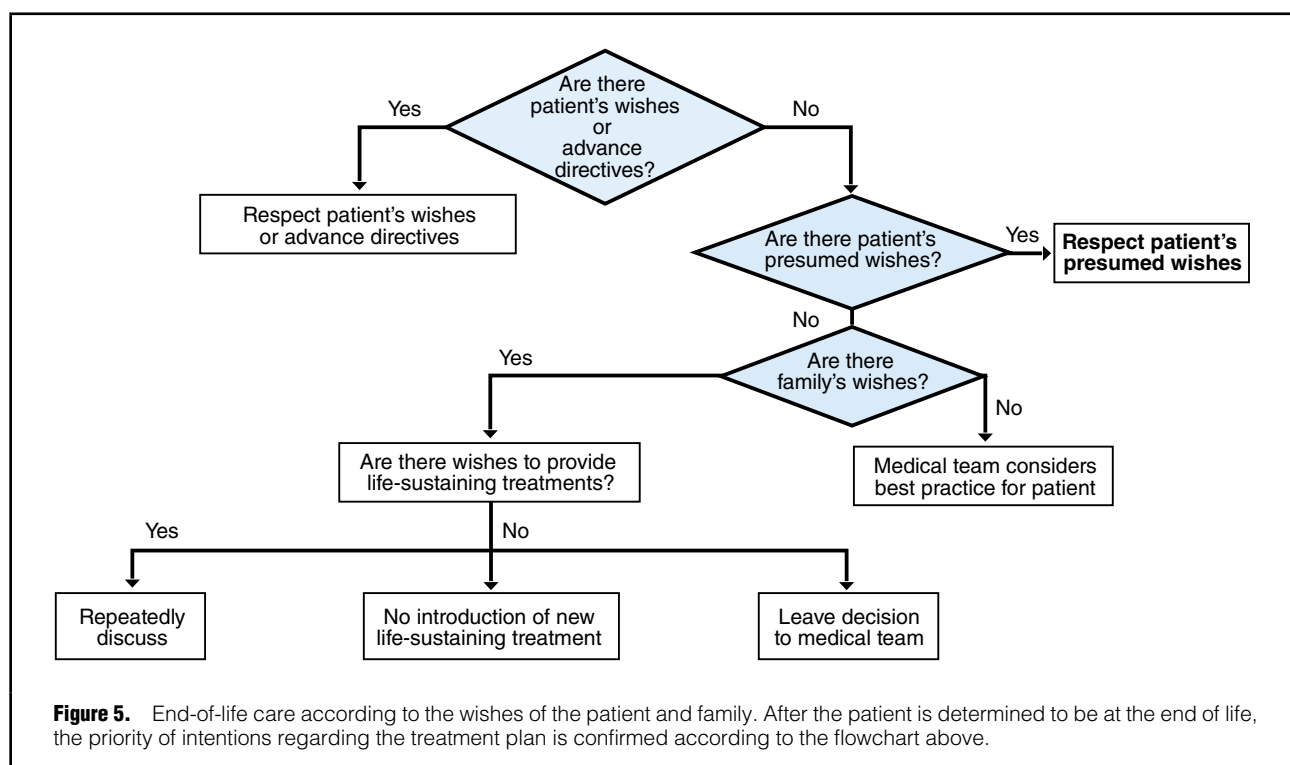
Even when a patient is deemed to be at the end of life, continuation of appropriate treatments for CVD is essential to alleviate symptoms.⁵ However, clear definitions of appropriate treatment are still lacking. Pharmacotherapy with diuretics, vasodilators, and inotropes is used to provide symptomatic relief. Occasionally, less invasive mechanical treatments such as noninvasive positive-pressure ventilation are considered if likely to prove beneficial for symptom relief. As mentioned above, cardiac intensive care is often initiated even when the background of the patient is unclear. Healthcare providers thus need to try to understand the background of the patient while providing treatment. In addition, the healthcare provider should provide sufficient explanation to the patient and their key family members that: (1) the patient is in an end-of-life condition with little chance of survival even with the best intensive care; and (2) further treatments may become life-sustaining treatments that may compromise the dignity of the patient.

5.4.1 Response to the Patient at End of Life Depending on the Wishes of the Patient or Family

The medical team responds as follows depending on the wishes of the patient and family (Figure 5).

a. Patient With Capacity to Make Decisions or Has Advance Directive

If the patient has the capacity to make decisions or has an



advance directive (AD) in place, these should be respected. The medical team should carefully assess the decision-making capacity of the patient. If the patient is found to possess the capacity to make decisions, the healthcare provider should provide sufficient explanation about current and future treatment options in the context of what is medically reasonable. A treatment plan is then made.

Advance Directive With this document, the patient describes in advance what end-of-life treatments are acceptable, before their consciousness becomes impaired and they cannot make decisions regarding treatment. Although medical treatment requires not only medical appropriateness, but also consent, patients in an end-of-life state sometimes undergo invasive treatments that they would not have elected to receive. ADs may resolve this problem. The SUPPORT study, a randomized study of 9,000 participants from 5 American centers, evaluated the utility of ADs. The study examined whether differences existed in outcomes such as days from acquisition of Do Not Attempt Resuscitation to death, pain and patient satisfaction between groups with and without ADs, but no significant differences were identified.⁷⁹ The main problem with ADs is that they do not represent the wishes of the patient at the time treatment is about to begin and thus may not accurately reflect the wishes of the patient. Advanced care planning, representing a process of discussing the preferences and expectations of a patient for the medical care that they would like to receive as the condition progresses and death approaches, may be more useful than the creation of an AD.⁸⁰

b. Wishes of the Patient Cannot Be Confirmed, But Can Be Presumed

If the family members can presume the wishes of the patient, these presumed wishes should be respected.

c. Wishes of the Patient Cannot Be Confirmed or Presumed

If the wishes of the patient cannot be confirmed or presumed, the medical team repeatedly explains the current situation to the family as the surrogate decision-maker and helps them to make decisions.

- i. If the family of the patient wishes the patient to receive life-sustaining treatment: The medical team explains in simple terms that the life of the patient is difficult to save even with the best treatment and that any further invasive treatments may be life-sustaining treatments that may compromise the dignity of the patient. Until the wishes of the family are reaffirmed, current treatments should be maintained.
- ii. If the family of the patient does not wish to introduce life-sustaining treatment: The medical team repeatedly holds discussions with the family to make the best choice for the patient. As a result, the decision may be made to withhold life-sustaining treatments.
- iii. If the family of the patient leaves the decision to the medical team or is unable to contact the surrogate decision-maker (e.g., because of non-identification): The medical team considers the best option for the patient and tries to reach a consensus with the family members, as surrogate decision-makers.

Because changes in the wishes of the patient and family members are not uncommon, the medical team should respond appropriately to such changes and provide multiple opportunities for discussion.

5.4.2 Withholding Life-Sustaining Treatment

The medical team responds to life-supporting devices and medications by: (1) maintaining current treatment and withholding new treatment; (2) reducing current treatment; or (3) withdrawing current treatment.

In cardiac intensive care, terminating a current treatment is difficult if this termination will lead to a worsening of patient's symptoms. In contrast, continuation of treatment may become life-sustaining if the patient is at the end of life. Particularly in the case of MCS such as ECMO or pVAD, maintaining treatment is sometimes difficult due to complications. Discontinuation of such treatments should be performed after providing sufficient explanation about the possibility that the condition may deteriorate rapidly and lead to cardiac arrest within a short time.

Little evidence has been accumulated regarding decision support in cardiac intensive care. We are in the process of identifying optimal methods to support decision making by the patient. In contrast, palliative care in cardiovascular medicine has received a great deal of attention and has been actively introduced to many hospitals. A large amount of evidence is expected to be accumulated in the near future.

6. Quality Indicators of Palliative Care in Cardiovascular Disease

6.1 Introduction

6.1.1 Palliative Care in Cardiovascular Diseases

Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and appropriate assessment and treatment of pain and other physical, psychosocial and spiritual problems. Palliative care should be considered for all life-threatening diseases including noncancer disease.⁸¹ In fact, cardiovascular diseases (CVD), as well as cancer, are associated with a wide range of pain, and the need for palliative care in this field is reported to be very high.^{1,82}

On the other hand, palliative care has developed for patients with cancer and it has not matured for noncancer patients. Therefore, when considering palliative care for CVD patients, we have to consider issues specific to CVD, in addition to traditional palliative care for cancer patients.^{83,84}

6.1.2 Quality of Care

Quality of care is defined as the extent to which healthcare services provided to individuals and patient populations improve desired health outcomes. In order to achieve this, health care must be safe, effective, timely, efficient, equitable and people-centered. High-quality care means that the "standard care", which is based on the best available evidence, is practiced in the clinical setting. In the area of palliative care in CVD, various efforts are being made with reference to evidence and the guidelines of palliative care in cancer. However, these efforts are made at the level of individual healthcare providers and institutions, and there is a lack of well-established consensus regarding the content and timing of cardiovascular palliative care. Although it is not easy to identify whether high-quality cardiovascular palliative care is practiced in clinical settings or not, this attempt is necessary to ensure the quality of cardiovascular

palliative care. Therefore, it is important to assess the quality of care and whether appropriate treatment of CVD is provided as a prerequisite for providing cardiovascular palliative care.

In aging societies, the prevalence of CVD continues to increase and the need for palliative care is also steadily increasing.^{85,86} In this context, it is impossible for palliative care specialists to handle all aspects of palliative care in CVD, and thus general cardiologists should practice basic palliative care in the clinical setting. Although cardiovascular palliative care is currently dependent on each health-care provider and institution, we should evaluate the quality of these practices and improve them.

As mentioned above, the quality of care is a “degree” and requires certain criteria. To evaluate the quality of care, we generally establish a standard care, called a quality indicator, and thereafter established quality indicators should be measured in clinical settings. Several quality indicators have already been established and widely used in the palliative care practice of cancer patients.

6.2 Quality Indicators

6.2.1. Differences Between Guidelines and Quality Indicators

In recent years, the concept of evidence-based medicine has become widespread, and evidence-based guidelines have been developed in various fields of CVD. However, real-world clinical practice is not always performed based on these guidelines and there is a gap between guidelines and usual care. One of the methods to filling this gap and providing high-quality care is to establish and evaluate quality indicators, which are criteria for evaluating the quality of care based on important issues and evidence. By using quality indicators, we can quantitatively measure the quality of care in actual clinical practice, and thus ensure and raise the quality of care.

6.2.2 Donabedian Model

The 3 frameworks proposed by Donabedian are widely

accepted in the understanding of the concept of quality indicator. The 3 frameworks are “structural indicator,” “process indicator,” and “outcome indicator.”⁸⁷ The quality of care can be evaluated based on these 3 frameworks. In addition, as a characteristic of quality indicators, they should be measurable, because they are used to quantitatively evaluate and improve the quality of care.

Using acute myocardial infarction as an example, the structural indicator is, “Is the institution capable of performing emergency percutaneous coronary intervention?” Structural indicators are measures of whether the subject institution is well-resourced, and are mainly “yes” or “no” indicators. The process indicator, to give an example, is “the percentage of patients admitted for acute myocardial infarction who are receiving antiplatelet drugs”. In other words, it is a measure of the medical treatment to be performed on the subject patients. Specific denominator and numerator are defined for the subject diseases and can be measured in numerical form. One example of an outcome indicator is the “in-hospital mortality rate of patients hospitalized for acute myocardial infarction”. In-hospital mortality rates and the number of days of hospitalization are common outcome indicators, but quality of life and satisfaction of the bereaved families can also be outcome indicators.

6.3 Quality Indicators of Palliative Care in Cancer

There is paucity of information regarding quality indicators of palliative care in CVD, and the field of cancer palliative care has taken the lead. However, it is assumed that many of the quality indicators in cardiovascular palliative care will share many of the same items as those of cancer palliative care, so most of the indicators may be applicable in CVD.

Using a survey of medical records, 30 quality indicators of end-of-life cancer care have been developed in Japan, based on 4 domains as follows: (1) symptom control, (2) decision making and preference of care, (3) family care and (4) psychosocial and spiritual concerns.⁸⁸

Domain	Quality indicators	Classification
Patient-reported quality of life	Cancer patient's physical conform	Outcome indicator
	Cancer patient's pain	Outcome indicator
	Cancer patient's psychological conform	Outcome indicator
Bereaved family-reported quality at end-of life	Dying in a favorite place	Outcome indicator
Family care	Caregiving consequences	Outcome indicator
Place of death	Home mortality	Outcome indicator
	Nursing home mortality	Outcome indicator
Bereaved family-reported quality of palliative care	Physical care by medical staff	Process indicator
Specialized palliative care services	Utilization of specialist palliative care services	Process indicator
Opioid utilization	Oral, rectal and dermal opioid use	Process indicator
Public perception about palliative care	Public perception of palliative care	Process indicator
	Public perception of opioids	Process indicator
Palliative care education for primary care providers	Number of doctors who participated in based palliative care training	Structure indicator
Specialist palliative care services	Staffing to palliative care services of certified nurse specialist and certified nurse	Structure indicator
Regional palliative care	Implementation of whole-region interdisciplinary conferences	Structure indicator

(Source: Prepared based on Nakazawa Y, et al. 2016.⁸⁹)

Table 9. Quality Indicators of Palliative Care in Heart Failure (HF)		
Domain	Quality indicator	Classification
1: Structure and process of disease care	1. Presence of multidisciplinary team	Structure indicator
	2. Availability of multidisciplinary team	Structure indicator
	3. Regular discussion by multidisciplinary team	Process indicator
	4. Intervention by multidisciplinary team	Process indicator
2: Appropriate heart failure treatment and care	5. Consideration of beta-blocker prescription	Process indicator
	6. Consideration of ACE-I/ARB prescription	Process indicator
	7. Consideration of MRA prescription	Process indicator
	8. Explanation of ICD therapy	Process indicator
	9. Explanation of CRT therapy	Process indicator
	10. Consideration of cardiac transplantation	Process indicator
	11. Evaluation of coronary artery disease and valvular heart disease	Process indicator
	12. Education for secondary prevention	Process indicator
	13. Consultation service for ICD implantation	Structure indicator
3: Total pain management	14. Preparation of screening sheet for total pain	Structure indicator
	15. Description of goals of total pain management	Process indicator
	16. Symptom evaluation using quantitative scales	Process indicator
	17. Management of physical pain	Process indicator
	18. Preparation of opioid instruction	Structure indicator
	19. Opioid therapy for patients with refractory dyspnea	Process indicator
	20. Evaluation of constipation during opioid therapy	Process indicator
	21. Evaluation of nausea and vomiting during opioid therapy	Process indicator
	22. Screening for psychological symptoms	Process indicator
	23. Availability of psychiatrist	Structure indicator
	24. Grief care for family members	Process indicator
	25. Survey of family structure	Process indicator
	26. Conferencing for discharge support	Process indicator
	27. Consideration of withholding or withdrawing life-prolonging treatment	Process indicator
	28. Multidisciplinary discussion about ICD deactivation at the end of life	Process indicator
	29. ICD deactivation prior to death	Process indicator
	30. Multidisciplinary team discussion about palliative sedation	Process indicator
	31. Informed consent of palliative sedation	Process indicator
4: Decision support and ethical issue management	32. Preparation of instruction for the illness trajectory of HF	Structure indicator
	33. Preparation of medical manual about advance care planning	Structure indicator
	34. Multidisciplinary team discussion about life-prolonging treatment	Process indicator
	35. Advisory committee for consultation of ethical issue	Structure indicator

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid receptor antagonist. (Adapted from Hamatani Y, et al. 2020.⁹²)

The National Cancer Center has also developed quality indicators for cancer palliative care.⁸⁹ Using the 3 frameworks proposed by Donabedian, 15 quality indicators have been developed based on 11 domains (Table 8). Of note, these quality indicators are not for medical institutions, but for the general population; however, they contain important elements for providing palliative care and may be applicable to the practice of palliative care in CVD.

In the absence of established quality indicators in cardiovascular palliative care, a systematic review of the existing literature on quality indicators of cancer palliative care was conducted to extract those indicators that can be adapted to CVD. This review proposed the indicators including structural indicators such as palliative care team and human resources, process indicators such as palliative

care needs screening and documentation on symptom relief, and outcome indicators such as quality of life, place of death and survey of bereaved families.⁹⁰ They can be very useful for the implementation of cardiovascular palliative care.

6.4 Quality Indicators of Palliative Care Specific to CVD

The quality indicators of palliative care in cancer can be applicable to cardiovascular palliative care, but it should be noted that CVD has different characteristics from cancer. In fact, the illness trajectories of heart failure (HF) are far different from those of cancer. Prediction of prognosis is more difficult in the case of HF than that of cancer,

Problem	Cancer (%)	Chronic heart failure (%)
Fatigue	23–100	42–82
Pain	30–94	14–78
Nausea-vomiting	2–78	2–48
Dyspnea	16–77	18–88
Insomnia	3–67	36–48
Confusion	2–68	15–48
Depression	4–80	6–59
Anxiety	3–74	2–49

(Source: Prepared based on Moens K, et al. 2014.⁹⁴)

because the disease progressively worsens with repeated exacerbations and remissions, and sudden cardiac death sometimes occurs.⁹¹

In addition, treatment for HF, such as inotropes and diuretics, is itself palliative. Therefore, it is difficult to consider the timing of palliative interventions with opioids and steroids, as are usually used in patients with cancer, in HF patients. Importantly, CVD differs from cancer in which surgical intervention or chemoradiation therapy is rarely performed in the terminal phase. Namely, CVD requires continuous appropriate treatment until the end of life not only to improve prognosis but also to alleviate symptoms.

Advances in medical technology have led to the development of many minimally invasive treatments for CVD. Although these therapies are less invasive and can lead to symptomatic relief, they are often expensive and can lead to certain complications.

In Japan, being aging society, the decision-making process for cardiovascular palliative care has become more diverse and complex than that for cancer. In addition, the decision to terminate implantable cardioverter defibrillators and ventricular assist devices at the end-of-life is an issue specific to CVD. In providing high-quality cardiovascular palliative care, it is necessary to take into account these unique characteristics and challenges of CVD. Therefore, in addition to quality indicators for cancer palliative care, quality indicators for cardiovascular palliative care that incorporates these characteristics are strongly warranted.

6.5 Quality Indicators of Palliative Care in HF

Although the need for palliative care in HF has been increasing, neither the methodology nor the timing of intervention has been established in this important clinical arena. In this situation, quality indicators for palliative care in HF have been developed (Table 9).⁹² In this initiative, 35 quality indicators of palliative care in HF were developed based on “basic palliative care to be provided by general cardiologists”, though these indicators need to be evaluated objectively in the future.

These quality indicators consist of 4 domains as follows: (1) structure and process of disease care, (2) appropriate treatment and care, (3) total pain management and (4) decision support and ethical issue management.⁹² These quality indicators describe the importance of a multidisci-

plinary team, and a lot of indicators have been adopted for the relief of total pain, which is the mainstay of palliative care. The domain of appropriate treatment and care, which is a specific domain for palliative care in HF, has also been adopted, emphasizing the need to consider continuous treatment in the palliative care of HF even at the end of life.

6.6 Quality of Palliative Care in CVD

Due to the nature of CVD, the emphasis has been historically on survival benefit, and the perspective of palliative care remains far from prevalent. On the other hand, the need for cardiovascular palliative care will become increasingly important as the population ages. CVD is common, and high-quality palliative care should ideally be available “by any healthcare provider” and “at any healthcare institution”. To promote and ensure the quality of cardiovascular palliative care, quality indicators are useful, and they should be widely used in the future.

7. Evaluation and Care of Physical Symptoms

7.1 Palliation of Symptoms During Endstage Heart Failure


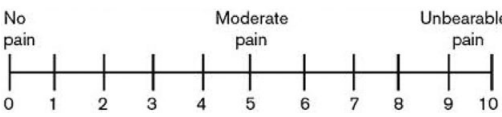
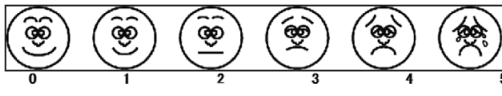
7.1.1 Symptom Evaluation

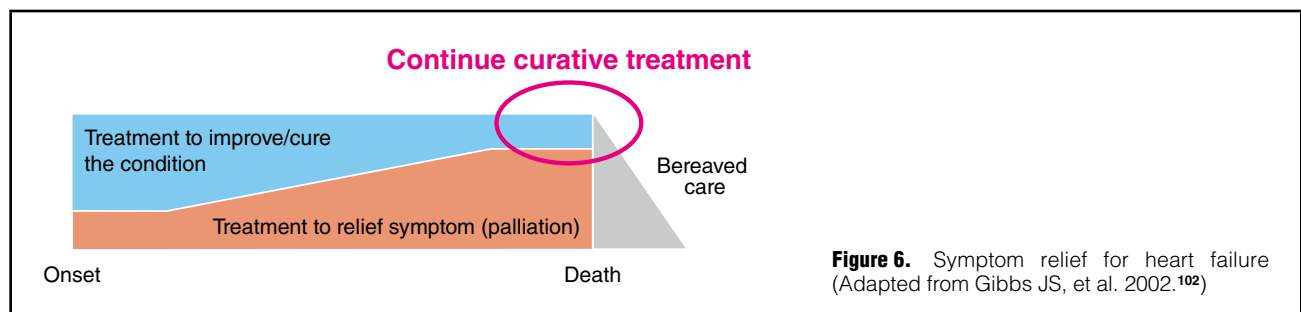
Patients with heart failure (HF) show various symptoms, including dyspnea, pain, malaise, depression, anxiety, sleep disorders, cognitive impairment, loss of appetite and weight loss.⁹³ Both the physical and mental symptoms are not less than those of cancer (Table 10).⁹⁴ It is reported that most endstage HF patients have 6 or 7 symptoms in average.⁸² On the other hand, nearly 70% of patients are aware of the lack of symptom relief,⁹⁵ and currently symptom relief is insufficient compared with cancer in the terminal stage. The reasons for insufficient symptomatic relief of HF are that symptoms are complicated with many comorbidities (vascular disease, chronic obstructive pulmonary disease, diabetes, arthritis, renal failure, depression, etc.),⁹⁶ and many side effects and restrictions on the use of drugs.

Physical symptoms in HF not only reflect the various comorbidities, but also have psychological, social, and spiritual aspects (the pain that results from the existence of self and the loss of meaning) and quality of life (QOL) worsens.⁹⁷ Therefore, because each aspect of the symptoms of HF is closely related and influences each other,⁹⁸ when assessing the symptoms, the perspective of total human distress, including physical, psychological, social, and spiritual distress, should be considered and evaluated from various aspects.

7.1.2 Multifaceted Assessment and Assessment Tools in HF

The New York Heart Association (NYHA) Cardiac Function Classification is used as a simple symptom assessment tool for HF, but it cannot be used for multifaceted assessment because of the large variability among evaluators, so a health-related QOL assessment tool using a questionnaire is used for multifaceted symptom evaluation. The Medical Outcome Study Short Form 36-Item Health Survey (SF-36)⁹⁹ is a frequently used health-related QOL questionnaire in the field of cardiovascular medicine. The Minnesota Living with Heart Failure questionnaire (MLHF)¹⁰⁰ and the Kansas City Cardiomyopathy Questionnaire (KCCQ)¹⁹ are disease-specific questionnaires that

Table 11. Subjective Symptom Assessment Tool	
Assessment tool	Measurement method/features
<p>VAS: Visual Analog Scale</p> 	On a straight line of 100 mm, write the extreme conditions at either end, and mark on the line that best describes own situation
<p>NRS: Numeric Pain Scale</p> 	<p>Patient show their own symptom at a numerical level of pain using 11 levels from 0 to 10 with 0 and 10 at the end.</p> <p>0: no symptoms, 1–3: light symptom, 4–6: moderate symptom, 7–10: severe symptom.</p> <p>It is more reproducible than VAS</p>
<p>Wong-Baker Faces Pain Rating Scale</p> 	<p>Faces show symptom from "smile" to "grimace" and "crying face" in 6 levels from 0 to 5.</p> <p>If the patient has anxiety or worries, the more difficult face will tended to be selected rather than the correct symptom. So careful evaluation is required.</p> <p>0: very happy with no symptoms, 1: just a bit of symptom 2: light symptom, a little painful, 3: moderate symptom, painful 4: severe symptom, very much painful, 5: unbearable symptom</p>



focus on the symptoms of HF. Each questionnaire can evaluate not only physical function but also social life function and psychological aspects, and they are useful for continuous evaluation.

Subjective Symptom evaluation tool are known as Visual Analog Scale (VAS), Numerical Rating Scale (NRS), Verbal Rating Scale (VRS), Wong-Baker Faces Pain Rating Scale,¹⁰¹ and Borg scale etc. (Table 11). With these scales, the intensity of each symptom can be quantitatively evaluated, and therapeutic effect can be also evaluated. For more information on each indicator, refer to **Chapter I.1: Importance of Palliative Care and Assessment of Total Pain.**

7.2 Dealing With Treatment-Resistant Pain

As mentioned above, the physical and mental symptoms in the end stage of HF are as diverse as those in cancer, leading to a decline in QOL. Physical symptoms are often improved with the use of diuretics, vasodilators, inotropes, etc., but if symptoms continue with such treatment, additional medication such as opioid use or non-drug therapy such as oxygen therapy is required. And if unbearable distress is present, it is an option to consider the use of analgesics and sedatives after determining the appropriateness (Figure 6).¹⁰²

It is important to understand the cause of both physical and mental symptoms, treat the cause, and repeat the evaluation of symptoms over time.

7.2.1 Dyspnea

Dyspnea is the most common symptom in patients with HF and often requires treatment even at the end of life. Although it is mainly related to the progression of HF, it may increase due to fatigue and anxiety, so a comprehensive evaluation (physical, psychological/spiritual, social), including a clinical evaluation (comorbidity, panic attacks, pleural effusion and ascites, etc.), should be done.

Diuretics, inotropes, and vasodilators are used according to the patient's condition, and noninvasive positive-pressure ventilation (NPPV), positioning, cold air ventilation to the face, environmental adjustment (humidity adjustment, comfortable environment), breathing exercises and physical exercise, fluid balance evaluation and education, psychological intervention, additional efficacy of non-drug therapy such as yoga and drug therapy such as opioids (morphine codeine, etc.) can be used for treatment-resistant dyspnea.^{103,104}

Evidence for opioid use in endstage HF is less than that for acute HF, and there is insufficient evidence of the appropriate volume to use, although in the oncology field, it is less in palliation of dyspnea than in pain,¹⁰⁵ and it is currently used in small amounts in HF as well.

Table 12 summarizes the drugs that can be used in Japan and the initial administration method. Because there is abundant evidence for symptom relief for refractory dyspnea, and there is no insurance indication for HF in Japan, it can be used for insurance treatment of severe

Drug	Dosage	Note
Codeine phosphate*	10 mg as needed, or 3 times a day	Depending on prescription amount, treated as narcotic
Oral morphine hydrochloride**	2.5mg as needed, or 4 times a day	Start with half dose in renal failure
Continuous injection of morphine hydrochloride**	5–10mg/day continuous intravenous or subcutaneous injection	Start with half or quarter dose in renal failure

*Cough associated with respiratory diseases is covered by insurance, but not with heart failure. **Although not covered by insurance for heart failure, it can be used for severe coughing symptoms. Oral morphine hydrochloride, which can be used in Japan, is a 10-mg tablet, which requires use as a powder.

cough and pain, so morphine hydrochloride intravenous/subcutaneous injection or powder are prescribed. Because morphine hydrochloride is a renal metabolizer, it is necessary to be reduced to half or one-fourth the dose during renal failure.

Tables 13,14 shows side effects associated with opioid administration and how to deal with them.^{106,107} Adjust the dose appropriately while evaluating the strength and side effects of the opioid using a scale as the VAS or NRS. Because opioids are not sedatives, drugs such as midazolam should be considered for the purpose of sedation for intolerable distress. Overdose can be avoided by targeting the extent to which QOL is not deteriorated by daily exertion without completely eliminating dyspnea. Although opioids may have side effects even during acute use, side effects may be carefully evaluated because they may be used for a longer period of time with consequent accumulation. It is recommended to consider dose reduction if the breathing rate of the patients reduced less than 10 times per minutes or if disordered consciousness is prolonged. For delirium and gastrointestinal symptoms, if oral administration is difficult, haloperidol may be co-injected with opioid at a dose of ≈ 2.5 mg/day.^{106,107} There are reports that oxycodone is effective against dyspnea, and it may be considered for patients with renal impairment, but it is not covered by insurance in Japan as of 2019 and caution is required.

Often in the early phase
Nausea/vomiting
Somnolence
Dizziness/light-headedness
Delirium
Often during long term
Constipation
Nausea/vomiting
Dry mouth
Sometimes during long term
Suppression of Hypothalamus-pituitary system
Suppression of the immune system
Infrequent
Neurotoxicity
Myoclonus
Allodynia
Hyperalgesia
Cognitive impairment
Hallucination
Sweating
Itchiness
Very infrequent
Respiratory depression
Mental dependence

(Adapted from Twycross R. 2013.¹⁰⁷)

In Japan, experience of using morphine hydrochloride for 43 patients with NYHA IV refractory dyspnea in advanced HF with the intervention of a palliative care team has been reported.¹⁰⁸ The median initial dose of morphine was 5mg for both oral and intravenous administration, and the median duration of use was 5 days without fatal adverse events related to drug use. Morphine therapy might be feasible for refractory dyspnea as palliative care in advanced HF patients.¹⁰⁸ However, efficacy evaluation is not sufficient with only 8 cases, and further knowledge is awaited.

7.2.2 Pain¹⁰⁹

Patients with HF may have various pains, such as anginal pain, arthralgia, neuropathic pain, and those associated with catheter/tube insertion for therapeutic purposes, and it is necessary to deal with the pain according to the cause. To deal with symptoms, first consider oral or intravenous acetaminophen administration, and consider the use of gabapentin or pregabalin as an analgesic aid. If these drugs are still ineffective, consider using an opioid such as morphine. The instruction and side effects of using opioids for pain are similar to that of dyspnea (**Tables 12,13**). However, for pain, a sufficient amount is required compared with the use for dyspnea, and it is often used for a long period of time. The use of fentanyl patches is an option if there is no dyspnea, and has insurance coverage for moderate to severe chronic pain (can be used with noncancer). However, there is compulsory e-learning, and patients must sign their name on the prescribed document. The administration of nonsteroidal anti-inflammatory drugs to patients with HF should be avoided because they exacerbate renal dysfunction, promote water retention, and thus worsen HF.

7.2.3 Fatigue

Fatigue associated with HF is a treatment-resistant symptom, and factors such as hypokalemia, β -blocker use, sleep disorder, anemia, depression, and deconditioning should be evaluated and treated. Potassium replacement, diuretics and β -blocker dose reduction or discontinuation, blood transfusion, antidepressant drug administration, psychotherapy, rehabilitation, etc. can be considered as additional treatments. Diuretics and β -blockers are sometimes used as standard treatments for HF, so consider the therapeutic effect obtained by continuing the drug and the effect on symptom relief expected with discontinuation. Steroid medication should be avoided because of exacerbation of water retention and delirium.

7.2.4 Use of Sedatives for Intolerable Pain

If unbearable pain persists even with various methods, including drug and non-drug therapies, the use of sedatives

Symptom	Approach
Nausea	During movement → diphenhydramine 1 tablet 3 times a day
	Postprandial → metoclopramide 5–10 mg 3 times a day
	During the day → haloperidol 0.75–1 mg once daily before sleep
Constipation	Magnesium oxide 1.5–3 g, lactulose 30–60 mL
	Sennoside 1–4 tablets, sodium picosulfate 3–30 drops
Somnolence	Natural relief within a few days
	Search and treat causes other than opioids (antiemetics, psychotropic drugs, hypoxemia)
Delirium	Search and treat causes other than opioids
	Administration of psychotropic drugs (e.g., haloperidol)
Involuntary movement	Diazepam, midazolam 5 mg, lorazepam 0.5 mg
Hyperalgesia	Acetaminophen, gabapentin
Respiratory depression	Opioid dose reduction/discontinuation
	Naloxone (opioid antagonist) administration

(Source: Prepared based on Japan medical association 2017.¹⁰⁶ Twycross R. 2013.¹⁰⁷)

is an option after a multidisciplinary examination and sufficient discussion with the patient and their family.¹¹⁰ Commonly used injectable drugs include midazolam, dexmedetomidine hydrochloride and propofol. At home, suppositories such as diazepam, phenobarbital, and bromazepam can be used. Midazolam is a renal metabolizer and may accumulate in patients with renal impairment; propofol is more likely to cause respiratory depression and lower blood pressure; less respiratory depression is associated with use of dexmedetomidine compared with midazolam and propofol. Therefore, although dexmedetomidine is useful when continuing treatment when there is no respiratory depression, such as when using NPPV, there is a high risk of bradycardia and it is generally difficult to maintain a deep sedation level.

Depending on the purpose, the appropriate drug is selected and the target depth of sedation and time are decided. The depth of sedation should be evaluated with a scale such as the Richmond Agitation-Sedation Scale. Furthermore, consider switching to continuous deep sedation as needed, even after the start of drug use, and gradually increase or decrease.

Because the use of sedatives when there is unbearable distress in the endstage of HF is a treatment that intentionally lowers the level of consciousness, it is necessary to confirm the validity of treatment resistance and confirm that the expected life prognosis is short. If sedation is ethically appropriate, it is desirable to share the target sedation level among healthcare staff and start treatment (Figure 7).¹¹⁰ Regarding the use of sedatives, as in the case of narcotics, there are few reports targeting HF, and further knowledge is required.

8. Evaluation and Care of Psychiatric Symptoms

8.1 Management of Psychiatric Symptoms

Heart failure (HF) is a chronic, progressive, and ultimately fatal disease. Patients with advanced HF suffer from various

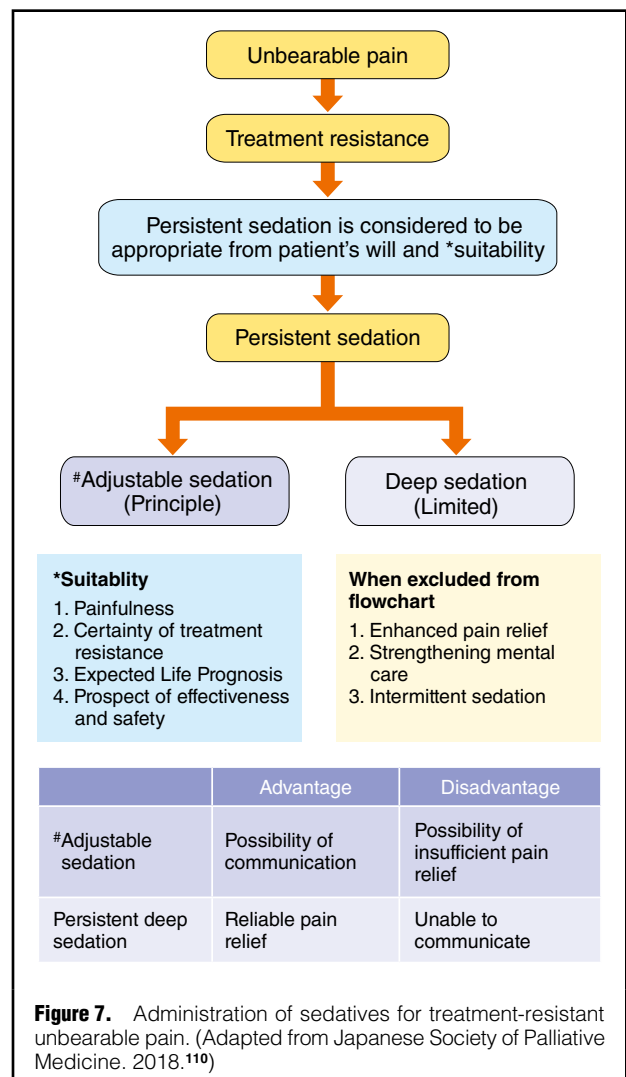


Figure 7. Administration of sedatives for treatment-resistant unbearable pain. (Adapted from Japanese Society of Palliative Medicine. 2018.¹¹⁰)

Table 15. Multifaceted Stressors in Patients With Heart Failure

1. Physical symptoms Dyspnea, cough, edema, malaise, pain
2. Complications Diabetes mellitus, renal disease, cerebrovascular disorders
3. Critical situation Loss of physical function, experience of cardiac arrest
4. Stressors associated with self-care behaviors Diet, behavior restrictions, medication adherence
5. Stressors associated with devices Sense of incongruity of foreign body, defibrillation (shock) experience
6. Social stressors Economic problem, difficulties in working and school, change of role within family

physical symptoms, including dyspnea, edema, and fatigue. Furthermore, advanced HF patients experience pain of an all-encompassing holistic nature, including physical, social, psychological, and spiritual pain. These multifaceted experiences of pain in HF patients are similar to those of patients with cancer or other illnesses requiring palliative care. However, some stressors are HF-specific, such as fear of sudden death, as well as device-related stressors, including fear of shock (defibrillation) (Table 15). These stressors can lead to the development of various psychiatric symptoms.

Psychiatric disorders are frequently complex in HF patients, including depression, anxiety disorder, post-traumatic stress disorder (PTSD), and delirium.^{111,112} Increasing evidence indicates that these disorders can have a substantial effect on the morbidity and mortality outcomes of HF.^{112–114} In addition, patients with the comorbidity of HF and cognitive disorders require additional support because cognitive disorders affect self-care and decision-making ability.¹¹⁵

Management of psychiatric symptoms should include good communication between the patient, their family, and healthcare professionals regarding pharmacotherapy, nonpharmacotherapy, and exercise/cardiac rehabilitation. Although the effect of each of these therapeutic options is not sufficient alone, the effectiveness of a multidisciplinary collaborative care approach has recently been reported.¹¹⁶ We review the evidence regarding the management of psychiatric symptoms in patients with advanced HF.

8.2 Psychiatric Symptoms in Patients With HF

8.2.1 Depression and Anxiety

A meta-analysis demonstrated that depression detected by questionnaires was present in 34% of HF patients, and depression detected by diagnostic interview was present in 19% of HF patients. Rates of depression varied between patient groups with HF of different severity, according to the New York Heart Association (NYHA) definition of HF: 11% in Class I, 20% in Class II, 38% in Class III, and 42% in Class IV.¹¹² In addition, depression is reported to occur in 29% of patients with a myocardial infarction.¹¹⁷

Another meta-analysis demonstrated elevated symptoms of anxiety in 56% of HF patients, and the prevalence rates of anxiety disorders vs. probable clinically significant anxiety were 13% vs. 29%, respectively.¹¹⁸ Less is known about the clinical features of subcategories of anxiety dis-

orders (e.g., panic disorder, specific phobias, or general anxiety disorder) in HF patients.

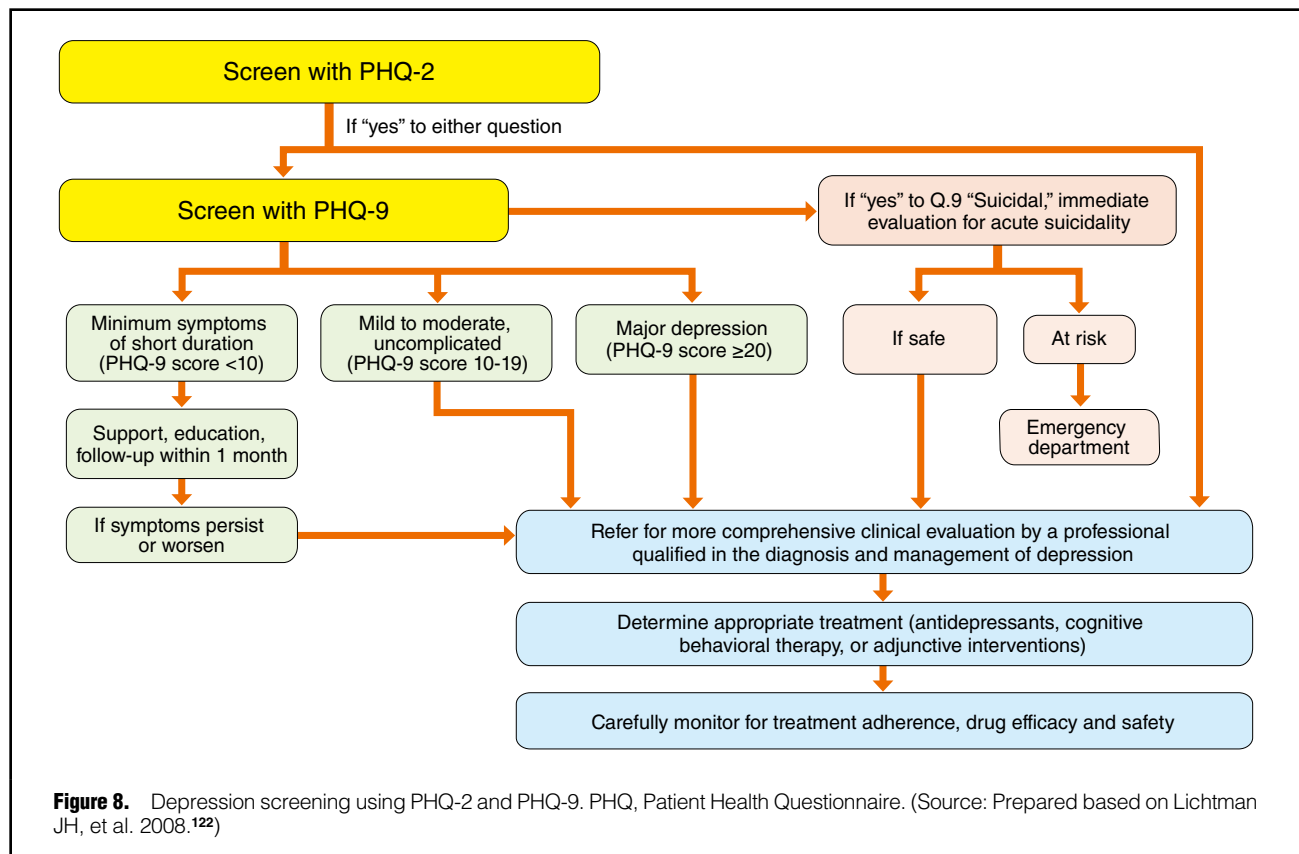
In addition, device-related psychological issues have been well documented, including issues related to the use of implantable cardioverter defibrillators (ICDs). One study reported that between 11% and 28% of patients with ICD exhibited a depressive disorder, and 11–26% exhibited an anxiety disorder.¹¹⁹ It is also reported that depression also increase the risk of appropriate ICD shocks.¹¹⁹ Shocks are potential traumatic stressor in patients with ICD. A preliminary study in Japan reported that PTSD was present in 26% of ICD patients, and experience of appropriate ICD shocks was one of the risk factors of PTSD.¹²⁰

Screening protocols for psychiatric disorders such as depression in HF patients have not been established. For patients with coronary artery disease, the American Heart Association (AHA) recommends routine screening for depression with a 2-stage implementation of the Patient Health Questionnaire (PHQ)-2 and PHQ-9 (Figure 8).^{121,122} The PHQ-2, a 2-item tool, and the PHQ-9, a 9-item tool, were designed for primary care providers to aid in the diagnosis of depression according to the Diagnostic and statistical manual of mental disorders, 5th edition. If the answer is “yes” to either or both questions in the PHQ-2, it is recommended that all 9 items (PHQ-9) are asked. Patients with screening scores that indicate a high probability of depression or risk of suicide should be referred for more comprehensive clinical evaluation by a professional qualified in the diagnosis and management of depression. With a cutoff score of 10, the PHQ-9 has reported 70% sensitivity and 92% specificity in identifying depressive symptoms in HF patients.¹²³ The self-administered 21-item Beck Depression Inventory has also been reported as a reliable instrument for assessing depression in HF patients.¹²⁴ Nevertheless, detecting depression in HF patients continues to be challenging because of the considerable overlap in symptoms (e.g., weakness, fatigue, or insomnia). Differential diagnosis of secondary depression or anxiety is crucial, considering comorbid physical illnesses including thyroid gland disease, and medications. Among cardiovascular drugs, methyldopa (3.6%) and reserpine (6–15%) have been reported to cause depression, and nifedipine (unknown frequency), verapamil (unknown frequency), diltiazem (unknown frequency), clonidine (1.5%), and digitalis (unknown frequency) also have been reported to cause depression and/or anxiety.¹²⁵ A number of recent studies have observed no significant association between β -blockers and depressive symptoms.¹²⁶

8.2.2 Cognitive Dysfunction (Including Delirium)

Cognitive dysfunction results from dementia, mild cognitive impairment (MCI), and delirium.

Cognitive dysfunction is present in 25–75% of patients with HF.¹²⁷ A large-scale cross-sectional study using Medicare claims in the USA reported that the prevalence of dementia in older adults with HF was 15%, and the prevalence of MCI was 24%.¹²⁸ Numerous mechanisms have been shown to contribute to cognitive dysfunction in HF, including cerebral hypoperfusion due to decreased cardiac output and HF-related cardioembolic stroke.^{129,130} Both the prevalence and severity of cognitive dysfunction in HF patients are reported to be positively correlated with the severity of HF.^{131,132} For detecting cognitive dysfunction in HF, the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) are widely used.



The MoCA has high sensitivity and specificity for detecting MCI.^{127,133}

Delirium, an acute condition characterized by disturbance of attention, awareness, and cognition, often occurs in HF patients. Delirium is considered an acute brain failure. A retrospective study reported that delirium occurred in 17% of 883 consecutive patients >65 years of age admitted with HF.¹¹⁵ Causes of delirium in HF include decreased cardiac output, cerebral hypoperfusion, metabolic abnormalities, abnormal electrolyte levels, infection, and benzodiazepines (BZDs).^{117,134} Studies have observed that diagnosis of delirium in patients with physical illnesses may be a challenge for physicians.^{135,136} Half of the cases of heart delirium, associated with HF, may not be recognized, and in such cases patients may not receive appropriate treatment.¹³⁷

Comorbidity of delirium in HF has been reported to be associated with increased risk of death and rehospitalization, as well as longer stays in hospital.^{115,138,139} Therefore, timely detection and treatment of delirium are crucial in HF patients.

8.3 Effect of Psychiatric Symptoms on Clinical Outcome and Decision Making

8.3.1 Effect of Psychiatric Symptoms on Outcome of HF

Comorbid depression in HF patients is associated with higher rates of death and secondary events (e.g., heart transplantation, new cardiac events) (risk ratio=2.1) and higher rates of hospitalization and emergency room visits.¹¹² In patients >65 years of age, depression predicts all-cause death.¹¹³ Although anxiety alone does not appear to have

a strong effect on death among HF patients, recent studies reported that a combination of depression and anxiety was associated with worse outcomes than depression alone in patients with HF.^{114,140}

Several pathophysiological factors (e.g., autonomic, hypothalamic-pituitary-adrenal axis, inflammatory, platelet, endothelial, and immune dysfunction), as well as behavioral (e.g., nonadherence [medications, low sodium diet, weight monitoring, or regularly attending a hospital], insufficient exercise, obesity, or smoking) have been found to cause adverse outcomes in HF patients with concomitant depression (**Figure 9**).¹⁴¹

Concomitant cognitive disorders in HF patients also negatively affect clinical outcomes, including rehospitalization and death.^{142,143} Cognitive disorders affect HF self-care behaviors, including self-monitoring of HF symptoms, adherence to prescribed HF therapies, and managing or seeking health advice when changes occur.¹⁴⁴

8.3.2 Effect of Psychiatric Symptoms on Patient's Decision-Making

Patients with advanced HF are required to make decisions about their treatment and healthcare choices (e.g., highly invasive treatment, place for medical care, or discontinuation of treatment at end of life) in a similar way to patients with cancer or other life-threatening illnesses. In addition, HF-specific therapeutic options include ICD, VAD, and heart transplantation.

Concomitant psychiatric disorders can affect the ability of HF patients to make decisions.¹¹⁵ Dementia and MCI, as well as delirium, can affect remembering, understanding and processing information. Anxiety and/or depression

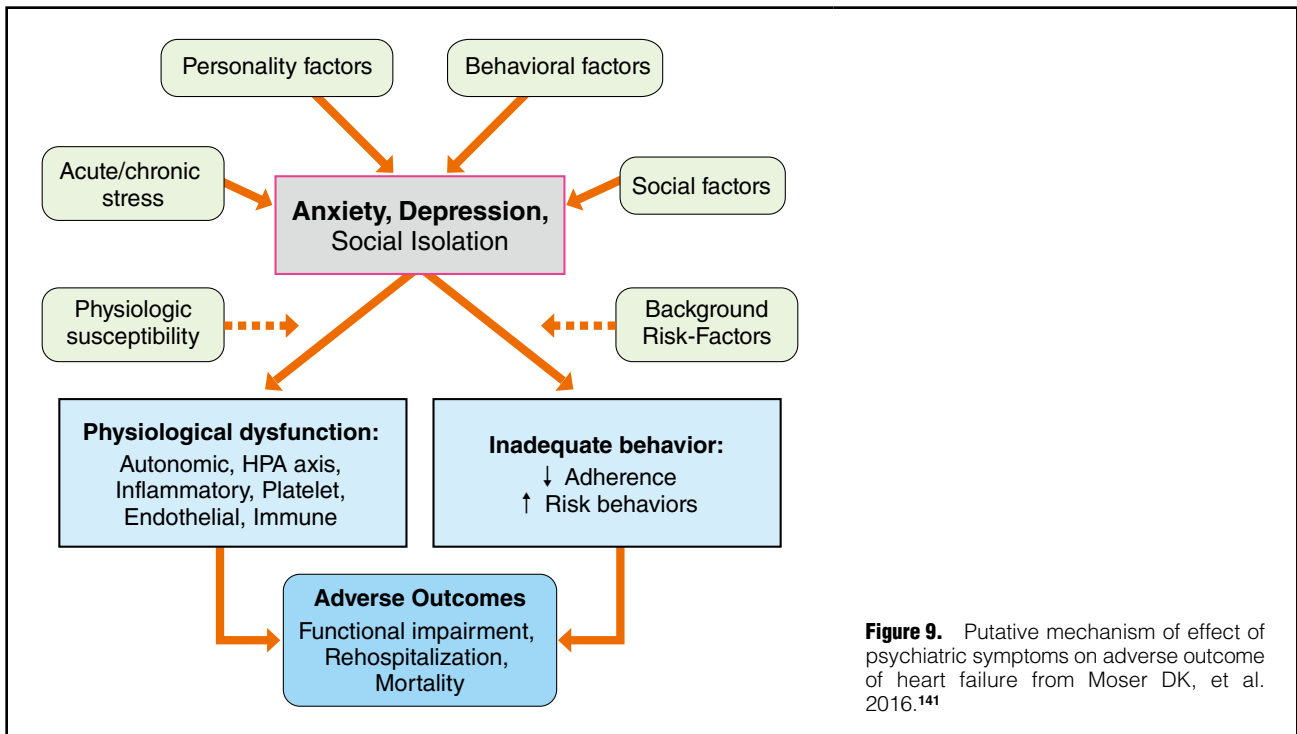


Figure 9. Putative mechanism of effect of psychiatric symptoms on adverse outcome of heart failure from Moser DK, et al. 2016.¹⁴¹

Table 16. Stepped Care for Depression in Heart Failure Patients		
	Target symptoms for intervention	Details of intervention
Step 4	<ul style="list-style-type: none"> • Severe and complicated depression • Life crisis • High degree of self neglect 	<ul style="list-style-type: none"> • Drug therapy • Highly intensive psychotherapy • Electroconvulsive therapy • Crisis intervention • Combination of the above • Treatment by psychiatric healthcare specialists including hospitalization
Step 3	<ul style="list-style-type: none"> • Moderate to severe disease • Mild illness that does not respond to initial intervention • Moderate depression • Persistent subthreshold depression* 	<ul style="list-style-type: none"> • Drug therapy • Highly intensive psychotherapy • Combination of the above • Intervention in multidisciplinary collaboration • Introduction to psychiatry healthcare specialists
Step 2	<ul style="list-style-type: none"> • Mild depression • Persistent subthreshold depression* 	<ul style="list-style-type: none"> • Mild psychosocial intervention • Psychotherapy • Drug therapy • Consider referral to a psychiatric professional
Step 1	<ul style="list-style-type: none"> • All symptoms of depression 	<ul style="list-style-type: none"> • Screening assessment • Supportive support • Psychology education • Active observation • Consider referral to a psychiatric professional

*Subthreshold depression: depressive symptoms without meeting the full criteria of major depression. (Source: Prepared based on NICE guideline. 2009.¹⁴⁸)

also can impair a patient’s decision making, especially in severe cases. The ability to appreciate the significance of information for one’s own situation has been shown to be primarily impaired by depression.¹⁴⁵

As mentioned above, the prevalence and severity of both cognitive and depressive disorders positively correlate with the severity of HF. Therefore, it may be important for advanced care planning (ACP), in which patients communicate their preferences for their own future treatment and healthcare choices with their families and healthcare

providers, to be undertaken as early as possible in the progression of HF. People with cognitive disorders are a particularly important target group for ACP. It is necessary to support patients to understand information in relation to decisions according to the degree of cognitive decline. In cases of severe dementia, healthcare professionals presume the patient’s intent in conjunction with the family, and support alternative consent by families.^{146,147}

If marked depression and/or anxiety are present, adequate evaluation and treatment of such symptoms are

needed. However, patients may be required to make serious decisions before these symptoms have sufficiently improved. In such cases, in parallel with treating depression/anxiety, patients' decision making must be supported while considering their negative or pessimistic thinking.

8.4 Management of Psychiatric Symptoms in Cardiovascular Disease

8.4.1 Stepped-Care Model for Depression and Anxiety

The National Institute for Health and Care Excellence (NICE) guidelines in the UK recommend a stepped-care model for patients with depression and chronic physical health problems, including heart disease (Table 16).¹⁴⁸ This model comprises 4 steps. Step 1: screening of depression and interventions for all symptoms of depression to prevent its progression; Step 2: early treatment focusing on psychosocial intervention and psychotherapy for mild depression; Step 3: psychiatric pharmacotherapy and/or highly intensive psychotherapy, as well as, if possible, collaborative care for moderate to severe depression or mild illness that does not respond to initial treatment; and Step 4: intensive treatment by psychiatric specialists, including hospitalization for severe and complicated cases of depression.

Many HF patients experience depression and anxiety associated with the above-mentioned multifaceted stressors that occur during treatment for HF (Table 15), corresponding to Step 1. Medical staff involved in HF treatment play a central role in recognizing and managing Step 1 depression and anxiety, rather than specialized psychiatric professionals. Medical staff include not only the attending doctor, but also many other healthcare professionals in a variety of settings, such as nurses, occupational and physical therapists involved in rehabilitation, and dietitians. All healthcare professionals should pay attention to the psychological state of patients, in addition to the patients' physical symptoms.

8.4.2 Pharmacotherapy for Depression and Anxiety

a. General Principles for Using Psychotropic Drugs in HF Patients

HF patients are at high risk of serious side effects of psychotropic drugs (e.g., sedation, delirium, and hypotension).¹⁴⁹ Several conditions commonly occur in HF patients, such as gastrointestinal edema, decreased renal and hepatic perfusion, decreased glomerular filtration, decreased absorption, metabolism and excretion, and altered drug distribution. Therefore, lower doses compared with routine doses for psychotropic drugs are initially used in HF patients. The doses may be gradually increased with careful monitoring of side effects. It is important to minimize the number of drugs used, and to avoid long-acting drugs or drugs that cause prolonged QT syndrome.¹⁴⁹⁻¹⁵¹ Table 17 summarizes the risk of prolonged QT syndrome associated with psychotropic drugs.¹⁵⁰

b. Pharmacotherapy for Anxiety/Anxiety Disorders

Selective serotonin reuptake inhibitors (SSRIs) are the first choice for treating anxiety disorders and for PTSD that fulfils the diagnostic criteria (discussed in detail below).¹⁵¹

If the symptoms of anxiety are considerable, or, if there is severe subjective suffering, a BZD is used.¹⁵¹ BZDs are frequently used in HF patients because they act immediately to alleviate anxiety-related tachycardia and myocardial

Table 17. Psychotropic Drugs That Can Prolong the QT Interval

Generic name	Risk
Antipsychotics	
Aripiprazole	A
Olanzapine	A
Perphenazine	A
Clozapine	B
Levomepromazine	B
Paliperidone	B
Quetiapine	B
Risperidone	B
Sulpiride	B
Haloperidol	B*
Pimozide	B*
Tricyclic antidepressants	
Amitriptyline	B
Clomipramine	B
Imipramine	B
Antidepressant (Other)	
Paroxetine	A
Sertraline	A
Duloxetine	A
Mirtazapine	A
Citalopram	B
Escitalopram	B
Venlafaxine	B
Mood stabilizers	
Carbamazepine	A
Lamotrigine	A
Valproic acid	A
Lithium	B
Other	
Benzodiazepines	A
Gabapentin	A
Pregabalin	A

A: No risk of QT prolongation, or the risk is negligible. B: The patient is at risk for QT prolongation. B*: Obvious prolonged QT syndrome or torsades de pointes. (Source: Prepared based on Fanoë S, et al. 2014.¹⁵⁰)

irritability.¹⁵² In addition, BZDs have no negative effects on the cardiovascular system. However, they do have other side effects, including drug dependence, cognitive dysfunction and falls. In addition, the efficacy of long-term administration has been questioned. For this reason, BZDs should only be used in the short-term, and at the minimum dose.

Caution is required when using long-acting BZDs (e.g., diazepam, chlorthalidopexide and clonazepam), or BZDs with active metabolites, because side effects may be prolonged. In addition, unlike other BZDs, lorazepam exhibits glucuronic acid conjugation without being affected by cytochrome P450 (CYP) metabolism (phase I reaction),^{149,151} so there are very few changes in drug metabolism. Lorazepam is relatively safe for HF patients.

c. Pharmacotherapy for Depression/Depressive Disorder

Although antidepressants are typically used to treat depres-

Table 18. Cardiac Effects of Antidepressants (Excluding Those for Prolonged QT Syndrome)

Antidepressants	Orthostatic hypotension	Hypertension	Tachycardia	Bradycardia	Antiplatelet action	Weight gain
Tricyclic	++++	–	+++	–/+	–	++++
SSRI	+	+	+	–/+	+ ^a	++ ^b
SNRI	+/ ⁺ +++	+/ ⁺ ++++ ^c	++	–	+ ^d	–/ ⁺ e
Mirtazapine	+	+	–	–	–	++++
Tradzon	+++	+	+	+	–	++ ^f

SNRI, serotonin/noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor. ++++: Strong, +++: secondary, ++: weak, +: very weak, –: none. ^aIn particular, paroxetine, sertraline, and escitalopram. ^bIn particular, paroxetine. ^cDose-dependent reinforcement. ^dIn particular, duloxetine. ^eVenlafaxine also causes weight loss. ^fWeight loss is also observed. (Modified from Teply RM, et al. 2016.¹⁵⁵)

sion, there is no consensus regarding pharmacotherapy for depression in HF patients,¹⁵³ and the efficacy of antidepressants was not supported by a network meta-analysis.¹⁵⁴ Several reasons have been proposed for the lack of efficacy of antidepressants in HF patients, including the similarity of symptoms between HF and depression, such as fatigue, the fact that depressive symptoms appear as side effects of HF drugs, and the inability to sufficiently increase antidepressant dosage in HF patients.¹⁵⁵

Typical antidepressants include SSRIs (which are also used to treat anxiety), noradrenergic and specific serotonergic antidepressants (NaSSAs), serotonin-noradrenaline reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs). SSRIs are typically the first choice for treating HF patients. Among the SSRIs, sertraline¹⁵⁶ and escitalopram¹⁵⁷ were found to be safe in the Sertraline Against Depression and Heart Disease in Chronic Heart Failure (SADHART-CHF) and the Morbidity, Mortality and Mood in Depressed Heart Failure Patients (MOOD-HF) randomized clinical trials of HF patients, respectively. However, both drugs involve a risk of prolonged QT syndrome, particularly escitalopram. There is evidence that mirtazapine (a NaSSA) is safe for patients who have suffered from myocardial infarction,¹⁵⁸ and mirtazapine can provide a second-line treatment when SSRI treatment fails in HF patients. SNRIs may cause tachycardia and hypertension due to their effects on noradrenaline. Thus, caution is advised when treating HF patients. TCAs cause hypotension (α 1-adrenergic receptor blocking) and bradycardia (cholinergic receptor blocking), as well as ventricular arrhythmias and torsade de pointes due to quinidine-like effects. For this reason, the use of SNRIs should be avoided in HF patients. **Table 18** shows the cardiovascular effects of antidepressants.¹⁵⁵

For HF patients using antidepressants, drug interactions must be considered. Fluvoxamine (SSRI), which exerts moderate to major inhibitory effects on the CYP enzymes 1A2, 2C9, 2C19 and 3A4. Paroxetine (SSRI) exerts powerful inhibitory effects on CYP 2D6. As a result, the serum level of drug metabolized by these enzymes may increase. For example, because β -blockers are metabolized by CYP 2D6, HF patients on low doses of these drugs should avoid using paroxetine.

As mentioned above, no consensus regarding antidepressants for treating depression in HF patients has been established. The efficacy of sertraline and escitalopram was not supported in randomized clinical trials.^{156,157} However, subanalysis of the SADHART-CHF trial demonstrated significant improvements in physical function and quality of life (QOL) in HF patients receiving sertraline as a

treatment for depression.¹⁵⁹ Meanwhile, another subanalysis of the SADHART-CHF trial demonstrated risk factors in patients who did not respond to sertraline, including ICD (often complicated by PTSD) and high anxiety scores, suggesting that intervention should focus on concomitant anxiety.¹⁶⁰

In addition, a systematic review suggested that antidepressants do not contribute to improving HF prognosis.^{157,161} However, a previous study reported that HF prognosis improved if depression was controlled appropriately using antidepressants.¹⁶²

8.4.3 Psychotherapy for Depression and Anxiety

Cognitive behavioral therapy (CBT) has been shown to be effective for depression in addition to antidepressants. In general, CBT is useful when patients have intolerance of antidepressants, or when patients refuse drug therapy. Combination therapy using CBT and pharmacotherapy has been found to be more effective than monotherapy using each therapy alone. CBT is also effective for treating depression in HF patients, although some reports indicate that it does not contribute to improving the prognosis (readmission or death).¹⁶³

8.4.4 Exercise/Cardiac Rehabilitation in HF Patients With Depression and Anxiety

Aerobic exercise and cardiac rehabilitation not only improve cardiovascular function, but are also known to improve depression.^{164–166} However, patients with depression typically exhibit reduced motivation for exercise and rehabilitation. It should be noted that exercise and rehabilitation improve depression for such patients, and families should promote participation.

8.4.5 Management of Delirium

In general, basic strategies for management of delirium consist of: (1) ensuring safety (e.g., removing dangerous items from the environment), (2) identifying causative physical factors or substances, including medications, then treating or eliminating them, (3) nonpharmacological interventions (e.g., moderating the circadian rhythm, or minimizing immobilization), (4) pharmacological interventions, and (5) sharing information about delirium with families. However, determining the cause of delirium is often not straightforward, and it can take a substantial period of time to treat or eliminate it. Thus, pharmacotherapy is usually administered for the symptomatic treatment of hyperactive delirium presenting as agitation or excitement. No consensus regarding pharmacotherapy

for hypoactive delirium has been established. Overall, there is extremely limited evidence for safe and effective pharmacotherapy in delirium complicated by HF.

a. Antipsychotics

First-line pharmacotherapy for delirium is the use of antipsychotics, although this treatment is off-label. Although haloperidol, a first-generation antipsychotic, is the gold standard treatment for delirium, second-generation antipsychotics (risperidone, quetiapine, olanzapine or aripiprazole), which have fewer extrapyramidal side effects, have become increasingly widely used in recent years.

According to the general principles of administration of antipsychotics, drugs are administered at the lowest adequate dosage, and agents with a shorter half-life are preferred. Once the symptoms of delirium have reduced, the dose may be decreased, or the antipsychotic may be withdrawn, and antipsychotic treatment should not be continued without monitoring.

In patients with HF, cardiovascular side effects of antipsychotics should be particularly closely monitored. Quetiapine and risperidone cause hypotension due to α -1 adrenoceptor blockade. All antipsychotics can prolong the QT interval (**Table 17**). Haloperidol, especially with intravenous use, can cause an increased risk of torsade de pointes. Olanzapine and aripiprazole have a very low risk of cardiovascular issues or prolonged QT syndrome; therefore, these drugs may be useful in HF patients. Careful ECG monitoring should be regularly performed in the treatment of delirium in HF patients.¹⁴⁸

b. Other Psychotropic Drugs

A meta-analysis demonstrated that yokukansan may be effective and safe for treating the behavioral and psychological symptoms of dementia,¹⁶⁷ suggesting that it may also be useful for delirium treatment in HF patients. Because BZDs can cause delirium by themselves, use of these agents should be avoided in the treatment of delirium, as well as for treating insomnia in patients with an increased risk of delirium (e.g., worsening HF symptoms). It has been suggested that ramelteon, a melatonin receptor agonist, and suvorexant, an orexin receptor antagonist, may prevent delirium,^{168,169} and thus may be useful for treating insomnia in HF patients.

8.4.6 Collaborative Care

Standard pharmacotherapy for depression in HF is not only associated with sufficient recovery of depression, but also improving prognosis.^{156,157,160} The situation is similar to that in patients with depression complicated by coronary artery disease or diabetes mellitus.¹⁷⁰ In recent years, collaborative care has gained increasing attention, particularly in North America, as a new care model for such chronic disorders.¹⁷¹ In summary, depression care managers (trained nurses, clinical psychologists and social workers) play a key role in caring for patients with depression. These staff work together with primary care physicians and provide treatment of depression under the supervision of psychiatrists. Specifically, they assess psychiatric symptoms comprehensively, propose an evidenced-based treatment plan, and follow-up the patient from the start of treatment. Importantly, depression care managers emphasize inclusive support on an individual basis (case management).

Collaborative care was reported to not improve specific health status in HF patients according to the Kansas City

Cardiomyopathy Questionnaire, although it was found to improve depressive symptoms and fatigue.¹¹⁶ In addition, a meta-analysis suggested that collaborative care improves QOL, anxiety and physical function in people with HF, compared with normal care.¹⁷²

9. Multidisciplinary Team Building

Nowadays, healthcare professionals are commonly engaged with patients and their family members in specialized positions as medical technologies become more complex. Furthermore, because patients and their families have diverse views on medical care, team-based medical care is becoming more important.

Team-based medical care is defined as “provision of medical care responding adequately to patient’s condition by a team of healthcare professionals from different professions with the use of each profession’s high-level expertise, in which members of the team collaborate and supplement with each other, while sharing the work, with the common goal and information”.

Team-based medical care enables multidisciplinary healthcare professionals to provide quality care for patients and their families through integration of information and experience from each professional. To practice palliative care, especially, a multidisciplinary team-based approach is quite important, because total pain must be treated comprehensively.¹⁷³

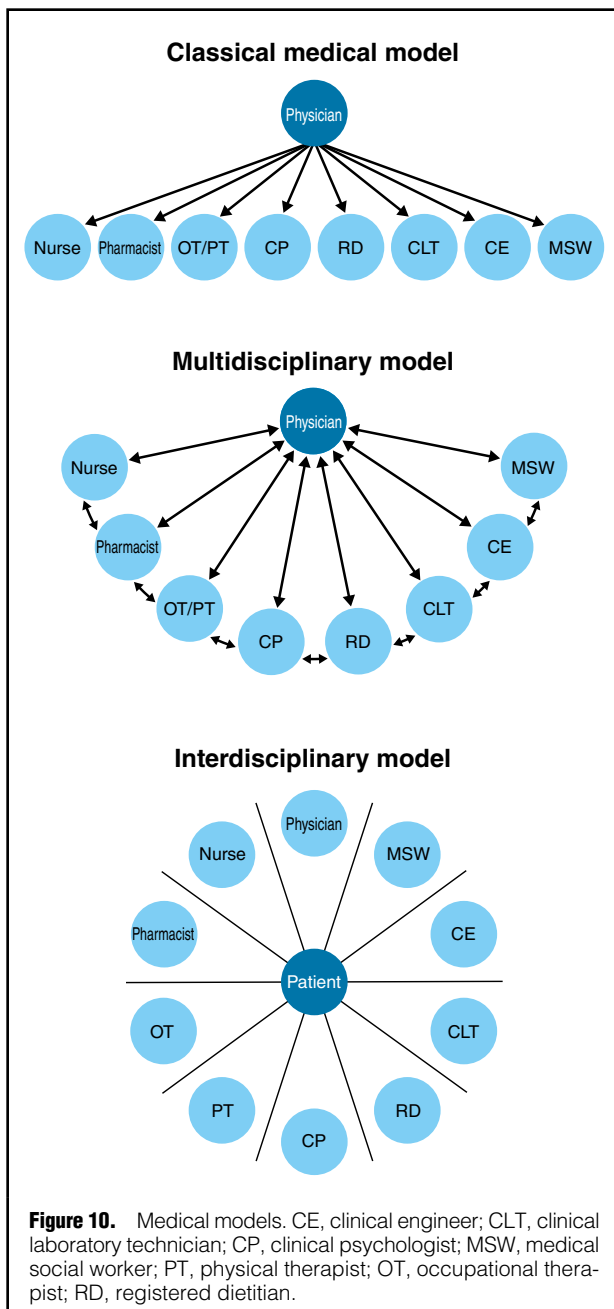
9.1 Structure of Multidisciplinary Team

To maximize the benefit of palliative care, it is important to organize a well-balanced multidisciplinary team with clarification of roles such as leader and coordinator. The structure of the multidisciplinary team, and of medical models, has changed over time. Previously, the classical medical model prevailed, in which medical care was provided by each healthcare professional in response to the physician’s order. As medical advances have required cooperation among healthcare professionals, the multidisciplinary model has spread, in which medical care is provided by healthcare professionals in response to the mutual physician’s order. More recently, the interdisciplinary model prevails, in which healthcare professionals involved with the patient provide medical care with the use of each specialty (**Figure 10**). Also, the transdisciplinary model has been developed, in which healthcare professionals provide medical care supplemented with other professionals beyond the specialty. In this way, the structure of the multidisciplinary team is important to provide palliative care for patients; however, the individual skill and experience of healthcare professionals, especially their professionalism and communication skills, determine the quality of palliative care.

9.2 Role of Individual Healthcare Professionals

9.2.1 Physicians

To maximize the benefit of palliative care, physicians are expected to (1) set the goal of the multidisciplinary team based on the needs of their patients and families, (2) elicit diverse opinions from each healthcare professional, (3) form a consensus of the team, and (4) advice the opinion to the attending physicians. In addition to physicians,



psychiatrists are indispensable for the multidisciplinary team to evaluate the patient's mental status and support their mental and medical therapies.

9.2.2 Nurses

As a care coordinator, nurses are expected to share important information with other team members, because nurses usually stand by patients and families and tend to obtain lots of information regarding their values and needs of medical care. Therefore, nurses are especially required to develop a trusting relationship with patients and families, in addition to perceptive observation, that enables detection of minor changes in the patients' mental and physical state.

9.2.3 Pharmacists

Pharmacists are expected to support the multidisciplinary team in terms of practicing appropriate medical treatment. In particular, pharmacists play a critical role in risk avoidance of adverse events with a drug's administration and prescription support for nutritional treatment.

9.2.4 Occupational Therapists and Physical Therapists

Occupational therapists (OT) contribute to the improvement of basic activities as well as quality of life (QOL) through physical therapies such as exercise therapy and thermal therapy. Physical therapists (PT) contribute to the restoration of patient's own life through household labor and community activities. OT/PT support the patient in living as independently as possible. Therefore, OT/PT are in the team required to provide advice and guidance on the patient's ability to live independently.

9.2.5 Clinical Psychologists

Clinical psychologists (CP) discover potential mental issues for the patient through counseling and psychological tests, and assist the patient in working through difficult thoughts and feelings. CP play an important role in reporting the patient's mental status to the multidisciplinary team.

9.2.6 Registered Dietitians

Registered dietitians (RD) evaluate the patient's nutritional status and recommend a nutritional management plan depending on the patient's disease stage in order to prevent impaired metabolic capability due to imbalanced nutritional status. Especially in the terminal stage of cardiovascular diseases, RD play a critical role in the maintenance of nutritional status, because sarcopenia can worsen heart failure. RD are required to assess each patient's feeding condition accurately, because patients tend to lose their appetite as heart failure progresses.

9.2.7 Clinical Laboratory Technicians

Clinical laboratory technicians contribute to precision guarantee in the assessment of the patient's pathological condition and therapeutic efficiency through the use of clinical laboratory tests and physiological function tests such as echocardiography.

9.2.8 Clinical Engineers

Clinical engineers (CE) play a key role in maintenance of multimodal life-sustaining devices such as respirators, pacemakers, and defibrillators. CE also contribute to the instruction and maintenance of continuous infusion pumps administering narcotic analgesic agents.

9.2.9 Medical Social Workers

Medical social workers (MSW) serve as a mediator between the medical service and social welfare. MSW play an important role in supporting the utilization of social security systems based on economic, psychiatric, and social issues raised by patients and families. MSW are expected to share information among team members to resolve any issues in the context of social welfare.

9.3 Implication of Multidisciplinary Team

To build a viable multidisciplinary team, each member should (1) improve professional skills, (2) widen the field of work, and (3) collaborate with and supplement each

other, while sharing the work at regular multidisciplinary meetings.

An educational resource that is useful for building and improving the multidisciplinary team is TeamSTEPPS (Team Strategies and Tools to Enhance Performance and Patient Safety).¹⁷⁴ This is an evidence-based set of teamwork tools, aimed at optimizing patient outcomes by improving communication and teamwork skills among healthcare professionals, which was developed by the Agency for Healthcare Research and Quality in the USA. The program directs mastery in 4 core competencies (Leadership, Situation monitoring, Mutual support, and Communication) to enhance the performance of teamwork skill.

10. Palliative Care for Heart Failure at Home

Heart failure (HF) is a syndrome that causes systemic organ damage, including the heart, and is a chronic disease for which curative treatment is a challenge. Therefore, when physicians engage in treatments for HF, it is critical not only to focus on interventions of the heart as an organ, which we call the “disease model,” but we should also focus on the living environment and quality of life (QOL) of the patient, the “life model.” From this perspective, it is necessary for us to build a local medical-caregiving structure that considers the entity, living, and life of the patient in collaboration with hospital medical care. To consider palliative care for cardiovascular disease (CVD) at home, we will look at the differences between hospital medical care and home medical care (**Table 19**).

Basically, hospital medical care is for life saving and extending life and not intended as long-term care. Therefore, in reality it is often switched to terminal care at the hospital. On the other hand, home medical care is intended to maintain QOL despite disabilities, which sets less hurdles in transitioning to palliative care. Although hospital medical

care and home medical care are not reciprocal medical models, it is interesting that the strengths of each model transform into weaknesses of each other. It is important to understand these differences when we provide palliative care for noncancer CVD in our daily practice.

10.1 Home Medical Care and Utilization of Social Resources in the Community

The roles of home medical care for heart failure are (1) discharge from long-term hospitalization, (2) prevention of rehospitalization, (3) treatment for acute exacerbations, and (4) caregiving at home. These roles help clarify the role of the acute care hospital, prevent rehospitalization of HF patients, and allow continuation of home medical care. Home medical care in the community is supported by many other organizations that provide medical and nursing such as home-visit nursing, home-visit rehabilitation, pharmacies, and dental clinics in addition to hospitals and clinics. The list of social services available in a community is summarized in **Table 20**.

Home medical care is covered by medical insurance, and is defined as “a physician visits and provides medical care for a patient at home for those having difficulties making hospital visit due to illness or injury” (2018 medical fee revision). The basics of the social services of a community are to harmonize medical insurance and nursing insurance. Among these, effective utilization of home-visit nursing is important. Home-visit nursing is covered by either nursing insurance or medical insurance depending on the disease and its stage. In order to use home-visit nursing in the community, we need to pay attention to the following issues. (1) When implementing home-visit nursing care, nursing insurance is prioritized over medical insurance, so it is difficult for patients with a low degree of support-needs defined by nursing insurance to fully utilize home-visit nursing. In particular, the application of medical insurance

	Hospital medical care	Home medical care
Goal/target	Health promotion Social participation	Guarantee of independence and dignity
Objective	Disease treatment, lifesaving, life extension	Improving quality of life
Target/subject	Disease (maintaining physiological normality)	Disability (maintaining daily activities)
Team	Single facility, same medical professionals	Multiple facilities, medical caregivers, family members
Strength	Medical specialists, emergency response, less burden of care	Familiar place, ease of reflecting will of the patient/family, more time with family

Social services	Insurance
Home-visit medical care	Medical insurance
Home-visit nursing	Medical insurance or nursing insurance
Home-visit rehabilitation	Medical insurance or nursing insurance
Periodic and needs-based home-visit care	Patients can receive both periodic emergency visit with integrated care and nursing. Nursing insurance only (1st degree or higher needed)
Home-visit acupuncture and massage	Aim to improve and relieve pain and autonomic symptoms by providing massage, acupuncture and functional trainings. Medical insurance only

Table 21. Information Sharing Between Community and Hospital	
Medical information	Progress of medical treatment in the community Medical condition, patient's understanding and acceptance of the symptoms Requests for hospital medical care When to return to the community
Background	ACP and living will in the community Patient's values and characters Patient's family situation Patient's daily living activities
Administrative information	Contact information of patient's family and related institutions Contact information of medical caregivers

ACP, advance care planning.

was approved for endstage cancer, but not for endstage HF at the time of revision of the medical fee in 2018. (2) Awareness among hospital medical professionals of the instruction sheet for home-visit nursing and special home-visit nursing. (3) Home-visit nursing staff require instructions to include medical prescriptions in case of exacerbation, and the criteria stating the circumstances when they should contact hospital medical professionals. In the local medical field, it is necessary to have a multi-facility, multidisciplinary team to provide medical care. Any differences in knowledge of the disease among multidisciplinary team members can cause differences in how they perceive the patient. Therefore, it is important for the medical staff to see things through eyes of the caregiver who supports the patient's daily life and work together for the best interests of the patient and the patient's family.

10.2 Hospital and Clinic Cooperation

Because HF has repeated exacerbations, it is necessary to enhance the hospital and clinic cooperation in the community. Rehospitalization of HF is known to be bimodal: immediately after discharge and at the end stage.¹⁷⁵ Therefore, proper home medical care will facilitate home care. We should keep in mind that the cause of rehospitalization immediately after discharge is often exacerbation of HF, and rehospitalization at the end stage is often for non-HF factors such as aspiration pneumonia, falls, and care burden. HF is a chronic disease characterized by fluctuations in the patient's condition. Therefore, it is important to communicate and share information such as disease stage, treatment plan, and care policy among facilities. Before discharge, a "Discharge adjustment conference" is held where the patient's medical conditions and special needs are communicated from the hospital to the local clinics to ensure a smooth transition from discharge to home medical care. In addition, a "personnel meeting" is held in the community where local medical caregivers can directly discuss the patient with each other. If a patient needs to be hospitalized, a "pre-hospitalization conference" is held where all the necessary information about the patient is communicated from the local clinics to the hospital to set the goals of the hospitalization, which may reduce the burden on the hospital (Table 21). Human resources are often limited in the community and advanced web conferences utilizing Information and Communication Technology (ICT) is expected.

10.3 Social Distress

Being conscious of "distress prevention" is important for

home palliative care. Just like the terminal stage of cancer, HF causes distress from not only physical symptoms such as dyspnea and general malaise, but also an aggregation of grief composed of social, mental, and spiritual aspects that require comprehensive total care. HF patients need support with everyday living but their need for support is often underestimated, because of the fluctuations in their health, and many do not receive adequate services.

To endure adequate home care and prevent social distress, it is necessary to understand the patient's situation in advance.

Some of the critical social distress issues are (1) burden on caregivers and family relationships; (2) selecting appropriate home care; (3) finances; (4) aspects of the local community.¹⁷⁶ Of these social distresses, the burden on caregivers is one of the major causes of discontinuation of home care. In-home medical care, it is necessary to pay attention not only to the patient but also to caregivers. Caregivers living with the patient are required to be ready for 24h a day and also play important roles not only as family members, but also as therapists, nurses, and decision-maker for the patient. Even if each task is small, the cumulative effect may lead to a great burden for caregivers. Because these burdens often increase, especially for endstage HF, appropriate prognostic assessment of the patient could lessen the caregiver's mental burden. In addition, in order to reduce the burden of caregivers, we should share information among facilities and healthcare providers, alleviate patient symptoms, solve issues that caregivers are facing, listen attentively to them, strengthen resources including personnel, and secure respite care.

10.4 Physical Distress

There are various symptoms of endstage HF, and adequate judgment on their quality and quantity is important. For dyspnea, which occurs in $\geq 90\%$ of HF patients, (1) judge the quality and quantity, (2) search for treatable causes, (3) observe the presence of hypoxic respiratory failure, and (4) pay attention to whether the patient feels anxiety. If the dyspnea symptoms are not relieved with non-drug treatment (home oxygen therapy, home mechanical ventilation, symptomatic rehabilitation, nursing care, etc.) or drug treatment (heart failure medication, opioids), consider sedation.

In visiting rehabilitation for patients with endstage HF, we should focus on "sleeping, eating, excreting, separating clean space and unclean area", as well as the usual rehabilitation to relieve the symptoms. For example, for a patient who does not wish to use a portable toilet, for the dignity of the patient, we should validate physical need of the

patient, consider aid equipment, and instruct the family how to help so that the patient can use a regular toilet. Details on opioids usage are given in a different chapter, but their usage for dyspnea with tachypnea in HF patients is effective in relieving symptoms and improving QOL. Sedation is the last resort for pain relief.

It is important to explain to the patient's family that sedation is the last resort to relieve pain, not to shorten the prognosis, and also the possibility of loss of communication. Benzodiazepine suppositories are often used in-home medical care. It is necessary for the physician to clarify the usage as "symptom relief" or "sedation".

In the elderly, it is sometimes difficult to judge the patient's condition as HF or senility at the end of life. Senility is the deterioration of mental and physical abilities with aging, but a definition of "death from senility" is not medically clarified. Although senility cannot be improved by medical treatment, HF can be. Although it is sometimes challenging even for an experienced cardiologist to judge whether to continue the treatment for HF or manage it as senility for severe HF patients, careful judgment must be made to provide care for the increasing number of HF patients in the community, including by primary care physicians.

II. Detailed Exposition

1. Heart Failure

Heart failure (HF) is the terminal stage of any cardiovascular disease (CVD), and the number of patients with HF is expected to increase. Therefore, HF is considered as a significant CVD requiring palliative care.¹⁷⁶ For the relief of total pain in patients with HF, as illustrated in **Figure 11**, palliative care should be provided with standard treatment in Stage C HF. In this section, we review the overall picture of palliative care in HF, and then focus on Stage D HF, in which palliative care will be a more substantial part of the patient care.

1.1 Palliative Care in HF

Palliative care in HF should be provided from Stage C in addition to standard treatment. To balance active treatment and palliative care for HF, it is crucial for patients to fully understand disease progression from Stage C to Stage D. However, standard treatments often relieve the symptoms of acute worsening of HF, and patients are likely to favorably view their prognosis.² Therefore, it is essential to provide patients and their families with an opportunity to understand the disease trajectory of HF in the early phase of the disease process. With a better understanding of the disease trajectory, advance care planning (ACP), a means to share decision making, is a crucial step to prepare patients and their families for future changes in the disease condition (see **Chapter I.2: Advance Care Planning and Advance Directive** for details).

During the disease trajectory, patients with HF demonstrate various physical and psychological symptoms, including dyspnea, general malaise, pain, depression, anxiety, and delirium. Standard treatment for HF, such as diuretics, vasodilators, and inotropes, can improve these symptoms. However, if adequate symptom relief is not achieved, additional pharmacologic and nonpharmacologic interventions for these symptoms should be added to the standard treatment for heart failure (see **Chapter I.7: Evaluation and Care of Physical Symptoms and Chapter I.8: Evaluation and Care of Psychiatric Symptoms** for details).

In addition to physical and psychological symptoms, patients with HF also suffer from social and spiritual pain, which should be viewed as part of the patient's total pain, including from the nursing and welfare perspectives, and to approach its treatment in a multifaceted and compre-

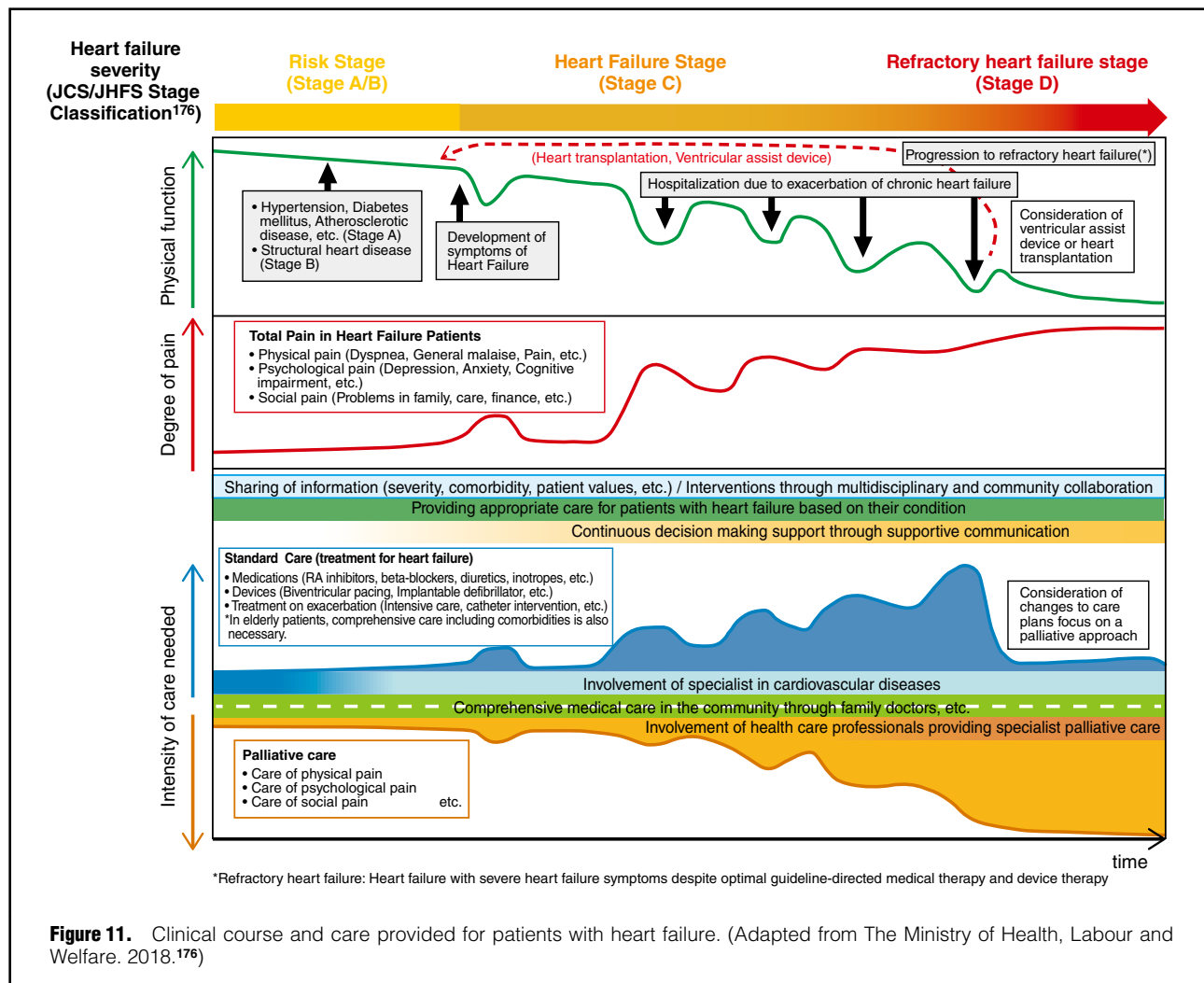
hensive manner. For this reason, healthcare professionals should support patients with HF in a multidisciplinary setting that includes collaboration with nursing and welfare professionals (see **Chapter I.9: Multidisciplinary Team Building and Chapter I.10: Palliative Care for Heart Failure at Home** for details).

Collectively, in providing palliative care for the total pain of patients with HF, it is important to understand the disease trajectory from the early stages and to provide appropriate support, including ACP, active treatment for HF, and symptomatic relief for distress, by the multidisciplinary team.

1.2 Diagnosis and Treatment of Stage D HF

In the JCS 2017/JHFS 2017 Guideline on diagnosis and treatment of acute and chronic heart failure, Stage D was defined as "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 non-pharmacologic therapy with proven efficacy, and are hospitalized for heart failure at least twice a year".⁵ Therefore, the diagnosis of Stage D is based on appropriate guideline-directed medical therapy. However, because patients with HF worsen with repeated hospitalization for acute exacerbations, the diagnosis of Stage D is often tricky. Besides, even if patients do not appear to be improving from NYHA III, appropriate therapeutic interventions can improve their symptoms. Therefore, accurate evaluation of treatable conditions and the responses to these conditions is essential. A thorough assessment of the etiology of HF, optimal medical therapy, and nonpharmacological treatment should be performed before making a Stage D determination.

On the other hand, the indication for heart transplantation as a treatment to improve long-term prognosis should be evaluated simultaneously. In Japan, criteria for evidence 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.⁵ However, patients with exclusion criteria are not eligible for heart transplantation, including over 65 years old, systemic diseases other than the heart, severe irreversible organ failure, and inadequate understanding of heart transplantation by patients and family.



1.3 Balancing Active Treatment and Palliative Care for Stage D HF Patients

Endstage cancer patients often do not receive aggressive treatment. In contrast, patients with HF may require the same standard treatment as for Stage C heart failure when they are at the endstage of the disease due to a clinical course of HF with repeated hospitalizations. Therefore, it is necessary to balance standard treatment for HF symptoms and additional palliative care, depending on the individual patient's condition. Patients with Stage D heart failure are highly symptomatic due to congestion and organ hypoperfusion. Therefore, palliative care to relieve symptoms should be initiatively provided, following standard treatment for HF.

In several USA, European, and Japanese guidelines, diuretics are recommended to reduce congestion symptoms in patients with HF with reduced ejection fraction, but their effects on mortality and morbidity have not been determined.^{5,177,178} In addition, the 2016 ESC guidelines for the diagnosis and treatment of acute and chronic HF state that diuretic management can be used to relieve severe congestion in palliative and end-of-life care.¹⁷⁷ In the management of Stage D patients with severe congestive symptoms, including severe dyspnea and edema, a sufficient dose of diuretics should be considered.

In the 2013 ACCF/AHA guideline for the management of heart failure, intravenous inotropes should be considered in such patients with systolic dysfunction who have low cardiac index and evidence of systemic hypoperfusion and/or congestion. Continuous intravenous inotropic support may be regarded as palliative therapy for symptom control in select patients with Stage D HF who are not eligible for either mechanical circulatory support or heart transplantation (Class IIb recommendation).¹⁷⁸ When considering the use of intravenous inotropes in patients with Stage D HF, the purpose of intravenous inotropes should be clarified.

Palliative care for distress, including physical and psychological symptoms, should be provided in conjunction with the curative treatments for HF such as diuretics and intravenous inotropes, to relieve the symptom burden in patients with Stage D HF (see **Chapter I.7: Evaluation and Care of Physical Symptoms** and **Chapter I.8: Evaluation and Care of Psychiatric Symptoms** for details).

1.4 Implantable Left Ventricular Assist Device (LVAD) for Stage D HF Patients

1.4.1 Palliative Care With LVAD Therapy

In Japan, LVAD therapy has been approved as a bridge to transplantation for patients with refractory HF who are

eligible for heart transplantation.⁵ Patients with LVADs need to be managed from various perspectives, including self-management of HF, device management, and wound management. Therefore, LVAD therapy requires guidance for both the patient and family members (family members include those who are not related to the patient but are significant others to the patient). A multidisciplinary team approach is needed from preoperative to postoperative and for in-home care. LVAD therapy may allow patients with Stage D HF to have improved survival and symptoms in the short-term. However, there remains a risk of complications, including infections, bleeding episodes, and stroke. A catastrophic LVAD complication and progression of a new malignancy may leave patients in the end stage with the device in place.¹⁷⁹ Such situations may prompt ethical questions of device deactivation. Hence, it is important that patients and families are well informed about LVAD deactivation at the end of life prior to LVAD implantation and are supported continuously after LVAD implantation.¹⁸⁰ Therefore, management of patients on LVAD should be performed by a multidisciplinary team that includes cardiovascular surgeons, cardiologists, other physicians (e.g., pediatrics, intensive care, palliative care), clinical engineer specialist for the VAD, VAD coordinators, nurse specialists (e.g., cardiology, intensive care, palliative care), and other specialists (e.g., pharmacist, psychologist, social worker). In the management of patients on LVADs, continuous involvement of palliative care specialists from the early stage of LVAD therapy can further help relieve symptoms, provide psychological support, and facilitate ACP.¹⁷⁹

1.4.2 Palliative Care for Patients With Destination Therapy (DT)

In other countries, LVAD therapy has been approved as destination therapy (DT); that is, long-term use of the LVAD as an alternative to heart transplantation.^{177,178} In Japan, the use of LVADs as DT is expected to be approved in the future, and we need to move forward with the discussion about appropriate palliative care in DT patients.

In the 2013 International Society for Heart and Lung Transplantation guidelines for mechanical circulatory support, the palliative care consultation should be a component of the treatment of endstage HF during the evaluation phase for patients being implanted with a LVAD as DT (Class IIa recommendation). Also, consultation with a palliative care team should be considered before LVAD implantation to facilitate discussion of end-of-life issues and establish advance directives (Class I recommendation).¹⁸¹

a. Advance Care Planning and Advance Directives Before DT

All patients with DT will eventually die with the LVAD in place. For this reason, before DT, ACP should be conducted to prepare for future changes in the patient's condition, including the end of life. ACP is a process for sharing decisions about future care goals and desired therapies before the patient becomes unable to make his or her own decisions. ACP may include the preparation of advance directives (AD), documents that describe the patient's preference for end-of-life care. The multidisciplinary team should support patients in making decisions about therapeutic options throughout the DT process after informing the patient of the expected clinical course of DT.

In these decision-making processes, it is desirable to establish ADs indicating the desired therapies at the end of life, including analgesia, sedation, tube or intravenous feeding, artificial respiration, dialysis, implantable cardioverter defibrillators, pacemakers, and mechanical circulatory support. At this time, healthcare providers should know that patients can change the contents of ADs at any time, and patients should be also informed of this choice.

1.4.3 End-of-Life Care in LVAD Therapy

From the report of the Bioethics Panel of the Japan Medical Association, it is assumed that end-of-life is "a situation that needs to be considered in the limited time to death" and is often primarily "the last months or years of life".¹⁰ Based on these concepts, the definitions of end of life in LVAD therapy are thought to be as follows: (1) progressive functional decline (physical and mental) and dependence in most activities of daily living, (2) severe HF symptoms with poor quality of life despite optimal pharmacologic and nonpharmacologic therapies, (3) frequent hospitalizations but no indication for heart transplantation or further VAD therapy, and (4) cardiac cachexia. The multidisciplinary team will make end-of-life decisions based on these factors.

In the management of LVAD at the end of life, it is essential to provide adequate relief of the patient's distress (e.g., dyspnea, general malaise, depression, anxiety). In addition, the goals of care should be addressed with the highest regard for the patient's wishes. If patients become unable to make their own decisions, healthcare providers should presume the patient's wishes by referring to the ADs and other information, together with the family members.²⁵

Withdrawing life-sustaining treatment at the end of life in CVDs should be discussed in accordance with the guidelines from several academic societies in Japan and procedures established in each institution with the best respect for the patient's wishes or presumed wishes.^{5,180,182} If the patient's intentions have not been made clear, the multidisciplinary team should decide the best treatment strategy for the patient through full discussion with the family members. In this situation, healthcare professionals should support family members in their decision making and provide them with emotional care throughout the patient's end-of-life process. With regards to helping the patient's family members, the Japanese Society of Intensive Care Medicine guidelines will be helpful.¹⁸³ In cases where it is difficult for the medical team to make decisions, such as when the patient has a secure request to deactivate the LVAD even though the patient is not at the end of life, consulting with the ethics committees of each institution is recommended.

2. Arrhythmias – Devices

2.1 Introduction

The goal of treating arrhythmia in patients with cardiovascular diseases (CVDs) is the prevention of sudden cardiac death (SCD), the improvement of symptoms due to arrhythmia, and the improvement of quality of life (QOL). Conventionally, antiarrhythmic drugs have been mainly used for the treatment of arrhythmias, but with progress in nonpharmacologic treatment, pacemaker therapy for bradyarrhythmia, catheter ablation therapy for tachyarrhythmia, and implantable cardioverter defibrillators (ICD) for the prevention of SCD, cardiac resynchronization

therapy (CRT) for heart failure (HF) associated with cardiac dyssynchrony, and the combination of these therapies, are performed.

SCD is the leading cause of death in patients with CVD, as well as death from HF, and its prevention is crucial for improving the prognosis for patients at high risk. An ICD is one of the most effective treatments for improving prognosis regardless of primary or secondary prevention of SCD. In Japan, the ICD was approved in 1996, and thereafter, along with the progress in electronic engineering, the development of smaller and lighter ICD generators and multifunctionality, as well as the development of remote monitoring systems, have made it easier to implant these devices and manage them after implantation. The number of ICD implantations is increasing.¹⁸⁴

Even if the therapeutic indication is greatly expanded due to such technological progress, all patients will eventually come to the end of their lives. For example, it is known that approximately 20% of patients who have an implanted ICD experience shock-induced pain within a few weeks prior to death,¹⁸⁵ which leads to reduced QOL.^{185,186} In addition, the negative problems associated with such treatment may occur not only at the end of life but also at the time when the treatment is started in patients who have been implanted with a cardiovascular implantable electronic device (CIED). In that sense, palliative care that relieves the patient's physical and psychosocial distress and improves QOL is needed at any time during CIED treatment. The CIED that is implanted in the body cannot be stopped by the patients themselves, and if termination of the treatment is required, it must be changed or stopped from outside the body by a specialist or a device-removal operation must be performed. Therefore, it is necessary to fully discuss this option with the medical staff, the patient and the patient's family (or substitute decision-maker) and for each party to understand each other's position regarding this action. This is also a matter that must be discussed between a patient and the medical staff before CIED implantation.

2.2 Psychological Problems and Palliative Care for ICD Patients

The ICD is a useful therapeutic device for improving prognosis in patients at high risk for SCD, and it is known that ICD implantation improves QOL for most ICD patients.^{187,188}

However, previous studies have shown that depressive symptoms are observed in 24–33% of ICD patients.¹⁸⁹ In particular, shock therapy is a risk factor for depressive symptoms in ICD patients. Depressive symptoms in ICD patients are also related to younger age (<50 years), female sex, a history of psychiatric disorders, and poor social support.^{188,189} In addition, depression persists in patients who experience repeated ICD shock therapy, suggesting that shock therapy itself also contributes to maintaining depressive symptoms.¹⁹⁰ However, there are reports that ICD patients perform avoidance behaviors caused by anticipatory anxiety, such as spatial fear and agoraphobia, and these behavior patterns are associated with depressive symptoms.¹⁹¹ HF is a common underlying disease in ICD patients, and the relationship between HF and depressive symptoms in patients has been previously pointed out. The frequency of depressive symptoms in patients with severe HF reaches 42%, and the prevalence of depression increases with an increased grade of NYHA functional

class.¹¹²

Therefore, treating depressive symptoms in ICD patients is an important part of palliative care. It has not been verified whether suppression of ICD shock therapy through combined use of antiarrhythmic drugs alleviates depressive symptoms, but it remains an important option. The effect of antidepressants is unknown. On the other hand, anxiety is reportedly observed in 24–87% of ICD patients, and ICD shock therapy has been found to increase the level of anxiety from pain and fear.¹⁸⁹ Furthermore, apart from ICD shock therapy, anxiety about the device itself and the presence of a Type D personality (finding it easy to have negative emotions and to suppress one's emotions in society to avoid criticism from others) are also reported to be associated with increased anxiety in ICD patients.¹⁹² Anticipatory anxiety that ICD shocks may be discharged greatly limits patients' daily activities. Although there are few studies of therapeutic interventions for anxiety in ICD patients, we have often found that cognitive behavioral therapy is effective in improving anxiety (particularly anticipatory anxiety).

In addition, it has been reported that 20% of ICD patients who experience ICD shock therapy have post-traumatic stress disorder (PTSD).¹⁸⁹ Selective serotonin reuptake inhibitors are the first-line treatment for PTSD, and cognitive behavioral therapy is also useful. It is necessary for cardiologists to be aware of psychological problems in ICD patients and to alleviate patients' symptoms with the assistance of psychiatrists and clinical psychologists.

For patients who use a CIED such as an ICD, the preimplantation explanation is important in terms of confirming the patient's acceptance of the device. It is necessary to fully explain not only the benefit of preventing SCD but also the possibility of malfunction, risk of CIED infection, types of ICD therapies and the contexts of setting programs, and psychological support such as drug therapy and cognitive behavior therapy if anxiety accompanying ICD therapy occurs. The important step after hospital discharge is to explain how to contact the hospital staff and how to deal with family members when ICD shock therapy occurs. Recently, home monitoring systems that constantly monitor the operating status and lead status of CIEDs at home have become widespread, and their effects can be expected to include the early prevention of frequent ICD shock or inappropriate therapy. If the patient is old, it is necessary to fully explain to the caregiver's family the location of the transmitter installed at home, the operating method, and how to contact the installer.

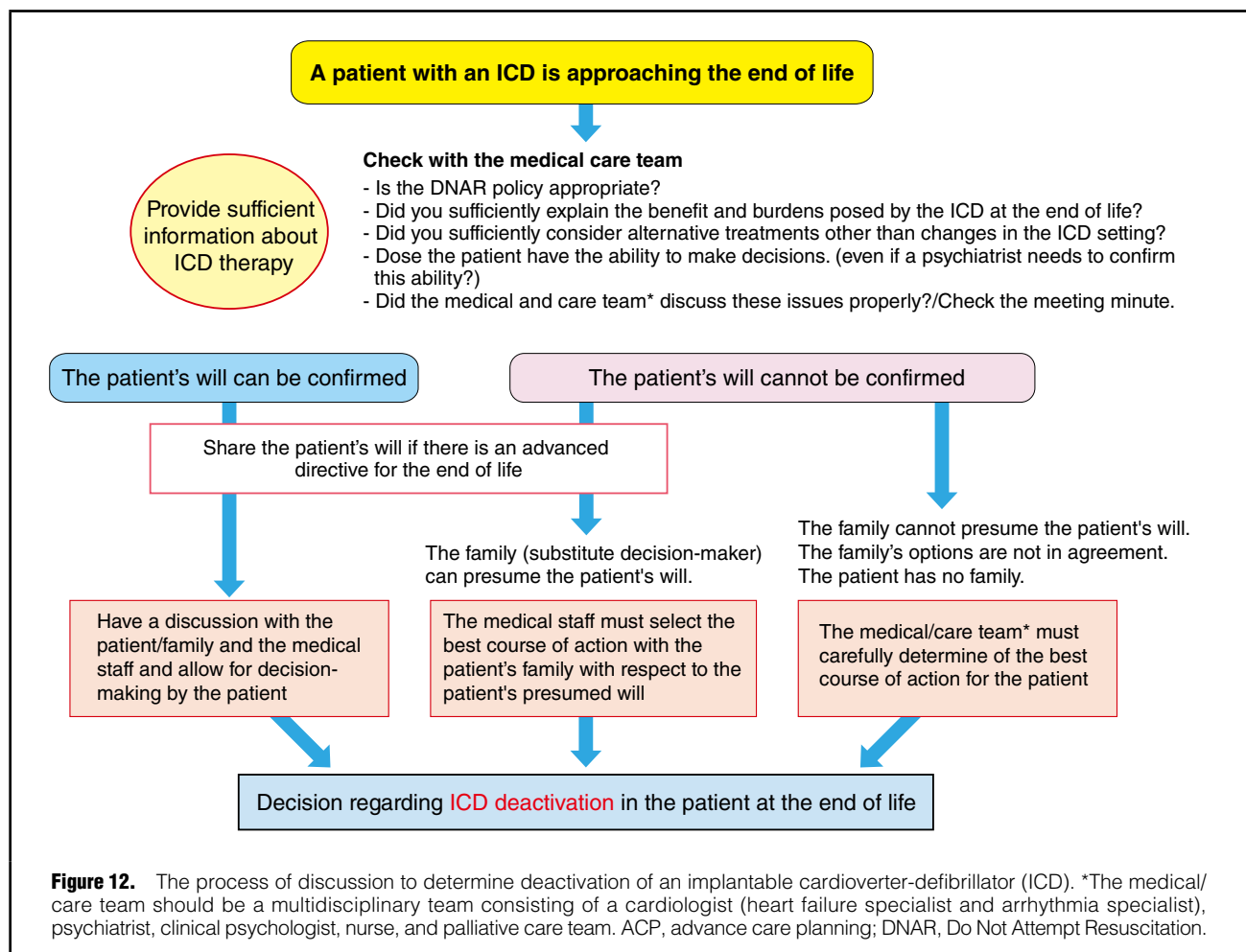
2.3 CIED Treatment and ICD Activation Status in Terminally Ill Patients

The purpose of pacemaker treatment for bradyarrhythmia is to relieve symptoms associated with bradycardia, but guidelines do not mention issues specific for endstage patients. However, decisions should be made considering the patient's general condition and the risk of pacemaker implantation. On the other hand, CRT is not recommended for patients in whom life expectancy is not expected to be more than 1 year (Class III) and is also not recommended for drug-resistant severe congestive HF in patients with NYHA functional class IV who are not candidates for heart transplantation, CRT, or LVAD (Class III).¹⁸⁴ Therefore, new implantation of CIED for endstage patients is not considered in principle.

On the other hand, the problem is whether or not to deactivate CIED treatment that has been initiated and continued before the patient is considered to be in the end stage. In patients with CVDs, including HF, even if endstage status is determined, all cardiovascular treatments are not discontinued, such as in patients with malignancy, because the treatments themselves contribute to symptom improvement. However, ICD treatment has only the purpose of preventing SCD, and shock therapy not only causes pain in the patient but also distresses the family members who provide their care, which contradicts the purpose of palliative care in terminally ill patients. In patients with HF, the clinical course towards the end of life is relatively slow, and even if the symptoms worsen, they improve promptly with acute treatment. Therefore, this causes a tendency to overestimate the life expectancy rather than identify the actual status.² Because the condition may suddenly worsen, even if the patient appears to be more stable, it is often difficult to predict the time-course prognosis. For this reason, it is difficult to determine the timing of ICD deactivation in the clinical setting.

There are few reports on the therapy status of ICD patients who are judged to be end stage. A retrospective observational study¹⁹³ of 49 ICD patients who were considered near the end of life, regardless of the type of CVD, reported that 42.9% of patients experienced ICD activation

within 1 year before death. Moreover, ICD therapy was not deactivated in 24.5% of patients even after an end-of-life diagnosis was made (in particular, this figure was approximately 20% within 1 month before death). Only one-third of patients were deactivated.¹⁹⁴ A subanalysis of MADIT-II reported the ICD therapy status of 98 terminally ill patients. Of the 83 patients without deactivation of ICD, 47 did not have Do Not Attempt Resuscitation (DNAR) orders, 6 (13%) experienced ICD shock therapy within 1 week before death, and 9 (19%) experienced ICD shock therapy within 24 h before death. In addition, 37 (37%) of 98 patients did not deactivate ICD therapy even after obtaining DNAR orders, and among them, 3 patients (8%) experienced ICD shock therapy.¹⁹⁵ A Swedish observational study reported that 32 of 65 ICD patients with DNAR orders had deactivated ICD, but 10 patients experienced ICD shock therapy within 24 h before death.¹⁹⁶ Of the 51 ICD patients who were diagnosed with endstage HF at the Tokyo Women's Medical University Hospital between 2010 and 2019, 39 had a DNAR order. Among them, only 12 (24%) patients underwent ICD deactivation. In addition, 21 (41%) patients experienced ICD shocks within 3 months before death, 14 (27%) patients experienced ICD shocks within 1 month before death, and 12 patients (24%) experienced electrical storms within 1 month before death.¹⁹⁶ Physicians as well as patients and families initiated requests for deactiva-



tion.^{194,196} The reasons for deactivation included avoidance of pain, intolerance of frequent shocks, and reduction of anxiety.¹⁹⁶

2.4 Response to End-of-Life Conditions in Patients With CIED

Regarding ICD deactivation at the end of life, shared decision making should be provided with sufficient information based on the ethical background and ACP, and additional explanations such as unnecessary physical and psychological distress caused by ICD shock therapy at the end of life and the disadvantages of not being treated for a life-threatening arrhythmia because of changed settings in the ICD should be discussed with the multidisciplinary team including cardiologists, heart-failure nurses, arrhythmia specialists, psychiatrists, clinical psychologists, palliative care staff members, etc. It should also be conveyed to the patient and family that the decision can be subsequently changed. If the patient's will cannot be confirmed, the medical staff should select the best choice for the patient together with the family members with sufficient information about the ICD with respect to the patient's presumed will through the intervening family members. If the patient's presumed will cannot be confirmed, a multidisciplinary medical/care team should carefully determine it (Figure 12).

The Heart Rhythm Society expert consensus statement states that communication about CIED deactivation is essential during an ongoing process that starts when informed consent is obtained prior to ICD implantation and continues over time as the patient's condition and treatment goals change with disease progression.¹⁹⁷ However, there is a report that only 4% of patients discussed deactivation of the ICD with their physician in the clinical setting.¹⁹⁸ From a survey of ICD patients with cancer whose prognosis was relatively easy to predict, it was reported that 35.3% of patients with stage IV cancer underwent ICD deactivation.¹⁹⁹ Thus, there are several possible reasons for the dissociation between the recommendations and the actual clinical situations. Medical staff do not actively discuss end-of-life topics and tend to postpone issues such as the deactivation of ICDs until just before death.²⁰⁰ A survey of 278 ICD patients in the USA reported that 26% of clinicians thought that deactivation itself was ethically linked to suicide assistance, and 22% thought that a DNAR order did not mean that the ICD should be deactivated.¹⁹⁸ From the viewpoint of palliative care, the avoidance of painful shocks is important when considering ICD deactivation.

On the other hand, in patients with pacemakers (including the pacing function of ICDs) and CRT who depend on pacing, the deactivation of therapy leads directly to death, unlike ICD deactivation. This is the same problem as that presented by the discontinuation of mechanical ventilation and hemodialysis treatments in Japan, and it can be difficult to make a judgment in the clinical setting if the ethical and legal backgrounds are not established. Unless pacing causes patient distress, pacemaker or CRT treatment is often continued.

In patients with refractory endstage HF who have received adequate pharmacologic and nonpharmacological treatments, deactivation decisions should be made in close cooperation with clinical psychologists, psychiatrists and palliative care teams based on a full examination of the psychological and physical stresses caused by ICD treat-

ment and the maintenance of good communication with the patient's family.

3. Coronary Artery Disease/Peripheral Artery Disease

3.1 Acute Coronary Syndrome

In patients with acute coronary syndrome (ACS), comprehensive palliative care is important in addition to the appropriate pharmacological and nonpharmacological therapy based on clinical guidelines.^{201–204} Even if the patients do not wish to receive invasive treatment, including percutaneous coronary intervention (PCI) and coronary artery bypass grafting, for reasons such as personal request or the living will of the patient, we should provide palliative care for physical pain, psychological distress, and social pain of both the patient and the family members. Regarding intensive care, the importance of comprehensive management of pain, agitation, and delirium has been focused on.²⁰⁵ On the other hand, because it was reported that the in-hospital mortality within 30 days of an OASIS study was 7.1%,²⁰⁶ the HIJAMI study reported 9.4%,²⁰⁷ and the J-MINUET study was 7.1% for ST-elevation myocardial infarction and 7.8% in non-ST-elevation myocardial infarction, grief counseling for families should be considered.

3.1.1 Palliative Care for Physical Pain: Analgesia

Analgesia is necessary for pain of the puncture site following PCI, and changing body position and early ambulation are necessary for lower back pain while in the dorsal position. Relieving physical pain is effective for prevention of anxiety, insomnia and delirium. For pain management, it is necessary to evaluate pain. If the patient's consciousness is clear, the Visual Analog Scale (VAS) and Numeric Rating Scale (NRS)²⁰⁸ are used. When consciousness is not clear, in cases such as patients under mechanical ventilation, the Behavioral Pain Scale (BPS) and Critical-care Pain Observation (CPOT) are recommended.^{205,209} In the case of NRS >3 or VAS >3, or BPS >5 or CPOT >2, the presence of pain is suggested, and pain management is required.¹⁰⁵ A change in physiological signs reflects increased sympathetic nervous activity, such as tachycardia and elevated blood pressure, and sweating is useful for the judgment of the presence of physical pain.²¹⁰ All medical staff should share information on patients' pain, as well as pain management. Analgesia should be considered prior to procedures when patients are receiving mechanical treatment accompanied by pain (e.g., intra-aortic balloon pumping, percutaneous cardiopulmonary support, or respirator).

3.1.2 Palliative Care for Psychological and Social Distress, and Measures for Delirium in the Acute Phase

ACS patients and their families experience psychological distress, including major anxiety complex. In the coronary care unit (CCU), distress can be caused by factors including the constant monitoring, machine noise, urethral catheter use, physical restriction, insomnia, and etc. These distressing factors can lead the patient into a depressed and delirious state.²¹¹ Delirium disturbs the treatment of patients, and is associated with prolongation of the CCU stay,^{212–215} cognitive dysfunction,^{216,217} and increased risk of death.^{212–215,218} For treatment and improvement of prognosis, as well as respect for human rights, preventing the occurrence of

delirium is important.

To manage delirium, we should consider assessment of patient factors (e.g., advanced age, dementia, visual impairment, and hearing loss), disease-associated factors (e.g., hemodynamic change, respiratory disorder, and infection) and treatment-associated factors (e.g., environmental change, analgesia, physical restriction, catheter insertion, and inappropriate sedation). A comprehensive approach to managing delirium by medical staff is important. To manage the ACS patient, we should especially consider several aspects including remaining pain, anxiety, resistance to sedatives, withdrawal symptoms of sedatives, insufficient circulation, hypoxemia, hypercapnia, acidosis, electrolyte abnormality, hypoglycemia, uremia and infection.

Sedation has several advantages, including (1) a sense of comfort or safety, (2) a decrease in oxygen consumption and basal metabolism, and (3) improved ventilation and a decrease in barotrauma. However, excessive sedation results in an extension of the mechanical ventilation period and length of CCU stay,²¹⁹⁻²²² and is associated with later occurrence of post-traumatic stress disorder (PTSD) and deconditioning following CCU discharge, as well as worse prognosis. After treatment for pain control, minimal doses of sedative agents should be considered.^{205,210} Attention is required for respiratory impairment and circulatory suppression following the administration of sedative agents. With respect to sedation depth, deep sedation can cause muscular dystrophy, muscle weakness, pneumonia, respirator-dependency, thromboembolism, nerve compression, pressure sores, and delirium.²²³⁻²²⁵ Thus, light sedation is recently being recommended.²⁰⁵ Although patient stress with light sedation can lead to an increase in catecholamines and oxygen consumption,^{226,227} myocardial ischemia does not occur.^{226,228} The Richmond Agitation-Sedation Scale (RASS) and the Sedation-Agitation Scale (SAS) are useful for the evaluation of sedative depth and quality.²²⁹⁻²³¹ RASS=-1 to -2 or SAS=3 for light sedation, and RASS=-3 to -5 or SAS=1-2 for deep sedation are the appropriate indices.

3.1.3 Palliative Care for Psychological and Social Distress, and Measures for Insomnia and Depression in the Recovery Phase

Patients have anxiety about the recurrence of ACS or death, as well as socioeconomic anxiety due to the burden of care and the medical costs. The family may also experience anxiety, and therefore psychological care is necessary for both patients and their families. Anxiety influences the development of PTSD, insomnia, depression, and worsening quality of life (QOL).

Chest pain or dyspnea due to ischemia or heart failure (HF), can cause insomnia. Furthermore, medication for ACS and/or HF, such as β -blockers, calcium-channel blockers, angiotensin II receptor antagonists, may also result in insomnia or nightmares. In addition, other drugs, such as lidocaine, β -blockers, digitalis etc., are associated with the occurrence of delirium and dementia. Thus, symptoms due to ACS or the treatment for ACS might cause mental and psychological distress. During comprehensive cardiac rehabilitation, counseling for psychological and social distress, as well as management of the coronary risk factors, should be considered.

The prevalence of anxiety is high among ACS patients, and the incidence of depression is reported to be approximately 3-fold higher than in control subjects. Thus psycho-

logical support is important. In a randomized trial for elderly patients with coronary artery disease, skeletal muscle strength of the lower limbs, SF-36 scale and anxiety status significantly improved with 6 months of cardiac rehabilitation; however, the depressed state did not improve.²³² Intervention by a clinical psychologist, which includes cognitive behavioral therapy, is important to alleviate the depressive state.

3.1.4 Palliative Care for Psychological and Social Distress, and Grief Counseling in the Terminal Phase

Even with the serious stage of ACS (e.g., shock), there can be an improvement in QOL that is considered as a return to normal daily life through optimal ACS management (e.g., early reperfusion therapy, mechanical cardiac support, and depressed body temperature therapy).²⁰¹⁻²⁰⁴ On the other hand, some patients suffer adverse events such as irreversible encephalopathy, heart failure, or etc., or even die. In such situations, palliative care is required to reduce the pain of the patients, and grief counseling to support the family. We should respect the process of agreement formation among the patient, family and medical staff. The medical staff perform continuous ACP with the patient and family, and provide support for interfamily decisions.

3.2 Peripheral Artery Disease of the Lower Extremities

Patients with peripheral artery disease (PAD) present with claudication, ulcers on the skin and necrosis, and have an adverse prognosis.^{233,234} In addition to appropriate treatment, palliative care for physical pain, psychological distress and social pain should be provided. PAD patients have a high incidence of complications of cardio- and cerebrovascular diseases, as well as the risk of revascularization and amputation of the lower limbs.^{233,234} Even in patients with stable PAD, death within 1 year is approximately 4%. It is important to discuss the prognosis with both the patient and the family.

Critical limb ischemia (CLI) is a clinical condition with pain at rest due to chronic ischemia or an ulcer and necrosis.^{233,234} Patients who undergo amputation of a lower extremity are at increased risk for undergoing further amputations.²³⁵⁻²³⁷ After a diagnosis of CLI, the 5-year mortality rate rises to 80%.²³⁴ After a major amputation, patients can experience both physical and phantom pain, and social pain because of loneliness, accompanied by a decrease in the ability to perform activities of daily living. The social pain of both the patient and the family can be relieved by cooperation with social workers to utilize the welfare and insurance systems.

4. Valvular Disease

4.1 Introduction

Heart failure (HF) patients with severe valvular disease, who are treated with medical treatment alone, have a poor prognosis.²³⁸ However, if their surgical risk is high, physicians and/or patients often decide to avoid surgery, even if it is indicated.²³⁹ Recently, minimally invasive catheter intervention, such as transcatheter aortic valve implantation (TAVI) or percutaneous edge-to-edge mitral valve repair with MitraClip® (TMVR), is widely used in clinical appli-

cations, and can save the lives of HF patients with endstage valvular disease. However, HF patients who are candidates for TAVI or MitraClip® are older, and have impaired cardiac function, multiple comorbidities, and frailty. Thus, therapeutic interventions do not always contribute to improvement of symptoms, quality of life (QOL), or prognosis in these patients.^{240–245} If the treatment is not sufficiently effective, then physical, mental, and social support is essential for these patients after the procedure. We describe the decision support for endstage HF patients who are candidates for TAVI or TMVR.

4.2 Evaluation of the Benefits and Futility of TAVI and TMVR

When considering the indications for TAVI or TMVR, the first thing that should be done is to discuss the merits and demerits of each treatment based on objective medical information and evidence (Table 22).

4.2.1 TAVI

a. Left Ventricular Systolic Function

A stroke volume index (SVI) <35 mL/m² is associated with a high risk of death regardless of the left ventricular ejection fraction (LVEF).^{246,247} Low SVI and low mean aortic valve velocity (mean aortic valve pressure gradient <40 mmHg) with preserved LVEF, paradoxical low flow/low gradient severe aortic stenosis (LFLGAS), has a particularly poor prognosis.^{246,247} There was accompanying ATTR amyloi-

dosis in 16% of patients who underwent TAVI, and showed the LFLGAS phenotype.²⁴⁸ Thus, we have to find ATTR amyloidosis hiding in LFLGAS. In HF patients with low LVEF and low SVI, no cardiac reserve on dobutamine stress echo (no increase in cardiac output of >20%) is a poor prognosis for surgical aortic valve replacement. However, it is not necessarily a risk factor for TAVI, and an indication for TAVI in low LVEF patients should be considered in individual cases.²⁴⁹

b. Comorbid Valvular Diseases

It is controversial whether moderate–severe mitral regurgitation (MR) is a poor postoperative prognostic factor or not.^{250–252} MR may improve after TAVI in some patients, such as those with functional MR (FMR), those without atrial fibrillation, and those without pulmonary hypertension.^{250,251} Moderate–severe tricuspid regurgitation is a poor postoperative prognostic factor in patients with a LVEF ≤40%.²⁵³

i. Pulmonary Hypertension

Pulmonary hypertension is an independent prognostic determinant. The mortality rate is particularly high in cases of combined pre- and postcapillary pulmonary hypertension.²⁵⁴

ii. Frailty, Malnutrition, and Dementia

Mortality is higher in patients with frailty, as assessed by a Clinical Frailty Scale score ≥7,²⁵⁵ and in cases of malnutri-

Table 22. Factors Associated With Outcomes After TAVI or TMVR	
Risk factors after TAVI	
LV systolic function	SVI <35 mL/m ² Low transvalvular gradient
Myocardial fibrosis	Delayed contrast enhancement by cardiac MRI
Comorbid valve disease	Moderate-severe mitral regurgitation (MR) or tricuspid regurgitation
Pulmonary hypertension (PH)	Pulmonary systolic pressure >60 mmHg Precapillary or combined PH (mean PAP >25 mmHg)
Risk score	STS >15%, MAGGIC score >30 Partner-TAVI-score
Comorbidities	Chronic lung disease, chronic kidney disease, liver cirrhosis
Frailty	Clinical frailty scale ≥7, Katz index <6 6-min walk distance <150 m
Malnutrition	GNRI <82
Cognitive function	MMSE <16
Risk factors after TMVR	
Severity of heart failure	NYHA class IV, NT-proBNP >10,000 μg/L
Residual MR	MR ≥3+
Etiology of heart failure	Ischemic cardiomyopathy
LV function	LVEF <30%, LVESV >110 mL
Right ventricular function	TAPSE <15 mm, PSVtdi <9.5 cm/s Severe tricuspid regurgitation
Comorbidities	eGFR <30 mL/min/1.73 m ² Anemia, peripheral artery disease

BNP, B-type natriuretic peptide; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESV, endsystolic volume; GNRI: Geriatric Nutritional Risk Index; LV, left ventricular; MAGGIC: Meta-Analysis Global Group in Chronic Heart Failure; MMSE: Mini-Mental State Examination; MRI, magnetic resonance imaging; NYHA: New York Heart Association; PAP, pulmonary artery pressure; PSVtdi, peak systolic velocity tissue Doppler imaging; TDI, tissue Doppler imaging; STS, Society of Thoracic Surgeons; TAPSE, tricuspid annular plane systolic excursion; TAVI, transcatheter aortic valve implantation; TMVR, transcatheter mitral valve replacement; SVI, stroke volume index.

tion, as assessed by the Geriatric Nutritional Risk Index (GNRI <82).^{256,257} Comorbidity of dementia (Mini-Mental State Examination score <16) is also a poor prognostic factor.²⁵⁸

iii. Risk Score

The Society of Thoracic Surgeons (STS) risk score, an assessment for cardiac surgery, is also useful for predicting outcomes after TAVI.²⁴³ In the PARTNER I trial, it was reported that patients with STS >15% had a poor prognosis. A risk score has been developed to identify patients with poor improvement in QOL after TAVI based on data from the PARTNER trial.²⁵⁹

4.2.2 TMVR

The benefit of MitraClip® for HF patients with reduced LVEF and severe FMR has not been well established.^{244,245}

a. Severity of Heart Failure

Patients with severe HF, who are NYHA IV or have high levels of NT-proBNP (>10,000 pg/mL) have a poor prognosis.^{260,261}

b. Residual MR

Residual MR after TMVR is a strong prognostic determinant, and severe MR is associated with a high mortality rate.²⁶⁰

c. LV Remodeling and LVEF

The primary pathology of FMR is LV dysfunction, and the prognostic benefit of reducing MR is limited in patients with progressive LV remodeling and reduced contractility. The prognostic effect of TMVR is particularly poor in HF patients with ischemic cardiomyopathy and endsystolic volume >110 mL,²⁶² or those with LVEF <30%.²⁶⁰

d. Right Ventricular Dysfunction

Decreased right ventricular function, as assessed by echocardiographic indicators such as tricuspid annular plane systolic excursion (TAPSE), is a prognostic factor.^{263,264}

e. Comorbidities

Comorbidities such as renal dysfunction (estimated glomerular filtration rate <30 mL/min/1.73 m²), peripheral arterial disease, and anemia are associated with a higher risk of death.²⁶⁰

f. Guideline-Directed Pharmacotherapy

In the COAPT trial that showed the benefit of TMVR, standard HF medications and doses were optimized throughout the preoperative and postoperative periods. In that study, there was a significant increase in β -blocker dose after treatment with MitraClip®, and the cardioprotective effect of increased β -blocker dose may have contributed to the improvement in prognosis.²⁶⁵ Therefore, continuous and appropriate medication titration before and after TMVR is essential to improve prognosis.

4.3 Importance of Shared Decision Making

Even though sufficient medical information is provided, it is not easy for patients and their families to make their own decisions with a proper understanding of the information. Therefore, it is necessary to fully understand the patient's needs and to support decision making. Each patient's values

and outlook on life will vary according to the individual case.²⁶⁶ If the benefit or risk of catheter intervention is not acceptable in terms of the patient's wishes and values, conservative treatment is considered the best treatment option. However, we should not choose futile treatment or withhold treatment because of inadequate decision support, such as (1) inadequate medical consideration, (2) insufficient understanding by the patient of medical information, and (3) healthcare providers' insufficient understanding of patient's wishes.

4.4 Importance of Clinical Ethics

Appropriate decision making requires a fair and non-biased discussion based on medical ethics, incorporating the broader perspectives of the medical professionals and patient, as well as family and social perspectives. This includes conflict of interests between patients and their families and among healthcare providers, as well as issues of socially effective use of limited healthcare resources. The "Four-Quadrant Approach in Clinical Ethics" is a methodology in which patient information is classified into 4 categories to organize the situation: (1) indications for medical intervention, (2) preferences of the patient, (3) quality of life, and (4) contextual features. The use of this classification enables a multidisciplinary team to discuss the case and seek appropriate solutions with the common view of "what is best for the patient," which has been found to be effective in promoting systematic and fair decision making.^{53,240}

4.5 Palliative Care in Parallel With Aggressive Treatment

Patient candidates for TAVI or TMVR have endstage HF, and are accompanied by a variety of pain, including physical pain, psychological pain, social pain, and spiritual pain. Whether the intervention is performed or not, we need to alleviate holistic distress and support patients in living their lives in their own way.

5. Hypertension/Aortic Disease

5.1 Hypertension

Hypertension is a known risk factor for developing cardiovascular diseases (CVDs) such as heart failure (HF), stroke, aortic disease, and peripheral vascular disease. The risk of cardiovascular events (fatal/nonfatal arrhythmias, fatal/nonfatal stroke, fatal/nonfatal HF, cardiovascular death, acute coronary syndrome, obstructive artery disease, aortic aneurysm) in the strict treatment group (average achieved blood pressure of 131.4/76.5 mmHg) is significantly lower than in the normal treatment group (average achieved blood pressure of 140.3/80.7 mmHg).²⁶⁷ However, antihypertensive

Table 23. Patients to Be Considered for Discontinuation or Dose Reduction of Antihypertensive Drugs

Elderly frail patients
Elderly patients at end of life
Cancer patients requiring end-of-life care
Dementia patients with blood pressure too low

Drugs	Expected survival 2–12 months	Expected survival <2 months
ACE inhibitor or ARB	Consider dose adjustment	Gradually reduce if normal BP
Beta-blocker	Consider dose adjustment	Gradually reduce if normal BP
Alpha-blocker	Cease	Cease
Diuretic	Consider dose adjustment	Gradually reduce if normal BP

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BP, blood pressure. (Excerpted from Pasiński T. 2017.²⁷¹)

Points
<ul style="list-style-type: none"> • Treatment according to the individual • Work closely with multiple disciplines • Continuation of blood pressure and pain control leads to palliative care as well as suppression of disease progression • Strive to provide medical care that meets the wishes of the patient, even at the end of life
Problems
<ul style="list-style-type: none"> • Unable to confirm patient's intention • Difficulty for family to accept the medical condition • Lack of medical staff

therapy is not required by all patients, and in some patients, treatment interruption should be considered. In this section, we describe the patients who should cease antihypertensive therapy.

5.1.1 Patients for Whom Discontinuation and Dose Reduction of Antihypertensive Therapy Should Be Considered (Table 23)

a. Elderly Patients at the End of Life

Diuretics for elderly patients over 80 years of age suppress all deaths and deaths due to CVD.²⁶⁸ In contrast, among nursing home residents with severe physical impairment, strict antihypertensive therapy may worsen their prognosis. Those with systolic blood pressure (SBP) <120 mmHg have a higher mortality rate than those with SBP 120–139 mmHg.²⁶⁹ In addition, it has been reported that the survival prognosis is better in hypertensive patients than in those with normal blood pressure among the elderly with a walking speed <0.8 m/s when performing the 6-min walk test.²⁷⁰ So, strict BP control for elderly patients needs to be individualized.

The recommendations for antihypertensive therapy in elderly people at the end of life are as follows: hypertensive emergency; development of symptoms related to hypertension; worsening of symptoms due to increased BP. On the other hand, discontinuation should be positively considered when it is for prognosis improvement even if antihypertensive drugs have been administered for a long time.

b. Terminal State of Cancer

Patients with cancer who require palliative care as end-of-life care will use more drugs, but may not get the benefits from antihypertensive drugs before death. Therefore, it is necessary to consider for how long the antihypertensive drug should be used.

A review of pharmacotherapy for CVD in cancer patients requiring palliative care discussed the prognosis of cancer patients and the continuation of antihypertensive drugs.²⁷¹ All patients undergoing palliative care should be evaluated for the need for antihypertensive drugs and should be considered for discontinuation if only a few benefits are expected. If the end-of-life prognosis is fewer than 2 months, reducing and discontinuing all antihypertensive drugs should be considered if BP is normal. In particular, α -blockers induce orthostatic hypotension and increase the risk of falls, so those are not recommended when life expectancy of 2–12 months is predicted (Table 24).

c. Dementia

It is suggested that treatment with antihypertensive drugs preserves cognitive function in elderly hypertensive patients, but there is no firm evidence. On the other hand, there is concern that antihypertensive drugs may cause an excessive decrease in BP, which may adversely affect cognitive function. Therefore, it is recommended that antihypertensive drug doses be adjusted to remain within the target range. Calcium-channel blockers, diuretics, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and β -blockers are recommended for use in patients with dementia, but α -blockers are not recommended and should be avoided.²⁷²

5.2 Aortic Disease

Acute aortic dissection and aortic aneurysm are the most common aortic diseases requiring palliative care. In the acute phase, it is possible that various organ disorders can occur and the status changes rapidly. Therefore, there are some points in palliative care, but many problems also exist (Table 25). In contrast, there are some cases in which the disease is relatively stable and progress must be observed chronically. Thus, palliative care for aortic disease should be performed according to the patient's condition.

5.2.1. Acute Aortic Diseases

a. Palliative Care for Acute Aortic Diseases

Acute aortic diseases, such as acute aortic dissection and ruptured aortic aneurysm, are severe and often require emergency surgery. In acute aortic dissection especially, patients in whom the level of consciousness is lowered due to organ perfusion disorder, extensive multi-organ ischemia, and shock state must be treated as soon as possible. Despite advances in medical technology, the perioperative mortality rate is still high at 25%,²⁷³ but surgical treatment is associated with lower mortality than medical treatment.²⁷⁴ Prognosis of patients undergoing surgery for ruptured

abdominal aortic aneurysms has been studied using prognostic scores, but this method is not sufficiently accurate and it is unclear which patients should undergo surgery. Therefore, the rate of surgical intervention should be increased.²⁷⁵ For these reasons, it is difficult to explain to patients and their families what treatment to choose and what the prognosis will be.

Sometimes the patient is unconscious or unable to confirm their wishes because of the emergency situation. In such cases, it is necessary to sufficiently explain the disease state and future prognosis to the families and have them decide how to deal with sudden deterioration. However, family acceptance of illness is not easy because of the limited time to draw conclusions. Therefore, it is desirable that not only doctors but also medical staff such as nurses be present at the time of the explanation. In addition, because the patient's medical condition changes suddenly, doctors are often required to perform urgent care, and the role of medical staff is important. However, the number of medical staff is limited, and there are many problems with how to support patients and their families.

If the surgical risk is high because the patient's general condition is poor, the patient may be treated conservatively without surgery. In patients with aortic dissection, it has been clarified that conservative treatment has a much worse prognosis than surgical treatment.⁷ If surgery is not possible, the patient may become unconscious or need intensive care, which may prevent the patient from making decisions. The family should be given sufficient explanation to make decisions about future treatment plans. In that case, multidisciplinary intervention and close cooperation are required on how to carry out family care.

b. Blood Pressure Management and Pain Control for Palliative Care

Blood pressure control and pain control are important in the treatment of acute aortic disease. Although emergency surgery is considered for acute aortic dissection, drugs for pain relief and BP control are recommended for all patients. In aortic dissection, reduction of the shear stress of the aorta can be expected to suppress the expansion of the dissection space. Therefore, control of both BP and pulse rate is required. As a result, lowering the BP leads not only to progression of the disease but also to pain relief. Systolic BP of ≤ 120 mmHg is recommended as the target level. Beta-blockers, non-dihydropyridine calcium channel blockers are selected as medical therapy. Beta-blockers have not only antihypertensive effects but also pulse rate reducing effects. Continuous intravenous infusion of non-dihydropyridine calcium channel blockers can lower the BP more quickly.

Among patients with type A aortic dissection, 80% complain of chest pain, 40% complain of back pain and 25% of abdominal pain. On the other hand, patients with type B dissection have 70% of abdominal pain and 70% of back pain. Pain may move from its origin to other sites and follow the pathway of aortic dissection.²⁷⁶ Pain increases BP and pulse rate, which may lead to expansion of the dissection space. Therefore, pain control not only provides pain relief but also has an effect of suppressing the elevation of BP and pulse rate. In other words, pain control itself suppresses the progression of the disease and leads to palliative care.

There is insufficient evidence for the drugs used to control pain in aortic disease. Opioids such as morphine and

fentanyl are commonly used. However, because aortic dissection may be combined with other organ disorders such as renal dysfunction, it is necessary to select therapeutic drugs according to the degree of organ disorder. Nonsteroidal anti-inflammatory drugs should be used with caution because they increase the risk of bleeding and embolism.

c. Aortic Diseases With Organ Dysfunction at the End of Life

Patients with aortic diseases with organ damage are not indicated for surgery and may be treated mainly with end-of-life care. In such cases, pain control plays a central role. Antihypertensive treatment should not be suddenly discontinued, because it may reduce the risk of developing arterial rupture or dissection and reduce pain. However, when organ ischemia is caused by a decrease in BP, it is necessary to carefully judge whether or not to continue with the drugs.

If the intentions of the patient can be confirmed, their condition should be fully explained and medical care should be provided according to the patient's wishes. However, some patients have rapidly progressive disease, and treatment will be different in each case.

5.2.2 Chronic Aortic Diseases

Chronic aortic disease includes uncomplicated type B aortic dissection and inoperable thoracic and abdominal aortic aneurysms. In both cases, generally conservative treatment is given by reducing BP while evaluating lesions with repeated imaging follow-up. Excessive exercise should be avoided, and lifestyle guidance is important. Although the condition is often stable without the appearance of symptoms, the prognosis becomes very severe if the aorta ruptures. It is necessary to explain this sufficiently to the patient, including the performing of emergency surgery. On the other hand, it may be difficult to perform surgery in very elderly patients or patients with underlying conditions that increase the risk of surgery. When the patient's condition is stable and their intention can be confirmed, it is necessary to fully explain the medical condition, including with the family, and discuss with them what to do if the condition worsens.

6. Pulmonary Hypertension and Adult Congenital Heart Disease

6.1 Pulmonary Hypertension

6.1.1 Palliative Care Needs in Pulmonary Hypertension

Pulmonary hypertension (PH) is a disease with varied etiology causing vasoconstriction of the pulmonary arteries and progressive remodeling of the pulmonary vasculature, with increased pulmonary arterial pressure leading to right heart failure and reduced survival. PH is classified into 5 groups based on similarities in pathophysiology, clinical presentation, and therapeutic options: Group 1, pulmonary arterial hypertension (PAH); Group 2, PH due to left-sided heart disease; Group 3, PH due to lung diseases and/or hypoxia; Group 4, chronic thromboembolic pulmonary hypertension; Group 5, PH with unclear or multifactorial etiology.²⁷⁷ The effect of PH on the patient's health-related quality of life (HRQOL) is significant. The most common symptom is dyspnea at rest or during exercise; other symptoms include easy fatigue, chest discomfort, leg edema, abdominal bloating, and anorexia. Although 7.5–53% of

Table 26. Specific PAH Medications and Typical Side Effects	
Phosphodiesterase type 5 (PDE-5) inhibitor	Gastroesophageal reflux, jaw pain, skin flushing, and headaches
Endothelin receptor antagonist (ERA)	Nasopharyngitis/nasal congestion, headache, anemia, liver failure, and lower extremity edema
Prostaglandin	Skin flushing/hot flashes, nausea, headache, peripheral neuropathy, and diarrhea
Soluble guanylate cyclase (sGC) stimulator	Headache, skin flushing, hot flashes, systemic hypotension, and syncope

PAH, pulmonary arterial hypertension.

PH patients have depression and 19–51% have anxiety and panic disorders,²⁷⁸ psychiatric symptoms are often overlooked,²⁷⁹ even though the disease often causes social and financial problems for patients and their families. As with heart failure (HF), a palliative care approach early in the disease trajectory of PH may be effective in improving HRQOL, but there is a lack of awareness of both palliative care and its delivery.²⁸⁰ This section focuses on Group 1 PAH, which presents the most typical clinical picture of PH. Although there is insufficient evidence on the effectiveness of combining standard and palliative care for PAH, this does not negate the potential benefits of palliative care for patient and family distress symptoms and HRQOL. PAH guidelines published by the American College of Chest Physicians in 2019 “suggest” the inclusion of palliative care services in the treatment of PAH.²⁸¹

6.1.2 PAH Treatment and Palliative Care

PAH-specific agents currently available are prostacyclin pathway agonists, endothelin receptor antagonists, and nitric oxide (NO)-cGMP enhancers. These drugs will also be considered for use in Groups 4 and 5, but are rarely used in Group 2 or 3. They have been demonstrated to reduce readmission rates, decrease disease progression, and improve HRQOL in patients with PAH.^{282–284} On the other hand, specific PAH therapies produce a variety of side effects (Table 26) during the induction process and their effect on HRQOL is not small. In particular, continuous intravenous or continuous subcutaneous administration of prostanooids is highly invasive and has a significant effect on the patient’s HRQOL. For example, epoprostenol is delivered continuously through a permanently implanted central venous catheter using a portable infusion pump. Patients are required to dissolve and load the drug into the pump under sterile conditions every 1–2 days, and there is a risk of thrombosis, infection, and pump-related problems. Treprostinil can be administered subcutaneously, as well as through continuous IV infusion, but one-quarter of patients discontinue the medication because subcutaneous administration is likely to cause pain at the injection site.²⁸⁵ Oxygen therapy is also associated with lower HRQOL.²⁸⁶ Compared with HF, standard therapies to improve hemodynamics are more likely to compromise HRQOL in patients with PH. To maximize treatment, it is important to provide symptom relief and decision-making support for the introduction of these therapies in parallel with treatment. PAH-SYMPACT (Pulmonary Arterial Hypertension-Symptoms and Impact),²⁸⁷ emPHasis-10,²⁸⁸ and CAMPHOR (Cambridge Pulmonary Hypertension Outcome Review)²⁸⁹ are known tools for assessing HRQOL in patients with PAH.

6.1.3 Prognosis Prediction and Decision-Making Support for Patients With PH

The disease trajectory of PH progresses through a series of exacerbations and remissions of decompensated HF, leading to a relatively rapid terminal stage.²⁹⁰ There is also a risk of sudden death, with 80% of cardiopulmonary resuscitations being unsuccessful and only 6% of patients surviving 90 days or more with good neurological outcomes.²⁹¹ Predicting an accurate prognosis for PH is very difficult,²⁹² and as a result, we often miss the timing of the benefits of palliative care by focusing on aggressive treatments and not discussing with patients how they want to spend the end of their lives. According to reports from the USA, 52–83% of PAH patients who die in hospitals die in intensive care units.²⁹³ Enhanced communication between healthcare providers and patients is the basis of palliative care, allowing for greater knowledge of the disease, understanding the trajectory of the disease, and knowing the prognosis. It should also be considered that patients with PAH are relatively young and predominantly female. From the time of the diagnosis of PH, the prognostic discussion should be considered, explaining treatment options and risk considerations, depending on the patient’s condition. Rather than focusing on the negative aspects of prognosis, we should encourage advance care planning (ACP) that allows patients to make the best choices.²⁹³ The variables presented in the Guidelines for Treatment of Pulmonary Hypertension (JCS 2017/JPCPHS 2017) (Table 27)²⁹² may be helpful in considering severity and prognosis, and may be useful in determining when to conduct an assessment of palliative care needs, including ACP and symptom relief as well as treatment modification.

6.1.4 Relief of Symptoms in Patients With PAH

PH is highly symptomatic at the end of life and there is a significant decline in QOL, as with COPD, renal failure, and treatment-resistant cancer patients.²⁹⁵ Dyspnea is a particularly strong symptom, but maximum treatment of PH is a prerequisite for symptom relief. Although the efficacy and safety of opioids for refractory dyspnea symptoms have been reported,²⁹⁶ there is insufficient evidence in patients with PH. Also note that the use of opioids, antipsychotics, and tricyclic antidepressants concomitantly with specific PAH medications can cause hypotension due to drug interactions.²⁹⁷ Many patients with advanced PH also present with symptoms associated with fluid retention, but because of intestinal edema, oral diuretics may not be fully absorbed, and intravenous diuretics must be administered as needed to relieve symptoms. Constipation and severe cough can lead to syncope from increased intrathoracic pressure, so these symptoms need to be aggressively treated. Specific PAH medications

Prognostic factor (estimated mortality rate at 1 year)	Low risk (<5%)	Medium risk (5–10%)	High risk (>10%)
Clinical sign of right-sided heart failure	Absent	Absent (or present)	Present
Symptom exacerbation	Absent	Slow	Rapid
Syncope	Absent	Incidental	Repeated
NYHA/WHO functional class	I, II	III	IV
6-minute walk distance	>440 m	165–440 m	<165 m
Cardiopulmonary exercise load test	peak $\dot{V}O_2$ >15 mL/min/kg (>65% predicted) $\dot{V}E/\dot{V}CO_2$ slope <36	peak $\dot{V}O_2$ 11–15 mL/min/kg (35–65% predicted) $\dot{V}E/\dot{V}CO_2$ slope 36–44.9	peak $\dot{V}O_2$ <11 mL/min/kg (<35% predicted) $\dot{V}E/\dot{V}CO_2$ slope \geq 45
BNP NT-proBNP	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–300 ng/L NT-proBNP 300–1,400 ng/L	BNP >300 ng/L NT-proBNP >1,400 ng/L
Imaging (echocardiography, heart MRI)	Right atrium area <18 cm ² No endocardial fluid	Right atrium area 18–26 cm ² No or little endocardial fluid	Right atrium area >26 cm ² Endocardial fluid present
Hemodynamics (catheterization)	Mean right atrial pressure <8 mmHg Cardiac index \geq 2.5 L/min/m ² SvO ₂ >65%	Mean atrial pressure 8–14 mmHg Cardiac index 2.0–2.4 L/min/m ² SvO ₂ 60–65%	Mean atrial pressure >14 mmHg Cardiac index <2.0 L/min/m ² SvO ₂ <60%

HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension. (Adapted from Japanese Circulation Society and the Japanese Pulmonary Circulation and Pulmonary Hypertension Society Joint Working Group. 2019.²⁹⁴)

are very expensive, and depending on the place of care, it may be difficult to continue them. On the other hand, abrupt discontinuation of these medications may lead to rapid functional decline or death, so careful multidisciplinary review is necessary.

6.2 Adult Congenital Heart Disease

6.2.1 Considerations for Palliative Care

Due to advances in medical science, many patients born with congenital heart disease (CHD) now die in adulthood rather than in infancy.²⁹⁸ Adult congenital heart disease (ACHD) patients differ from the usual adult HF patients because they have a lifelong chronic disease, often die young in severe cases, and have a strong parental commitment to decision making. In typical HF, comprehensive care often begins with the onset, but CHD begins at birth, sometimes earlier thorough support to parents after a fetal diagnosis of complex CHD.²⁹⁹ Furthermore, the symptoms, clinical course, and prognosis of patients with ACHD vary widely among individuals with each disease (e.g., patients with asymptomatic postoperative atrial septal defects and failed Fontan patients with multi-organ failure). The prognosis for patients with ACHD is difficult to predict and they are often actively treated during the last hospitalization of their lives.²⁹⁹

6.2.2 Decision-making Support for Patients With ACHD

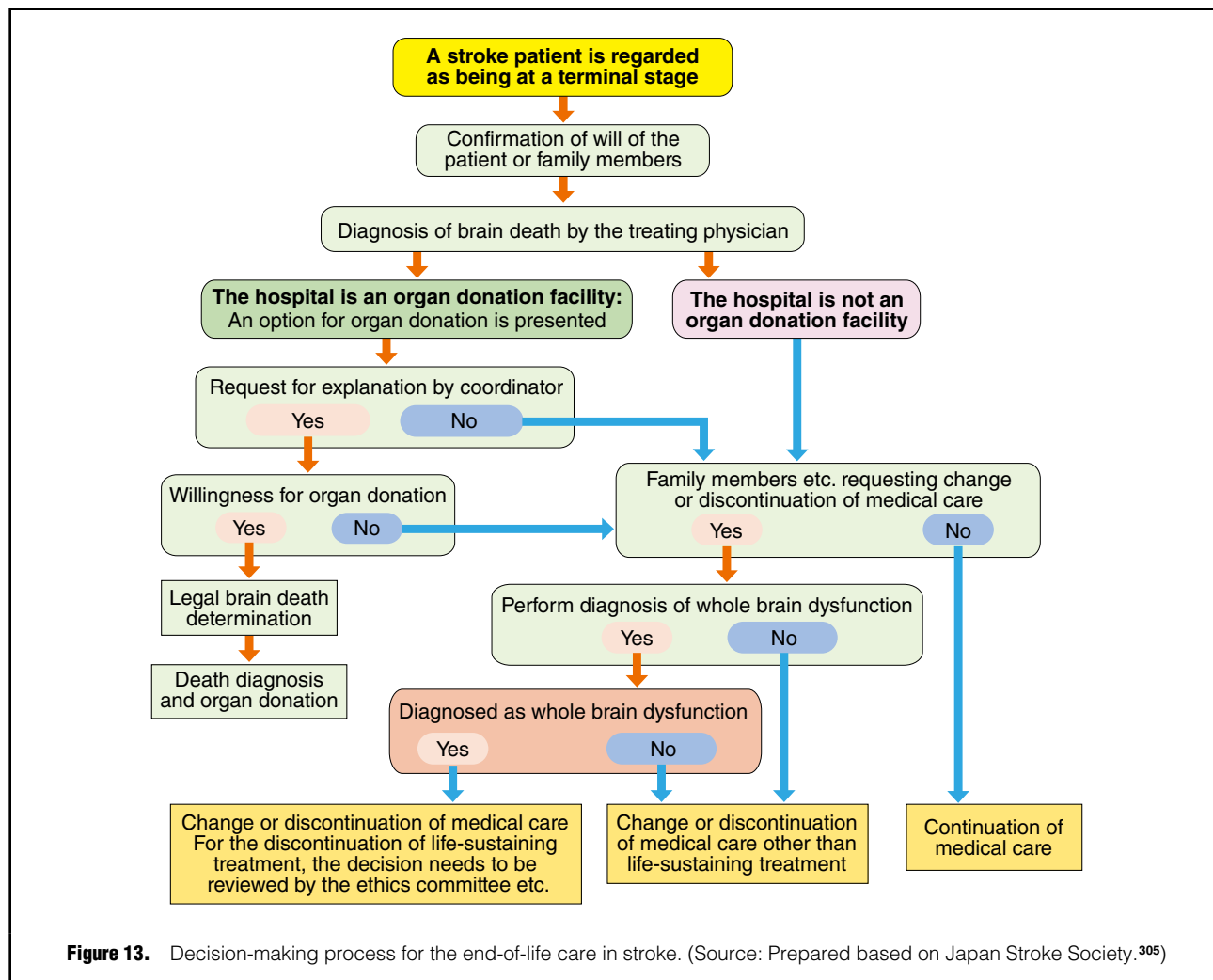
2018 AHA/ACC guideline for the management of adults with congenital heart disease states that it is beneficial for patients with ACHD or their surrogates to discuss end-of-life issues and advance directives (Class IIa, level of evidence: B-NR).³⁰⁰ Although there are currently insufficient prospective studies examining the benefits of ACP for ACHD, a systematic review of ACP in patients with ACHD found that while patients expressed a strong interest in it, only a small number of patients had the opportunity for ACP.³⁰¹ It is also reported that many patients with positive attitudes toward ACP want to have the opportunity for ACP early in their disease and that interest in ACP was

independent of disease severity.³⁰² For patients with ACHD who have undergone life-threatening surgeries and other treatments since childhood and have lived with various complication risks after surgery, the challenge is how to respect their wishes as they approach the end of their lives. Many patients with ACHD are exposed to social and psychological problems that affect their HRQOL.³⁰³ These psychosocial problems may be a result of the nurturing environment, including a lack of maturity in interpersonal relationships with friends as a result of prolonged hospitalization from an early age and a high degree of dependence on parents. As a result, patients with ACHD often have diminished ability to solve social problems and independence, and in addition to being highly dependent on their parents, they may have problems with their decision-making ability.³⁰⁴ Patients with ACHD may have associated chromosomal abnormalities and mental developmental delays, and may also have neurocognitive deficits due to persistent hypoxia and surgical complications from childhood. In these cases, social independence is even more difficult and there is a high degree of dependence on parental and family support. If there are difficulties with decision-making support, work with the palliative care team, psychiatrist, or clinical psychologist as appropriate. Besides, as patients with ACHD transition from pediatric to adult care, multidisciplinary support should also facilitate subsequent ACP by sharing the disease process with the patient and allowing the patient to progressively contribute to decisions about treatment options.

7. Stroke

7.1 Care for Stroke Patients

The term “stroke” refers to an acute cerebrovascular disorder. However, stroke is not a single entity but a heterogeneous condition with different etiologies, such as ischemic cerebrovascular disease, cerebral hemorrhage, and subarachnoid hemorrhage, and has widely varying clinical course and outcomes. Unlike terminal cancer or



chronically ill patients, some stroke patients may die within hours or weeks. However, the mortality is low in the post-acute phase, and the prediction of life prognosis is often difficult. Patients with severe stroke may eventually develop a prolonged consciousness disorder and become bedridden for a long time. The sequelae of stroke include paralysis, dysphagia, language disorder, and higher brain dysfunction. Although these sequelae are not life-threatening, they can severely affect the quality of life (QOL) of patients.

There is no established method for predicting the prognosis in patients with stroke, although there are several prediction models for functional and survival outcomes. Currently, the functional and survival outcomes are predicted by attending neurologists or neurosurgeons based on clinical information together with their clinical experience and knowledge.

The degree of brain injury, focal neurological signs, and severity of the neurological deficit vary among patients. Therefore, when considering the palliative care needs of stroke patients, it is all the more essential to assess each patient's disease state, as well as physical, psychological, and social problems, and the burden of families and caregivers, while having compassion and empathy for them. Palliative care is required for patients with varying backgrounds, and it is estimated that many stroke patients need palliative care.

The Ministry of Health, Labour and Welfare has developed the Guidelines on the decision making process for end-of-life care (revised in 2018).²⁵ These emphasize the importance of a shared decision-making process in end-of-life care, stipulating that, in principle, the decision should be made by the patient after a thorough discussion with the healthcare team. However, in the case of severe stroke in which an advance directive or advanced care plan is not available, the patient may not be able to communicate with healthcare professionals or family members because of coma, aphasia, or prolonged consciousness disturbance, and the will of the patient cannot be confirmed by family members because of the sudden disease onset. In order to solve these problems, further discussion is required in Japan.

7.2 Irreversible Dysfunction of the Whole Brain Due to Stroke

The Japan Stroke Society has developed their Guidelines for the end-of-life care in stroke (released in December 2018),³⁰⁵ which addresses the issue of end-of-life care in stroke patients with whole-brain dysfunction. Healthcare professionals are recommended to use the guidelines to support the decision-making process in the end-of-life care in consideration of the characteristics of stroke patients.

Stroke patients at the end of life can present with widely varying conditions and symptoms, including irreversible dysfunction of the whole brain, persistent vegetative state, and a bedridden status due to recurrent stroke or exacerbation, and be facing imminent death. Further discussion is required to provide palliative care tailored to meet each patient's need. In this section, we address the issue of "whole-brain dysfunction due to stroke" in end-of-life care in accordance with the guidelines.

Definitive diagnosis of "whole-brain dysfunction due to stroke" requires the following: (1) deep coma; (2) apnea; (3) fixed and dilated pupils (both pupils have a diameter ≥ 4 mm); (4) disappearance of brainstem reflexes (light, corneal, ciliospinal, oculocephalic, vestibular, pharyngeal, and cough reflexes); and (5) flat brain waves on electroencephalogram. These criteria are in accordance with the "brain death diagnosis" in the Legal Brain Death Determination Manual. "Whole-brain dysfunction" is equivalent to the condition of "brain death" in the Legal Death Determination Manual, and a stroke patient with whole-brain dysfunction is regarded as being in the terminal stage. The final diagnosis is established by 2 physicians. A healthcare professional attends the diagnostic meeting and records the results.

The detailed procedure described in the Guidelines for end-of-life care in stroke is summarized as follows (Figure 13). If a patient is diagnosed with "brain death", the treating physician should consider and respect the will of the patient and determine the best treatment for the patient through a discussion with family members. In addition, the physician is expected to provide information about organ donation (presenting options for organ donation) and its procedure to family members using a written information sheet. If the family members request an explanation, it is given by a coordinator at the relevant organizations, such as the Japan Organ Transplant Network. It should be noted that the physician must not force family members to listen to the coordinator's explanation. If the family members do not request an explanation, the physician asks whether or not they would consider a change or discontinuation of medical care. If they request this, the physician presents the option of "definitive diagnosis of whole-brain dysfunction". If the definitive diagnosis of "whole-brain dysfunction" is made, the current medical care is changed or discontinued after a thorough discussion with family members. When performing discontinuation or withdrawal of the life-sustaining treatment (cardiopulmonary resuscitation at cardiac arrest; mechanical ventilation; pacemaker therapy [including changing the setting of an implantable cardiovascular defibrillator]; use of a lifesaving defibrillator, such as assisted circulation apparatus; and blood purification therapy, such as hemodialysis; administration of vasopressors or blood products, transfusion, and artificial nutrition), approval of the hospital director after a review by the ethics committee of each institution is necessary. If the family members do not request a change or discontinuation of medical care, the treating physician continues to provide the best treatment for the patient. It is important to record in writing the process and discussion in detail.

7.3 Palliative Care for Physical, Mental, and Social Problems in Stroke Patients

Many stroke patients not diagnosed with whole-brain

dysfunction may still have impaired ability to perform activities of daily living (ADL) and decreased QOL. Their physical, mental, and social problems can be managed with palliative care. Strategies for medical and palliative care should be carefully determined with consideration of the values of the patient and family members. The decision is based on consensus among the members of the multidisciplinary healthcare team, including physicians, nurses, social workers, clinical psychologists, etc. The important precautions (1–7) are listed.

- (1) Members of the multidisciplinary healthcare team need to have appropriate communication skills and knowledge in order to address the physical, mental, cultural, psychological, and social needs of patients receiving palliative care.
- (2) The healthcare team holds regular meetings with patients and family members in order to discuss the issues of end-of-life care, such as whether or not the patient's life can be saved, whether or not there is a possibility of functional recovery, and whether or not pain relief and palliative care should be prioritized, with consideration of the patient's condition and the severity of stroke. Treatment and palliative care plans are changed if necessary.
- (3) The healthcare team provides psychological support to family caregivers.
- (4) The topics of discussion include discontinuation of a medical intervention, actions in emergency situations (resuscitation etc.), and the site of palliative care.
- (5) The healthcare team records the results of each meeting.
- (6) Because the patient's condition will change over time, the suitability of the care plan should be confirmed whenever there is a change in the patient's condition and when members of the healthcare team have changed.
- (7) The patient or family members can change the goal of care.

Based on the guidelines in Canada³⁰⁶ and the USA,³⁰⁷ the assessment items that are useful for palliative care in Japan were developed and include the following: pain due to stroke; nutrition and fluid administration for patients with dysphagia; dyspnea and respiratory tract secretion; delirium; incontinence; nausea; vomiting; constipation; bedsores; convulsion; psychiatric symptoms (anxiety/depression); easy fatigability; and social difficulties. In the case of severe stroke and imminent death, actions in emergency situations (resuscitation etc.) and the advantages and disadvantages of life-sustaining methods, such as mechanical ventilation, enteral/parenteral nutrition, and intravenous infusion, are discussed. When withholding life-sustaining treatment, the following issues are discussed: re-evaluation of drug therapy (including discontinuation), frequency of vital sign assessment, discontinuation of blood testing and imaging study, and who to contact in the case of death. The site of care is also an issue to be discussed (home, medical long-term care sanatorium, care facility, etc.).

In Japan, further discussion and accumulation of clinical data are necessary to establish the method of palliative care. The healthcare team needs to evaluate the appropriateness of the palliative care they are providing in order to improve the quality of services. It is desirable to consult a palliative care specialist when difficult problems arise (difficulties in symptom control, end-of-life decision making, and management of psychosocial distress, etc.). However, such consultations are not always possible because of the

lack of human resources; therefore, more palliative care specialists are needed in Japan.

8. Principles of Drug Therapy

8.1 Drugs Used in Palliative Care

The endstage of cardiovascular disease (CVD) is defined as treatment-resistant disease and endstage heart failure (HF). Such patients usually have various symptoms, such as dyspnea, general malaise, pain, loss of appetite, and depression. According to previous reports of patients with endstage HF, 60–88% have dyspnea, 69–82% have general malaise, and 35–78% have pain.^{111,308,309} Terminally ill patients often suffer from mental health disorders such as depression, anxiety, and insomnia; 70% of patients with endstage HF who require hospitalization are reported to have depressive symptoms.¹¹² Drug therapy is sometimes required to alleviate such symptoms during HF treatment.

Based on the common premises that palliative care is applicable for diseases other than cancer, the drugs used in endstage CVD are the same as those used in patients with cancer. Acetaminophen, morphine, and anxiolytics are used for respiratory distress and pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) should not be used in patients with CVD because of the risks of gastrointestinal disorders, exacerbation of renal dysfunction and acceleration of fluid retention.⁷⁸ For insomnia, melatonin receptor agonists, orexin receptor antagonists, benzodiazepines (BZDs) and non-BZDs are used. Antipsychotics and benzodiazepines are used for delirium. The main drugs for antidepressive treatment are BZDs, anxiolytics, antidepressants, selective serotonin reuptake inhibitors (SSRIs), and serotonin-noradrenaline reuptake inhibitors (SNRIs).

8.2 Pharmacokinetics and Precautions in HF Patients

In patients with HF, the gastrointestinal absorption of oral drugs is often reduced due to decreased peristalsis of the digestive tract, prolonged gastric stasis, intestinal edema, and decreased blood flow in the absorption site. Treatment with oral drugs is limited, especially in patients with decompensated HF who require intensive care. Hepatic blood flow decreases, and the hepatic metabolic capacity generally decreases due to degeneration of liver parenchymal cells and a decrease in metabolic enzyme activity in patients with HF. Therefore, drugs that are metabolized in the liver (both flow-limited drugs and metabolic, capacity-limited drugs) may show a high blood concentration in HF.³¹⁰

On the other hand, in patients with HF, decreased cardiac output and increased sympathetic nerve activity cause changes in tissue blood flow, the distribution of blood flow to each tissue, and the distribution of blood flow within each tissue, and these changes lead to changes in the distribution of the drug. In general, the distribution of a drug in plasma increases, and the volume of distribution decreases (the volume of distribution seems to increase with edema, but the circulating blood volume decreases; therefore, the blood drug concentration increases). Furthermore, when the plasma albumin level decreases due to HF, the free form of any drug that binds to albumin increases, and the pharmacological effect is increased in patients with HF. However, the concentration of α 1-acid glycoprotein, which is an inflammatory protein, rises in HF, so that the

free form of drugs that bind to α 1-acid glycoprotein decreases and the pharmacological effect is decreased.³¹⁰

In HF, renal clearance of a drug decreases because low cardiac output reduces renal blood flow (prerenal failure), glomerular filtration rate in addition to causing renal parenchymal and tubule disorders (renal failure). Therefore, the elimination half-life of renally excreted (highly water-soluble) drugs is reduced, and the blood concentration is also increased. On the other hand, loop diuretics and thiazide diuretics are secreted from the proximal tubule into the urine and act from the tubular lumen to inhibit transport mechanisms, so a high dose may be required in patients with HF.

For patients with HF, it may be safer to start with a lower dose than the usual dose because blood concentrations tend to be high as a function of pharmacokinetics. In addition, if the pharmacological effect is not sufficiently obtained, changes in the administration route or reconsideration of the dose are necessary. Furthermore, patients with CVD often take concomitant medications, which may cause unexpected enhancement of the pharmacological effects or the occurrence of adverse reactions, and drug interactions should always be monitored with caution.

8.3 Opioids in Patients With Endstage CVD

Dyspnea, severe pain, and malaise are common symptoms in patients with endstage HF.³¹¹ Hospice care, including opioids, is recommended as appropriate symptomatic relief for patients with endstage HF.³¹² Opioids act to improve the abnormal ventilation pattern of HF, resulting in relief from the dyspnea and pain. In previous studies in patients with HF, oral opioids were reported to yield both short-term and long-term relief of dyspnea in patients with chronic HF and with no adverse effects.^{104,313,314} However, the use of opioids for dyspnea and pain relief in patients with endstage HF has not been established. Because pain can come from various parts of the body, it is necessary to identify cardiogenic factors (e.g., musculoskeletal pain, gout, peripheral vascular disorder, lower leg edema, ascites).³¹⁵ Fatigue may be caused by reversible factors such as hyperdiuresis due to diuretics, fatigue associated with β -blockers, sleep disorders and anemia, and therefore, an assessment of the cause is important.

Concomitant medications such as oxycodone/acetaminophen are generally not recommended because they may prevent opioid dose escalation. Short-acting opioids such as morphine and codeine are switched to sustained-release formulations after the total daily requirement is determined. Short-acting opioids can be used as needed even in patients using sustained-release opioid formulations. Methadone is effective for chronic pain, but caution should be taken regarding prolonged QT as well as the development of torsades de pointes. Meperidine, morphine, and codeine should be used cautiously in patients with impaired renal function. If orally administered opioids are difficult to use, transdermal (fentanyl) or subcutaneous (morphine or hydromorphone) opioids can be used.

8.4 Polypharmacy and Deprescribing

Polypharmacy is common in the treatment of CVDs, because many are multifactorial, and there are several evidence-based therapeutic strategies to control the underlying risk factors. In addition, in elderly patients with

HF, the number of drugs consequently increases with an increase in comorbidities and concomitant diseases. However, we should not forget that the risk of adverse reactions increases as well with an increased number of concomitant drugs.

For patients with CVD who have a long history, it is necessary to reset the patient's treatment goals as the patient's situation changes. In palliative care, the improvement of QOL is the main goal, and avoidance of pain is required. For that purpose, reconsideration of prescribed drugs for each patient and for each phase of disease is an important process.

The protocol proposed by Scott et al as a deprescribing method for polypharmacy is also useful in the treatment of CVD.³¹⁶

- (1) Identify all drugs the patient is currently taking and the reasons for each one. Patients should be asked about any regularly prescribed drugs that are not being taken and, if so, why not.
- (2) Consider the overall risk of drug-induced harm in individual patients in determining the required intensity of a deprescribing intervention. Consider drug factors: number of drugs (the single most important predictor), use of high-risk drugs, past or current toxicity and patient factors: age >80 years, cognitive impairment, multiple comorbidities, substance abuse, multiple prescribers) and nonadherence.

- (3) Assess each drug for its eligibility to be discontinued:
 - No valid indication
 - Part of a prescribing cascade (use of antitussives for cough caused by angiotensin-converting enzyme inhibitors)
 - Actual or potential harm of a drug that clearly outweighs any potential benefit
 - Ineffective disease and/or symptom control by the drugs, or complete resolution of symptoms (antacids, digestives, etc.)
 - Preventive drugs that are unlikely to confer any important benefits over the patient's remaining lifespan (e.g., statins, etc. for terminally ill patients)
 - Drugs that impose an unacceptable treatment burden (difficulty in ingestion, great expense, increased blood sampling, etc.)
- (4) Prioritize drugs for discontinuation (drugs with the greatest harm and least benefit, drugs that are easiest to discontinue, e.g., have the lowest likelihood of withdrawal reactions or disease rebound, and drugs that the patient is most willing to discontinue first)
- (5) Implement and monitor the drug discontinuation regimen. Explain the management plan and reach an agreement with the patient, and then communicate this plan and its contingencies to all health professionals and other relevant parties (caregivers, family) involved in the patient's care.

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Appendix 1. JCS/JHFS Joint Working Group

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External Evaluation Committee

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- Yoshihiko Saito, Department of Cardiovascular Medicine, Nara

- Medical University
- Yoshiki Sawa, Department of Cardiovascular Surgery, Osaka University Graduate School of Medicine
- Hiroyuki Tsutsui, Department of Cardiovascular Medicine, Kyushu University Graduate School of Medical Sciences
(Listed in the order of the alphabetical; affiliations as of March 15, 2021)

**Appendix 2. Disclosure of Potential Conflicts of Interest (COI):
JCS/JHFS 2021 Statement on Palliative Care in Cardiovascular Diseases**

Author	Potential COI of the participant									Potential COI of the marital partner, first-degree family members, or those who share income and property	Declaration about the head of your affiliated organization/department (if the participant is conducting joint research with the head of the organization/department)	
	Employer / leadership position (private company)	Stock or stock options	Intellectual property / royalties	Speakers' bureau	Payment for manuscripts	Research grant	Scholarship (educational) grant	Endowed chair	Other rewards			Research grant
Chair: Toshihisa Anzai				AstraZeneca K.K. TOA EIYO LTD. Novartis Pharma K.K. Bayer Yakuhin, Ltd. Pfizer Japan Inc. Bristol-Myers Squibb Ono Pharmaceutical Co., Ltd. Otsuka Pharmaceutical Co., Ltd. Daiichi Sankyo Company, Limited Mitsubishi Tanabe Pharma Corporation Nippon Boehringer Ingelheim Co., Ltd. Takeda Pharmaceutical Company Limited		Bristol-Myers Squibb	Otsuka Pharmaceutical Co., Ltd. Abbott Medical Japan L.L.C Boehringer Ingelheim GmbH Boston Scientific Japan K.K. Daiichi Sankyo Company, Limited Nippon Boehringer Ingelheim Co., Ltd. Japan Lifeline Co., Ltd. Takeda Pharmaceutical Company Limited	WIN INTERNATIONAL CO.,LTD. BIOTRONIK Japan, Inc. HOKUYAKU TAKEYAMA Holdings, Inc. MEDICAL SYSTEM NETWORK Co., Ltd. Medtronic Japan Co., Ltd.				
Member: Yoshihiro Fukumoto				Actelion Pharmaceuticals Japan Ltd. AstraZeneca K.K. Novartis Pharma K.K. Bayer Yakuhin, Ltd. Janssen Pharmaceutical K.K. Ono Pharmaceutical Co., Ltd. Otsuka Pharmaceutical Co., Ltd. Daiichi Sankyo Company, Limited		Alnylam Pharmaceuticals Inc. Actelion Pharmaceuticals Japan Ltd. Daiichi Sankyo Company, Limited Nippon Shinyaku Co., Ltd.	MSD K.K. Astellas Pharma Inc. Abbott Medical Japan L.L.C Eisai Co., Ltd. Novartis Pharma K.K. Bayer Yakuhin, Ltd. Shionogi & Co., Ltd. Kowa Pharmaceutical Co., Ltd. Mochida Pharmaceutical Co., Ltd. Teijin Pharma Limited Japan Lifeline Co., Ltd. Takeda Pharmaceutical Company Limited					
Member: Chisato Izumi				Edwards Lifesciences Corporation Novartis Pharma K.K. Otsuka Pharmaceutical Co., Ltd. Daiichi Sankyo Company, Limited		Daiichi Sankyo Company, Limited						
Member: Yoshiyuki Kizawa				Daiichi Sankyo Company, Limited Kyowa Hakko Kirin Co., Ltd. Chugai Pharmaceutical Co., Ltd.								
Member: Masatoshi Koga				Bayer Yakuhin, Ltd.								
Member: Katsuji Nishimura				MSD			Sumitomo Dainippon Pharma Co., Ltd.					
Member: Mitsuru Ohishi				AstraZeneca K.K. Novartis Pharma K.K. Ono Pharmaceutical Co., Ltd. Otsuka Pharmaceutical Co., Ltd. Daiichi Sankyo Company, Limited Nippon Boehringer Ingelheim Co., Ltd. Takeda Pharmaceutical Company Limited			Nippon Boehringer Ingelheim Co., Ltd. Takeda Pharmaceutical Company Limited Daiichi Sankyo Company, Limited					

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	Employer / leadership position (private company)	Stock or stock options	Intellectual property / royalties	Speakers' bureau	Payment for manuscripts	Research grant	Scholarship (educational) grant	Endowed chair	Other rewards		Research grant	Scholarship (educational) grant
Member: Yasushi Sakata				AstraZeneca K.K. Novartis Pharma K.K. Bayer Yakuhin, Ltd. Otsuka Pharmaceutical Co., Ltd. Daiichi Sankyo Company, Limited Nippon Boehringer Ingelheim Co., Ltd. Medtronic Japan Co., Ltd. Mitsubishi Tanabe Pharma Corporation		Biosense Webster Bristol-Myers Squibb Actelion Pharmaceuticals Japan Ltd. Amgen Astellas BioPharma K.K. Abbott Medical Japan L.L.C. Sony Corporation Nipro Corporation Nipro Corporation Bristol-Myers Squibb Roche Diagnostics K.K. Shionogi & Co., Ltd. JIMRO Integral Corporation REGIMMUNE Co., Ltd. Nippon Boehringer Ingelheim Co., Ltd. FUJIFILM RI Pharma Co., Ltd.	Cardinal Health Japan Astellas Pharma Inc. Abbott Medical Japan L.L.C. Edwards Lifesciences Corporation Johnson & Johnson K.K. St. Jude Medical Japan Co., Ltd. Novartis Pharma K.K. Bayer Yakuhin, Ltd. BIOTRONIK Japan, Inc. Boston Scientific Japan K.K. Kowa Company, Ltd. Kowa Pharmaceutical Co., Ltd. Ono Pharmaceutical Co., Ltd. Taisho Biomed Instruments Co., Ltd. Otsuka Pharmaceutical Co., Ltd. Daiichi Sankyo Company, Limited Teijin Pharma Limited Mitsubishi Tanabe Pharma Corporation Biosensors Japan Co., Ltd. Nippon Boehringer Ingelheim Co., Ltd. Medtronic Japan Co., Ltd. Takeda Pharmaceutical Company Limited					
Member: Tsuoyoshi Shiga				Ono Pharmaceutical Co., Ltd. Bristol-Myers Squibb Daiichi Sankyo Company, Limited		Daiichi Sankyo Company, Limited	Ono Pharmaceutical Co., Ltd.					
Member: Yasuchika Takeishi				MSD K.K. Bayer Yakuhin, Ltd. Bristol-Myers Squibb Otsuka Pharmaceutical Co., Ltd. Daiichi Sankyo Company, Limited Mitsubishi Tanabe Pharma Corporation Nippon Boehringer Ingelheim Co., Ltd. FUJIFILM RI Pharma Co., Ltd. Novartis Pharma K.K.		CANON MEDICAL SYSTEMS CORPORATION Mitsubishi Corporation	MSD K.K. Astellas Pharma Inc. Philips Respironics GK. Ono Pharmaceutical Co., Ltd. Otsuka Pharmaceutical Co., Ltd. Sumitomo Dainippon Pharma Co., Ltd. Teijin Pharma Limited Nihon Medi-Physics Co., Ltd. Medtronic Japan Co., Ltd. FUJIFILM Toyama Chemical Co., Ltd. Takeda Pharmaceutical Company Limited FUJIFILM RI Pharma Co., Ltd. Philips Japan, Ltd.	Actelion Pharmaceuticals Japan Ltd. Abbott Medical Japan L.L.C. St. Jude Medical Japan Co., Ltd. BIOTRONIK Japan, Inc. Fukuda Life Tech Co. Ltd. Fukuda Life Tech Minamitohoku Co. Ltd. Fukuda Denshi Co., Ltd. Fukuda Denshi Minamitohoku hanbai Co., Ltd. Nihon Kohden Corp.				
Member: Kazuhiro Yamamoto				Otsuka Pharmaceutical Co., Ltd. Pfizer Japan Inc. Ono Pharmaceutical Co., Ltd. Mitsubishi Tanabe Pharma Corporation Nippon Boehringer Ingelheim Co., Ltd. Novartis Pharma K.K.			Abbott Medical Japan L.L.C. Novartis Pharma K.K. Novo Nordisk Pharma Ltd. BIOTRONIK Japan, Inc. Fukuda Denshi Co., Ltd. Boston Scientific Japan K.K. Medtronic Japan Co., Ltd. LifeScan Japan Kowa Pharmaceutical Co., Ltd. Ono Pharmaceutical Co., Ltd. Otsuka Pharmaceutical Co., Ltd. Daiichi Sankyo Company, Limited Teijin Pharma Limited Mitsubishi Tanabe Pharma Corporation Japan Lifeline Co., Ltd. Nihon Kohden Corp. Takeda Pharmaceutical Company Limited					

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	Employer / leadership position (private company)	Stock or stock options	Intellectual property / royalties	Speakers' bureau	Payment for manuscripts	Research grant	Scholarship (educational) grant	Endowed chair	Other rewards		Research grant	Scholarship (educational) grant
Member: Satoshi Yasuda				CSL Behring K.K. Bayer Yakuhin, Ltd. Bristol-Myers Squibb Kowa Company, Ltd. Daiichi Sankyo Company, Limited Takeda Pharmaceutical Company Limited		IQVIA Services Japan K.K. JSR Corporation NEC Solution Innovators, Ltd. Actelion Pharmaceuticals Japan Ltd. Abbott Vascular Japan Co., Ltd. Bayer Yakuhin, Ltd. Kowa Company, Ltd. Daiichi Sankyo Company, Limited Takeda Pharmaceutical Company Limited	Abbott Medical Japan L.L.C Amicus Therapeutics, Inc. Bayer Yakuhin, Ltd. Roche Diagnostics K.K. Kowa Company, Ltd. Otsuka Pharmaceutical Co., Ltd. Sumitomo Dainippon Pharma Co., Ltd. Takeda Pharmaceutical Company Limited	Abbott Medical Japan L.L.C Sound Wave Innovation CO., LTD. ZEON MEDICAL INC. Teseo TERUMO CORPORATION Shionogi & Co., Ltd. Kowa Company, Ltd. Mochida Pharmaceutical Co.,Ltd. Ono Pharmaceutical Co., Ltd. Otsuka Pharmaceutical Co., Ltd. Nippon Boehringer Ingelheim Co., Ltd. Medtronic Japan Co., Ltd. Japan Lifeline Co.,Ltd. Nihon Kohden Corp. Nippon Shinyaku Co., Ltd. Takeda Pharmaceutical Company Limited				
Collaborator: Naoki Ishimori								MEDICAL SYSTEM NETWORK Co., Ltd. HOKUYAKU TAKEYAMA Holdings,Inc.				
Collaborator: Toshiyuki Nagai				Novartis Pharma K.K. Daiichi Sankyo Company, Limited	MEDIC MEDIA Co., Ltd.							
Collaborator: Shogo Oishi				Daiichi Sankyo Company, Limited Otsuka Pharmaceutical Co., Ltd.								
Collaborator: Katsuki Okada				Bayer Yakuhin, Ltd.								
Collaborator: Tatsuhiko Shibata				Otsuka Pharmaceutical Co., Ltd. Daiichi Sankyo Company, Limited								
Collaborator: Akiomi Yoshihisa								Fukuda Denshi Co., Ltd Fukuda Life Tech Co. Ltd. Fukuda Denshi Minamitohoku hanbai Co., Ltd Fukuda Life Tech Minamitohoku Co. Ltd.				
Collaborator: Dai Yumino				Daiichi Sankyo Company, Limited Novartis Pharma K.K.								
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External Evaluation Committee: Yasuki Kihara				Daiichi Sankyo Company, Limited Otsuka Pharmaceutical Co., Ltd. Nippon Boehringer Ingelheim Co., Ltd. TEIJIN HOME HEALTHCARE LIMITED Takeda Pharmaceutical Company Limited Teijin Pharma Limited		Teijin Pharma Limited EP-CRSU Co., Ltd. Mebix, Inc.	MSD K.K. Astellas Pharma Inc. Daiichi Sankyo Company, Limited Sanofi K.K. Boston Scientific Japan K.K. Nippon Boehringer Ingelheim Co., Ltd. BIOTRONIK Japan, Inc. AKANE-kai Senoo hospital Federation of National Public Services and Affiliated Personnel Mutual Aid Associations Kure Kyosai Hospital					

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External Evaluation Committee: Takeshi Kimura				Abbott Vascular Japan Co., Ltd. Sanofi K.K. Bristol-Myers Squibb Boston Scientific Japan K.K. Kowa Company, Ltd. Nippon Boehringer Ingelheim Co., Ltd.		Edwards Lifesciences Corporation EP-CRSU Co., Ltd. Pfizer Japan Inc. Kowa Company, Ltd. Daiichi Sankyo Company, Limited	Astellas Pharma Inc. MID.Inc. Otsuka Pharmaceutical Co., Ltd. Daiichi Sankyo Company, Limited Mitsubishi Tanabe Pharma Corporation Nippon Boehringer Ingelheim Co., Ltd. Takeda Pharmaceutical Company Limited					
External Evaluation Committee: Yoshihiko Saito				Novartis Pharma K.K. Pfizer Japan Inc. Otsuka Pharmaceutical Co., Ltd. Daiichi Sankyo Company, Limited Mitsubishi Tanabe Pharma Corporation		Amgen K.K. TERUMO CORPORATION Novartis Pharma K.K. Roche Diagnostics K.K. Kowa Pharmaceutical Co., Ltd. Daiichi Sankyo Company, Limited	Astellas Pharma Inc. Novartis Pharma K.K. Bayer Yakuhin, Ltd. Bristol-Myers Squibb Shionogi & Co., Ltd. Kyowa Kirin Co., Ltd. Ono Pharmaceutical Co., Ltd. Otsuka Pharmaceutical Co., Ltd. Sumitomo Dainippon Pharma Co., Ltd. Daiichi Sankyo Company, Limited Teijin Pharma Limited Mitsubishi Tanabe Pharma Corporation Nihon Medi-Physics Co., Ltd. Takeda Pharmaceutical Company Limited					
External Evaluation Committee: Yoshiaki Sawa						Edwards Lifesciences Corporation Cuorips Inc. JTEC Corporation Century Medical, Inc. DAIKIN INDUSTRIES, LTD. TERUMO CORPORATION Nacalai Tesque, Inc. Nipro Corporation HeartLab, Inc. LivaNova Japan K.K. ROHTO Pharmaceutical Co., Ltd. Sun Medical Technology Research Corp. Mediphus Pharma, Inc. Sumitomo Riko Company Limited Ono Pharmaceutical Co., Ltd. Taki Chemical Co., Ltd. Dai Nippon Printing Co., Ltd. Sumitomo Dainippon Pharma Co., Ltd. Daiichi Sankyo Company, Limited Teijin Pharma Limited Medtronic Japan Co., Ltd.	Abbott Medical Japan L.L.C Edwards Lifesciences Corporation Smith & Nephew KK Century Medical, Inc. TERUMO CORPORATION Nipro Corporation Paramedic Japan Co., Ltd. JMS Co., Ltd. Myoridge Co., Ltd. Konishi Medical Instruments Co., Ltd. Ono Pharmaceutical Co., Ltd. Otsuka Pharmaceutical Co., Ltd. Abiomed Japan K.K. Medtronic Japan Co., Ltd.	Medtronic Japan Co., Ltd.				
External Evaluation Committee: Hiroyuki Tsutsui				AstraZeneca K.K. Novartis Pharma K.K. Bayer Yakuhin, Ltd. Pfizer Japan Inc. Kowa Company, Ltd. Ono Pharmaceutical Co., Ltd. Otsuka Pharmaceutical Co., Ltd. Daiichi Sankyo Company, Limited Teijin Pharma Limited Mitsubishi Tanabe Pharma Corporation Nippon Boehringer Ingelheim Co., Ltd.	Nippon Rinsho Co., Ltd.	IQVIA Services Japan K.K. OMRON HEALTHCARE Co., Ltd. Medical Innovation Kyushu MEDINET Co., Ltd. Daiichi Sankyo Company, Limited Mitsubishi Tanabe Pharma Corporation Japan Tobacco Inc. Nippon Boehringer Ingelheim Co., Ltd.	St. Mary's Hospital. Daiichi Sankyo Company, Limited Teijin Pharma Limited TEIJIN HOME HEALTHCARE LIMITED Mitsubishi Tanabe Pharma Corporation Nippon Boehringer Ingelheim Co., Ltd.	Actelion Pharmaceuticals Japan Ltd.				

Notation of corporation is omitted.
No potential COI for the following members.
Member: Akihiko Sakashita
Collaborator: Takahiro Abe
Collaborator: Rie Akaho
Collaborator: Yasuhiro Hamatani
Collaborator: Hayato Hosoda
Collaborator: Mika Kato
Collaborator: Yoshiharu Kingasa
Collaborator: Takuro Kubozono
Collaborator: Takuma Sato
Collaborator: Atsushi Suzuki
Collaborator: Tsuyoshi Suzuki
Collaborator: Yasuko Takada
Collaborator: Masahito Takagi
Collaborator: Kenkichi Tsuruga