

Clinical Perspectives on Cardiac Rehabilitation After Heart Failure in Elderly Patients with Frailty: A Narrative Review

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Abstract: The purpose of this narrative review is to examine rehabilitation modalities for patients with heart failure and Frailty who require comprehensive intervention. Ischemic heart disease is the leading cause of death worldwide, accounting for 16% of global mortality. Due to population growing and aging, the total number of heart failure patients continues to rise, a condition known as the heart failure pandemic. Furthermore, frailty has been associated with an increased risk for heart failure and increased morbidity and mortality. The 2021 update of the 2017 ACC expert consensus decision pathway for optimization of HF treatment has become more concerning, citing frailty as one of the 10 most important issues associated with heart failure with reduced ejection fraction (HFrEF). Frailty and heart failure share common pathological mechanisms and are associated with poor clinical outcomes. Most studies of frailty in patients with heart failure primarily focus on physical frailty, and associations between psycho-psychological and social factors such as cognitive dysfunction and social isolation have also been reported. These results suggest that a more comprehensive assessment of frailty is important to determine the risk in patients with heart failure. Therefore, mechanisms of the three domains, including not only physical frailty but also cognitive, psychological, spiritual, and social aspects, should be understood. In addition to interventions in these three domains, nutritional and pharmacological interventions are also important and require tailor-made interventions for the widely varied conditions associated with heart failure and frailty. Although several studies have shown a relationship between frailty and prognosis in patients with heart failure, interventions to improve the prognosis have not yet been established. Further information is needed on frailty intervention by a multidisciplinary team to improve the prognosis.

Keywords: frailty, heart failure, rehabilitation, cardiovascular diseases

Introduction

Ischemic heart disease is the leading cause of death worldwide, accounting for 16% of all deaths.¹ Worldwide, it is estimated that approximately 64.3 million people are living with heart failure, and an estimated mortality rate of 13.5% at 1 year and 43.3% at 5 years.² HF is not a single pathological diagnosis, but a clinical syndrome consisting of cardinal symptoms (eg breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (eg elevated jugular venous pressure, pulmonary crackles, and peripheral oedema).³ Due to population growing and aging, the total number of HF patients continues to rise, a condition known as the HF pandemic.⁴ The 2021 update of the 2017 ACC expert consensus decision pathway for optimization of HF treatment has become more concerning, citing frailty as one of the 10 most important issues associated with HF with reduced ejection fraction (HFrEF).⁵

Frailty is recognized as an age-related clinical condition that is typically observed by a deterioration in the physiological capacity of several organ systems, and that causes an increased susceptibility to stressors.⁶ Frailty is generally recognized as a physical condition that precedes the development of a disability,^{7,8} but frailty and disability can coexist.⁹ With the rapid aging of society, the number of frailty elderly people is increasing, placing a heavy burden on the

world's health care systems.¹⁰ Frailty has been associated with an increased risk for HF and increases morbidity and mortality.¹¹

Comprehensive treatment of HF and frailty, including not only physical but also cognitive, psychological, psychosocial, nutritional, and pharmacological factors, is essential. The purpose of this narrative review is to examine rehabilitation modalities for patients with HF and Frailty who require comprehensive intervention.

Frailty in HF

Frailty and HF share common pathological mechanisms and are associated with a worsening clinical outcome (Figure 1).¹² In FRAIL-HF,¹³ a cohort study of 450 non-caring patients with worsening HF aged ≥ 70 years, the presence of frailty was closely associated with an increased risk of mortality, rehospitalization, and declined cardiac function at 1 year. In addition, a study examining the risk of heart failure rehospitalization in a conditional vulnerability model found that age, female sex, non-manual work, better medical compensation, longer QRS duration, and treatment with percutaneous coronary intervention increased the risk of heart failure rehospitalization.¹⁴ Furthermore, patients with HF and frailty more frequently complained of dyspnea, sleep disturbance, and depression than non-frail patients, and their quality of life is significantly impaired.¹⁵ In contrast, most studies on frailty in patients with HF have mainly focused on physical frailty,¹⁶ but not on cognitive dysfunction¹⁷ and social isolation.^{18,19} Those results indicate the importance of conducting a more comprehensive assessment of frailty to confirm the risk in patients with HF and are consistent with the publication from the heart failure association/European society of cardiology.²⁰ Therefore, a more comprehensive assessment of frailty in patients with HF is needed to better understand the risk. To promote a comprehensive approach, incorporation vulnerability assessment into prognostic and treatment models for HF is strongly emphasized.²¹ In summary, three domains of HF include not only physical frailty but also cognitive, psychological, and social aspects.

Three Domains: FRAGILE-HF

We present the FRAGILE-HF trial²² that aimed to investigate the frequency of three domains of frailty in elderly patients with HF, the extent of their overlap, and the extent of their influence on death and rehospitalization. Of the 1180 hospitalized patients enrolled (median age 81 years, 57.4% male), physical frailty was found in 56.1%, social frailty in 66.4%, and cognitive decline in 37.1%. Of these three frailty domains, 13.5%, 31.4%, 36.9%, and 18.2% of all patients

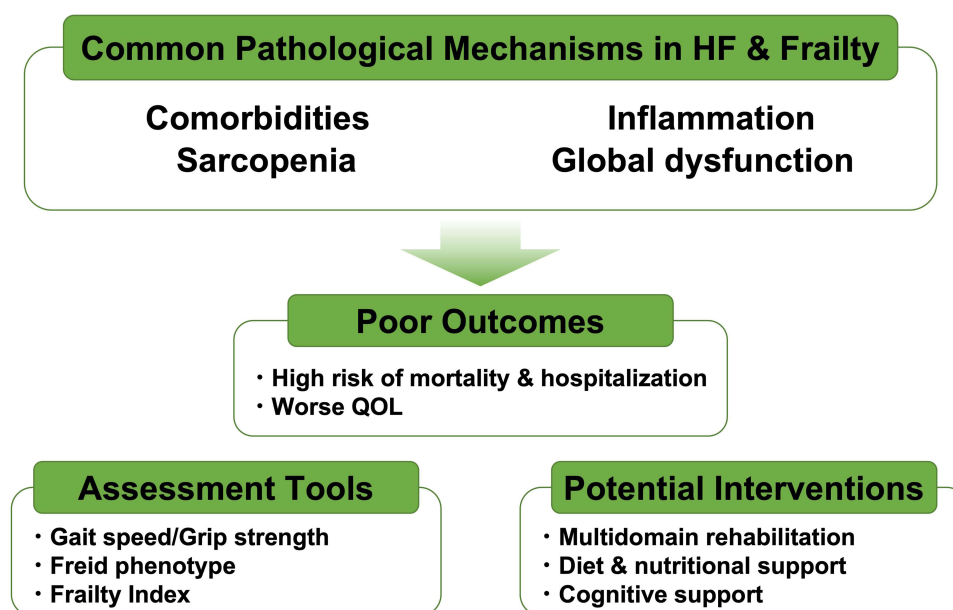


Figure 1 Commonalities between heart failure and frailty.

Notes: Adapted from *JACC Heart Fail*, 7(12), Pandey A, Kitzman D, Reeves G. Frailty Is Intertwined With Heart Failure: Mechanisms, Prevalence, Prognosis, Assessment, and Management. 1001-1011, copyright (2019), with permission from Elsevier.¹²

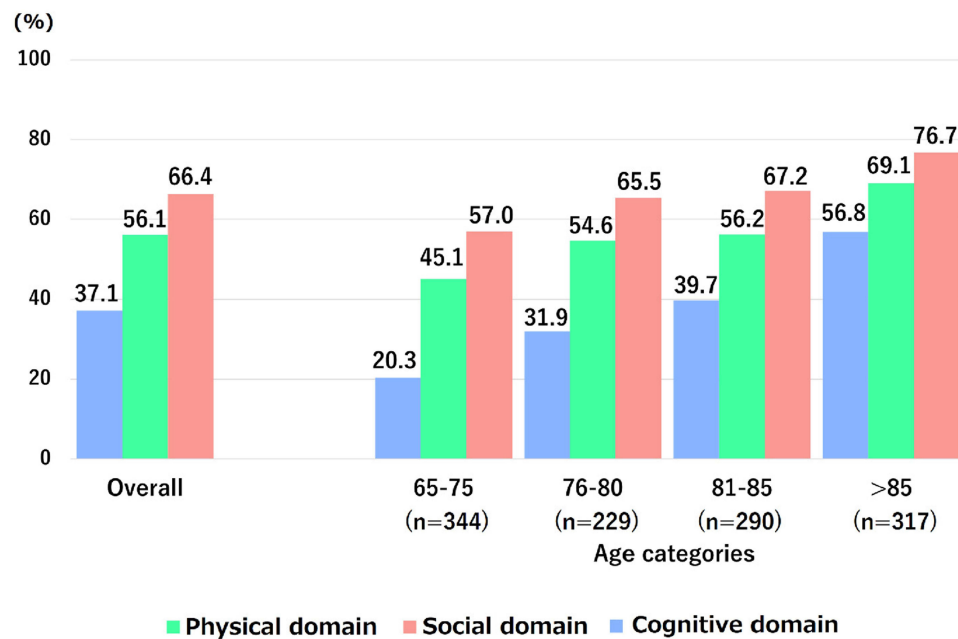


Figure 2 Prevalence of impairment in each frailty domain in the total cohort and according to age category. Reprinted from Matsue Y, Kamiya K, Saito H, et al. Prevalence and prognostic impact of the coexistence of multiple frailty domains in elderly patients with heart failure: the FRAGILEHF cohort study. *Eur J Heart Fail.* 2020;22(11):2112-2119. © 2020 European Society of Cardiology.²²

had 0, 1, 2, and 3 domains, respectively (Figure 2). These results indicate that 86.5% of elderly patients with HF had at least one frailty domain. During the follow-up period, the composite end-point occurred in 383 patients, and based on patients without evidence of frailty in any region, patients with one, two, and three regions of frailty were reported to be 1.38, 1.60, and 2.04 times more likely to have a composite end-point in a year, respectively (Figure 3). The assessment tools used in this trial are the cardiovascular health study (CHS) criteria, the questionnaire to define social frailty status (QSFS) of Makizako et al, and the Mini-Cog for the physical, social, and cognitive domains, respectively.

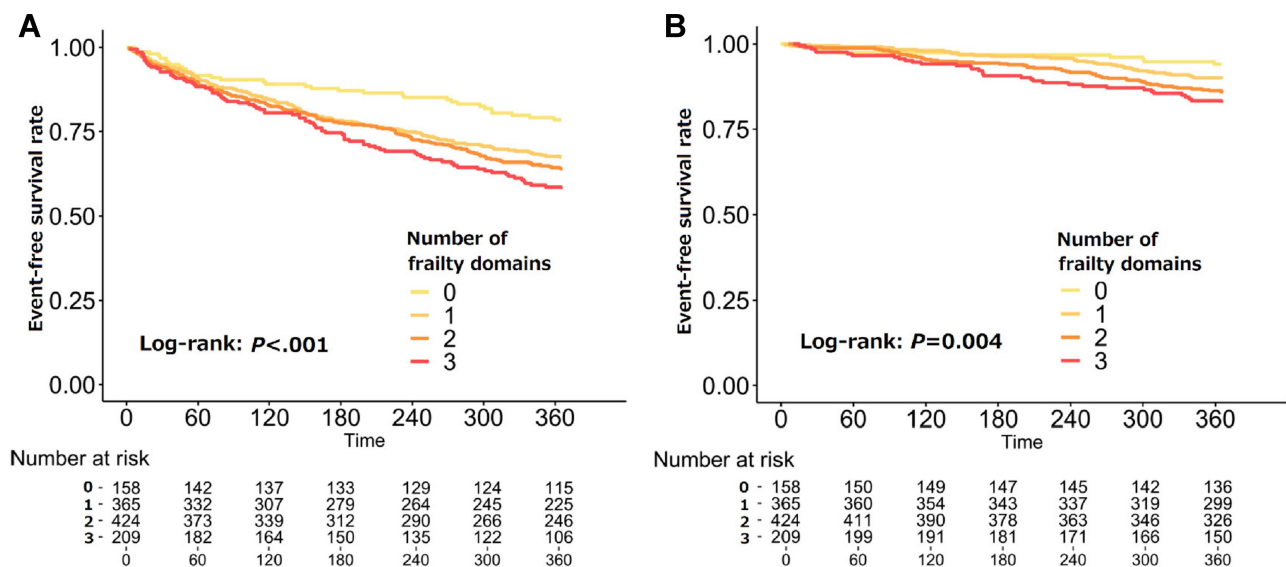


Figure 3 Kaplan-Meier curves in FRAGILE-HF for (A) the combined endpoint of all-cause death and heart failure rehospitalization, and (B) all-cause death according to the number of frailty domains. Reprinted from Matsue Y, Kamiya K, Saito H, et al. Prevalence and prognostic impact of the coexistence of multiple frailty domains in elderly patients with heart failure: the FRAGILEHF cohort study. *Eur J Heart Fail.* 2020;22(11):2112-2119. © 2020 European Society of Cardiology.²²

Comparison of Physical Frailty Assessment Tools

The Frailtools Project²³ in five European countries (Spain, France, Italy, the United Kingdom, and Poland) conducted a comparative study of eight commonly used frailty assessment tools in older adults aged ≥ 75 years. Results showed the FRAIL scale (99.4%), SHARE-FI (98.3%), and GFST (95.0%) as the three most feasible scales. The three shortest average implementation times were clinical frailty scale (CFS) (24 s), GFST (72 s), and FRAIL scale (90 s). Agreement between tools was best for the CFS, and most of them were good.

Physical Frailty

Mechanism

The muscle hypothesis, shown in Figure 4, has been proposed as the cause of muscle weakness in patients with HF. First, decreased cardiac output reduces peripheral tissue perfusion, resulting in skeletal muscle atrophy. Furthermore, autonomic nervous system activity is impaired by increased catabolism due to increased production of inflammatory cytokines, increased oxidative stress, and immobility. All these factors induce skeletal muscle dysfunction, a veritable vicious cycle that results in further functional impairment. In other words, in addition to aging, low skeletal muscle perfusion in cardiovascular diseases (CVD) can easily lead to muscle weakness.

Cardiac cachexia is a condition that results in weight loss in patients with HF²⁴ and is characterized by anorexia, inflammation, insulin resistance, abnormal anabolism and catabolism, and anemia triggered by HF (Figure 5). In particular, intestinal edema due to HF directly causes anorexia, which leads to weight loss.²⁵ Intestinal edema also leads to decreased digestive and absorption capacity of the gastrointestinal tract. Furthermore, patients with cardiac cachexia have reduced blood flow to the superior mesenteric artery, inferior mesenteric artery, and celiac artery compared to healthy participants and patients with HF without cardiac cachexia.²⁶ Cardiac cachexia is closely associated with physical frailty in HF.

Prevalence and Diagnosis

In the aforementioned FRAIL-HF,¹³ 76% of patients with HF meet the physical frailty criteria, and to prevent frailty, the screening tool must first be understood. The screening tools for frailty widely varied (Table 1). Although no uniform

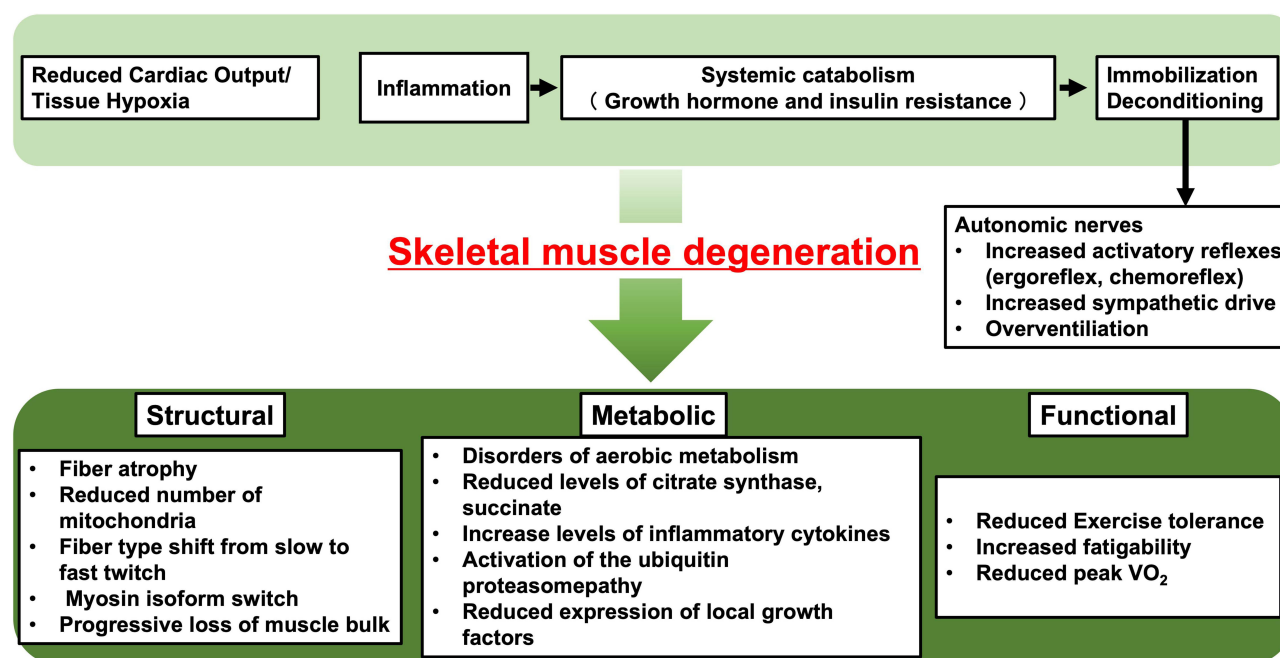


Figure 4 Cardiovascular disease and skeletal muscle degeneration.

Notes: Adapted from Piepoli MF, Coats AJS. The "skeletal muscle hypothesis in heart failure" revised. *Eur Heart J*. 2013;34(7):486-488, by permission of Oxford University Press.¹³⁴

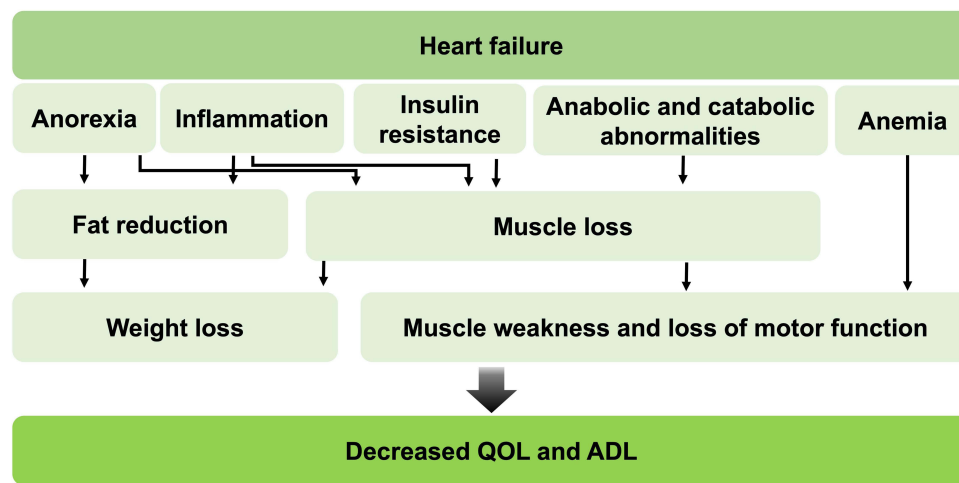


Figure 5 Concept of Cardiac Cachexia.

Notes: Adapted from *Clin Nutr*, 27(6), Evans WJ, Morley JE, Argilés J, et al. Cachexia: a new definition. 793–799. Copyright 2008, with permission from Elsevier.²⁴

standards have been established for diagnostic procedures, frailty screening is important to identify patients with HF and frailty and to provide multidomain interventions. We will present some of the most commonly and widely used tools, along with their prevalence.

The diagnostic methods in physical frailty can be broadly divided into the CHS criteria⁸ based on the Phenotype model by Fried et al and the frailty index²⁷ based on the accumulated deficit model by Rookwood et al. Fried et al considered that five factors, shrinking, exhaustion, low activity, slowness, and weakness, become apparent in frailty (phenotypic model). The authors propose to evaluate these factors using alternative indices (unintentional weight loss, fatigue, physical activity, normal walking speed, and grip strength). This assessment method is called the CHS criteria as it was first used in the CHS. The criteria for the five alternative indices are as follows: frail, if three or more of the five items are met, and pre-frail, if one or two of the five items are met. Since this model does not include items associated with psycho-psychological and social frailty, it is used only to diagnose physical frailty and is the most widely used assessment method worldwide to date. In contrast, the frailty index based on the accumulated deficit model by Rookwood et al is a comprehensive assessment method based on the concept of comprehensive geriatric assessment. The frailty index is calculated by summing up the number of impairments in 70 items, including activities of daily living (ADLs), psychosocial risk factors, and geriatric syndromes. Considering its use in clinical situations and the application of previous studies in clinical practice, we believe that the CHS criteria should be used for physical frailty.

Self-reported questionnaires are easy to use in clinical practice regardless of facility. Yamada et al developed the frailty screening Index, a five-item self-reported questionnaire to predict disability in elderly patients.²⁸ Nozaki et al reportedly evaluated whether the FRAIL scale questionnaire is consistent with the Fried criteria, can predict all-cause mortality, and reflects disability in patients with HF.²⁹ Results showed that the FRAIL scale was moderately consistent with the Fried criteria, predicted all-cause mortality, and reflected clinically significant disabilities. The simplicity of the self-reported questionnaire, its reported validity and usefulness, and the fact that it does not require special instruments suggest that it will be used in the future.

For risk stratification and prognostic prediction in physical frailty of patients with HF, a multicenter prospective cohort of 2721 patients (median age: 76 [interquartile range 67–83] years, men: 60.5%) who were ambulatory at discharge was used. The FLAGSHIP study is instructive: usual walking speed of <0.98 m/s, 4 points; grip strength of <30.0 kg (men) or 17.5 kg (women), 5 points; PMADL-8 of ≥21, 2 points; SEW-7 of ≤20, 3 points and assigned a cutoff value and score for each indicator. Based on the total score, patients were classified into four categories: Category I, ≤3 points; Category II, 4–8 points; Category III, 9–13 points; and Category IV, 14 points. Results showed that the composite outcome (prevalence and cumulative incidence) of rehospitalization and death within 2 years increased with an

Table I List of Frailty Screening Tools

Type	Instrument	Criteria
Physical frailty	CHS Criteria (Phenotype model)	≥ 3 of the following components of the hypothesized cycle of frailty: Shrinking/weight loss, Weakness, Poor endurance and energy, Slowness, Low physical activity level
	Frailty Index (Accumulated deficit model)	70 items including ADLs, psychosocial risk factors, and geriatric syndromes are evaluated, and the Frailty Index is calculated by summing the number of impairments.
	FTS-5	A scale consisting of 5 components: nutritional status assessed with BMI, balance assessed with the Romberg test, activity evaluated using the Physical Activity Scale for the Elderly, poor handgrip strength, and slow gait speed.
	FTS-3	A scale consisting of 3 components: BMI, balance, and activity
	FI-35	The index is expressed as a ratio of deficits present to the total number of deficits considered (n=35). A cut-point of ≥ 0.25 was used to consider a participant as frail.
	SHARE-FI	A scale consisting of 5 components: slowness as measured by walking difficulties, weakness as measured by handgrip strength, exhaustion, loss of appetite, and low physical activity.
	CFS	Classified into 9 stages: Mild frail, Healthy, Maintaining good health with health care, Frail, Mild frail, Moderate frail, Severe frail, Very severe frail, and End stage of disease.
	GFST	An 8-item questionnaire to help identify frailty in community residents 65 years of age and older.
Cognitive and Psychological frailty	CDR	$0.5 \leq$ is cognitive impairment.
	Mini-Cog	$2 \geq$ is suspected dementia.
	GDS15	$5 \leq$ are depressive tendency and $10 \leq$ are depressed.
Social frailty	SFP	Assessment using gender, age, and marital status.
	QSFS	Assessed with five simple questions: live alone, go out less often than in the previous year, visit friends occasionally, feel useful to friends and family, talk to someone every day
	SFI	Consists of four questions on economic hardship, living alone, social behavior, and social needs, categorized as social robust, pre-social frailty, and social frailty.
Self-report questionnaire	The FRAIL Scale	Questionnaire with 5 components: fatigue, resistance, ambulation, illness, and loss of weight.
	Frailty Screening Index	The index includes simple yes/no questions concerning nutrition/shrinking, physical function, physical activity, forgetfulness, and emotions/ exhaustion. It then consisted of 5 items, which are rated as 0 or 1 by the participants.

Abbreviations: BMI, Body Mass Index; CDR, Clinical Dementia Rating; CHF, Clinical Frailty Scale; CHS Criteria, Cardiovascular Health Study Criteria; FI-35, 35-item Frailty Index; FTS-5, 5-item Frailty Trait Scale; FTS-3, 3-item Frailty Trait Scale; SHARE-FI, Frailty Instrument of the Survey of Health, Ageing and Retirement in Europe; GDS15, Geriatric depression scale 15; GFST, Gerontopole Frailty Screening Tool; SFP, Social Frailty Phenotype; QSFS, Questionnaire to define Social Frailty Status; SFI, Social Frailty Index.

increasing score. Remarkably, these results were used for Asian patients, excluding patients with dementia with mini mental state examination (MMSE) of ≤ 17 points.

The involvement of sarcopenia as a cause of physical frailty has also attracted attention, and its diagnostic criteria are suggestive. Rosenberg proposed the term sarcopenia, from the Greek sarco = muscle and penia = loss, for the decrease in skeletal muscle mass associated with aging, which had been the case for about 30 years.³⁰ Subsequently, The European working group on sarcopenia in older people (EWGSOP)³¹ and the Asian working group for sarcopenia (AWGS)³² proposed diagnostic criteria for sarcopenia in 2010 and 2014, respectively. They were subsequently updated to EWGSOP2³³ and AWGS2019³⁴ in 2018 and 2019, respectively. The major change between the two is the diagnostic process. The first step is to screen the elderly for possible sarcopenia based on the SARC-F questionnaire (cutoff point ≥ 4) and clinical symptoms. It also provides clear cutoff points for measuring muscle strength and physical performance, which are commonly used in bed release. The cutoff points in the EWGSOP2 are grip strength < 27 kg for men and < 16 kg for women, chair stand test > 15 seconds, gait speed ≤ 0.8 m/s, short physical performance battery (SPPB) ≤ 8 , timed-up and go test (TUG) ≥ 20 seconds, 400-m walk test ≥ 6 minutes. The cutoff points in AWGS2019 are grip strength for men < 28 kg women < 18 kg, chair stand test ≥ 12 seconds, gait speed ≤ 1.0 m/s, and SPPB ≤ 8 . Although

these are indicators of sarcopenia, they are simple indicators commonly used in rehabilitation settings and are useful in the assessment of physical frailty.

Cognitive and Psychological Frailty

Mechanism

Elderly patients with HF are thought to be more prone to cognitive dysfunction, leading to frailty.^{35,36} HF is often associated with CVD such as coronary artery disease and other complications including hypertension and diabetes, which can also be considered risk factors for cognitive dysfunction (Figure 6).³⁷ Changes in the neuroendocrine axis, such as elevated cortisol and catecholamines in the blood and activation of the renin-angiotensin system associated with HF, also promote cognitive dysfunction.³⁸ Decreased cardiac output due to HF directly results in reduced cerebral blood flow. Furthermore, age-related microvascular disorders and disrupted autoregulation of the cerebral blood flow associated with hypertension, diabetes mellitus, and other conditions accelerate the reduced cerebral blood flow. In particular, decreased blood flow to the ventral hippocampus, the brain region responsible for memory, is associated with cognitive dysfunction and depression severity in patients with HF.³⁹

In addition to cognition, psychiatric symptoms of frailty include depression, apathy, and anxiety.^{40–43} Moreover, depression exacerbates sarcopenia via an extremely decreased activity level and elevated corticotropin-releasing factor adrenocorticotrophic hormone levels.⁴⁴ The presence of such psychiatric symptoms can exacerbate physical frailty.

Prevalence and Diagnosis

In the systematic review and meta-analysis of cognitive dysfunction and HF by Jane A Cannon et al, data from four prospective cohorts (n = 2513 patients) suggested a long-term cognitive decline in patients with HF compared to those without.⁴⁵ Data showed that HF is associated with cognitive dysfunction in the long term. In a case-control study describing the presence or absence of HF (n = 4 articles, 1414 patients), the odds ratio for cognitive impairment in patients with HF was 1.67 (95% confidence interval [CI], 1.15–2.42). The prevalence of cognitive impairment in the HF cohort was 43% (95% CI, 30–55) (n = 26 studies, 4176 patients). Currently, cognitive frailty is defined by an international consensus group as meeting the following two criteria: (1) the presence of physical frailty and cognitive

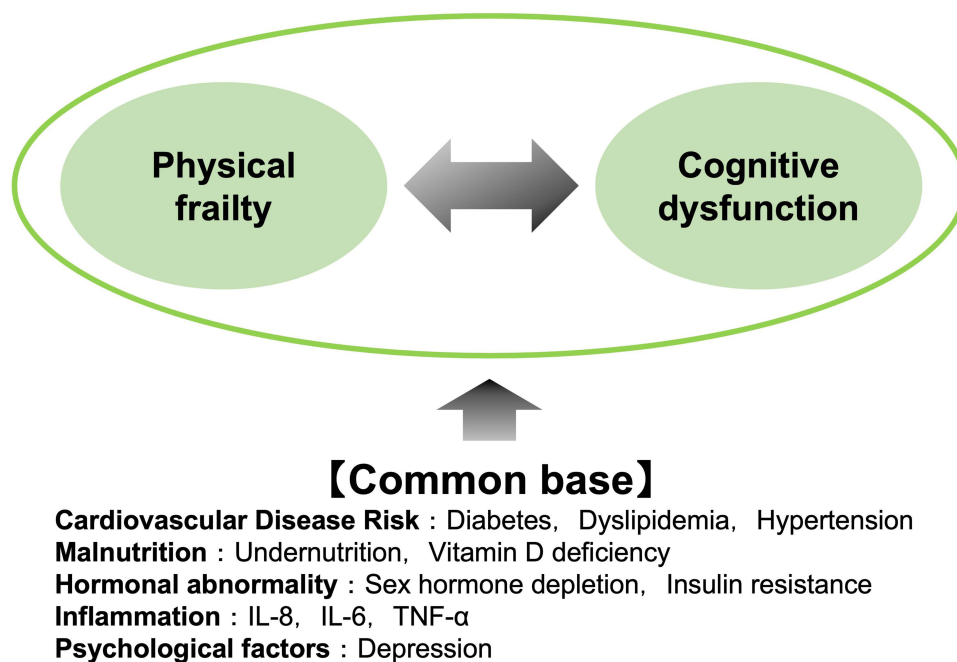


Figure 6 Commonalities between Physical Frailty and Cognitive dysfunction. Data from Kelaiditi et al.³⁷

impairment and (2) the absence of Alzheimer's disease or other dementia.³⁷ Cognitive impairment in this context is defined as a clinical dementia rating of 0.5.

Two expert meetings were held to develop a conceptual framework for frailty, and a consensus document was produced. Therefore, psychological frailty was defined as a decline in cognition, mood, and coping.⁴⁶ However, international definitions of psychological and mental frailty have not yet been established. Shimada et al conducted a longitudinal study of psychological frailty, defined as the coexistence of physical frailty (J-CHS criteria) and depressed mood (≥ 5 on the geriatric depression rating scale), in Japanese community-dwelling elderly people.⁴⁷ Their results showed that the hazard ratio of elderly people with physical frailty alone to be certified for long-term care was 1.69, whereas that for the elderly people with psychological frailty was as high as 2.24. Another study of 179 frailty elderly Italian subjects, age 65 years and older, with a Montreal Cognitive Assessment (MoCA) score of less than 26 points, found a strong and significant correlation between MoCA score and the 5-m walking speed test (r 0.877; $p < 0.001$).⁴⁸

Social Frailty

Mechanism

Social frailty is the most unexplored concept among the three domains. To date, no standardized definition of social frailty has been proposed; however, it has been conceptualized as the loss or risk of losing social support, activities, and resources needed to meet social needs.⁴⁹ Social interactions are critical to human health. Previous studies have shown that social frailty is associated with physical functioning, cognition, depression, and prediction of mortality.⁵⁰ Exercise intolerance and depression are common factors associated with HF and social frailty. HF induces exercise intolerance and depression and may lead to disconnection from society because of reduced opportunities to go out and interact with others. This can result in social frailty, with the loss of social activities needed to meet social needs. Because social activities often require the integration of higher-order physical and mental abilities than basic activities of daily living, social frailty may occur relatively early during the frail process. Recently, the prevailing view is that social frailty is caused by the interaction of independent factors in four areas summarized by Bunt et al in their scoping review: meeting basic social needs, social resources, social behaviors and activities, and general resources.⁵¹

Prevalence and Diagnosis

Saito et al reported that among the 148 patients with HF (80 ± 8 years, 51% male), 73 (49%) were socially isolated.¹⁹

As mentioned above, social frailty is the most unexplored concept among the three domains. Therefore, there is no consensus on assessing social frailty. A systematic review that examined assessment tools for social frailty reported 27 assessment tools that include at least one or more social questions.⁵² However, as of 2018, tools focusing solely on social frailty only include the following: the social frailty phenotype,⁵³ the QSFS⁵⁴ of Makizako et al, and the social frailty index.⁵⁵

In patients with HF, the QSFS of Makizako et al is frequently used. In the sub-analysis of FRAGILE-HF,⁵⁶ the QSFS was also used, showing that 825 (66.5%) of 1240 participants had social frailty, which was associated with all-cause mortality and rehospitalization at 1 year post-discharge. The QSFS is recommended for the assessment of social frailty in patients with HF due to multiple reports and its simplicity with only five questions. Conversely, studies using the Tilburg frailty indicator,⁵⁷ a comprehensive tool including physical, psychological, and social aspects, have reported that social frailty in elderly patients with HF negatively affects self-care, and therefore, different uses should be considered for different purposes.

Intervention Strategies for Patients with HF and Frailty

Various interventions for frailty have been proposed (Table 2). As mentioned above, frailty is composed of three domains, and a wide range of interventions are required. Although intervention strategies associated with physical frailty have dominated the reports, nutritional, cognitive, psycho/psychological/cognitive, and pharmacologic interventions are also important. Here we review the intervention strategies, particularly in patients with HF.

Table 2 Interventions in Elderly Frail Patients with Heart Failure

First Author	Year	Type of Study	Subjects	Frailty Instrument	Intervention	Control	Outcomes
Davis KK ¹²⁷	2012	RCT	125 patients hospitalized for exacerbation of HF who screened positive for MCI	MoCA with scores of 17–25	A targeted self-care teaching intervention using principles of cognitive training	Usual care	Improved HF knowledge scores in the intervention group. There was no difference in readmission rates between the groups.
Gharacholou SM ¹²⁸	2012	RCT	309 inpatients previously diagnosed with HF	Defined by multifaceted clinical characteristics	GEM provided by multidisciplinary teams	Usual care	Length of stay for GEM was significantly greater than usual care, but total costs at 1 year were not different.
Kamiya K ¹²⁹	2020	Multicenter retrospective cohort study	3277 patients admitted with acute HF	Frailty Index	Outpatient CR	Nonparticipant outpatient CR by Propensity scores matching	Outpatient CR participation was related to reduced risks of all-cause death and readmission because of HF.
Kitzman DW ⁶²	2021	RCT	349 patients ≥60 years of age admitted with ADHF	Modified Fried frailty criteria SPPB hand-grip strength	An early, transitional, tailored, progressive physical rehabilitation program	An attention control	SPPB score at 3 months was significantly greater than an attention control. At 6 months, the rates of rehospitalization for any cause were lower than an attention control.
Mudge AM ¹³⁰	2021	Secondary analysis of RCT	256 patients hospitalized with acute HF	Frailty Index	Center-based ET within a CR program including home exercise prescription and monitoring	A CR program including home exercise prescription and monitoring without center-based ET	Participants who were more frail had significantly greater improvements in Frailty Index compared with not-frail participants and were often able to achieve PA guidelines, both in intervention and control groups.
Pulignano G ¹³¹	2010	RCT	173 HF patients ≥70 years of age discharged home after a hospitalization	Modified frailty score	Multidisciplinary DMP	Usual care	Intervention was significantly cost saving in moderately frail, but not in nonfrail or severely frail patients.
Witham MD ¹³²	2005	RCT	82 outpatients ≥70 years of age with CHF	Functional Limitations profile scores	Group-based exercise training (0 to 3 months) and exercises at home (3 to 6 months)	Usual care	The significant increase in everyday PA measured by accelerometry in the exercise group at 6 months.
Yun S ¹³³	2022	Sub-analysis of RCT	178 patients with CHF	8 frailty-related dimensions	Multidisciplinary HF management programme using TM (telemonitorization and teleintervention using videoconference)	Multidisciplinary HF management programme by usual care (the basis of face-to-face on-site encounters)	The positive effect of TM compared to usual care strategy was consistent across 5 different frailty phenotypes. The risk of experiencing non-fatal HF events after 6 months of inclusion was significantly lower in patients that underwent allocation to the TM arm compared to usual care.

Abbreviations: ADHF, acute decompensated heart failure; CHF, chronic heart failure; CR, cardiac rehabilitation; DMP, disease management programs; ET, exercise training; GEM, geriatric evaluation and geriatric management; HF, heart failure; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; PA, physical activity; RCT, randomized controlled trial; SPPB, short physical performance battery; TM, telemedicine.

Physical Intervention

The goals of exercise therapy are to improve subjective symptoms and exercise tolerance, improve life expectancy, improve the quality of life, and reduce cardiac events. These goals have been achieved with exercise therapy. However, the majority of studies on exercise therapy in HF were obtained from studies on chronic HF and HFrEF. The HF-ACTION trial,⁵⁸ a large clinical trial funded by the National Institutes of Health and enrolling 2331 ambulatory patients with HF (LVEF 35%, NYHA class II–IV) from 82 centers, randomized patients to be treated with a combination of standard medical therapy and aerobic exercise and found that combination of both therapies was effective at 30 months. The quality of life was compared between the two groups. Results showed a greater improvement in the quality of life in the exercise group. Furthermore, adjustment for background factors showed a lower risk of all-cause mortality and hospitalization and cardiovascular mortality and rehospitalization. ExTraMACH study⁵⁹ has shown that exercise therapy improves survival and hospitalization rates. On the other hand, the ExTraMACH II study,⁶⁰ which increased the number of randomized controlled trials (RCTs) analyzed to 18, including 3912 patients, to account for cluster (or trial-level) data characteristics, showed no significant effects on the risk of death or hospitalization. The study using individual participant data in the HF-ACTION trial reported that physical activity was a predictor of death and rehospitalization,⁶¹ whereas the ExTraMACH II study did not provide physical activity data; therefore, future analysis is warranted.

Unlike the studies described herein, we present the REHAB-HF trial,⁶² comprising 53% of patients having HFpEF. In the REHAB-HF trial, the intervention was started early after hospitalization for HF, and rehabilitation in the outpatient and home settings was also introduced at the early stage. Interventions are divided into four domains, such as muscle strength and balance, and the rehabilitation content is determined in detail based on the patient's level. The main outcome, SPPB, improved by 1.5 (0.9–2.0) points in the intervention group over the control group. However, since this RCT included 349 out of 27,300 patients who met the criteria, whether results can be truly applied in clinical practice remains to be elucidated.

Exercise therapy primarily consists of aerobic exercise and resistance training. In recent years, whether aerobic exercise or resistance training should be recommended for elderly patients with HF and frailty remains controversial. First, aerobic exercise is recommended based on the following reasons: 6 months of aerobic exercise (3 months of supervised exercise and 3 months monitored by telephone after) for patients with HF aged ≥ 70 years has been associated with a 6-min walking distance (6MWD), ADL score, risk of rehospitalization, and quality of life.⁶³ Aerobic exercise in CVD also improves the vascular endothelial function, promotes vascular remodeling and angiogenesis, improves autonomic balance, and is myocardioprotective.⁶⁴ Compared with resistance training, aerobic exercise has a greater maximal oxygen uptake (VO_2 max) improvement^{65–67} (Table 3). Collectively, HFrEF and HFpEF have been reported to have different improvement mechanisms in exercise tolerance; HFrEF has been attributed to improvements in cardiac pump function, vascular function, and muscle fiber and mitochondrial function, whereas HFpEF is attributed to increased oxygen extraction capacity (arteriovenous) in the peripheral skeletal muscle.⁶⁸ However, the duration of aerobic exercise intervention in all studies has been notably long, ie several months. Considering the improvement mechanism, the manifestation of effects takes time, and some believe that it is not suitable for elderly patients with HF who are seeking happiness in the present study. Above all, most elderly people are not athletes in the real world and most elderly patients with HF have frailty, which often precludes effective aerobic exercise at 60% of the maximal load. Moreover, the OptimEx-Clin study⁶⁹ conducted at five centers in Germany and Norway also reported no significant differences in high-intensity interval training or medium-intensity continuous training compared to guideline-based physical activity for patients with HFpEF, which brings into focus the importance of resistance training. A systematic review and meta-analysis of resistance training in patients with HF demonstrated that it produces statistically significant improvements in peak VO_2 and 6MWD measurements without harming the cardiac structure and function.⁷⁰ Early resistance training can be safely performed even after STEMI, and quality of life improvements, exercise tolerance, and endothelial function have been observed.^{5,71,72} Based on these points, resistance training can be easily introduced to elderly patients with HF and frailty at various risks. Furthermore, resistance training has been reported to improve not only muscle strength but also muscle quality, such as inter- and intramuscular coordination, which may be effective against sarcopenia.⁷³ To date, we have discussed patients who underwent either aerobic exercise or resistance training. Resistance training in addition to exercise is known to improve cardiopulmonary function and quality of life,⁷⁴ and

Table 3 Effects of Aerobic Exercise and Resistance Training

	Aerobic Exercise	Resistance Training
Body composition		
Bone density	↑↑	↑↑
Body fat percentage	↓↓	↓
Lean body mass	→	↑↑
Skeletal muscle strength	→ or ↑	↑↑↑
Glucose metabolism		
Insulin response to sugar load	↓↓	↓↓
Insulin level	↓	↓
Insulin sensitivity	↑↑	↑↑
Serum lipid and Lipoprotein		
HDL cholesterol	↑ or →	↑ or →
LDL cholesterol	↓ or →	↓ or →
Neutral fat	↓↓	↓ or →
Circulatory dynamics		
Resting heart rate	↓↓	→
Stroke volume	↑↑	→
Heart rate (resting)	→	→
Heart rate (maximum exercise)	↑↑	→
Systolic blood pressure (resting)	↓ or →	→
Diastolic blood pressure (resting)	↓ or →	→
Exercise tolerance		
Maximum oxygen uptake	↑↑↑	↑ or →
Exercise duration at maximal and submaximal exercise load	↑↑↑	↑↑
Double product under maximum exercise load	↓↓↓	↓↓
Basal metabolic rate	↑ or →	↑
Health-related quality of life	↑ or →	↑ or →

Notes: ↑ Indicates values increase; ↓, values decrease; →, values remain unchanged; 1 arrow, small effect; 2 arrows, moderate effect; 3 arrows, large effect; From Williams MA et al.⁶⁵

Abbreviations: HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol.

we believe that elderly patients with HF with a wide range of exercise tolerance and comorbidities need tailor-made interventions based on the discussed knowledge.

Nutritional Intervention

Nutritional disorders are characteristic findings of sarcopenia and cachexia in physical frailty. In HF, hyponutrition develops due to anorexia, increased physical inactivity and resting energy demands, intestinal edema due to congestion, and circulatory failure. As mentioned, weight loss in patients with HF is known as cardiac cachexia. The prognosis for cardiac cachexia is extremely poor, with a reported 3-year survival rate of 50%.⁷⁵ Therefore, nutritional intervention and assessment are important. Nutrition assessment tools include the prognostic nutritional index), subjective global assessment, controlling nutritional status, nutritional risk index), geriatric nutritional risk index (GNRI), mini nutritional assessment), mini nutritional assessment-short form), and the above tools. The global leadership initiative on malnutrition (GLIM) is a tool used to assess malnutrition. In a systematic review that evaluated the prediction of all-cause mortality in HF using nutrition tools other than GLIM, HRs for all-cause mortality were MNA (HR = 2.62, 95% CI 1.11–6.20, P = 0.03] and MNA-SF (HR = 1.94, 95% CI 1.40–2.70, P < 0.001) were reported to be the best.⁷⁶ Among them, the GLIM criteria, released in 2018, are the world's first international criteria for diagnosing undernutrition, with four societies from Europe, the United States, Asia, and South America participating in their development, and are an evaluation index for evaluation. Compared to the widely used GNRI, the GLIM criteria are partly recommended because they do not include

serum albumin, which is greatly affected by inflammation and volume overload in HF. The following information is a summary of the study results.

Nutritional therapy for patients with HF is not yet well established, and even the 2020 meta-analysis reported a few valid articles. Thus, further RCTs are needed to accumulate evidence.⁷⁷ A few representative trials are presented below. The PICNIC study⁷⁸ showed that a 6-month personalized nutritional support provided by specialists reduced the HF-related 1-year mortality and rehospitalization rates compared to a control group. The study patients had a mean age of 79.2 years, BMI of 25.2 kg/m², and included HFpEF. Notably, a sub-analysis of patients with and without renal dysfunction (GFR, <60 mL/min/1.73 m²) showed that the study was effective even in patients with renal dysfunction who were considered protein limited. The second is the EFFORT trial⁷⁹ for patients with HF at risk for low nutrition. The median age was 78.8 years and a Nutritional Risk Screening 2002 (NRS-2002) score of ≥ 3 was the inclusion criterion. Patient-specific nutritional support included interventions, such as energy intake, protein (1.2–1.5 g/kg/day), multi-vitamins, and disease adjustments. Results showed a low risk of death and cardiovascular events within 30 days. Evidence on energy requirements of elderly patients with HF is lacking, and further accumulation of evidence is essential.

Several reports have been made in recent years on the quality of protein. Compared to vegetable proteins, animal proteins are more efficiently utilized, contain important nutrients, and are expectedly effective in preventing and improving muscle strength and muscle mass loss.⁸⁰ On the other hand, animal protein foods contain high saturated fatty acids and cholesterol levels.⁸¹ Increased animal protein intake has also been reportedly associated with total mortality, death from CVD, cancer death,⁸² and diabetes occurrence.^{83,84} Conversely, vegetable proteins contain phytochemicals and have been shown to have antioxidant benefits.⁸⁵ Protein selection should be tailored to the patient's cardiovascular and renal function and diabetes mellitus. In a review article on HF and diabetes mellitus (DM), he states that coronary microvascular inflammation with endothelial dysfunction is considered the common denominator of HFpEF, DM, and obesity and can explain the synergistic relationship between the pathogenesis of HFpEF, DM and obesity. He also states that lifestyle modification is very effective in improving the quality of life of patients with asymptomatic diastolic dysfunction and HFpEF. Therefore, we believe that patients with HFpEF presenting with DM and renal insufficiency need not only nutritionally therapy but also additional exercise therapy.⁸⁶

Finally, we present a study reporting that L-arginine, a semi-essential amino acid involved in many biological processes, enhances the effects of cardiac rehabilitation.⁸⁷ L-arginine is the substrate used by nitric oxide (NO) synthase to produce NO and is known to have beneficial effects on the endothelium that promote vasodilation, it is known to inhibit inflammation and improve physical function. In this previous study, patients were assigned, with a 2:1 ratio, to add to their standard therapy one bottle containing 1.66 g of L-arginine or one bottle of identical aspect apart from not containing L-arginine, twice a day orally for 3 weeks. Patients completed the 6-Minute Walk Test (6MWT) and were evaluated with the Borg Modified 0–10 Cognitive Exertion Evaluation (BRPE) before and at the end of treatment. 75 patients who received L-arginine and 35 patients who received placebo successfully completed the study. The 6MWT distance was significantly increased in the L-arginine group compared to both baseline and placebo ($P < 0.0001$). In addition, there was a significant improvement in BRPE in the L-arginine group, but not in the placebo group. These results indicate that L-arginine enhances response to cardiac rehabilitation regardless of age, gender, baseline functional capacity, or comorbidities. Thus, reports of improved therapeutic outcomes with various nutrients, not limited to energy intake and protein inoculation, have been increasing in recent years, and their clinical application is expected.

Psycho-Psychological and Cognitive Interventions

Genetic factors are known to increase the risk of dementia. However, a study examining the extent of offsetting by lifestyle factors reported that a healthy lifestyle with regular exercise, combined with non-smoking, a healthy diet, and moderate alcohol intake, was associated with a lower risk of dementia, regardless of the genetic risk.⁸⁸ As shown in this report, the effects of combined interventions on the cognitive decline are often tested. Some of the most representative trials are described below. First, the effects of a multidomain intervention (diet, exercise, cognition, and vascular risk management) and regular health advice were tested using a neuropsychological test battery as an outcome in 1260

Finnish patients aged 60–77 years at risk for dementia. The FINGER trial⁸⁹ showed that it was effective in maintaining or improving cognitive function. In contrast, the pre-DAVA trial,⁹⁰ a cluster RCT of 3526 Dutch subjects aged 70–78 years that tested the effects of nurse lifestyle guidance (smoking, diet, physical activity, weight, and blood pressure) every 4 months, showed no effects on cognitive function. Moreover, no cognitive function effect was found in the MAPT trial⁹¹ that tested the effects of Supplement $\omega 3$ and group sessions (cognitive training, physical activity, and nutrition) in 1680 patients without dementia aged ≥ 70 years in France and Monaco. The FINGER trial, the only trial with positive effects, involved a very high frequency of interventions by physiotherapists, nurses, nutritionists, and psychologists during the 2-year intervention period, and the content was very rich, making it difficult to generalize to the real world. We would like to note this point.

Focusing on multidomain interventions, we now consider the extent of a single exercise intervention in benefiting the cognitive function. First, the DAPA trial⁹² that examined the effects of a moderate- to high-intensity aerobic and strength exercise training program in 494 patients with dementia with a mean age of 77 years, concluded that only improvements in physical fitness were observed, without cognitive function effects. On the other hand, a meta-analysis of 36 studies comprising patients aged ≥ 50 years, excluding studies comprising patients with neurological and psychiatric disorders, found that aerobic exercise, strength training, multi-component training, and tai chi all improved cognitive function.⁹³ These two studies differ in terms of whether participants are patients with dementia or elderly in general. Patients who already have dementia may have had difficulty learning and generalizing exercise in the first place and therefore may not have been able to successfully approach the cognitive function. For patients who already have cognitive decline, interventions such as the FINGER trial that forcefully stimulate the activity of external factors may be a good idea. Since high activity is known to have a positive effect on brain capacity and A β , not only the amount of exercise during the intervention but also to increase it in daily life should be managed.^{94,95} For the cognitive function of elderly patients with mild cognitive impairment or dementia, the amount of exercise and cognition, such as in the dual-task, should be increased. Some meta-analyses have found combined exercise and cognitive training interventions, such as the dual-task, to be effective for cognitive function in elderly patients with mild cognitive impairment or dementia; therefore, incorporating these interventions is an option for patients with cognitive decline.⁹⁶

In summary, the effectiveness of exercise therapy alone versus multiple interventions including nutritional guidance varies depending on the patient and the method used. The trend was that in elderly patients without cognitive decline, even exercise therapy alone was likely effective because the content of the instruction could be generalized in daily life. Conversely, in patients with declined cognitive, the content of instruction cannot be generalized in daily life; thus, they should be forced to exercise through external factors. Since lifestyle guidance, including diet and nutrition, is not easily habit-forming, regular exercise therapy externally provided is considered most reliable for elderly patients with dementia. Combining intervention of exercise and cognitive training, eg, a dual task, could be provided within the exercise therapy.

Social Intervention

Social frailty worsens physical and cognitive functioning and depression and predicts mortality.^{50,97} The prevalence and prognostic impact of weak social networks in patients with HF has been addressed in previous studies; however, results have been inconsistent.⁹⁸ Although this is an area that seems to summarize all frailty areas, it is the least studied area, and only a few RCTs reported effective intervention methods. Previous studies have shown that those without physical frailty but with social frailty have a higher risk of subsequently developing physical frailty.⁹⁹ Furthermore, the mortality rate has been reportedly lower if the patient has physical frailty but not social frailty than those with both; thus, intervention for social frailty is important.¹⁰⁰ Here, we present an approach that may be effective.

Eighty pre-frail and frail adults aged ≥ 65 years (mean age 83) in a community study in Australia showed that non-professional, home-based physical training, nutrition, and social support interventions were effective for malnutrition and frailty.¹⁰¹ In this study, non-professional visits by volunteers were made twice a week for 12 weeks and focused on social aspects that activated the cognitive function, such as encouraging excursions and conversation exchanges. Remarkably, social support alone effectively improves malnutrition and frailty in this study. Intervention studies focusing on supervised group exercise have also reported that group activities may reduce or resolve social frailty by promoting

social interaction and physical factors.¹⁰² Participation in gatherings that promote social interaction, such as group-based social support programs (eg, salon activities), has been found to strengthen social connections and reduce the incidence of disability.^{103,104}

Therefore, the promotion of a population approach that does not cause social disconnection is believed to be the preferred coping method. If social disconnection has already occurred, social connections can be re-established using the latest technology, specifically video calls and social networking services, among others. Other exercises using virtual reality (VR) have also been investigated and have been reported to significantly enhance physical and cognitive functions.¹⁰⁵ Other studies have examined tablet-based applications and exercises that combine VR and stationary bikes for frail elderly people.^{106,107} The TELEREH-HF trial, which examined the effects of hybrid comprehensive telerehabilitation, consisting of remote monitoring of training at home in patients with HF, significantly improved the peak oxygen consumption and quality of life.¹⁰⁸ As these technologies become more widespread, social disconnection can be solved by allowing patients to dine with friends or go for a walk in the comfort of their own homes. Some studies have reported that satisfaction with significant activities, including a wide range of activities from daily life to work, social life, and leisure time activities important, enjoyable, and rewarding for the individual patient, is associated with social frailty. During the acute phase and hospitalization, patients tend to focus only on physical and cognitive functions; however, early acquisition of meaningful activities beyond these functions may help correct social frailty.

Pharmacological Intervention

Effective drugs for HF have been developed over the years. In the 2022 AHA/ACC/HFSA guideline for the management of HF: executive summary, each drug is listed with a high recommendation class and evidence level.¹⁰⁹ The ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure, revised in 2021 for the first time in five years, revised the treatment algorithm for HFrEF. The new algorithm includes angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor-neprilysin inhibitors (ARNIs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), sodium-glucose co-transporter 2 inhibitors (SGLT-2Is), fluid retention improving loop Diuretics were positioned as drugs that should be administered to all patients.³ Here, we will focus on the impact of drugs on frailty including the fantastic four (ARNIs, beta-blockers, MRAs, and SGLT2Is), which have been increasingly investigated in recent years.¹¹⁰

A study investigating the effects of ARNIs on physical frailty as assessed by a modified version of Fried's frailty phenotype in patients with advanced HFrEF on the heart transplant waiting list found not only physical frailty but also improved 6MWT and VO₂ max and NT-pro-BNP¹¹¹ and improved depressive symptoms in the same patients.¹¹² In those with HFrEF, ACE-Is and angiotensin receptor blocker to ARNIs, along with 6MWT, significantly improved depression, anxiety symptoms, and functional status.¹¹³ In frail elderly patients with diabetes mellitus and HFpEF, the study of SGLT2Is showed significant improvements in the 5-m walk test and cognitive function.¹¹⁴

We have discussed the efficacy of pharmacotherapy in patients with HFrEF, and the ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure also state that “there are no large RCTs that have met their primary endpoints, and no treatment currently has demonstrated reliable efficacy for patients with HFpEF.” However, the EMPEROR-Preserved trial showing the efficacy of empagliflozin in HFpEF was published in ESC 2021, although not in time for the guideline revision process.¹¹⁵ Empagliflozin reduced the combined risk of cardiovascular death, hospitalization for heart failure, and emergency/urgent heart failure requiring intravenous treatment (432 versus 546 patients [empagliflozin versus placebo, respectively]; hazard ratio, 0.77 [95% CI, 0.67–0.87]; $P<0.0001$). In addition, Empagliflozin reduced the total number of heart failure hospitalizations that required intensive care (hazard ratio, 0.71 [95% CI, 0.52–0.96]; $P=0.028$) and the total number of all hospitalizations that required a vasopressor or positive inotropic drug (hazard ratio, 0.73 [95% CI, 0.55–0.97]; $P=0.033$).

As mentioned above, although pharmacologic interventions are effective in preventing frailty, multiple drug use in HF is a risk factor for frailty. The frailty and comorbid elderly population are at utmost risk due to the prevalence of polypharmacy is increasing rapidly and their resistance to all diseases and infections is impaired.

It is also essential to identify frail older individuals with polypharmacy; a study reported a significant correlation between the frailty index score and both potentially inappropriate prescribing and adverse drug reactions in hospitalized elderly

patients.¹¹⁶ Polypharmacy is defined as “the use of six or more multiple drugs”, and polypharmacy is known to be common in patients with HF, with a significantly higher risk of adverse events.^{117–123} One of the reasons why polypharmacy is common in patients with HF is that appropriate polypharmacy occurs due to medical necessity. In 2022, six drugs are recommended by the AHA/ACC/HFSA guideline for the management of HF: executive summary, and the addition of drugs for comorbid conditions could result in multiple drug combinations.¹⁰⁷ Another reason is the high incidence of inappropriate polypharmacy due to unnecessary prescriptions for elderly patients. The frailty and comorbid elderly population is at utmost risk due to the prevalence of polypharmacy is increasing rapidly and their resistance to all diseases and infections is impaired.¹²⁴ To evaluate the medication appropriateness in 231 elderly patients with HF attending the University of Michigan in the United States, 50–70% of prescriptions were inappropriate.¹²⁵ In a study on the number of drug prescriptions and taste sensitivity in patients with HF, the polypharmacy group with ≥ 8 prescriptions had a significantly higher rate of all four types of taste disorder complications and a significantly lower energy intake rate.¹²⁶ These results suggest that polypharmacy can lead to poor nutrition, frailty, and cachexia. Thus, not only physicians and pharmacists but also nurses and rehabilitation-related professionals should evaluate the daily dietary intake, weight changes, and physical function changes and make efforts to detect polypharmacy.

Conclusion

To introduce evidence and well-known studies, the explanation was divided by domain. However, because frailty spans multiple domains, interventions should not be divided into exercise, nutrition, and drugs, but rather, interventions should further be evaluated to multiple domains such as psycho-psychological, cognitive, and social to compensate for deficiencies. This is because we believe that such tailor-made interventions are more necessary than single interventions for the various symptoms associated with heart failure and frailty. Several studies have shown a relationship between frailty and HF prognosis; however, interventions that improve prognosis remain unclear. Future information regarding interventions aimed at improving the prognosis for multidomain frailty is needed.

Abbreviations

ADLs, activities of daily living; ARNI, angiotensin receptor-neprilysin inhibitors; CFS, Clinical Frailty Scale; CHS, Cardiovascular Health Study; CVD, cardiovascular diseases; DAPA, Dementia and Physical Activity; EFFORT, Effect of Early Nutritional Therapy on Frailty, Functional Outcomes and Recovery of Undernourished Medical Inpatients Trial; FINGER, The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; GLIM, Global Leadership Initiative on Malnutrition; GNRI, Geriatric nutritional risk index; HF, heart failure; HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart Failure with Reduced Ejection Fraction; MAPT, Multidomain Alzheimer Preventive Trial; MMSE, Mini Mental State Examination; QSFS, Questionnaire to define Social Frailty Status; RCT, randomized controlled trials; VR, virtual reality.

Disclosure

The authors report no conflicts of interest in this work.

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