Japanese Heart Failure Society 2018 Scientific Statement on Nutritional Assessment and Management in Heart Failure Patients

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In Japan, heart failure patients continue to be increasing rapidly, and the state is called a “heart failure pandemic”. Heart failure is basically impairment of cardiac function, but its pathology is greatly influenced by non-cardiac factors including complications, and this constitutes a difference compared with cancer. In such circumstances, attention is directed to nutritional disorders, a non-cardiac factor, as a new target of therapeutic approaches to heart failure patients. Nutritional disorders have been shown by a number of epidemiological studies to be a risk factor for heart failure and events subsequent to heart failure. After heart failure, a negative spiral is considered to be set off with not only progression of heart failure exacerbating nutritional disorder but also exacerbation of nutritional disorder accelerating progression of heart failure. Nutritional disorders are also a factor of frailty, which is a problem in recently increasing aged heart failure patients.

Presently, however, the accumulation of scientific knowledge remains insufficient for the preparation of guidelines for nutritional management of heart failure patients. Therefore, the Japanese Heart Failure Society prepared this statement as a summary of expert consensus at the current level based on the knowledge available at present with participation by experts in various fields of many disciplines. It is our wish that this statement urges medical service workers to reflect deeply about nutritional support of heart failure patients, consequently promotes the evolution of new knowledge, and eventually contributes to the development of this field, which is presently an unexplored territory, into a rich and productive discipline.
Chapter I. What Is Nutrition?

Section 1. Nutrition and Nutrients

In humans, nutrition is defined as supporting life by maintaining vital phenomena such as respiration, digestion and absorption, excretion, exercise, growth, and reproduction, taking in materials necessary for healthy daily living from the environment and using them, and excreting wastes. Therefore, nutrition is a phenomenon rather than materials. In contrast, nutrients are materials which must be taken in from the environment to sustain vital phenomena, examples of which are protein and calcium. Thus, nutrition and nutrients differ clearly but are occasionally confused or misunderstood.

Section 2. Intake of Nutrients and Their Physiological Activities

Nutrients essential for living are classified into five groups, namely, proteins, lipids, carbohydrates, vitamins, and minerals. Each nutrient bears physiological activities and roles necessary to sustain life. Of these nutrients, proteins, lipids, and carbohydrates are called energy-yielding nutrients, because they produce energy in the body. Carbohydrates and proteins produce about 4 kcal/g of energy, and lipids produce about 9 kcal/g of energy. Therefore, the amount of energy contained in a particular food item or dish or nutritional preparation is determined by the amounts of various energy-yielding nutrients. Vitamins and minerals do not produce energy in the body, but they are indispensable for structuring of biological tissues and regulation of vital functions. Also, since water is closely involved in digestion, absorption, excretion, and structuring of biological tissues as well as control of body temperature, it is regarded as a material comparable to a nutrient.

Deficiency or excess (imbalance) of nutritional intake is widely known to not only invite disorders but also strongly affect the development and progression (exacerbation) of diseases. Therefore, appropriate nutritional intake is indispensable for sustaining or promoting health and preventing and treating diseases. However, we usually ingest nutrients as meals rather than plain nutrients. Therefore, the contents, amount, and balance of diet are important (Figure I-1).

Section 3. Nutritional Disorders, Deficiencies, and Excesses

Lack of nutrients necessary for an individual and consequent inability to maintain normal physiological functions is called nutritional deficiency. Also, the inability to maintain normal physiological functions due to excessive nutritional intake is called nutritional excess. In addition, physical disorders caused by nutritional deficiency or excess are called nutritional disorders.

Nutritional disorders are caused by not only excessive or deficient intake of essential nutrients for some reason but also malabsorption, impairment of utilization, increases in consumption or demand, and disorder of excretion alone or in combination. Nutritional disorders may also be caused by the effects of drugs on absorption, utilization, or metabolism of nutrients.

A. Nutritional Disorders Due to Protein or Energy Deficiency

A nutritional disorder caused by the lack of protein is called
kwashiorkor. It results from qualitative and quantitative inadequacy of protein and has been reported to be observed in infants in regions with a low standard of living, but is recently considered also to be caused by protein deficiency combined with factors such as infection and trauma. Nutritional disorder caused by simultaneous deficiency of protein and energy is called marasmus. It is observed in adults and older people as well as infants in regions with a low standard of living and is considered to be caused primarily by low energy intake associated with an absolute lack of food intake.³

\[ \text{B. Vitamin Deficiency and Excess} \]

Vitamins consist of four lipid-soluble vitamins (vitamins A, D, E, and K) and nine water-soluble vitamins (vitamins B₁₂, B₆, B₃, niacin, pantothenic acid, folic acid, biotin, and vitamin C).

Lipid-soluble vitamin deficiency is caused by decreases in intake of lipid-soluble vitamins and lipid absorption. Also, if lipid-soluble vitamins are ingested or administered in excess, they are accumulated in the liver and fat and may cause hypervitaminosis.

Since water-soluble vitamins are readily excreted, their storage in the body is low. Therefore, they may be deficient, and disorders due to their excess are rare.³⁴

\[ \text{C. Mineral Deficiency and Excess} \]

Minerals include sodium, potassium, calcium, phosphorus, and magnesium, which are classified as macro-minerals, and iron, zinc, copper, manganese, chromium, iodine, molybdenum, and selenium, which are classified as trace elements (called micro-minerals in the Dietary Reference Intakes for Japanese (2020)). The time until deficiency or excess becomes apparent varies widely among minerals.³⁵

\[ \text{D. Interrelations Among Nutrients} \]

In iron deficiency anemia, which is frequently observed in Japan, for example, appropriate intake of vitamin C is necessary to promote absorption of dietary non-heme iron along with increased intake of iron for symptomatic relief. Thus, approaches with sufficient consideration of interrelations among nutrients are required for the prevention and treatment of nutritional deficiency or excess.

The amount a nutrient necessary for a person (minimum amount necessary to avoid deficiency) is unknown in many cases, because its accurate determination is extremely complex and practically impossible. Even if the sex, age, height, and activity level are assumed to be the same, necessary amounts of nutrients vary, and consideration of individual differences is necessary. Therefore, the current nutrition science predicts and organizes deficits and surpluses of intakes and recommendable intakes of nutrients based on scientific evidence including the results of nutrient consumption and expenditure studies and nutritional surveys and by introducing approaches of probability theory. In Japan, this is implemented in the Dietary Reference Intakes for Japanese compiled by the Ministry of Health, Labour and Welfare.

In the Dietary Reference Intakes for Japanese (2020),⁶ indices are adopted from three viewpoints, namely 1) avoidance of insufficient intake, 2) avoidance of health damage due to excessive intake, and 3) prevention of lifestyle-related diseases.

There are three indices adopted for the avoidance of insufficient intake. The estimated average requirement (EAR) is considered to be the amount that meets the requirement in half the population (the probabilities of fulfillment and lack are both 50%). The recommended dietary allowance (RDA) is adopted as an index that complements EAR. RDA is considered the amount that meets the requirement in most people (probability of fulfillment: 97.5%). In addition, the adequate intake (AI) is used if EAR or RDA cannot be determined due to the lack of scientific evidence. AI is considered the amount sufficient to maintain a nutritional level at or above which the risk of deficiency is nearly zero.

As the index aiming at avoidance of health damage due to excessive intake, the tolerable upper intake level (UL) is adopted.

In addition, as the intake that current Japanese should provisionally aim at for the prevention of lifestyle-related diseases, the tentative dietary goal for preventing lifestyle-related diseases (DG) is adopted.

A conceptual diagram that helps with the understanding of these indices is shown in Figure I-2.⁶ Concerning energy, the body mass index (BMI) is
adopted as an index to check the balance between intake and consumption of energy (energy balance). However, BMI is difficult to apply to school children, because both the height and weight change with growth. Therefore, it is necessary to understand and confirm the condition including changes with time using objective indices such as the obesity assessment and growth curve used in school health statistical survey by the Ministry of Education, Culture, Sports, Science and Technology. In the Dietary Reference Intakes for Japanese (2020), a provisional range of BMI that should be targeted is determined based on comprehensive judgments in consideration of the relationships of the overall mortality and incidences of various diseases with BMI and the relationships between causes of death and BMI reported by observational epidemiological studies as well as the reality of BMI in Japanese (Table I-1). Particularly, in those aged 65 years and above, there was a gap between BMI at which the overall mortality was lowest and the reality, and the provisional target range of BMI is set at 21.5–24.9 kg/m² partly because of the necessity to consider the prevention of both frailty and lifestyle-related diseases.

Incidentally, check of energy balance using BMI does not lead to practical measures without a specific guidelines or recommendation about energy intake. Therefore, the Dietary Reference Intakes for Japanese (2020) presents a formula (method) for the calculation of the estimated energy requirement (EER) as a product of basal metabolic rate and physical activity level based on monitoring of the condition of each person.

### Section 5. Evaluation of Nutrient Intakes

The amounts of nutrients that we ingest as diet constantly fluctuate. Therefore, it is not appropriate to evaluate nutrient intakes by checking the dietary contents on a particular day. The Dietary Reference Intakes for Japanese recommends the evaluation by determining the mean intakes of nutrients over a period of about 1 month as habitual intakes except those that vary widely and comparing them with the reference intakes. However, it is fairly bothersome to weigh dietary contents and record them for 1 month. Thus, in practice, methods in which the dietary contents are weighed and recorded on a few separate days, and the habitual intakes are estimated from the values obtained, or in which the amounts of food groups ingested over a given period and the frequency of their intakes are asked, and the nutrient intakes during the period are estimated (food intake frequency survey method) are often employed. However, since there are advantages and disadvantages in any nutritional/dietary survey method, one or several survey methods and evaluation procedures that are appropriate must be selected depending on what are evaluated and for what purpose they are evaluated. Also, comprehensive assessment by measuring, if necessary, the serum albumin level and amounts of urinary excretion of urea nitrogen and sodium is often performed.

### Section 6. Recommendable Nutrient Intakes

Based on the results of the National Health and Nutrition Survey conducted annually by the ministry of Health, Labour and Welfare and many other nutritional/dietary surveys, nutrients that may be underingested or overeaten have generally identified from the dietary contents of average Japanese people. Therefore, from this perspective, measures and management to encourage strict adherence to EAR, RDA, or AI are necessary. However, actual dietary nutrient intakes are not so simple. Many foods contain several nutrients, and meals are prepared as dishes consisting of one or more foods. Thus, if excessive attention is paid to nutrients that may be under- or overeaten, meals themselves become less appetizing, and dietary intakes as a whole may decrease, or meals may even cease to be meals. For optimal nutrient intakes, habitual intakes should be adjusted to remain in a tolerable range rather than confining the intake of energy or each nutrient to a set value. Specifically, the intakes of nutrients that may be underingested should be maintained at or above EAR, and the intakes of nutrients ingested above UL by the use of oral nutrition supplementation (ONS), should be controlled by stopping or reducing the intake of ONS, aiming both to bring them closer to RDA or AI (Figure I-3).

Incidentally, the sodium (salt) intake of Japanese is higher than the global average. According to the Dietary Reference Intakes for Japanese (2020), EAR of sodium in adults is 600 mg/day (equivalent to 1.5 g/day of salt). The sodium intake of Japanese is not usually considered to fall below this level without marked perspiration if they can eat normally. Instead, it is more important to reduce the sodium intake, and DG as salt is set at <7.5 g/day for males and <6.5 g/day for females.

### Section 7. Changes in Energy and Nutrient Requirements With Growth and Aging

It is necessary that humans ingest amounts of energy and nutrients appropriate for changes in physical conditions from birth to death.

According to the Dietary Reference Intakes for Japanese (2020), the basal metabolism reference value (kcal/kg body weight/day) that serves as the basis for estimation of basal metabolism, which is the minimum necessary amount of energy to sustain life, is 61.0 and 59.7 in males and females,
respectively, for 1–2-year-olds, 37.4 and 34.8 for 10–11-year-olds, 23.7 and 22.1 for 18–29-year-olds, and 21.5 and 20.7 for those aged ≥75 years, showing decreases with aging. However, the height, which is another factor, also changes with growth and aging. Therefore, the basal metabolic expenditure varies with changes in these two factors. Individual EER can be calculated by multiplying the basal metabolic expenditure by the physical activity level. To calculate EER of a growing child, it is necessary to add the energy needed for the increased tissue to the energy required for physical activities and tissue synthesis. In adults, also, for pregnant women, it is necessary to add the sum of the change in total energy consumption due to pregnancy and the accumulated amount of energy. For breast-feeding women, the energy for breast-feeding must be added to EER before pregnancy.

Special attention is needed for nutrition in many women, because additional nutrient intakes may be necessary in consideration of menstruation, pregnancy, and breast-feeding.

Section 8. Characteristics of Nutritional Therapy for Treatment

The Dietary Reference Intakes for Japanese (2020) is prepared in consideration of the prevention of undernutrition and frailty in older people as well as the prevention of lifestyle-related diseases and their progression. It is also targeted to healthy individuals and a population consisting primarily of healthy individuals including people with risk factors for lifestyle-related diseases, older people with risk factors for frailty capable of generally independent living, and a population consisting primarily of such people. For these reasons, it practically concerns only nutrients and energy contained in orally ingested foods.

On the other hand, for the management of energy and nutrient intakes for therapeutic purposes in individuals and groups with diseases or at a high risk for diseases, it is necessary to use guidelines for nutritional management, such as treatment guidelines for particular diseases with the understanding of basic principles of the Dietary Reference Intakes toward energy and nutrient intakes, and, eventually, the utmost priority is given to the judgments and instructions of the physician in charge. Naturally, there are situations in which nutritional methods including enteral and intravenous nutrition are employed alone or in combination in addition to situations manageable by ordinary oral nutrition alone. In nutritional therapy for treatment, the prescribed (provided) amounts of energy and nutrients vary with not only the physical characteristics but also the pathologic condition of the patient. In addition, the tolerable ranges of the amounts of energy and nutrients are usually narrower than those in healthy individuals. Moreover, in those with critical conditions or complications, the ranges are further narrowed, and more strict management is necessary.
Chapter II. Nutritional Disorders in Heart Failure

Figure II-1. In heart failure patients, low BMI is an independent risk factor for overall mortality and cardiac death. (Adapted from Hamaguchi S, et al. *Circ J* 2010 with permission.)

Figure II-2. Asian Working Group for Sarcopenia 2019 algorithm for Sarcopenia. F, Female; M, Male. (Adapted from Chen LK, et al. *J Am Med Dir Assoc* 2020 with modifications. ©2019 AMDA - The Society for Post-Acute and Long-Term Care Medicine, with permission from Elsevier.)
Section 1. Paradigm Shift From Restrictive Nutritional Guidance

In the general population, obesity has been shown to be an independent risk factor for heart failure as well as future events of cardiovascular disease. However, Anker et al. reported that, in heart failure patients, loss of body weight is a poor prognostic factor and that stability of body weight is associated with a good prognosis. Thereafter, similar evaluation was made by large-scale multicenter studies. As a low body mass index (BMI) was consistently associated with a poor outcome, heart failure guidelines in Western countries began to warn about a low body weight. Although there are physical differences between Western and Japanese people, similar phenomena have also been reported in Japanese (Figure II-1). Under these circumstances, the necessity of change in the direction of nutritional guidance from conventional restriction of energy intake to maintenance of BMI has begun to be recognized.

Section 2. Concepts of Sarcopenia, Frailty, and Cachexia

Sarcopenia, frailty, and cachexia are pathological conditions with low body weight and undernutrition. Sarcopenia means declines in muscle strength and physical functions due to loss of muscle mass. The diagnostic criteria for Asians by the Asian Working Group for Sarcopenia are shown in Figure II-2. Frailty means a state of increased vulnerability to health damage based on age-associated declines in various functions, and sarcopenia is an important element of frailty. Frailty contains the reversibility, i.e., the possibility of recovery of health. Along with the conventional diagnostic criteria for frailty shown by Fried (Table II-1), a basic check list incorporating the assessment of psychological and social aspects has also been proposed by the Ministry of Health, Labour and Welfare. Since low body weight and undernutrition in heart failure were considered historically to be caused primarily by cachexia, or alteration of humoral factors, the following discussion of the pathology centers around cachexia.

The literature on cachexia is growing but still somewhat limited. This is particularly true of specific diagnosis criteria. The criteria, below, represents the clinical experiences of the clinicians on the consensus panel and the limited data on patients with and without cachexia. The following needs to be excluded: starvation, malabsorption, primary depression, hyperthyroidism and age-related loss of muscle mass.

| Table II-1. Phenotypic Definition of Frailty |
|---------------------------------------------|
| 1. Weight loss A critical mass of characteristics, defined as three or more, had to be present for an individual to be considered frail. Those with one or two characteristics were hypothesized to be in an intermediate, possibly prefrail, stage clinically. Fried et al. developed a phenotypic definition of frailty based on readily identifiable physical aspects. |
| 2. Slow gait speed |
| 3. Weakness (grip strength) |
| 4. Exhaustion |
| 5. Low physical activity level |

Source: Prepared based on Fried L.P., et al. J Gerontol A Biol Sci Med Sci 2001.

| Table II-2. Diagnostic Criteria for Cachexia in Adults |
|------------------------------------------------------|
| Weight loss of at least 5%* in 12 months or less in the presence of underlying illness,** PLUS THREE of the following criteria: |
| • Decreased muscle strength (lowest tertile) |
| • Fatigue*** |
| • Anorexia*** |
| • Low fat-free mass index* |
| • Abnormal biochemistry |
| a) increased inflammatory markers CRP (>5.0 mg/L), IL-6 >4.0 pg/mL |
| b) Anemia (<12 g/dL) |
| c) Low serum albumin (<3.2 g/dL) |

The literature on cachexia is growing but still somewhat limited. This is particularly true of specific diagnosis criteria. The criteria, below, represents the clinical experiences of the clinicians on the consensus panel and the limited data on patients with and without cachexia. The following needs to be excluded: starvation, malabsorption, primary depression, hyperthyroidism and age-related loss of muscle mass.

*Edema-free.
**in cases where weight loss cannot be documented a BMI <20.0 mg/m² is sufficient.
***Fatigue is defined as physical and/or mental weariness resulting from exertion; an inability to continue exercise at the same intensity with a resultant deterioration in performance.
**Limited food intake (i.e. total caloric intake less than 20 kcal/kg body weight/d; <70% of usual food intake) or poor appetite.
*Lean tissue depletion (i.e. mid upper arm muscle circumference <10% percent for age and gender; appendicle skeletal muscle index by DXA (kg/m²) by DXA <5.45 in female and <7.25 in males.)

Adapted from Evans WJ, et al. Clin Nutr 2008. ©2008 Elsevier Ltd and European Society for Clinical Nutrition and Metabolism, with permission from Elsevier.

In healthy individuals, 250–350 g/day of muscle protein is degraded into amino acids. They are partly reused for protein synthesis and partly stored in the blood. Part of the amino acids in blood is converted in the liver by glycogenogenesis and used as energy. In heart failure, the blood levels of cortisol, catecholamines, and inflammatory cytokines increase, and insulin resistance and a decrease in testosterone are observed, suggesting imbalance between protein catabolism and anabolism (Figure II-3).

Section 3. Quantitative and Qualitative Declines in Skeletal Muscles

The decrease in adipose tissue observed in cachexia is considered to be caused by promotion of lipid degradation. The activity of lipoprotein lipase (LPL) in adipose tissue is enhanced by the actions of catecholamines associated with activation of the sympathetic nervous system and tumor necrosis factor (TNF)-α associated with promotion of inflammation, and fat in fat cells is degraded. Also, insulin inhibits lipid degradation, but insulin resistance is observed in heart failure, suggesting predominance of lipid degradation. Moreover, natriuretic peptides have been reported to have a lipid degrading activity.
Section 5. Modification of Disease Condition in Acute Heart Failure

In acute heart failure, the nutritional condition is considered to be more likely to deteriorate than in chronic heart failure (Table II-3). Albumin has a long half-life and exhibits mirror-image fluctuations of the fluctuations of C-reactive protein (CRP), which is an index of inflammation. Although it does not necessarily reflect the nutritional condition alone, progressive hypoalbuminemia observed in patients with acute heart failure after admission is related to exacerbation of the outcome.22

Table II-3. Factors That Exacerbate the Nutritional State in Acute Heart Failure (Compared With Chronic Heart Failure)

| Factor                                                                 |
|------------------------------------------------------------------------|
| 1. Increased protein catabolism and lipid degradation due to further activation of inflammatory cytokines, catecholamines, and natriuretic peptides |
| 2. Increased work of respiratory muscles due to labored respiration     |
| 3. Reduced albumin generation due to congestion of the liver            |
| 4. Reduced nutrient absorption due to intestinal edema                 |
| 5. Reduced dietary intake                                              |

Chapter III. Nutritional Assessment

Section 1. What Is Nutritional Evaluation?

Nutritional evaluation is can be divided into nutritional screening and nutritional assessment.23 Nutritional screening is performed to identify patients with malnutrition and those possibly at risk for nutrition-related disorders. Nutritional assessment, on the other hand, is a process in which clinical data, food intake data, body composition data, and biochemical data are collected, patients with malnutrition are identified, and appropriate nutritional therapy is designed. The JSPEN Guidelines for Parenteral and Enteral Nutrition- Guidelines for the Proper Use of Parenteral and Enteral Nutrition24 define nutritional assessment as “a method for comprehensive evaluation of the nutritional status using medical history, nutritional history, physical findings, body measurement data, clinical laboratory data, etc.” (Table III-1).

The more information is available for nutritional assessment, the more appropriate the assessment can be. The results of body measurements, biochemical tests, and physical function tests are usually used for nutritional assessment, but more detailed nutritional assessment can be made by collecting a wide variety of information including the family structure, living environment, economic status, oral environment, and state of medication as well as the age and sex of the patient.

Section 2. Nutritional Screening

Nutritional screening is performed to select patients at nutritional risk. As it is important to screen all patients, a method that can be performed readily in a short time even by non-experts with minimum interrater variation in the results is necessary.

Although the methods for nutritional screening unavoidably vary among institutions, it is important to extract...
Nutritional Assessment and Management in HF

Table III-1. Items of Nutritional Assessment

| Medical history       | History of present disease: Fever and cough, gastrointestinal symptoms, etc. When they occurred? |
|-----------------------|--------------------------------------------------------------------------------------------------|
|                       | Past history: Metabolic diseases (diabetes, chronic kidney disease, etc.)                          |
|                       | History of surgery, oral medications, socioeconomic condition, etc.                              |
|                       | Nutritional history: Appetite, dietary contents, changes in food intake, body weight changes, gastrointestinal symptoms, food preferences, food allergy, etc. |
| Physical examinations | Edema, ascites, findings related to deficiency of particular nutrients, etc.                       |
| Body measurements     | Height, body weight, BMI                                                                          |
|                       | Muscle mass (AC, TSF, AMC, AMA, CC, etc.)                                                          |
|                       | Body composition (DXA, BIA)                                                                      |
| Biochemical tests     | Transferrin (Tf), transthyretin, albumin, retinol-binding protein (RBP), total cholesterol, liver function tests, kidney function tests, etc. |
| Body function assessment | Respiratory function, swallowing function, ADL, etc.                                           |

Adapted from Japanese Society for Parenteral & Enteral Nutrition, JSPEN Guidelines for Parenteral and Enteral Nutrition (3rd edition), 2013 with modifications.

| Table III-2. Comparison of JASSO Obesity Classification and WHO Criteria |
|-----------------------------|--------------------------------------------------------------------------|
| BMI (kg/m²)                 | JASSO classification | WHO criteria |
| <18.5                       | Low body weight          | Underweight |
| 18.5≤ – <25                 | Normal body weight      | Normal range|
| 25≤ – <30                   | Obesity (grade 1)        | Pre-obese   |
| 30≤ – <35                   | Obesity (grade 2)        | Obese class I|
| 35≤ – <40                   | Obesity (grade 3)        | Obese class II|
| 40≤                         | Obesity (grade 4)        | Obese class III|

JASSO, Japan Society for the Study of Obesity; WHO, World Health Organization.

Note 1) Obesity (BMI ≥25 kg/m²) is not necessarily a condition that medically requires weight control. The standard body weight (ideal body weight; kg) is the value calculated as height (m)²×22, using a BMI of 22 kg/m², at which morbidity is lowest, as a reference.

Note 2) Severe obesity is defined as a BMI ≥35 kg/m².

Adapted from Japan Society for the Study of Obesity, Guidelines for the Management of Obesity Disease, 2016.

patients at risk for nutritional disorders and undernourished patients without omission. If the criterion of the risk of nutritional disorder is too high, patients who should be extracted may be overlooked, but if it is low, too many patients are extracted. Concerning the items examined for nutritional screening, those that can be readily obtained at each institution should be selected.

Section 3. Nutritional Assessment

A. Items of Nutritional Assessment

Medical History

Concerning the history of the present disease, whether there is a chronic lack of food intake or decline in activities of daily living (ADL) can be evaluated by carefully checking for the time of onset of fever, cough, and gastrointestinal symptoms. In taking a medical history, metabolic diseases are important, and diabetes mellitus and chronic kidney disease must be taken into consideration in calculating the nutrient requirements.

In heart failure patients, the number, frequency, and time of past hospitalization due to heart failure must also be checked. Nutritional therapy appropriate for the stage of heart failure is necessary.

Body Measurement Data

1) Body mass index (BMI)

Measurements of the body are important in nutritional assessment. The Guidelines for the Management of Obesity Disease, the Japan Society for the Study of Obesity 2016 defines a body mass index (BMI) of ≥25 kg/m² as obesity, which is classified by WHO as “pre-obese”, and obesity accompanied by health damage as obesity disease and proposes therapeutic intervention to be necessary (Table III-2).

Among studies in healthy individuals, there is a report that the incidence of heart failure increases with BMI.4 However, studies in the United States and Japan reported that the prognosis was more favorable in high BMI patients.26,27 This means that obesity is a risk factor for heart failure but that heart failure patients have a better prognosis as they tend to be obese. A meta-analysis also showed that the mortality rate and rehospitalization rate were higher in low-BMI heart failure patients.28 The mortality rate was reported to be higher in obese heart failure patients, if they lost 5% or more weight, than in non-obese patients.29

In heart failure patients, body weight changes are also important for the assessment of the disease state. A short-term body weight gain is useful as an index of fluid retention, and a weight gain of 2 kg or more within a few days strongly suggests acute exacerbation of heart failure.30 Also, if there is a weight loss over a long period, decreases in fat and muscle mass are suspected, and progression of undernutrition is suggested.

2) Arm circumference, triceps skinfold, arm muscle circumference, and calf circumference

From the arm circumference (AC) and triceps skinfold (TSF), the arm muscle circumference (AMC) can be determined, and, then, the arm muscle area (AMA) can be calculated (Figure III-1). These indices are useful for long-term follow-up of the nutritional state. The degree of depletion of muscle protein can be evaluated from changes in AC, and changes in the energy accumulation rate can be evaluated from changes in TSF. In addition, skeletal muscle mass can be evaluated from AMC and AMA.31 A study in
heart failure patients has suggested that the addition of AC to BMI as an evaluation item improves the prognostic accuracy. More appropriate nutritional assessment is made possible by combining multiple items rather than depending on a single evaluation item.

The calf circumference (CC) is effective for the evaluation of calf skeletal muscles and is reflected in ADL. It is important to measure CC along with the assessment of ADL, such as whether the patients can walk or sit, by interviews. However, heart failure patients often show calf edema, and caution is needed, because the assessment of muscle mass according to CC is inaccurate in patients with edema.

3) Body composition
The assessment of not only body weight but also body composition is needed. Methods for body composition assessment include dual energy X-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA).

DXA is considered to be the most reliable method for body composition assessment. BIA is a simple and minimally invasive assessment method. It is possible to know the tendency of body fluid retention by serially evaluating the same patient. There have been reports that the ratio between extracellular water (ECW) and total body water (TBW) determined by BIA (ECW/TBW) is useful for the assessment of body fluid distribution and prognosis of patients with heart failure or end-stage renal disease and critically ill patients. It is considered possible to evaluate increases or decreases in the amount of body fat in a particular patient and estimate changes in body fluid retention and nutritional status using the ECW/TBW ratio as a reference.
### Table III-4. Mini Nutritional Assessment-Short Form

#### Mini Nutritional Assessment

**MNA®**

| Last name: | First name: |
|------------|-------------|
| Sex: | Age: | Weight, kg: | Height, cm: | Date: |

Complete the screen by filling in the boxes with the appropriate numbers. Total the numbers for the final screening score.

#### Screening

**A** Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
- 0 = severe decrease in food intake
- 1 = moderate decrease in food intake
- 2 = no decrease in food intake

**B** Weight loss during the last 3 months
- 0 = weight loss greater than 3 kg (6.6 lbs)
- 1 = does not know
- 2 = weight loss between 1 and 3 kg (2.2 and 6.6 lbs)
- 3 = no weight loss

**C** Mobility
- 0 = bed or chair bound
- 1 = able to get out of bed / chair but does not go out
- 2 = goes out

**D** Has suffered psychological stress or acute disease in the past 3 months?
- 0 = yes
- 2 = no

**E** Neuropsychological problems
- 0 = severe dementia or depression
- 1 = mild dementia
- 2 = no psychological problems

**F1** Body Mass Index (BMI) (weight in kg) / (height in m)²
- 0 = BMI less than 19
- 1 = BMI 19 to less than 21
- 2 = BMI 21 to less than 23
- 3 = BMI 23 or greater

*IF BMI IS NOT AVAILABLE, REPLACE QUESTION F1 WITH QUESTION F2. DO NOT ANSWER QUESTION F2 IF QUESTION F1 IS ALREADY COMPLETED.*

**F2** Calf circumference (CC) in cm
- 0 = CC less than 31
- 3 = CC 31 or greater

#### Screening score (max. 14 points)

- **12 - 14 points**: Normal nutritional status
- **8 - 11 points**: At risk of malnutrition
- **0 - 7 points**: Malnourished

**References**

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For more information: [www.mna-elderly.com](http://www.mna-elderly.com)
Biochemical Tests
1) Serum albumin and transthyretin (prealbumin)
Serum albumin is widely used as an index of the nutritional status, particularly secondary to inflammation. Concerning the relationship between the serum albumin level and prognosis, the annual mortality rate was reported to be significantly higher when the serum albumin level was <3.4 g/dL in a study of 428 acute heart failure patients.38 Transthyretin has a shorter half-life than albumin and is used as an index for nutritional assessment in a shorter period. In a study of 514 heart failure patients, the mortality rate after 6 months was shown to be high when the transthyretin level was ≤15 mg/dL.39 Also, when used in combination with mini nutritional assessment (MNA)®, which is a nutritional assessment tool, transthyretin serves as a prognostic factor in patients with acute heart failure.40

2) Total cholesterol
The total cholesterol level is considered to reflect long-term nutritional disorders. In a study of 114 patients with chronic heart failure, the 3-year mortality rate was highest in the group with the lowest total cholesterol level (100.0–173.4 mg/dL) compared with other groups.41 However, when the total cholesterol level is used for nutritional assessment, it is also necessary to know whether drugs for treating dyslipidemia are used.

Assessment of Swallowing Function
Swallowing function is evaluated by the repetitive saliva swallowing test (RSST), modified water swallow test (MWST), and food test (FT)42 (Table III-3).
RSST is a simple test of counting the number of saliva swallowing that the subject can make during a 30-second period.
MWST is a test to evaluate respiratory changes and whether the subject chokes in addition to whether swallowing occurs after infusing 3 mL of cold water into the mouth.
In FT, the subject is asked to swallow a teaspoonful (3–4 g) of food, such as pudding, and the condition of swallowing is evaluated.
In videofluoroscopic examination of swallowing (VF), the processes from the entry of food into the mouth to swallowing are observed by videofluoroscopy by having the subject swallow a contrast medium.
In videoendoscopic evaluation of swallowing (VE), the condition of swallowing is observed directly with a transnasally inserted nasopharyngoscope.

### B. Tools for Nutritional Evaluation
It is recommended to combine multiple nutritional assessment items rather than using a single item, because more accurate evaluation of the nutritional status is possible by combining multiple evaluation items.

MNA® (Mini Nutritional Assessment)
MNA® was developed primarily for the early detection and early treatment of undernutrition syndrome in older patients.43 Presently, MNA®-short form (MNA-SF) is widely used (Table III-4).
In a study of 50 heart failure patients evaluated using MNA® and MNA®-SF, similar results were obtained, and the mortality rate and rehospitalization rate were higher in patients classified according to MNA®-SF in the undernutrition group.44 CC is an evaluation item in MNA®. Its cut-off value is originally 31 cm, but it is considered desirable to set the cut-off level at 28 cm for Asians.45

GNRI (Geriatric Nutritional Risk index)
The GNRI is an evaluation method reported by Bouillanne et al. in 2005, and it has been reported to be an accurate predictive index of the mortality rate in older people.46 The nutritional status is predicted according to the value obtained using a calculation formula consisting of the serum albumin level and body weight alone (Table III-5).

#### Table III-5. GNRI (Geriatric Nutrition Risk Index)

| GNRI formula is as follows: | Nutrition-related risk from GNRI values |
|-----------------------------|----------------------------------------|
| GNRI = [14.89 × Serum albumin (g/dL)] + 41.7 × (Weight/Ideal weight)] | <82: Major |
| or 14.89 × Serum albumin (g/dL) + 41.7 × (BMI / 22) | 82 to <92: Moderate |
|                             | 92 to <98: Low |
|                             | ≥98: Absent |

Source: Prepared based on Bouillanne O, et al. *Am J Clin Nutr* 2005.46

#### Table III-6. CONUT (Controlling Nutritional Status)

| Serum Albumin (g/dL) | Score | Total Lymphocytes (/μL) | Score | Total Cholesterol (mg/dL) | Score | Assessment | Screening Total Score |
|----------------------|-------|------------------------|-------|--------------------------|-------|------------|----------------------|
| ≥3.50                |       | ≥1,600                 |       | ≥180                     |       | Normal     | 0–1                  |
| 3.49–3.00            | 2     | 1,599–1,200            | 1     | 179–140                  | 1     | Light      | 2–4                  |
| 2.99–2.50            | 4     | 1,199–800              | 2     | 139–100                  | 2     | Moderate   | 5–8                  |
| 2.50–                 | 6     | ≥800                   | 3     | ≥100                     | 3     | Severe     | 9–12                 |

Source: Prepared based on Ignacio de Ulíbarri J, et al. *Nutr Hosp* 2005.48
http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S0212–161120050000100006&lng=en&nrm=iso
In a study of 152 heart failure patients with a mean age of 77 years, the mortality rate significantly increased when GNRI was <92.47

CONUT (Controlling Nutritional Status)
The CONUT was developed as a tool for the assessment of the nutritional status from 3 biological indices, i.e., protein metabolism, immunological competence, and lipid metabolism. The nutritional status is evaluated comprehensively and multifacetedly from the 3 biological indices (Table III-6).

CONUT has been reported to be an index useful in early screening of heart failure patients for undernutrition, but it must be carefully interpreted if the patient is taking a drug for treating dyslipidemia for such diseases including coronary artery disease.

PNI (Prognostic Nutritional Index)
PNI is a tool for nutritional evaluation using the serum albumin level and total lymphocyte count. In patients with acute heart failure, the PNI score is useful as a prognostic index, and its evaluation in combination with the CONUT score is recommended.48

SGA (Subjective Global Assessment)
SGA is a tool for nutritional evaluation reported by Detsky et al. in 1987. It can be performed readily by physical examinations alone without special equipment and is widely used. It is applicable to inpatients in the acute phase, patients admitted to care institutions, and home-cared patients and is also used for outpatient nutritional evaluation.

NRS (Nutritional Risk Screening) 2002
NRS 2002 is a tool for nutritional evaluation prepared by the European Society for Clinical Nutrition and Metabolism (ESPEN) and is characterized by evaluation based on scoring of the severity of nutritional disorder and disease. The severity of nutritional disorder is evaluated by scoring each of the body weight loss during a 3-month period, BMI, and weekly food intake 0–3 points.

Chapter IV. Methods for Nutritional Support

It is widely known that the patient’s nutritional status is a very important determinant of the onset and prognosis of heart failure. For nutritional management, oral nutrition, which is the most physiologic to the body, is recommended, and oral intake of food yields many benefits. However, patients difficult to orally ingest nutrients have increased with the increase in older patients, and poor dietary intake due to malaise and sense of dyspnea is often observed, particularly, in heart failure patients. Conventionally, such patients were managed by peripheral parenteral nutrition (PPN), but the problems such as insufficient energy intake were caused by the possibility of angitis and angialgia associated with an increase in osmotic pressure if the energy supply was increased. Therefore, since the 1960s, total parenteral nutrition (TPN) has become prevalent, resulting in improvements in the therapeutic results of many diseases. From the viewpoint of “When the gut works, use it!”, elemental diet has been developed for enteral nutrition, and the administration of readily absorbable high-energy, high-protein preparations became possible.

Presently, methods for nutritional support are classified into three major groups, namely, 1) oral nutrition, 2) enteral nutrition, and 3) parenteral nutrition. Each of them has advantages and disadvantages and must be selected appropriately alone or in combination for individual patients (Table IV-1).

| Table IV-1. Advantages and Disadvantages of Oral, Enteral, and Parenteral Nutrition |
|-----------------------------------------------|-----------------------------------------------|
| **Advantages** | **Disadvantages** |
| Oral nutrition | • The structure of the digestive tract can be physiologically maintained.  
• Blood oxygen supplied to the brain is increased by increased energy required by the stomach and intestine for digestion.  
• There are physical and psychological/social aspects.  
• One psychological/social aspect is activation of neurotransmitters in the brain.  
• Communication through eating develops.  
• The cerebrum is stimulated via receptors of vision, taste, smell, hearing, touch, etc.  
• Maintenance of oral hygiene is promoted.  
• It is impossible to provide all necessary nutrients because of preferences.  
• The amount of intake is affected by appetite.  |
| Enteral nutrition | • The structure of the digestive tract can be physiologically maintained.  
• Medical professionals can provide nutrients in planned amounts.  
• Necessary amounts of nutrients for different disease conditions can be provided.  
• There is concern over the development of gastrointestinal symptoms.  
• There is concern over self-extubation (accidental extubation).  
• There is a sense of discomfort about the tube.  |
| Parenteral nutrition | • Necessary water, electrolytes, and nutrients can be administered regardless of appetite.  
• Can be performed for patients with difficulty in using their digestive tract.  
• Long-term parenteral feeding may make it physiologically impossible to maintain the structure of the digestive tract.  
• Serious complications, such as hyperglycemia, phlebitis, and sepsis, may be induced.  |
Section 1. Outline of Nutritional Support Methods

A. Significance of Oral Nutrition
The fundamental principle of nutritional management is avoiding a meaningless fasting period by using the gastrointestinal tract as much as possible. Needless to say, oral intake is the best route of nutritional supply, and it is the ultimate goal of nutritional support. Eating from the mouth has physiological significance not confined to simple supply of nutrients.

B. Significance of Enteral Nutrition
Unlike TPN via the intravenous route, enteral nutrition is a physiological method for nutritional management, by which the dynamics of gastrointestinal hormones can also be maintained more normally. Enteral nutrition requires no special technique if nutritional preparations are administered by inserting a gastric tube orally or transnasally without creating a stoma to the stomach or intestine. Long-standing TPN is associated with the possibility of atrophy of the intestinal mucosal epithelium and consequent bacterial translocation, a phenomenon in which bacteria or endotoxin produced pass through the intestinal mucosa.

C. Significance of Parenteral Nutrition
Although oral or enteral nutrition should be selected preferentially, parenteral nutrition is the first choice for patients with severe swallowing disorder, gastrointestinal dysfunction, or circulatory instability. The recommendations of the guidelines for nutrition support therapy for critically ill patients by the Japanese Society of Intensive Care Medicine are: “The preference of enteral nutrition is strongly recommended (recommendation level: 1A)” to the clinical question, “Which route of nutritional support should be preferred between enteral and parenteral routes?”, but “Delaying the initiation of enteral nutrition is weakly recommended to patients with hemodynamic instability such as those administered a high dose of vasopressor or requiring massive fluid infusion or blood transfusion until resuscitation and stabilization of the hemodynamics (recommendation level: 2C)” to the clinical question, “Is enteral nutrition possible in hemodynamic instability?”.

Section 2. Oral Nutrition in Heart Failure

A. Taste Abnormality and Oral Nutritional Supplements
Taste is sensed by taste buds on the tongue surface or oral mucosa, but the total number of taste buds decreases with aging to about 1/2 to 1/3 in older people compared with neonates, and taste disturbance or disorder is a physiological phenomenon associated with aging. Older people are less sensitive to tastes of foods (Figure IV-1).
In heart failure patients difficult to eat orally due to malaise or respiratory distress, the lack of energy intake is usually complemented by oral nutrition supplementation (ONS).

B. Types of Oral Nutrition

Low-Salt Diet
Generally, low-salt diet is diet in which the salt content is restricted to prevent edema and reduce the renal burden. It is classified into 1) salt-free diet, 2) moderately low-salt diet (1–3 g/day), and 3) mildly low-salt diet (5–8 g/day). They are used for the treatment of conditions such as hypertension, congestive heart failure, and renal edema. The Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure (2017 edition) recommends a salt intake of “<6 g/day”.

Minced Diet
Minced diet is food cut into a masticable size for patients with declined mastication ability or muscle strength. The perception that minced food is inappropriate for patients with swallowing disorder is beginning to be established.

Blender Diet
Blender diet is prepared by processing ordinary or soft diet in a blender. It is prepared by adjusting the viscosity to about potage so it can be eaten without mastication. For patients with impaired swallowing ability, it is smoothed using a thickener (polysaccharide thickener), but caution is necessary as pharyngeal residue increases if the food is excessively thickened.

Dysphagia Diet
With progressive aging also of heart failure patients, many of them develop swallowing disorder. Dysphagia diet is prepared by adjusting the shape, thickness, and adherability of bolus according to the level of swallowing ability for patients with declined swallowing or masticatory function.

Section 3. Enteral Nutrition for Heart Failure

A. Types of Enteral Nutrition Products
In selecting enteral nutrition products, it is important to assess the abilities of digestion and absorption and consider the ratio of the 3 major nutrients, i.e., protein, lipids, and carbohydrates, and the type of each nutrient. Commercially
available enteral nutrition products can be classified into 1) elemental diets, 2) oligomeric formulas, 3) polymeric formulas, and 4) natural thickened liquids

**Table IV-2. Classification of Enteral Nutrient Preparations by the Nitrogen Source and Their Characteristics**

| Nitrogen source          | Elemental nutrients | Digested nutrient preparations | Half-digested nutrient preparations | Natural thick liquid diet |
|--------------------------|---------------------|--------------------------------|-------------------------------------|--------------------------|
| Amino acids              | Amino acids, dipeptides, and tripeptides | Polypeptides, protein          | Proteins                           |
| Lipids                   | Long-chain and medium-chain fatty acids | Long-chain and medium-chain fatty acids | Long-chain fatty acids            |
| Carbohydrates            | Dextrin             | Dextrin                         | Dextrin, etc.                       | Maltodextrin             |
| Fiber components         | None                | None                            | Water-soluble and insoluble dietary fiber added in many products | Water-soluble dietary fiber added |
| Characteristics          | Very low lipid content | Nitrogen source is primarily peptides | Rich in variety | Primarily natural foods are compounded |
| Digestion                | Unnecessary         | Partially necessary             | Necessary to an extent             | Necessary                |
| Absorption               | Necessary           | Necessary                        | Necessary                           | Necessary                |
| Residue                  | Very little         | Very little                     | Little                             | Large amount            |

**Elemental Diets**

Elemental diets have chemically definitive composition and need little digestion. Their major characteristic is that proteins are composed of non-antigenic amino acids. In long-term administration, attention to deficiency of vitamins and trace elements is necessary, and there is the possibility of the occurrence of selenium deficiency, in particular. Because of the very low lipid contents, the risk of essential fatty acid deficiency must also be considered.

**Oligomeric Formulas**

Since dipeptides consisting of 2 bound amino acid molecules and tripeptides consisting of 3 bound amino acid molecules are absorbed via peptide-specific peptide carriers, oligomeric formulas containing low-molecular-weight peptides as the nitrogen source require little digestion and show a short intestinal retention time.

**Polymeric Formulas**

Polymeric formulas range from general enteral nutrition products developed by adjusting the compositional ratio of the 3 major nutrients to the nutrient requirements or dietary reference intakes of Japanese to products prepared by adjusting the type and compositional ratio of each nutrient for various disease states. The preparations are enriched with vitamins and trace elements in addition to the 3 major nutrients, and many contain dietary fiber. A disadvantage is the possible occurrence of diarrhea if there is maldigestion or malabsorption. Also, the fat energy ratio is high in many products, and caution is needed if there is impairment of lipid absorption, but some products contain a high percentage of middle-chain fatty acids, which can be absorbed even in such cases. They are formulas appropriate for long-term management by total enteral nutrition, and new products that cater to individual disease states or compensate for defects of conventional formulas are developed at a rapid pace.

**Natural Thick Liquids**

Before natural thick liquids began to be commercially distributed, liquid meals prepared by stirring ordinary meals with a blender were used. Since natural thick liquids are made from natural foods, they have a low osmotic pressure and are less likely to cause diarrhea even if a large amount is administered in a short time. However, they are not indicated for patients with reduced digestion/absorption ability. Also, they are difficult to pass through a thin tube because of poor fluidity.

For these reasons, oligomeric and thick polymeric diets are recommended for enteric nutrition of heart failure patients. Many heart failure patients also require fluid restriction. Usual nutritional preparations are adjusted to 1.0 kcal/mL with a water content of about 80%. The energy content of thickened nutritional products is adjusted to 1.5–2.0 kcal/mL, and 10% of water intake can be reduced with a product at 2.0 kcal/mL, in which the water content is 70%, compared with usual nutritional products when the same amount of energy is administered. In addition, the daily energy requirement is high in heart failure patients, and thickened nutrition products are also advantageous from this viewpoint.

**B. Measures to Prevent Complications of Enteral Nutrition**

The greatest complication of enteral nutrition is gastrointestinal symptoms. To avoid them, it is recommended to initiate the administration at a low dose and to carefully increase the dose while concomitantly using parenteral nutrition to supplement the lack.

**Section 4. Parenteral Nutrition for Heart Failure**

Although evidence concerning nutritional management for patients with severe heart failure is insufficient, a few studies have been performed concerning critically ill patients who require intensive care such as those with sepsis.

There is also a report that the target dose of energy...
administration was reached by enteral nutrition in 40% of the patients using catecholamines, and intestinal absorption of nutrients is considered possible even in critically ill patients.

While enteral nutrition is also considered possible in patients using catecholamines, stabilization of the disease state such as stabilization of the blood pressure, completion of massive fluid administration or transfusion, and no need to increase the dose of catecholamines is considered necessary for the initiation of enteral nutrition. Usually, enteral nutrition induces increases in the oxygen consumption of the digestive tract and intestinal blood flow, but, in patients with low cardiac output or circulatory disorders, it is difficult to increase the intestinal blood flow, and enteral nutrition may trigger a decrease in blood pressure or even intestinal ischemia and necrosis. The prognosis of intestinal ischemia is poor, and the mortality rate has been reported to be 58% in an observational study. The Society of Critical Care Medicine (SCCM)/American Society for Parenteral and Enteral Nutrition (ASPEN) Guidelines recommend avoidance of the initiation of enteral nutrition during a large amount of catecholamines administration and massive fluid infusion until stabilization of the hemodynamics, with a mean blood pressure of 60 mmHg as a provisional criterion.

Chapter V. Outcome Indices and Evidence of Nutritional Therapy

Nutritional therapy is expected to benefit physical functions, quality of life (QOL), and outcome of chronic heart failure patients. In this chapter, the framework of outcome indices and present status of evidence in the efficacy evaluation of nutritional therapy are described.

A conceptual chart of outcomes used in phase III clinical trials in chronic and acute heart failure patients is shown in Figure V-1. In addition to these outcomes, outcomes related to the assessment of nutritional state, physical functions, frailty, sarcopenia, and cachexia are used in intervention with nutritional therapy. An outcome model of nutritional therapy for heart failure based on the outcome models by the Clinical Nutrition Guideline Group, European Society for Clinical Nutrition and Metabolism (ESPEN) is shown in Figure V-2. In these models, outcomes in nutritional therapy are classified into medical outcomes, patient-reported outcomes, medical economics outcomes, outcomes concerning medical guidelines, and complex outcomes. In many studies on nutritional therapy, medical outcomes were used as the primary indices, but comprehensive assessment with the concomitant use of other outcomes is recommended.

Interventional studies concerning nutritional therapy for stage C/D symptomatic heart failure patients are very few. More research results are awaited.

There have been a number of systematic reviews and meta-analyses of nutritional therapy for older and malnourished as well as heart failure patients, and they are summarized in Table V-1. According to the results of meta-analyses, there have been many reports of improvements in indices that reflect the nutritional state including energy intake, protein intake, body weight, body mass index (BMI), arm circumference (AC), and arm muscle circumference (AMC) as a result of some nutritional intervention such as ONS. However, the results of studies using muscle strength, activities of daily living (ADL), QOL, re-admission, or death as outcomes have not been consistent.

Concerning studies carried out for the prevention or treatment of sarcopenia, there have been some reports of synergy by the addition of nutritional supplementation to exercise, but the evidence remains insufficient. More research results are anticipated.

![Figure V-1](https://example.com/figure-v-1.png)

**Figure V-1.** Schematic of potential endpoints for phase III pivotal chronic heart failure trials (A) or acute heart failure trials (B). CV, cardiovascular; HF, heart failure; HRQOL, health-related quality of life. (Adapted from Zannad F, et al. *Eur J Heart Fail* 2013. ©2013 Faiez Zannad et al., with permission from John Wiley and Sons.)
### Table V-1. Evidence of Nutritional Therapy Primarily for Older People and Patients

| Outcome          | Outline                                                                 | Authors            | Study design   | Journals                      | Year  | Reference No. |
|------------------|--------------------------------------------------------------------------|---------------------|----------------|-------------------------------|-------|---------------|
| Nutritional state| Improvements are observed in indices of the nutritional state, such as energy intake, protein intake, body weight, BMI, AC, and AMC, due to nutritional support with oral nutritional supplements, etc. | Milne AC           | Meta-analysis  | Ann Intern Med                | 2006  | 71            |
|                  |                                                                          | Milne AC           | Meta-analysis  | Cochrane Database Syst Rev    | 2009  | 72            |
|                  |                                                                          | Cawood AL          | Meta-analysis  | Ageing Res Rev                | 2012  | 73            |
|                  |                                                                          | Beck AM            | Meta-analysis  | Clin Rehabil                  | 2013  | 74            |
|                  |                                                                          | Bally MR           | Meta-analysis  | JAMA Intern Med               | 2016  | 75            |
| Physical function| There are reports of some effects, but the increase in muscle strength due to nutritional supplements, such as protein, is not observed or not significant. | Milne AC           | Meta-analysis  | Ann Intern Med                | 2006  | 71            |
| (primarily muscle|                                                                          | Milne AC           | Meta-analysis  | Cochrane Database Syst Rev    | 2009  | 72            |
| strength)        |                                                                          | Cawood AL          | Meta-analysis  | Ageing Res Rev                | 2012  | 73            |
|                  |                                                                          | Cermak NM          | Meta-analysis  | Am J Clin Nutr                | 2012  | 76            |
|                  |                                                                          | Finger D           | Meta-analysis  | Sports Med                    | 2015  | 77            |
|                  |                                                                          | Bally MR           | Meta-analysis  | JAMA Intern Med               | 2016  | 75            |
|                  |                                                                          | Thomas DK          | Meta-analysis  | J Am Med Dir Assoc            | 2016  | 78            |
|                  |                                                                          | Beaudart C         | Systematic review | Osteoporos Int             | 2017  | 79            |
|                  |                                                                          | Yoshimura Y        | Meta-analysis  | J Am Med Dir Assoc            | 2017  | 80            |
| QOL              | No consistent results have been obtained.                               | Milne AC           | Meta-analysis  | Ann Intern Med                | 2006  | 71            |
|                  |                                                                          | Cawood AL          | Meta-analysis  | Ageing Res Rev                | 2012  | 73            |
| Re-admission     | No consistent results have been obtained.                               | Cawood AL          | Meta-analysis  | Ageing Res Rev                | 2012  | 73            |
|                  |                                                                          | Beek AM            | Meta-analysis  | Clin Rehabil                  | 2013  | 74            |
|                  |                                                                          | Stratton RJ        | Meta-analysis  | Ageing Res Rev                | 2013  | 81            |
|                  |                                                                          | Bally MR           | Meta-analysis  | JAMA Intern Med               | 2016  | 75            |
|                  |                                                                          | Deutz NE           | Double-blind RCT including 157 heart failure patients | Clin Nutr | 2016 | 82 |
| Death            | No consistent results have been obtained.                               | Milne AC           | Meta-analysis  | Ann Intern Med                | 2006  | 71            |
|                  |                                                                          | Milne AC           | Meta-analysis  | Cochrane Database Syst Rev    | 2009  | 72            |
|                  |                                                                          | Cawood AL          | Meta-analysis  | Ageing Res Rev                | 2012  | 73            |
|                  |                                                                          | Beek AM            | Meta-analysis  | Clin Rehabil                  | 2013  | 74            |
|                  |                                                                          | Bally MR           | Meta-analysis  | JAMA Intern Med               | 2016  | 75            |
|                  |                                                                          | Deutz NE           | Double-blind RCT including 157 heart failure patients | Clin Nutr | 2016 | 82 |

**Figure V-2.** The outcome models of nutritional therapy. (Source: Prepared based on Koller M, et al. *Clin Nutr* 2013, 68)
Chapter VI. Nutritional Therapy According to the Disease Stage

Section 1. Nutritional Therapy for Stage A/B Heart Failure

A. What Is Appropriate Salt Intake?

Excessive intake of salt increases the blood pressure and exacerbates the risk of cardiovascular disease. The World Health Organization (WHO) proposes a target salt intake of <5 g (2 g of Na) /day, and the American Heart Association (AHA) recommends a salt intake of <3.8 g (1.5 g of Na)/day for hypertensive patients.85

Japan ranks high in salt intake86 with a mean daily salt intake of about 10 g.87 A recent observational study reported that a low salt intake is also related to cardiovascular events.88 Since excessive salt restriction may also be harmful, the setting of the salt control goal remains controversial. According to Japanese guidelines, the target of salt reduction is set at <6 g/day for stage A/B heart failure patients such as those with hypertension and myocardial infarction in consideration of the Japanese dietary habit.89,90

B. What Is the Optimal Body Weight for the Prevention of Cardiovascular Events?

The WHO defines a body mass index (BMI) of ≥25 kg/m² as pre-obese and ≥30 kg/m² as obese.91 Since complications such as glucose intolerance, dyslipidemia, and hypertension increase when BMI exceeds 25 kg/m², a BMI of 18.5–24.9 kg/m² is defined as normal weight and ≥25 kg/m² as obesity25 (see Chapter III, Table III-2). In Japanese, the incidence of coronary artery disease increases two-fold in males and 1.58-fold in females with a BMI of ≥27 kg/m² compared with those with a BMI of 23.0–24.9 kg/m².92 Low body weight is also a problem, and the risk of cerebral infarction and cerebral hemorrhage increases in those with a BMI of <18.5 kg/m².92 Body weight gains after reaching adulthood is also important, and the risk of coronary artery disease doubles in those who had a BMI of <21.7 kg/m² in their 20s and gained 10 kg or more thereafter.93

C. Evidence About Various Foods for the Prevention of Cardiovascular Events

Red Meat

The harm of a meat diet has been emphasized as a risk factor of cardiovascular disease, but the relationship between the intake of red meat and the occurrence of cardiovascular disease is considered weak in recent reports.94,95 A study in Japanese showed that moderate meat intake (<100 g) does not lead to an increase in deaths due to cardiovascular disease.96 In contrast, intake of processed meat such as ham and sausage at ≥75 g/day increases the risk of heart failure 1.28-fold and the risk of death due to heart failure 2.43-fold compared with their intake at <25 g/day.97

Fish

Fatty blue-skinned fish contain large amounts of ω3 polyunsaturated fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and may the prevent coronary artery disease. The AHA recommends eating fish at least 2 times a week.85

Table VI-1. The DASH Eating Plan

| Food                      | Daily/Weekly servings | Serving indication                           |
|---------------------------|-----------------------|----------------------------------------------|
| Grains                    | 6 to 8 SVs per day    | 1 slice bread                                |
|                           |                       | 1 oz* dry cereal                             |
|                           |                       | 1/2 cup** cooked rice, pasta, or cereal      |
| Vegetables                | 4 to 5 SVs per day    | 1 cup raw leafy vegetable                    |
|                           |                       | 1/2 cup cooked vegetable                     |
|                           |                       | 1/2 cup vegetable juice                      |
| Fruits                    | 4 to 5 SVs per day    | 1 medium fruit                               |
|                           |                       | 1/4 cup dried fruit                          |
|                           |                       | 1/2 cup fresh, frozen, or canned fruit       |
|                           |                       | 1/2 cup fruit juice                          |
| Fat-free or low-fat milk  | 2 to 3 SVs per day    | 1 cup milk                                   |
| and milk products         |                       | 1 cup yogurt                                 |
|                           |                       | 1 1/2 oz cheese                              |
| Lean meats, poultry, and  | <6 oz per day         | 1 oz cooked lean meats, poultry, fish        |
| fish                      |                       | 1 egg                                        |
| Nuts, seeds, and legumes  | 4 to 5 SVs per week   | 1/3 cup (11/2 oz) nuts                       |
|                           |                       | 2 tbsp peanut butter                         |
|                           |                       | 1/2 cup cooked beans or peas                 |
| Fats and oils             | 2 to 3 SVs per day    | 1 tsp soft margarine                         |
|                           |                       | 1 tsp vegetable oil                          |
|                           |                       | 1 tbsp mayonnaise                            |
|                           |                       | 2 tbsp salad dressing                        |
| Sweets and sugars         | 5 or fewer SVs per    | 1 tsp sugar                                  |
|                           | week                  | 1 tbsp jelly or jam                          |

*1 oz=28 g, **1 cup=236 mL. Assuming the daily total energy intake as 2,000 kcal, the necessary intake of each food item is shown in the dietary unit of serving (SV). Source: Prepared based on National Institutes of Health. Description of the DASH Eating Plan.105
Vegetables/Fruits
Vegetables and fruits are rich in vitamins, minerals, and fiber\(^1\) and may reduce deaths due to cardiovascular disease.\(^{98\text{-}100}\)

Whole-Grain Cereals
Whole-grain cereals are rich in fiber, vitamin B, and minerals and have been reported to be effective for preventing coronary artery disease and reducing the risk of deaths due to cardiovascular disease.\(^{101}\)

Nuts
Nuts are rich in unsaturated fatty acids, fiber, vitamins, and minerals and have been reported to reduce the risk of coronary artery disease.\(^{102}\)

Alcohol
Mild intake of alcohol reduces the risk of heart failure.\(^{103}\) Regular drinkers are recommended to restrict drinking under 30g/day in terms of pure alcohol.\(^{89}\)

D. Evidence Concerning the Dietary Pattern for the Prevention of Cardiovascular Events
A regular diet consists of combinations of various food items, and evaluation based on the dietary pattern is important. Mediterranean diet\(^{104}\) and Dietary Approaches to Stop Hypertension (DASH) diet (Table VI-1) have been reported as useful dietary patterns to prevent cardiovascular events.\(^{105\text{-}106}\) Japanese food is attracting global attention as a healthy diet, and a relationship between the Japan Diet (characterized by low meat and fat intakes and high intakes of soybeans, fish, vegetables, seaweeds, mushrooms, and fruits\(^{107}\)) and reduced risk of death due to cardiovascular disease has been reported.\(^{108\text{-}109}\) The frequency of cardiovascular events is reported to be low in Japanese with a dietary pattern in compliance with the Japanese Food Guide Spinning Top (Figure VI-1)\(^{110}\) prepared by the Ministry of Agriculture, Forestry and Fisheries based on the Dietary Reference Intakes for Japanese.\(^{111}\)

E. Soft Drinks (Sweetened Beverages)
A high intake of soft drinks or sweetened beverages increases the risk of obesity and diabetes mellitus.\(^{85\text{-}112}\) In addition, so-called zero-calorie soft drinks containing artificial sweeteners may also be involved in the pathogenesis of diabetes.\(^{113}\)

F. Oral Nutritional Supplementation
The effectiveness of oral nutrition supplementation (ONS) has not been established, and the AHA is not recommending the use of ONS.\(^{85}\)

G. Evidence Concerning Fatty Acids
Fatty acids consist of atoms of 3 elements, i.e., carbon (C), hydrogen (H), and oxygen (O),\(^{114}\) and are divided into saturated fatty acids with no carbon double bonds and unsaturated fatty acids with carbon double bonds (Figure VI-2). Unsaturated fatty acids are divided into monounsaturated fatty acids with one carbon double bond and polyunsaturated fatty acids with multiple carbon double bonds, and...
polyunsaturated fatty acids are divided into ω3 and ω6 fatty acids depending on the position of the first double bond from the terminal methyl group (CH₃). Unsaturated fatty acids with hydrogen atoms on the same side of the double bond are called cis, and those with hydrogen atoms on different sides of the double bond are called trans-fatty acids.

**Saturated Fatty Acids**
Saturated fatty acids are contained in large amounts in animal fat in meat, dairy products, and vegetable oils such as palm oil used in processed foods. Excessive intake of saturated fatty acids is considered to increase the blood level of low density lipoprotein (LDL) cholesterol and promote atherosclerosis. Although recent meta-analyses have suggested that saturated fatty acids have no marked effect on atherosclerosis, cardiovascular events have been reported to be reduced by replacing saturated fatty acids with polyunsaturated fatty acids derived from vegetable oils.

**Unsaturated Fatty Acids**

1) **Monounsaturated fatty acids**
Oleic acid, a typical monounsaturated fatty acid, is contained in large amounts in animal fat and cooking oils such as olive oil. Compared with saturated fatty acids, monounsaturated fatty acids do not markedly increase LDL cholesterol and are considered to prevent cardiovascular disease. However, it has been reported that monounsaturated fatty acids derived from olive oil reduce deaths due to cardiovascular disease but that those derived from animals or vegetables have no such effect.

2) **Polyunsaturated fatty acids**
   a) **ω6 Fatty Acids**
Linoleic acid is a typical polyunsaturated fatty acid, and it is ingested primarily as vegetable oils such as soybean oil and corn oil. Since they may prevent cardiovascular diseases, they are recommended as substitutes for saturated fatty acids. However, as ω6 fatty acids are converted in the body to prostaglandins and leukotrienes, which cause inflammation, there is concern over the safety of their excessive intake, and the possibility of an increase in coronary artery disease due to their excessive intake has also been suggested.

   b) **ω3 Fatty Acids**
ω3 fatty acids include α-linolenic acid derived from cooking oil and EPA and DHA derived from fish. The effectiveness of EPA preparations for the secondary prevention of coronary artery disease has been reported. No consensus has been reached concerning their effectiveness for the primary prevention.

3) **Trans-Fatty Acids**
Trans-fatty acids are generated in the production of semi-solid or solid oils and fats from liquid vegetable or fish oils at room temperature by the processing technique called hydrogenation. Typical trans-fatty acids are margarine, fat spread, and shortening, and they are contained in bread, cake, doughnut, etc., as ingredients. If trans-fatty acids are ingested in large amounts, LDL cholesterol increases, high density lipoprotein (HDL) cholesterol decreases, and the risk of coronary artery disease increases.

Table VI-2 shows typical fatty acids, their relationships with cardiovascular diseases, and the foods that contain them in large amounts.

**H. Frequency and Timing of Eating**
In modern society, the daily schedule of activities is diversified, and mealtime is irregular. In those who skip breakfast, the risk of obesity, diabetes, and cardiovascular events increases. Also, eating late dinners in addition to skipping breakfast increases the risk of metabolic syndrome.
Section 2. Nutritional Therapies for Stage C/D Acute Heart Failure

A. Selection and Objectives of Parenteral and Enteral Nutrition

Some guidelines recommend enteral rather than parenteral nutrition as the route of nutritional support for critically ill patients. Enteral nutrition is considered to control infection, shorten the duration of hospitalization, and reduce the medical expenditure compared with parenteral nutrition although it does not improve the mortality rate. There has not been a randomized controlled study that compared parenteral and enteral nutrition in acute heart failure patients, and which of parenteral and enteral nutrition is more beneficial for acute heart failure patients is presently unknown (Table VI-3).

B. Determination of the Time of Initiation

In this section, the time of initiation of nutritional therapy for critically ill patients requiring intensive care is discussed. Whether these results can be applied to acute heart failure patients is unknown.
Time of Initiation of Enteral Nutrition
The Japanese Guidelines for Nutrition Support Therapy in the Adult and Pediatric Critically Ill Patients recommend the initiation of enteral nutrition within 24 hours as much as possible and within 48 hours at the latest after the beginning of treatment of critically ill patients. However, if the hemodynamics is unstable, the guidelines also consider it necessary to withhold the initiation of enteral nutrition. In severe heart failure, the hemodynamics often affects the use of the intestine, and enteral nutrition may invite intestinal ischemia or further exacerbation of hemodynamic instability. It is recommended that enteral nutrition should be withheld when the mean blood pressure is ≤60 mmHg due to cardiogenic shock and that its initiation should be evaluated after stabilization of the blood pressure and end of high-dose fluid supplementation or transfusion.

There is a report that the intestine could be used without complications such as intestinal ischemia when oral and enteral nutrition was initiated during treatment using hypertensive drugs, dialysis, and the intra-aortic balloon pump (IABP) in 70 patients after heart surgery using the heart-lung machine.

Time of Initiation of Parenteral Nutrition
Presently, no consensus has been reached about the time of initiation of parenteral nutrition. In the EPaNIC Trial, a group in which nutritional support was initiated within 48 hours by parenteral nutrition (early group) and a group in which parenteral nutritional support was not performed (late group) were compared and showed increases in the incidence of infection, and the durations of support with a respirator and stay in the intensive care unit (ICU) in the early group. In the Early PN Trial, on the other hand, the durations of support with a respirator and thrombocytopenia were shortened by initiating parenteral nutrition early after admission to the ICU.

It is difficult to directly apply the results of the EPaNIC Trial to Japanese patients, because intensive insulin therapy, which is not recommended at present, was used in the EPaNIC Trial, and because BMI of the patients in both studies was high around 28 kg/m².

C. Target Nutrient Intakes
Presently, research results that provide the basis for target nutritional intakes for acute heart failure patients are not available. In this section, target nutritional intakes for severely ill patients requiring intensive care are discussed.

Energy
First, to determine the target amount of energy to be administered, it is necessary to estimate energy expenditure. In heart failure patients, the resting energy expenditure (REE) is reported to be about 18% higher compared with healthy individuals. It is recommended to set the target amount of energy to be administered based on the measurement of the energy expenditure by indirect calorimetry or its calculation using an estimation equation.

For the calculation of the target amount of energy to be administered, a simplified formula assuming the energy expenditure per kg of body weight as 25–30 kcal/day and Harris-Benedict equation are widely used today. Indirect calorimetry can be substituted for estimation of the energy expenditure using an estimation equation.

In critically ill patients, it is recommended to administer energy at a dose smaller than the calculated target amount during the first week of the acute phase. In a group in which tolerable restriction of nutritional intake was imposed, the hospital death rate was significantly lower, durations of the stay in the ICU and the period of support using a respirator were shorter, and the incidence of hyperglycemia was lower compared with a group in which energy was administered to the target dose. In a study of the relationship between the fulfillment rate of the energy requirement with the mortality rate in ICU patients, a U-shaped curve was obtained, indicating that the risk of death was high when the energy intake was excessive or deficient.

Protein
In an observational study of patients admitted to the ICU, the mortality rate was shown to decrease inversely with protein intake. The administration of at least 1.2 g/kg/day of protein is necessary in patients in the acute phase of trauma to improve nitrogen balance. However, a systematic review indicated that the grounds concerning the optimal protein dose are insufficient. Since the subjects of these studies were not acute heart failure patients, the optimal protein intake for acute heart failure patients is unclear.

Salt
One of the exacerbating factors of chronic heart failure is excessive intake of salt, but there has been no study that showed the optimal salt intake in acute heart failure patients.

In patients capable of oral feeding, excessive salt restriction may invite anorexia, leading to energy deficiency due to insufficient dietary intake. According to an interventional study, there was no advantage in the combination of strict salt restriction and fluid restriction.

D. Types and Selection of Enteral Nutrient Preparations
In heart failure patients, the risk of diarrhea associated with enteral nutrition increases because of intestinal edema and reduced digestion/absorption ability.

There is no significant difference between oligomeric nutrient preparations (peptide type nutrient preparations) and polymeric nutrient preparations in the duration of hospitalization, incidence of infection, or mortality rate. Most of the nutrient preparations usable in Japan contain 1 kcal of energy per mL, but the use of concentrated products with energy content of 1.5 or 2 kcal/mL should be considered for acute heart failure patients with fluid restriction.

E. Management of Patients During Enteral Nutrition Therapy
Points of attention in the management of enteral nutrition in critically ill patients are described, although they are not specific to heart failure patients.

Body Position During Enteral Nutrition Therapy
Sufficient caution against aspiration is necessary during enteral nutrition therapy. In enteral feeding of tracheally intubated patients, the incidence of pneumonia can be reduced by placing them in the semi-Fowler’s position, in which the cranial end of the bed is elevated 30–45°. It is
recommended to maintain semi-Fowler’s position as much as possible in consideration of the risk of aspiration.

**Nutritional Management During Noninvasive Positive Pressure Ventilation**

During noninvasive positive pressure ventilation (NPPV), there is the possibility of aspiration if the gastric contents reach the oral cavity due to vomiting or gastroesophageal reflux, but the NPPV guidelines recommend enteral nutrition for patients incapable of oral feeding.

Even in patients requiring NPPV, avoidance of unnecessary fasting and early initiation of oral or enteral feeding are also recommended if the use of intestine is possible.

**Estimation of Gastric Residual Volume**

The amount of nutrient preparation and digestive juice retained in the stomach during the management of enteral feeding is called the gastric residual volume (GRV). Generally, GRV is measured every 4–6 hours.

GRV is used as an index for the assessment of gastric motility. There is a report that GRV is unrelated to the incidence of aspiration, but there was also a report that the frequency of aspiration was high when GRV was large. The joint guidelines by the Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN) recommend continuation of enteral feeding without interruption if GRV is ≤500 mL, however, careful management is required in Japanese patients even if GRV is ≤500 mL.

**Intermittent and Continuous Administration**

Comparison between intermittent and continuous administration showed that the target amount of energy administration could be reached more quickly by intermittent administration. However, it is necessary to consider that the subjects were American patients admitted to the trauma ICU and that they were young with a mean age in the 40s.

Although there has been no study in which intermittent and continuous administration was compared in heart failure patients, the frequency of diarrhea was reported to be lower by continuous administration in burn patients and older people. From these observations, continuous administration is recommended, if possible, for enteral nutritional management in the acute phase.

**F. Composition of Parenteral Nutrition**

In parenteral nutrition, the administration of at least the 3 primary nutrients, vitamins, and trace elements should be considered rather than glucose alone. In the Early PN Trial, the outcome was not exacerbated even when parenteral nutrition, which contained the 3 primary nutrients, was initiated early. The recommended doses of vitamins and trace elements for not only heart failure patients but also critically ill patients are presently unclear.
Section 3. Nutritional Therapy for Stage C/D Chronic Heart Failure

IA. Therapeutic Goals of Chronic Heart Failure and the Position and Basic Principles of Its Nutritional Therapy

Chronic heart failure is a progressive syndrome in which gradual progression of declines in cardiac function, physical functions, and nutritional state is observed with repeated alternation of exacerbation and remission. Exacerbation of the nutritional state, decreases in muscle mass and muscle strength, and declines in physical functions are considered to occur as results of phenomena due to circulatory insufficiency such as dysfunction of viscera and organs of the whole body, activation of the renin-angiotensin system and sympathetic nervous system, and activation of inflammatory cytokines.

While the stage of heart failure gradually progresses, physical functions and nutritional state change in parallel, and the nutritional state is exacerbated as the terminal phase approaches. The serum albumin and cholesterol levels and the nutritional state is exacerbated as the terminal phase approaches. The serum albumin and cholesterol levels have been reported to be prognostic factors independent of age or the severity of heart failure.38,41 The goal of nutritional therapy for chronic heart failure is to prevent exacerbation of heart failure and improve the outcome while maintaining the nutritional state and aiming to maintain or improve the ability of physical activities. To achieve this goal, it is important to reduce salt intake, which may increase fluid retention, while maintaining appropriate energy intake. Generally, since the nutritional state is often intact if chronic heart failure is stabilized in stage C, nutritional therapy often centers around modification of salt intake, i.e., nutritional guidance primarily consisting of salt restriction. However, if intake of a necessary amount of energy is difficult to secure due to salt restriction, priority should be placed on securing energy intake. In addition, there is a report that Mediterranean diet reduced the re-admission rate of heart failure patients while it did not have an effect on hospitalization.42 Moreover, a condition with increased vulnerability to health damage due to declines in various functions accompanied by impairment of cognitive function, psychological/psychiatric problems such as depression, and social problems such as solitary living and economic difficulties in addition to physical problems due to sarcopenia is defined as frailty,16 and the degree of frailty is correlated with the development of new heart failure159 and the outcome of heart failure patients.166

In the course of progression of heart failure, 5–15% of the patients lapse into a systemic wasting condition called cachexia (see Chapter II, Table II-2).18,161,162 Cardiac cachexia is an independent poor prognostic factor for heart failure.9 Dietary therapy and exercise therapy with reevaluation and optimization of drug therapy for heart failure are important for improving cardiac cachexia.163

IB. Sarcopenia, Frailty, and Cachexia Associated With Chronic Heart Failure and the Prognosis

Chronic heart failure is complicated by sarcopenia in 25–50% of the patients.157,158 Moreover, a condition with increased vulnerability to health damage due to declines in various functions accompanied by impairment of cognitive function, psychological/psychiatric problems such as depression, and social problems such as solitary living and economic difficulties in addition to physical problems due to sarcopenia is defined as frailty,16 and the degree of frailty is correlated with the development of new heart failure159 and the outcome of heart failure patients.166

IC. Chronic Heart Failure and Obesity, Optimal BMI

Presently, no evidence concerning the optimal BMI for chronic heart failure patients has been established. In heart failure patients, the prognosis has been reported to be poorer as BMI is lower and, inversely, to be better as BMI is higher, a phenomenon known as “obesity paradox”.9,14 However, no evidence concerning the relationship between intentional body weight gain or loss and the prognosis has been established in heart failure patients.

ID. Reality of Nutritional Therapy for Chronic Heart Failure

Energy Requirement

In nutritional therapy for chronic heart failure patients, consideration of energy intake, salt/water intake, and intakes of protein and vitamins/minerals is necessary. As the basic dietary pattern for chronic heart failure, the Mediterranean diet consisting primarily of fish, vegetables, fruits, wine, and whole-grain cereals is recommended. In heart failure patients, basal metabolism is increased,136 and the energy requirement is greater than usual.

For the estimation of the energy requirement, the REE is considered to be calculated most accurately by indirect calorimetry:

| Table VI-4. Estimation of Necessary Amount of Energy Using the Harris-Benedict Equation |
|------------------------------------------|---------------------------------|---------------------------------|
| Basal metabolic expenditure Male: 66.5 + (13.8 x body weight in kg) + (5.0 x height in cm) – (6.8 x age) Female: 655.1 + (9.6 x body weight in kg) + (1.8 x height in cm) – (4.7 x age) |
| Activity index Recumbent position: 1.0, wheelchair (resting on the bed): 1.2, walking (out-of-bed activities): 1.3–1.4, mild exertion: 1.5, moderate exertion: 1.7, heavy exertion: 1.9 |
| Stress index After surgery (no complications): 1.0, fever: 1.2–1.5, fracture: 1.15–1.3, bedsore: 1.2–1.6, cancer, COPD, pneumonia, sepsis: 1.1–1.3, use of steroid: 1.6–1.7, severe infection, multiple traumas: 1.2–1.4, multiple organ failure, burn injury: 1.2–2.0 |
| Necessary amount of energy Basal metabolic expenditure x activity index x stress index |

Source: Prepared based on Japanese Society for Parenteral & Enteral Nutrition. Guidelines for Parenteral/Enteral Nutrition for Comedicals. Nankodo; 2000.166
REE (kcal/day) = 
{(3.941 × VO₂ (mL/min)) + (1.106 × VCO₂ (mL/min))} × 1.44

VO₂: oxygen uptake, VCO₂: carbon dioxide output

or using a simplified formula:

REE (kcal/day) = 
{(3.94 × VO₂ (mL/min)) + (1.11 × VCO₂ (mL/min))} × 1.44

REE calculated using this formula multiplied by the activity index (Table VI-4) is the estimated daily energy requirement. However, as expired gas analysis, which is often difficult to perform, is necessary for indirect calorimetry, a method based on the Harris-Benedict equation is widely used as a substitute for the calculation of REE (Table VI-4). However, there is also no mention about the stress index of chronic heart failure patients in this equation. In addition, in Japanese, particularly, older women, the energy requirement calculated using this equation tends to be higher than the value obtained by indirect calorimetry.

As more convenient methods, a simplified formula for the calculation of basal metabolic rate in Japanese is widely used as a substitute for the calculation of REE (Table VI-4). However, there is also no mention about the stress index of chronic heart failure patients in this equation. In addition, in Japanese, particularly, older women, the energy requirement calculated using this equation tends to be higher than the value obtained by indirect calorimetry.

As more convenient methods, a simplified formula for the calculation of basal metabolic rate in Japanese [14.1 × current body weight (kg) + 620 for males, 10.8 × current body weight (kg) + 620 for females] and addition or subtraction of 25–30 kcal/kg depending on the degree of stress are also used frequently. Whichever estimation equation may be used for the calculation of energy requirement, assessment of the patient’s nutritional state must be repeated during the course of treatment.

If the actual body weight is ≥125% of the standard body weight (22 × height (m)^2), it is recommended to perform the calculation using the corrected body weight calculated as:

Corrected body weight (kg) =
{(actual body weight) − (standard body weight)} × 0.25 + standard body weight

Salt Restriction and Fluid Restriction

As salt increases fluid retention and the report that half-hearted salt/fluid restriction is the most frequent factor of re-admission due to exacerbation of heart failure, salt restriction is important in nutritional management of heart failure patients. However, no specific recommended intake of salt has been established. According to Japanese guidelines, a salt intake of <6 g/day is recommended, and more strict salt restriction should be evaluated for severe heart failure, but caution is necessary, particularly, in older patients, because excessively strict salt restriction reduces appetite and may lead to exacerbation of the nutritional state. It is recommended to reduce salt intake within a tolerable range by individually assessing the patient’s nutritional state and dietary intake and considering the actual salt intake without sticking to salt-restricted diet.

Guidance about the necessity of fluid restriction in heart failure is often similar to that about salt restriction, but intake of a certain amount of fluid is necessary to maintain fluid homeostasis. Generally, the daily fluid requirement is considered to be 30–40 mL/kg/day including dietary water content, but it varies with age, and the minimum requirement in those aged ≥75 years is considered to be 25 mL/kg/day. There is no clear evidence concerning fluid restriction in heart failure patients. In the European Society of Cardiology (ESC) guidelines, also, avoidance of excessive intake of fluid is recommended, but they only state that restriction of fluid intake to 1.5–2.0 L/day may be evaluated to alleviate symptoms and congestion in patients with severe heart failure and recommend adjustments such as increasing the fluid intake depending on the environment and physical condition. Furthermore, in older patients, appropriate support for fluid intake is necessary in consideration of the age-associated decline in thirst center function. However, fluid restriction is necessary if the patient with severe heart failure shows dilutional hyponatremia. The amount of water contained in food is often assumed to be about 400 mL per 1,000 kcal or about 600 mL per 1 kg of usual diet.

Protein Intake

In the absence of moderate or severe renal dysfunction, protein intake of patients with chronic diseases including chronic heart failure is recommended to be increased to 1.2–1.5 g/kg/day. If the estimated glomerular filtration rate (eGFR) is <60 mL/min/1.73 m^2, and if there is moderate or severe renal dysfunction with grade 3b chronic renal disease, protein restriction to 0.6–0.8 g/kg/day is considered. In such an event, also, it is recommended to ingest a sufficient amount of energy, or ≥30 kcal/kg, with attention to sarcopenia and frailty.

E. Possible Effectiveness of Oral Supplements in Heart Failure

Of the essential amino acids, branched-chain amino acids such as leucine, isoleucine, and valine (particularly leucine) are known to be substrates in muscle protein synthesis and, at the same time, promote protein synthesis. Many studies that evaluated the effects of nutritional supplementation therapy using oral amino acids to promote muscle protein synthesis in chronic heart failure reported increases in muscle protein synthesis and improvements in skeletal muscle mass and exercise tolerance. However, since each of these studies was performed in a small number of patients and did not show the evidence of improvement in prognosis, further evaluation is still necessary.

EPA and DHA, which are ω3 polyunsaturated fatty acids and essential fatty acids contained in large amounts in fish oil, are known to have anti-arteriosclerotic, anti-inflammatory, and anti-inflammatory cytokine actions and are expected to have suppressive effects on heart failure. In both the American College of Cardiology Foundation (ACCF)/AHA and ESC guidelines, intake of ω3 polyunsaturated fatty acids is recommended as nutritional supplementary therapy despite a difference in recommendation grade.

In chronic heart failure, deficiency of vitamins and trace elements is also likely to occur. Regarding ONS, the effects of agents such as coenzyme Q10, carnitine, antioxidants or hormone therapy using growth hormones and thyroid hormones have been reported. However, no evidence has been established.

F. Possibility of Synergy Between Exercise and Nutrition Therapies

The effectiveness of exercise therapy in chronic heart failure is well established, and various effects including improve-
Exercises recommended for heart failure patients are low-intensity resistance training and aerobic exercise such as walking, bicycle ergometer, and light aerobic exercise. If muscle weakness is severe, combining resistance training (low/moderate-intensity repetitious muscle-developing exercise) with systemic aerobic exercise is reportedly safe and effective for improving exercise tolerance and QOL. Generally, the importance of resistance training relative to aerobic exercise is greater as skeletal muscle mass and muscle strength are more reduced, and as exercise tolerance is more impaired. The exercise pattern that recovers loss of skeletal muscle mass is resistance training, and its combination with nutritional therapy is important. It has been found that synergistic effects were obtained in muscle mass and motor function by combining exercise therapy primarily consisting of low-intensity resistance training with amino acid supplementation therapy in older Japanese women with sarcopenia.

### Section 4. Diet in Palliative Care of Heart Failure Patients

In the terminal phase of heart failure, symptoms including anorexia, nausea/vomiting, respiratory distress, and a sense of abdominal fullness associated with the disease state are observed, and food intake decreases. This also causes a decrease in salt intake. There are also reports that suggest that excessive restriction of salt intake is related to a poor prognosis.

The objective of palliative care is to support patients to maintain QOL so that they can spend their remaining time as they wish. It is necessary to evaluate diet individually, and uniform excessive salt reduction should be avoided.

Although, eventually, patients show natural progressive loss of appetite, forced nutritional support should be avoided in this period. Also, uniform fluid infusion to compensate for reduced dietary intake is not recommended in the terminal phase, because it may exacerbate dyspnea and symptoms of congestion such as edema.

### Chapter VII. Team Care for Heart Failure in Nutritional Therapy

#### Section 1. Significance of Nutritional Therapy for Heart Failure by Multidisciplinary Collaboration

In conducting nutritional therapy for heart failure, it is necessary to consider social problems such as the family structure, presence or absence of caregivers, and economic state and problems other than the disease including mental/psychological condition in addition to the assessment of the nutritional state and understanding of the complex pathology. Multidisciplinary teamwork is important,

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**Figure VII-1.** Healthcare models in skill mix. (A) Classical medical model: Model initiated by orders given by the physician to each profession. (B) Interdisciplinary model: With the patient in the center, each profession approaches the problem equidistantly. Model in which cooperation among professions is closer. (Adapted from Takamasu T. The Japanese Journal of Pediatric Intractable Asthma and Allergic Diseases 2015 with modifications.)
because it is difficult to cope with nutritional disorders in heart failure by a single profession alone, which may result in inadequacy of medical services and operations and increased burden on medical workers.

The Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure of Japan also recommend a team approach for the management of heart failure patients (class I), and multidisciplinary inclusive nutritional intervention has been reported to improve the nutritional state in older people with a risk for malnutrition including heart failure patients. Team care means, “Care appropriate for the patient’s condition provided by a team of various medical professionals based on a high level of expertise of each member by sharing the objective and information, dividing duties, but collaborating and complementing each other”. This is consistent with the concept of “skill-mix”, which is also called “multidisciplinary collaboration”. Skill-mix is not simply division of roles among professionals but involves mutual complementation of roles, transfer of authority and responsibility, creation of new professionals, and functional differentiation (Figure VII-1).

Section 2. Stage-Specific Setting of Team Goals

A. Acute Phase (Acute Phase/Recovery Phase)

In the acute phase of heart failure, the team of nutritional therapy aims to quickly and accurately evaluate the nutritional state and perform nutritional support by an appropriate interventional method (enteral, parenteral, oral feeding). Once the intervention method has been determined, attention to fluid management is necessary simultaneously with the assessment of the nutritional state. After stabilization of heart failure, nutritional guidance is given early, and arrangements for nutritional management after discharge are made.

B. Chronic Phase (Maintenance Phase/Living Phase)

The mean duration of hospitalization of heart failure patients is 33.9 days, and it is difficult to improve the nutritional state during hospitalization or to form an appropriate habit of nutrient intake. Therefore, the team goals after discharge are: 1) to have the patients themselves fully understand the significance of nutritional therapy, 2) to provide information about necessary nutrient intake behavior, and 3) to continuously monitor the state of implementation of the therapy and nutritional state.

Section 3. Roles of Various Professions (Figure VII-2)

A. Roles of Physicians

Role of Physicians in Multidisciplinary Collaboration

Physicians play a coordinating role of communicating with members of the multidisciplinary team, making adjustments among professions by drawing out their opinions, issuing necessary instructions and advice to other professions according to the results of assessment of the disease and circumstances of the diagnosis of treatment, and transmitting the opinions shared within the team to the physician in charge.

Role of Physicians in Nutritional Assessment

In heart failure, the values of nutritional indices may change under the effects of systemic congestion and neurohumoral factors. For this reason, physicians must implement nutritional evaluation in consideration of the effects of the disease state of heart failure based on the results of nutritional assessment carried out by various professions.

Role of Physicians in Intervention With Nutritional Therapy

Risk management is important in nutritional management of heart failure, which exhibit complicated pathological...
conditions. Particularly, in hemodynamically unstable situations such as the acute phase and exacerbating phase of heart failure, physicians must evaluate risks in nutritional supplementation that require caution in the management of heart failure such as bowel rest and restriction of fluid intake and give other professions instructions about measures to take.

| B. Role of Registered Dietitians |

Registered dietitians play an important role in clinical practice as experts of nutritional management/guidance and nutritional evaluation/judgment. Registered dietitians evaluate the nutritional state by collecting a wide range of information concerning nutrition and draw up nutritional management plans. If the dietary intake is insufficient, registered dieticians propose the use of oral nutrition supplementation (ONS) and change of the route of administration by sharing information concerning eating function, disease state, treatment plan, and treatment environment, within the team and specifically showing expected effects and points of attention in the management. To cope with changing disease states, registered dietitians select the evaluation items and re-evaluate/re-design the contents of nutritional management in multidisciplinary approach.

In the acute phase, registered dietitians predict excess or deficiency of energy and nutrients according to the administration route in collaboration with pharmacists and design mutually complementary nutritional therapies. In the chronic phase, self-management of disease by the patients is important. If the patient’s self-management is inadequate, measures to obtain cooperation from family or caregivers must be taken. Depending on the treatment environment, home delivery of meals and home care service are proposed to the team as options. If adherence to dietary therapy is difficult to obtain, treatment should be conducted under conditions close to the actual dietary environment by proposing management according to the characteristics and preferences of the patient.

In the terminal phase, the approach to dietary therapy is evaluated together with the patient and family by taking their wishes in consideration and providing sufficient information including the risks of readmission and prolongation of hospitalization.

| C. Role of Nurses |

Collection of Information Concerning the Life Circumstances, Assessment of Problems With Nutritional Therapy, and Adjustment With Family and Other Professions

In introducing nutritional therapy, nurses play a central role in the assessment for the judgment of its technical and economic feasibility to the patient and family. Occasionally, nutritional therapy necessary for the patient cannot be implemented because of the lack of understanding or cooperation by the family living with the patient even if the patient himself/herself understands the necessity of nutritional therapy. In such situations, consideration of the family is also necessary.

Role of Deepening the Understanding of Patients

Since diet is closely related to emotions (see Chapter IV, Section 1-A), medical professionals must understand the values of the patient/family about diet, perception of the patient/family about nutritional therapy, and patient’s dietary practice. For this purpose, patients should be listened to. By talking, patients are also expected to reflect on the present status, sort out problems, and modify their behavior.

Evaluation of the Body Weight, Dietary Intake, and Salt Intake

It is necessary for nurses to monitor signs and symptoms of heart failure with serial evaluation of the body weight, body composition, daily dietary intake, and salt intake even after discharge of the patients. The absolute salt intake can also be estimated by examination of casual urine samples.

Assessment of Anorexia

Concerning decreases in dietary intake, the reality may be difficult to capture by medical interviews if there is cognitive impairment. The cause of anorexia may be postprandial hypotension or orthostatic hypotension, and observation by nurses, who have long contact with patients, is important.

| D. Roles of Physiotherapists, Occupational Therapists, and Speech Therapists |

Physiotherapists and Occupational Therapists

The nutritional state is closely related to physical functions and activities of daily living (ADL). Physiotherapists and occupational therapists assess physical functions and constitution, posture, cognitive function, and ADL and evaluate how they are related to the nutritional state. If impairment of physical function or ADL is observed, they formulate ADL supporting programs with exercise loads appropriate for the disease condition, nutritional state, and the state of physical functions. Older patients have low reserve of physical functions and exhibit complications and complex impairment of physical functions. Paying attention to the endurance of, and fatigue in, feeding activities, they propose appropriate posture and actions of eating, eating pace, and support equipment. They also assess the respiratory function including the ability to cough and respiratory reserve and provide guidance in coughing and respiratory training, if necessary, for the risk management against aspiration.

Speech Therapists

Speech therapists evaluate eating and swallowing disorders and devise programs for basic training in eating function and improving the functions of oropharyngeal and laryngeal organs. Eating/swallowing training can be classified into direct training in food ingestion and indirect training to improve the basic swallowing function. Speech therapists evaluate the indications of these training methods according to the level of consciousness, general condition, appetite, and cognitive function. In addition, they propose diets adjusted to the oral and swallowing functions.

| E. Roles of Pharmacists, Dental Hygienists, and Medical Social Workers |

Pharmacists

Pharmacists support nutritional therapy by helping with the selection of the feeding route and pharmaceutical formulation from pharmacological viewpoints. They propose nutritional preparations and proper methods for their use based on the knowledge of drug/food interactions. They
also provide explanation and guidance about the prevention of complications and avoidance of risks associated with the use of nutritional preparations.

Dental Hygienists
Dental hygienists examine and evaluate the state of oral hygiene and give expert oral care using medical devices and drugs. They also evaluate oral contamination, which may cause taste disorders, and the state of mastication environment or dentures, which affect bolus formation.

Medical Social Workers
Medical social workers play the role of coordinators for the use of social services. They help patients continue to have appropriate nutritional management through consultation, adjustment, and support concerning psychological, social, and economic problems that the patients and families encounter.

Section 4. Actual Nutritional Therapy by Multidisciplinary Collaboration

A. Multidisciplinary Collaboration in Nutritional Therapy for Severe Heart Failure
In severe heart failure, nutritional therapy must be conducted based on the understanding of each profession about the high hemodynamic variability and consequent destabilization of the general condition as well as the possibility of the occurrence of complications associated with nutritional therapy.

Nutritional Evaluation
Nurses and registered dieticians must hear from the patient or family about the nutritional state and ADL before admission and judge whether the patient was at risk or was in a state of malnutrition. It is also indispensible to collect information such as the dietary intake before admission and drinking history for the risk assessment of refeeding syndrome.

The results of body measurements are the basis of nutritional evaluation, and they are usually evaluated by registered dieticians, physiotherapists, and nurses. In severe heart failure, however, as heart failure itself affects the nutritional assessment items (see Chapter III, Section 3-A), nutritional evaluation in consideration of the physician’s evaluation of the disease state is necessary.

Selection of the Administration Method of Nutritional Preparations and Points of Attention
Monitoring of changes in hemodynamic indices (vital signs, urine volume) and checking of gastrointestinal symptoms after the beginning of enteral nutrition are made by nurses, who spend much time at the bedside, according to the physicians’ evaluation of the cardiac function and hemodynamics. If nutritional requirements cannot be fulfilled due to the difficulty in initiating or increasing enteral nutrition, registered dieticians or pharmacists must make proposals about indications of total parenteral nutrition (TPN) and peripheral parenteral nutrition (PPN).

Pharmacists must send reminders about the effects of drugs used on nutritional management while placing priority to the use of drugs for the management of heart failure and make relevant proposals if additions, reductions, or adjustment of the dose are necessary for nutritional management.

Nutritional Management in the Transition From the Acute Phase to the Recovery or Maintenance Phase
In conducting oral nutrition, speech therapists and nurses perform risk management against aspiration including the assessment of swallowing function. If the risk of aspiration, low output syndrome, or exacerbation of the hemodynamics is high, physicians must consider changing the feeding method, if necessary, by consulting with registered dieticians.

If the condition is confirmed to tolerate the transition to oral feeding, the settings of the amount of feeding and salt intake are re-checked. It is necessary to share the state of the patient’s activities in the ward and contents of rehabilitation among professions on the basis of evaluation of the general condition.

If anorexia is observed, its cause must be identified among the professions. Methods for the evaluation of anorexia include the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) Appetite Scale\(^\text{196}\) and, as simpler methods, the Council on Nutrition Appetite Questionnaire (CNAQ) and Simplified Nutritional Appetite Questionnaire (SNAQ)\(^\text{197}\).

Physicians must evaluate whether anorexia is caused by heart failure or not. Pharmacists must check the presence or absence of drugs with zinc chelator actions and evaluate the possibility of zinc deficiency, which may cause taste disorders,\(^\text{198}\) nurses and registered dieticians evaluate changes in the patient’s preferences, dietary contents, and eating environment (place, tableware) and, in cooperation with speech therapists and dental hygienists, evaluate the oral environment including oral dryness and unfit dentures.

When the cause of anorexia is identified, measures are devised multidiscidentally, and if the dietary intake does not fulfill the nutritional requirements, the addition of supplements, concomitant use of enteral/parenteral feeding should be evaluated, as necessary, under the initiative of registered dieticians. If the possibility of an involvement of depression or anxiety cannot be excluded, arrangements are made for intervention by psychiatrists or clinical psychologists from the viewpoint of mental health.

In severe heart failure, to sustain ADL and quality of life (QOL), it is very important to preserve or improve skeletal muscle mass and muscle strength (see Chapter VI, Section 3-F). The state of energy and protein intakes are evaluated under the initiative of registered dieticians, and physiotherapists conduct exercise therapy based on the pathological assessment primarily by physicians. In the nutritional management in the transition from the recovery to maintenance phase, the state of body weight management and salt/fluid intake are checked primarily by nurses and registered dieticians, and guidance is given to the patients and families. In patients with malnutrition or at risk of malnutrition, attention to decreases in dietary intake continues to be necessary. Since the patient’s general condition, personality and mental condition, living and economic status, and the presence or absence of caregivers greatly affect nutritional therapy for severe heart failure patients, it is recommended to formulate measures by consultation among all professions involved.

B. Collaboration With the Nutrition Support Team in the Treatment of Heart Failure
If there are difficulties in nutritional management, intervention by a team for safe and effective nutritional management in collaboration with many experts and professions trained in the Treatment of Heart Failure...
in nutritional management such as the nutrition support team (NST)\(^1\) should be considered. Since heart failure is accompanied by rapid changes in the disease state and body fluid volume, close collaboration is necessary. Intervention by an expert team is expected to have an educational effect on the staff of the heart failure team concerning nutritional management.

### C. Home Nutritional Therapy for Frail Patients

Heart failure patients are likely to progress into frailty (see Chapter II, Section 2, Table II-1)\(^1\). If a patient is judged to be frail, priority should be placed on securing the quality and quantity of nutrition and exercise rather than restriction of salt intake. For this, early detection of frailty is important. Nurses, who have long contact with patients, are expected to bear the role of frailty screening. Reliable interventional studies on frailty with nutritional therapy alone are still few.\(^{199,200}\) According to studies in average older people as references, measures such as increasing the intakes of energy, protein, and branched-chain amino acids including leucine and trace nutritional element supplementation are possible options.\(^{201-206}\) Home exercise therapy is also necessary to increase muscle mass and strength. Such interventions should be performed under the appropriate supervision of nutritionists and therapists.

For home management of frail heart failure patients, collaboration between the medical staff specializing in heart failure and home caregivers is indispensable.

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Conflicts of interest of the parties involved in developing the statement

The Japanese Heart Failure Society Expert Consensus Writing Committee for “A Scientific Statement on Nutritional Assessment and Management in Heart Failure Patients” clarifies that the conflict of interest status over the past one year from each committee member and author based on the following criteria regarding the financial relationship between the drafting committee members and companies involved in the relevant fields.

1. Compensation received for serving as an executive officer or consultant of companies or organizations (should be stated if the compensation from a single company / organization exceeds ¥1 million annually).

2. Holding shares of stock and earning profits from the stock (should be stated if profits earned from the stocks of a single company exceed ¥1 million annually, or holding ownership of 5% or more of the company’s entire share).

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8. Affiliating to a donated fund laboratory provided by a company or organization
9. Acceptance of travel expenses or gifts unrelated to research (should be stated if the total annual amount received from a single company or organization exceeds ¥50,000)

Notes
1: None
2: None
3: None
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The company names declared are as stated above (applicable period: April 1, 2017–March 31, 2018). Company names are as of March 2018 (in alphabetical order). Publishers and organizations in a neutral position were not included.

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(The affiliations of the members are as of February 2020)