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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Interventions for Frailty Among Older Adults With Cardiovascular Disease

JACC State-of-the-Art Review

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ABSTRACT

With the aging of the world's population, a large proportion of patients seen in cardiovascular practice are older adults, but many patients also exhibit signs of physical frailty. Cardiovascular disease and frailty are interdependent and have the same physiological underpinning that predisposes to the progression of both disease processes. Frailty can be defined as a phenomenon of increased vulnerability to stressors due to decreased physiological reserves in older patients and thus leads to poor clinical outcomes after cardiovascular insults. There are various pathophysiologic mechanisms for the development of frailty: cognitive decline, physical inactivity, poor nutrition, and lack of social supports; these risk factors provide opportunity for various types of interventions that aim to prevent, improve, or reverse the development of frailty syndrome in the context of cardiovascular disease. There is no compelling study demonstrating a successful intervention to improve a global measure of frailty. Emerging data from patients admitted with heart failure indicate that interventions associated with positive outcomes on frailty and physical function are multidimensional and include tailored cardiac rehabilitation. Contemporary cardiovascular practice should actively identify patients with physical frailty who could benefit from frailty interventions and aim to deliver these therapies in a patient-centered model to optimize quality of life, particularly after cardiovascular interventions. (J Am Coll Cardiol 2022;79:482-503) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

In the United States, as in the rest of the developed world, there is a rapidly growing older adult population, with adults 65 years or older composing 16.5% of the population in 2019.[1] This figure is projected to increase to 20.3% by 2030, when all baby boomers reach 65 years of age. By 2034, older adults will outnumber children, and nearly 1 in 4 Americans will be older than 65 years by 2060.[2] This has many implications for the practice of cardiovascular medicine because older adults

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HIGHLIGHTS

- Physical frailty syndrome is associated with poor outcomes after cardiovascular events.
- The etiology of frailty in older adults is multifactorial and patient specific.
- Multimodal interventions, including cardiac rehabilitation, can reduce frailty.

are disproportionately affected by cardiovascular disease (CVD). The prevalence of CVD increases with age, and outcomes are more detrimental for those older than 75 years with coexisting geriatric syndromes.[3] Between 2015 and 2018, the prevalence of CVD was 75% to 77% in those 60 to 79 years of age and 89% to 90% in those 80 years and older.[4] Very old patients have a higher mortality rate[5] and greater risk for disability after hospitalizations.[6] They are also more likely to have longer lengths of hospital stay and are less likely to be discharged back to their original places of residence.[4] This phenomenon of increased vulnerability to stressors because of decreased physiological reserves in older adults is termed frailty, which has recently gained great interest from cardiologists because of the changing demographics of the U.S. population.[7]

Frailty syndrome has been described over a spectrum ranging from the absence of frailty, termed robust, to prefrail, and then physically frail.[8] The prefrail state increases the risk for progression to frailty, and frailty increases the risk for disability, a state that is distinct from frailty.[9] Depending on the instrument used to assess for frailty, the prevalence of frailty among community-dwelling older adults ranges from 4.0% to 59.1%, and the prevalence of prefrailty ranges from 18.7% to 53.1%,[10] but the highest estimates are observed among older patients with CVD. There is a strong bidirectional association between CVD and

ABBREVIATIONS AND ACRONYMS

6MWD = 6-minute walk distance

CABG = coronary artery bypass grafting

CFS = Clinical Frailty Scale

CVD = cardiovascular disease

EFT = Essential Frailty Toolset

HF = heart failure

HMB = beta-hydroxy beta-methylbutyrate

MMSE = Mini-Mental State Examination

mTOR = mechanistic target of rapamycin

NHATS = National Health and Aging Trends Study

SPPB = Short Physical Performance Battery

TAVR = transcatheter aortic valve replacement

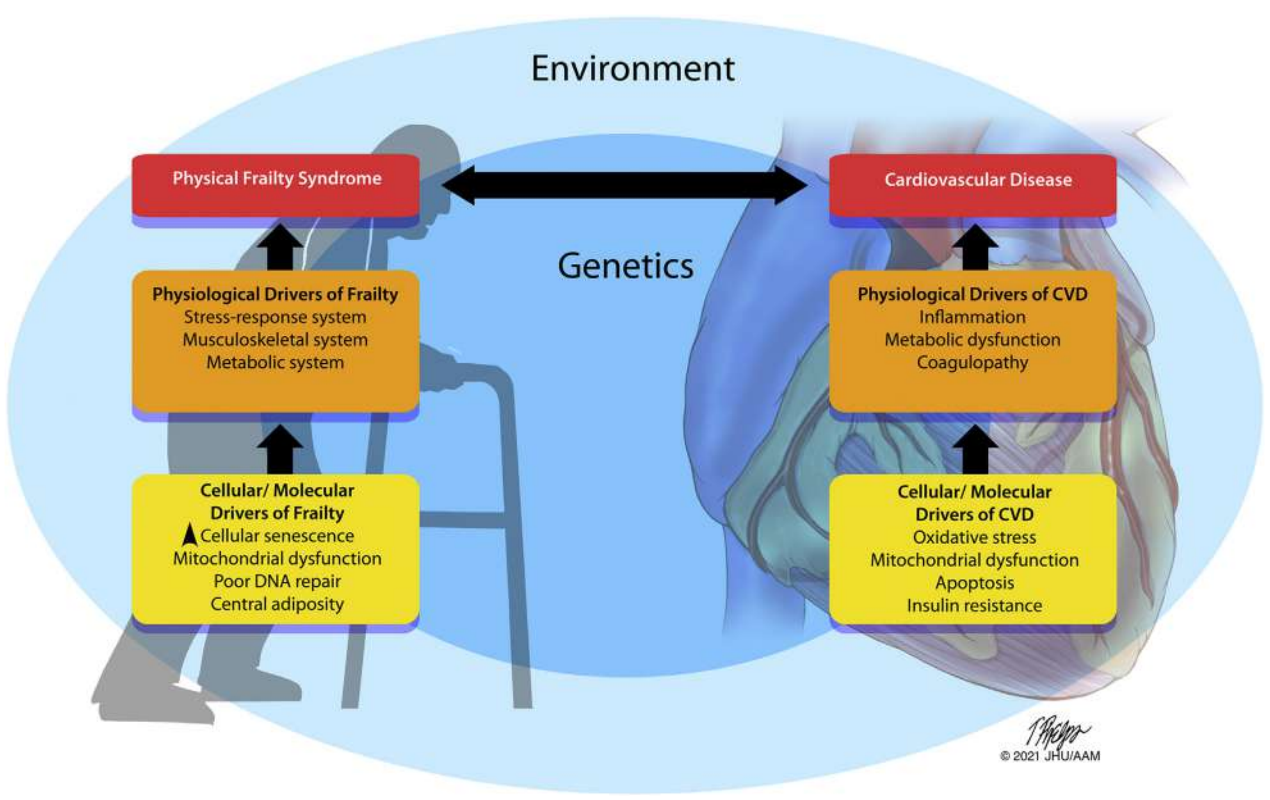
TUG = Timed Up and Go

TABLE 1 Conceptual Definitions of Frailty Syndromes Among Patients With Cardiovascular Disease

Frailty Type	Definition
Physical frailty	
Fried physical frailty phenotype	Clinical syndrome of increased vulnerability resulting from age-associated decline in reserve and function across multiple physiologic systems such that the ability to cope with everyday acute stress is compromised.
Consensus definition (*JAMDA*)	A medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiological function that increases an individual's vulnerability for developing increased dependency and/or death.
WHO definition	A clinically recognizable state in which the ability of older people to cope with everyday or acute stressors is compromised by an increased vulnerability brought by age-associated declines in physiological reserve and function across multiple organ systems.
Cognitive frailty	
Cognitive frailty/predementia syndrome	State of cognitive vulnerability exposed to vascular risk factors with an increased likelihood of progression to overt dementia.
IANA/IAGG definition	A heterogenous clinical manifestation characterized by the simultaneous presence of both physical frailty and cognitive impairment.
Ruan definition	A heterogenous clinical syndrome of cognitive impairment (CDR ≤0.5) that develops in older patients and is caused by physical factors (eg, physical frailty and pre-physical frailty) and is excluded from dementia resulting from AD or other conditions. The 2 subtypes are: • Reversible cognitive frailty: SCD and/or positive biomarkers resulting from physical factors when unrelated to an acute event or clinical diagnosis of neurodegenerative and mental conditions • Potentially reversible cognitive frailty: MCI (CDR = 0.5)
Psychosocial frailty	
Integral conceptual definition of frailty	A dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, social), which is caused by the influence of a range of variables and which increases the risk for adverse outcomes. • Psychological: declines in cognition, mood, and coping • Social: declines in social relations and social support
Social frailty	A continuum of being at risk for losing, or having lost, social and general resources, activities, or abilities that are important for fulfilling one or more basic social needs during the life span.
Nutritional frailty	
Nutritional frailty	A state commonly seen in vulnerable older adults, characterized by sudden, significant weight loss and loss of muscle mass and strength (sarcopenia), or an essential loss of physiologic reserves, making the individual susceptible to disability.

AD = Alzheimer's disease; CDR = clinical dementia rating; IAGG = International Association of Gerontology and Geriatrics; IANA = International Academy on Nutrition and Aging; *JAMDA* = *Journal of the American Medical Directors Association*; MCI = mild cognitive impairment; WHO = World Health Organization.

FIGURE 1 Theoretical Model of the Drivers of Frailty Syndrome and CVD



A combination of genetic and environmental factors cause dysfunction at a cellular/molecular scale **(yellow)**, driving physiological responses in different organ systems **(orange)**, resulting in clinical manifestations of cardiovascular disease (CVD) and/or the physical frailty syndrome **(red)**. Both are intertwined in a bidirectional relationship, as the presence of one entity drives the progression of the other. Revised with permission from Fried LP, Cohen AA, Xue Q-L, Walston J, Bandeen-Roche K, Varadhan R. The physical frailty syndrome as a transition from homeostatic symphony to cacophony. *Nat Aging.* 2021;1:36–46.

frailty, with a dose-dependent response seen from robust to frail. Prefrailty and frailty are independently associated with a higher risk for developing CVD.[11]

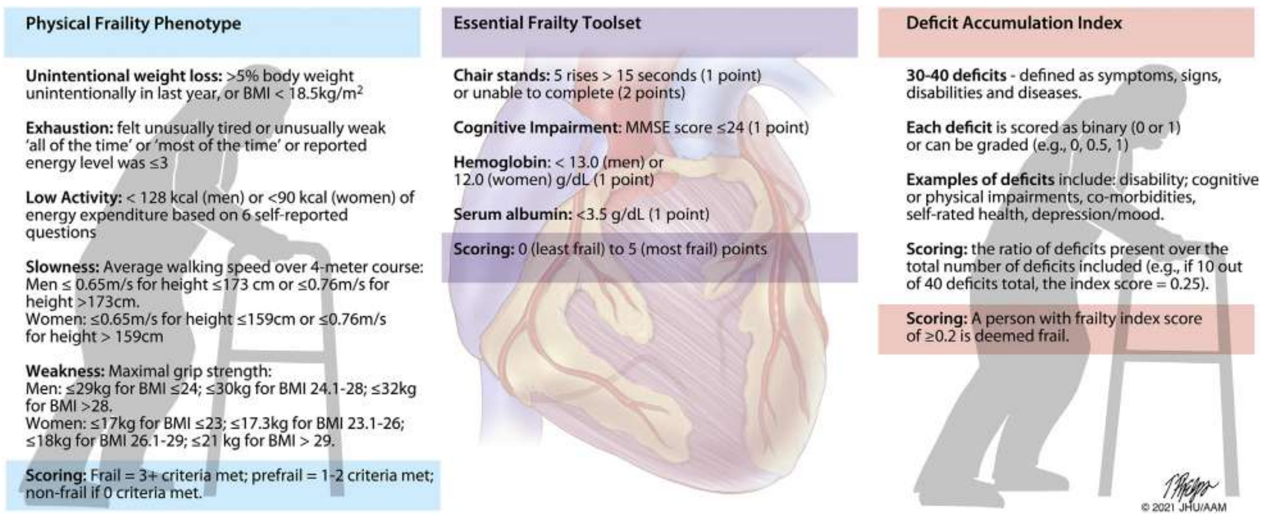
The hospital environment, with immobilization, fasting, sleep deprivation, and disorientation, can dramatically worsen physical frailty with rapid, severe loss of muscle mass and function. The result is “posthospital syndrome,” with high rates of rehospitalization, mortality, and nursing home admissions; prolonged physical disability; poor quality of life; and high health care costs.[12] Thus, interventions aimed at preventing, delaying, or reversing frailty may influence cardiovascular health in older patients. In this state-of-the-art review, we discuss the various definitions of frailty, the instruments used to measure frailty in practice, and proposed interventions to prevent, reverse, or slow the progression of frailty in patients with CVD.

DOMAINS AND DEFINITIONS

There are various proposed definitions and conceptual frameworks of frailty. As frailty involves dysregulation across many physiological systems,[13] with multifactorial etiologies, there is a wide range of clinical phenotypes. Therefore, frailty has been categorized into different functional domains: physical, cognitive, psychosocial, and nutritional (**Table 1**).

Physical frailty was defined by Fried et al[8] as “a clinical syndrome of increased vulnerability resulting from age associated decline in reserve and function across multiple physiologic systems such that the ability to cope with everyday acute stress is compromised.” This definition uses the presence of the following components to establish the diagnosis of frailty: shrinking, weakness, poor endurance and energy, slowness, and low physical activity level. Shrinking is defined by unintentional weight loss and

FIGURE 2 **Selected Instruments for Frailty Screening in Patients With Cardiovascular Disease**



In the physical frailty phenotype model, frailty is defined by meeting 3 or more of the 5 criteria of unintentional weight loss, exhaustion, low activity, slowness, and weakness. The Essential Frailty Toolset is scored from 0 (least frail) to 5 (most frail), on the basis of the following components: chair stands, cognitive impairment, hemoglobin, and serum albumin. The Deficit Accumulation Index is a deficit-accumulation approach based on the theory that vulnerability stems from the accumulation of health deficits. BMI = body mass index; MMSE = Mini-Mental State Examination.

alludes to the presence of sarcopenia contributing to the development of frailty.

Cognitive dysfunction leads to increased vulnerability; therefore, many investigators have proposed adding cognition to the definition of frailty. Cognitive frailty was first defined by Panza et al[14] as "a particular state of cognitive vulnerability in mild cognitive impairment and other similar clinical entities exposed to vascular risk factors and with a subsequent increased progression to dementia, particularly vascular dementia." A workshop on cognitive frailty was conducted by an international consensus group that defined cognitive frailty to be "a heterogenous clinical manifestation characterized by the simultaneous presence of both physical frailty and cognitive impairment."[15] Ruan et al[16] refined the definition by proposing subtypes of potentially reversible and irreversible cognitive frailty so that interventions could be accurately divided into primary prevention and secondary prevention.[16]

In an aim to develop a conceptual framework of frailty, 2 additional expert meetings took place that resulted in an integral conceptual model of frailty that included psychological frailty and social frailty. The consensus document defined frailty as "a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, social), which is caused by the influence of a range of variables and increases the risk of adverse outcomes."[17] Psychological frailty was defined as declines in cognition, mood, and coping, and social frailty was defined as declines in social relations and social support. Recognizing that social frailty is the most unexplored of all frailty domains, Bunt et al[18] defined it as "a continuum of being at risk of losing, or having lost, resources that are important for fulfilling one or more basic social needs during the life span" and suggested that not only the absence of resources but also the absence of social behaviors, social activities, and self-management abilities be included in the concept of social frailty.

Nutritional frailty was defined by Bales and Ritchie[19] as "rapid, unintentional loss of body weight and accompanying disability that often signals the beginning of a terminal decline in an older individual." Using this conceptual framework, numerous nutritional interventions to reverse frailty have been proposed.

Frailty can be a result of physical, cognitive, nutritional, and/or psychosocial vulnerabilities, and there is a lack of a comprehensive definition that incorporates all components of every domain, but several of these domains cannot be practically addressed in cardiovascular practice. As physical frailty can be measured objectively, investigators argue that physical factors should be identified by

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TABLE 2 Clinical and Administrative Instruments Used to Measure Frailty in Patients With Cardiovascular Disease

Type	Instrument	Criteria
Physical frailty	Fried frailty phenotype	≥3 of the following components of the hypothesized cycle of frailty: • Shrinking/weight loss • Weakness • Poor endurance and energy • Slowness • Low physical activity level
	Study of Osteoporotic Fractures frailty criteria	A frailty index using 3 components: weight loss, one's inability to rise from a chair 5 times without using the arms, and reduced energy level.
	Simplified Frailty Scale	A scale consisting of 5 components: slowness as measured by gait speed, weakness as measured by handgrip strength, exhaustion, low activity level, and weight loss.
	FIFA score	A frailty score based on data collected from a wearable health-monitoring device, including heart rate, preprocedural stress, and walking.
Deficit accumulation frailty	Frailty Screening Questionnaire	A self-report frailty measurement tool based on the modified Fried frailty components used to identify older adults with higher risk for adverse health outcomes.
	Brief Risk Identification of Geriatric Health Tool	An 11-item questionnaire composed of questions on health status, independence, fall risk, depression, and cognitive limitations. A score of 3 or more identifies those with disability-related needs.
	PRISMA-7	A 7-item questionnaire on age, gender, health problems, limitations, dependence, social support, and mobility. A score of 4 or more indicates frailty.
	Geriatric 8 frailty questionnaire	An 8-question screening tool to identify patients who could benefit from a comprehensive geriatric assessment. Evaluates appetite, weight loss, mobility, neuropsychological problems, BMI, medications, relative health status, and age.
	Hospital Frailty Risk Score	A risk score based on administrative hospital data (ICD-10 codes) used to identify frailty risk.
	Electronic Frailty Index	A risk score derived from automatically populated routinely collected data contained within the primary care electronic health record in the United Kingdom.
	The Johns Hopkins Claims-Based Frailty Indicator	A frailty indicator derived from Medicare claims that uses administrative data to classify patients as frail.
	Claims-based frailty index	An index calculated from Medicare data using the deficit accumulation approach.
	CSHA frailty index	Composed of assessments in 10 standard domains: cognitive status, mood and motivation, communication, mobility, balance, bowel function, bladder function, IADLs and ADLs, nutrition, and social resources. A count of 70 deficits including the presence and severity of current diseases, ability in ADLs, and physical signs from clinical and neurologic exams.
	Frailty Index of Accumulated Deficits	The proportion of deficits present in an individuals at the time of his or her health appraisal.
	Schoenenberger Frailty Index	A summary score of performance on various components, including MMSE, TUG test, Mini Nutritional Assessment, basic ADLs, and IADLs. Also includes an assessment of preclinical mobility disability.

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clinicians as they are more likely to be medically treatable.[20] Similar to other academic consortiums in cardiovascular medicine, a universal definition of frailty through a "frailty academic research consortium" is needed to improve the quality of research in the field and to accurately interpret the results of interventions aimed to prevent and reverse frailty as part of the comprehensive cardiovascular evaluation and management in older adults.

FRAILTY AND CVD: A BIDIRECTIONAL ASSOCIATION

Whereas CVD can lead to worsening frailty due to hospitalization, debilitation, and immobility, underlying systemic, metabolic, and hormonal dysregulation such as chronic low-grade inflammation, central adiposity, and insulin resistance can explain the molecular and physiological underpinnings of both physical frailty and CVD (**Figure 1**).[21,22] There is a strong association between frailty and adverse cardiovascular outcomes, which was explored in depth elsewhere.[23] Among patients who underwent percutaneous coronary intervention, frailty status was independently associated with increased mortality and adverse cardiovascular events.[24] In patients with non-ST-segment elevation myocardial infarction, an invasive strategy was associated with improved outcomes in nonfrail patients, but it also was associated with a higher incidence of procedural complications in frail patients.[25] In patients presenting with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention, frailty was associated with higher in-hospital mortality even with prompt revascularization strategies.[26] In patients with acute coronary syndromes, frailty was associated with lower adherence to quality metrics, including longer admission-to-balloon time, longer hospital stay, and higher 30-day and 1-year mortality.[27] Frailty is highly prevalent in patients with heart failure (HF), ranging from 36.2% to 52.8%,[28] and is a

TABLE 2 Continued

Type	Instrument	Criteria
Predisability frailty	CSHA function scale	Based on the Older American Resources Survey, with 12 IADL and ADL items. Scores patients on each of 12 ADLs as 0 (the patient is independent in carrying out this ADL), 1 (needs assistance), or 2 (is incapable).
	Frail Non-Disabled instrument	A 5-item questionnaire assessing mobility, disability, weight loss, exhaustion, and sedentary behavior that categorizes patients as disabled, frail, or robust.
	Edmonton Frailty Scale	Screening questionnaire assessing 9 domains of frailty: cognition, functional performance, general health status, functional independence, social support, pharmacological condition, nutritional aspect, mental condition and continence. Patients are classified into the following categories: no frailty, apparently vulnerable, and severe frailty.
	Bern scale	An 8-element frailty score, including the domains of cognition, instrumental activities of living, nutrition, energy level, weight loss, limb strength, comorbidities, and psychological factors, scoring patients on a scale of 0 (least frail) to 9 (most frail).
	11-Item Simplified Frailty Index	An index composed of 11 overlapping items from the CSHA frailty index and the ACS NSQIP: DM, lung problems, CHF, MI, cardiac problems, HTN, cognitive impairment, cerebrovascular problems, history of stroke, and PVD.
	Groningen Frailty Indicator	A screening instrument consisting of 15 self-report items in multiple frailty domains. A score of 4 of more indicates frailty.
	Health Deficits Index	Derived from a self-administered questionnaire of health deficits, this tool has been found to be associated with adverse health outcomes.
	Evaluative Frailty Index for Physical Activity	A 50-item multidomain questionnaire assessing physical functioning, psychological functioning, social functioning and general health.
	Frailty Risk Score	A risk score based on 16 factors derived from the electronic health record, including symptoms, syndromes, conditions, and serum biomarkers.
	Vulnerable Elders Survey	A function-based self-assessment tool consisting of age, self-rated health, independence, and physical performance for screening community-dwelling adults to identify the vulnerable, defined as a score of >3.
	Katz index	A simple scale composed of 6 items that evaluate basic daily activities to provide a measure of independence.
	Barthel index	A scale assessing mobility and performance in ADLs, with a higher number indicating greater independence and a lower number indicating that a greater degree of assistance is required.
	Gait speed	Gait speed <0.8 m/s is found to have high sensitivity (0.99) and moderate specificity (0.64) for identifying frailty.
	Handgrip strength	Reduction in handgrip strength is associated with functional decline, mortality, disability, and medical complications.
	Rising time from bed	Rising time from bed, measured within 2 days of admission, is an independent predictor of frailty at hospital discharge in elderly patients hospitalized for heart failure.
	Short Physical Performance Battery	A measure of lower limb function that can predict future risk of nursing home admission and mortality. It consists of 3 individual subtests: standing balance, 4-m gait speed, and 5-repetition sit-to-stand.
	6-minute walk test	A ≤300-m walk distance is a significant predictor of frailty in patients with CHF.
	5-m gait speed test	Gait speed ≥6 s over a 5-m distance has been proved to be a predictor of mortality and major morbidity in elderly patients undergoing cardiac surgery.
	Tinetti Performance Oriented Mobility Assessment	A task-oriented test composed of various maneuvers that measure gait and balance abilities.
	Knee extension strength test	A measure of lower extremity strength that is measured in a seated position with hips and knees at 90°, by a force transducer mounted in a chair.
	Appendicular lean mass	Quantified using bioimpedance analysis of body measurements, a measurement found to correlate with mortality in prefrail and frail adults.

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strong predictor of outcomes. The FRAILTY-AVR (Frailty Assessment Before Cardiac Surgery & Transcatheter Interventions) study showed that the prevalence of frailty was 26% to 68% in patients undergoing aortic valve replacement, which increased the risk for mid-term mortality, functional decline, and disability.[29] A study among patients undergoing percutaneous mitral valve repair showed that 45.5% of patients were frail, and frailty was associated with higher risk for mortality and HF decompensation during follow-up.[30]

The same biological underpinnings that cause CVD may also lead to the development of other chronic cardiovascular and noncardiovascular conditions in older patient populations that need to be carefully managed. These multiple chronic conditions, also known as multimorbidity, result in the introduction of several concurrent medications, or polypharmacy, which has long been associated with an increased risk for frailty, falls, and worsening cognitive impairment.[31] In addition to more data on optimal pharmacotherapy in older adults, individualized care informed by geriatric principles may reduce frailty risk in this patient population. Because of recognition that various pharmacotherapies in frail patients with CVD can result in adverse effects (eg, antiplatelet

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TABLE 2 Continued

Type	Instrument	Criteria
Mixed assessments	Fried+ scale	Consists of the Fried frailty phenotype components in addition to a cognition assessment as evaluated by the MMSE and mood as assessed by the short-form Geriatric Depression Scale.
	The CSHA Clinical Frailty Scale	Uses information from a clinical encounter to summarize a person's health on a scale from 1 (very fit) to 7 (severely frail).
	CSHA rules-based definition of frailty	Categorizes subjects as 0 (having no cognitive or functional impairment), 1 (isolated urinary incontinence), 2 (dependent in 1 ADL or having a diagnosis of CIND), or 3 (dependent in at least 2 ADLs, having mobility impairment, or having a diagnosis of dementia).
	Frailty Staging System	Evaluates the functional status of patients using carefully selected tests of vision, hearing, arm and leg function, urinary incontinence, mental status, instrumental and basic ADLs, environmental hazards, and social support system that are conducted using a brief questionnaire and easily observed tasks.
	Columbia scale	A frailty scale consisting of 4 items: gait speed, grip strength, serum albumin, and ADL disability.
	Green score	A frailty score based on serum albumin, independence in ADLs, gait speed, and handgrip strength.
	Essential Frailty Toolset	A brief, 4-item frailty scale based on evaluation of chair rise, cognition, hemoglobin, and serum albumin.
	Comprehensive Assessment of Frailty	A score composed of different items to quantify the physical performance and coordinative abilities of the patient in addition to biomarkers and scores that are already used to define frailty, such as the Fried criteria.
	Gérontopôle Frailty Screening Tool	An 8-item questionnaire evaluating a patient's status (living alone, involuntary weight loss, fatigue, mobility difficulties, memory problems and gait speed) in addition to the general practitioner's personal view about the frailty status of the individual.
	The Frailty Trait Scale	A 12-item multidimensional assessment on energy balance-nutrition, physical activity, nervous system, vascular system, strength, endurance, and gait speed.
	The Dutch Tilburg Frailty Indicator	Consists of 2 subscales, one comprising sociodemographic data and data about life events and chronic diseases. Another consists of physical, social, and psychological factors. A score of 5 or greater is associated with frailty.
	SHARE Frailty Instrument	An assessment tool composed of grip strength and 4 self-reported items (fatigue, loss of appetite and/or eating less than usual, difficulties climbing stairs and/or walking 100 m, and low-level physical activity) used to screen community-dwelling adults for frailty. It is based on the first wave of the Survey of Health, Ageing and Retirement in Europe.
	Comprehensive Geriatric Assessment	An interdisciplinary, multidimensional assessment of various domains of health, including medical conditions, mental health, functioning, social circumstances, and environment.
	FRAIL scale	A questionnaire composed of a self-assessment of 5 components (fatigue, resistance, ambulation, illness, and loss of weight), which categorizes patients as robust, prefrail, or frail.
	SARC-F	A 5-component questionnaire consisting of self-assessment of strength, assistance walking, rise from a chair, climb stairs, and falls.
	Sherbrooke Postal Questionnaire	A simple mailed questionnaire consisting of 6 items in multiple frailty domains. Those who score 2 or higher, or those who do not respond to the questionnaire, are assumed to be frail.
	Kihon checklist	A 25-item questionnaire including 7 categories: daily life, physical ability, nutrition, oral condition, the extent to which one is housebound, cognitive status, and depression risk.

ACS = American College of Surgeons; ADL = activity of daily living; BMI = body mass index; CHF = congestive heart failure; CIND = cognitive impairment no dementia; CSHA = Canadian Study of Health and Aging; DM = diabetes mellitus; FIFA = Fitness-Tracker Assisted Frailty-Assessment; FRAIL = fatigue, resistance, ambulation, illnesses, and loss of weight; HTN = hypertension; IADL = instrumental activity of daily living; ICD-10 = International Classification of Diseases-Tenth Revision; MI = myocardial infarction; MMSE = Mini-Mental State Examination; NSQIP = National Surgical Quality Improvement Program; PVD = peripheral vascular disease; SARC-F = strength, assistance walking, rise from a chair, climb stairs, and falls; TUG = Timed Up and Go.

therapy increasing the risk for bleeding in frail patients or polypharmacy secondary to guideline-directed medical therapy increasing the risk for adverse events),[32] frailty is becoming a forerunner of undertreatment or overtreatment among older geriatric populations. Hence, frailty can worsen cardiovascular outcomes, and efforts to address and prevent frailty syndrome in the setting of CVD are critical.

Taken together, cumulative evidence has shown that the high prevalence of frailty in patients with different forms of CVD is strongly associated with adverse clinical outcomes, but the association between frailty and CVD is bidirectional. Recent data from NHATS (National Health and Aging Trends Study) have shown that among patients with no known coronary artery disease, frailty was strongly associated with a high incidence of CVD outcomes, including mortality, myocardial infarction, stroke, and vascular disease, during 5-year follow-up.[11] Frailty and CVD are interconnected, and therefore integration of frailty in cardiovascular practice is necessary.

INSTRUMENTS TO MEASURE FRAILTY DURING CARDIOVASCULAR ILLNESS

Measuring frailty is important for prognostication and planning of an appropriate treatment plan in patients with CVD. However, numerous tools have been developed to measure frailty, some focusing on physical frailty as a construct and others incorporating cognitive and psychosocial domains of frailty. The most widely cited definition of frailty is the Fried physical frailty phenotype, which was developed from 2 large epidemiologic studies: the Cardiovascular Health Study and the Women's Health and Aging Study. It measured frailty as ≥3 abnormal domains of the following: shrinking or weight loss, weakness, poor endurance and energy (exhaustion), slowness, and low physical activity level (**Figure 2**).[8] However, other instruments detect physical frailty by measuring 1 or more components of the Fried phenotype combined with other metrics of functional decline. For example, the Green score is composed of gait speed and handgrip strength in addition to independence in activities of daily living and a biomarker, serum albumin.[33] There are other scales that include components to evaluate not only physical but also cognitive, psychosocial, and nutritional frailty.

Cognitive frailty can be measured using the Fried+ scale, which is composed of the criteria in the Fried frailty phenotype in addition to a cognitive assessment measured using the Mini-Mental State Examination (MMSE) and mood assessed using the short-form Geriatric Depression Scale.[29] Similarly, the Edmonton scale includes assessments of cognition, social support, and nutrition in addition to function.[34] Some tools use a deficit accumulation approach to formulate an index of frailty, one of which is the CSHA (Canadian Study of Health and Aging) frailty index. It is based on the accumulation of deficits, a 70-item list that encompasses physical, cognitive, and psychological domains (**Figure 2**).[35]

In addition to the large number of tools used to measure frailty, there is variability due to the subjective nature of some of these instruments. The CSHA Clinical Frailty Scale (CFS) is based solely on a clinician's judgment of a patient's functional status and independence.[36] In contrast, there are many questionnaires, including the FRAIL (fatigue, resistance, ambulation, illness, loss of weight) scale,[37] that are based solely on a subject's answers on a questionnaire. To address limitations related to subjective tools or complex instruments, the Essential Frailty Toolset (EFT) was developed by Afilalo et al.[29] The EFT is an objective and parsimonious instrument used to measure frailty in older patients with CVD. The components of the instrument include biomarkers such as serum albumin and hemoglobin combined with an evaluation of: 1) cognitive function using the MMSE or Mini-Cog scale; and 2) physical function using the chair-rise test (ie, the time it takes to perform 5 sit-to-stand repetitions without using arms) (**Figure 2**). The EFT was compared with the Fried scale, Fried+ scale, CFS, Short Physical Performance Battery (SPPB), Bern scale, and Columbia scale and demonstrated superior ability in predicting worsening disability at 1 year postoperatively and death at 30 days.[29] It has also been applied to patients undergoing coronary artery bypass grafting (CABG) and proved to be highly prognostic for short- and intermediate-term outcomes.[38] Because of ease of use and the objective nature of this tool, the EFT has been incorporated in research and practice.

Implementation of frailty scales can be challenging because of the time and resources required for measurement. Thus, many single-item measures of frailty are used, such as 5-m gait speed and handgrip strength.[39-41] However, these measures can be surrogates for predisability frailty or a single domain of frailty and do not represent physical frailty as a construct (**Table 2**).

To conclude, numerous tools are used to measure frailty; some are based on a single domain of physical frailty phenotype, and others are more comprehensive and aim to capture frailty as a construct. These comprehensive tools may be resource intensive, time consuming, and require additional training. To overcome this heterogeneity and balance that with accuracy in measuring frailty syndrome as a construct, the EFT can be used to measure frailty in older patients with CVD, which allows standardized frailty assessment in research and practice (**Figure 2**).

CHALLENGES IN MEASURING FRAILTY DURING ACUTE CVD

Despite the availability of numerous instruments (**Table 2**), the measurement of frailty during acute cardiovascular illness is challenging. For example, measuring physical domains such as gait speed and grip strength can be impaired in acute cardiovascular illness[42] and can even be impractical in critically ill patients in the intensive care unit.[43] To overcome this challenge, some questionnaire-based or simplified clinical instruments have been proposed. Prior work showed that the CFS required only 3 to 5 minutes to complete, and the FRAIL scale required 1 to 3 minutes to complete in acute settings.[42] Whereas the FRAIL scale is a questionnaire that can be administered by any staff member, the CFS requires clinical expertise. Although these questionnaires can be helpful, other challenges during acute cardiovascular illness among older adults include delirium, poor recall and memory, and inaccuracy in physical testing due to their bedbound status. As most frailty assessment tools were developed in outpatient settings, some investigators argue that new instruments to detect frailty during acute illness are needed that

TABLE 3 Frailty Interventions in Patients With Cardiovascular Disease

Type of Intervention	Type of Study	Intervention	Subjects	Frailty Instrument Used	Outcomes
Physical	RCT	Multicomponent cardiac rehabilitation[55]	136 patients with elective transcatheter aortic valve replacement and subsequent inpatient cardiac rehabilitation	Schoenenberger Frailty Index 6MWD Maximum workload in bicycle ergometry	Improved functional capacity, quality of life, and reduction in frailty
	RCT	Resistance and balance training in exercise-based cardiac rehabilitation[58]	252 patients admitted to cardiac rehabilitation early after valve surgery/ intervention	6MWD SPPB 5-min walk test Strength (one repetition maximum test for leg press)	Improved functional and exercise capacity, physical performance, muscular strength, and reduced physical frailty levels
	RCT	Cardiac rehabilitation[68]	89 patients with cardiovascular disease ≥65 y of age who participated in the outpatient cardiac rehabilitation program for 3 mo	Japanese Version of the Cardiovascular Health Study Standard Walking speed Maximal grip strength Lower extremity strength	Reduction in frailty and improved physical function
	RCT	Structured physical activity intervention after cardiac rehabilitation[67]	140 frail elderly patients who completed cardiac rehabilitation after elective cardiac surgery	SPPB	Improved physical function
	Observational study	Cardiac rehabilitation[56]	60 patients who underwent TAVR and were thereafter referred to cardiac rehabilitation	6MWD Cumulative Illness Rating Scale	Improvements in function, autonomy, and quality of life
	Cross-sectional study	Exercise-based cardiac rehabilitation[102]	78 patients who underwent TAVR vs 80 patients who underwent SAVR	6MWD	Enhanced independence, mobility, and functional capacity
	Retrospective observational study	Cardiac rehabilitation[103]	3,277 patients hospitalized for acute HF	CSHA frailty index	Improved physical functioning and exercise capacity with favorable long-term outcomes in frail patients with HF
	Observational study	4-wk inpatient cardiac rehabilitation[104]	160 patients 75 y and older referred to an outpatient cardiac rehabilitation unit after an acute coronary event or cardiac surgery	6MWD Peak torque (strength) using an isokinetic dynamometer	Improvements in all domains of physical performance, particularly in those with poorer baseline performance
	Prospective pilot study	8-wk combined endurance and resistance exercise training[105]	30 patients who underwent TAVR	Muscular strength 6MWD	Improved exercise capacity, muscular strength, and quality of life
	Retrospective study	3-wk cardiac rehabilitation[62]	442 patients after TAVR or SAVR who were referred to cardiac rehabilitation	6MWD Bicycle exercise test	Improved functional status and exercise capacity
	Retrospective cohort study	Cardiac rehabilitation program enhanced with psychological support[63]	523 elderly inpatients ≥75 y of age admitted to a cardiac rehabilitation ward for heart disease	Barthel index	Improvement in psycho-physical health of elderly subjects and significant delay in rehospitalization
	Observational study	Home-based preoperative rehabilitation[49]	22 patients planned to undergo CABG or valve surgery	Clinical Frailty Score 6MWD SPPB	Improved clinical frailty score, functional ability, and reduced hospital length of stay
	Retrospective analysis	Cardiac rehabilitation[64]	243 patients with cardiovascular disease who completed phase 2 cardiac rehabilitation program	Fried criteria	Improvements in multiple domains of physical function among frail patients, similar to or greater than those achieved by intermediate-frail and nonfrail patients
	Observational study	Patient-centered cardiac rehabilitation[106]	160 patients >70 y of age admitted in the cardiac rehabilitation unit soon after cardiac surgery	Not available	Improved objective and subjective functional status
	Retrospective study	Geriatric rehabilitation-cardio program[69]	58 patients hospitalized for cardiovascular disease	Functional status	Improved functional status and health-related quality of life

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TABLE 3 Continued

Type of Intervention	Type of Study	Intervention	Subjects	Frailty Instrument Used	Outcomes
	Retrospective study	Comprehensive cardiac rehabilitation, including nutrition, physical, exercise and medication[52]	322 inpatients with cardiovascular disease	Muscle mass (skeletal muscle index) Muscle strength (grip strength) Physical performance (gait speed)	Improved handgrip strength, gait speed, leg weight bearing index, and nutritional intake after exercise training in patients both with and without sarcopenia
	RCT	Prehabilitation (PREQUEL study)[51]	164 patients who were prefrail and frail, awaiting CABG with or without valvular repair/replacement	Clinical Frailty Scale 5-m gait speed Essential Frailty Toolset	Unpublished
	RCT	Personalized physiotherapy program in-hospital[53]	224 patients 70-87 y of age who underwent cardiac surgery	Tinetti Performance Oriented Mobility Assessment Get-Up-and-Go Test Mobility Balance Muscle strength	Improved independence and mobility and shorter length of hospital stay
	RCT	Preoperative rehabilitation (PREHAB study)[50]	244 patients ≥65 y of age who underwent elective cardiac surgery and had Clinical Frailty Scores of 4-7	Clinical Frailty Score	In process
	RCT	Physical activity intervention (HULK trial)[107]	Elderly (≥70 y) patients with ACS who had an uneventful first month and showed reduced physical performance	SPPB	In process
	Retrospective cohort study	Early mobilization in the CICU[54]	264 patients ≥60 y of age admitted to the CICU	Level of function 1-4 (bedbound to walk >50 ft) Rockwood's Clinical Frailty Scale	Improvement in functional status in both frail and nonfrail older adults
	Retrospective cohort study	Cardiac rehabilitation[108]	114 cardiac surgery patients who underwent cardiac rehabilitation	Clinical Frailty Scale Modified Fried criteria SPPB Functional Frailty Index	No change in frailty scores from baseline to 1 y postoperatively, but improvements in cognitive impairment and functional domains of the frailty criteria
	Pilot trial	6-mo cardiac rehabilitation (RECOVER-TAVR pilot)[57]	27 patients who underwent TAVR	6MWD Fried and Edmonton frailty scores	Improvement in outcome scores
	RCT	Cardiac rehabilitation with resistance training and special balance training[59]	173 patients ≥75 y of age who underwent CABG	6MWD TUG test Maximal isometric strength test	Improvements in all measured variables
	RCT	12-wk multidomain physical rehabilitation (REHAB-HF trial)[109]	360 patients ≥60 y of age hospitalized with ADHF	SPPB	In process
	Pilot study	12-wk multidomain physical rehabilitation (REHAB-HF)[60]	27 patients with ADHF ≥60 y of age hospitalized with ADHF	SPPB	Improved SPPB score and reduced all-cause rehospitalization rate
	RCT	Acute-phase intensive electrical muscle stimulation (ACTIVE-EMS trial)[71]	Frail patients ≥75 y of age with AHF	Quadriceps isometric strength Handgrip strength SPPB Gait speed 6MWD Digit symbol substitution test Mini-Cog MOS 36-Item Short-Form Health Survey physical functioning scale Frailty score SARC-F	In process
	RCT	Structured physical activity vs health education program (LIFE study)[110]	1,635 sedentary men and women 70-89 y of age who had physical limitations, defined as a score on SPPB of ≤9 but able to walk 400 m	Mobility disability defined by loss of ability to walk 400 m	Reduced major mobility disability in the structured, moderate-intensity physical activity program compared with a health education program

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TABLE 3 Continued

Type of Intervention	Type of Study	Intervention	Subjects	Frailty Instrument Used	Outcomes
Pharmacotherapy	RCT	Rapamycin, an mTOR inhibitor[84]	13 elderly patients undergoing cardiac rehabilitation	Physical performance Frailty	Some correlation between some senescence markers and physical performance but no reduction in frailty with rapamycin
	RCT	Testosterone (intramuscular)[76]	Men ≥70 y of age undergoing elective cardiovascular revascularization with extracorporeal circulation	Clinical and functional outcomes	In process
	RCT	Vitamin D_3[72]	64 patients with HF	6MWD TUG test Knee isokinetic muscle strength	No improvement in physical performance for patients with HF despite a robust increase in serum 25(OH)D
	RCT	Vitamin D and quadriceps resistance exercise (FITNESS trial)[74]	243 frail older people discharged from the hospital	Physical performance	Neither vitamin D supplementation nor a home-based program of high-intensity quadriceps resistance exercise improved outcomes in frail older people after hospitalization
	RCT	High omega-3 fatty acid multinutrient supplement (Efalex Active 50+) for 6 mo[77]	27 non-acutely ill postmenopausal women (60-84 y of age)	Mobility (habitual walking speed and fast walking speed) Cognitive performance	Improved cognition and mobility
	Cross-sectional study	Exposure to metformin[78]	763 community-dwelling veterans ≥65 y of age with type 2 diabetes	Frailty index	Exposure to metformin was associated with lower risk for frailty
	RCT	Metformin[79]	Adults >65 y of age who are prediabetic and not frail at baseline	Fried criteria SPPB	In process
	RCT	Antihypertensive medication reduction (OPTIMISE trial)[85]	540 adults ≥80 y of age with hypertension, prescribed ≥2 antihypertensive treatments	CSHA frailty index Electronic Frailty Index FRAIL scale	No significant differences in frailty
	RCT	Allogeneic human mesenchymal stem cells via intravenous delivery (CRATUS study)[81]	60-95 y of age showing signs of frailty	Activity (CHAMPS questionnaire) Mobility (4-m gait speed test and 6MWD, handgrip strength, SPPB) Exhaustion (multidimensional fatigue inventory questionnaire)	In process
	RCT	Testosterone supplementation with and without progressive resistance training[75]	167 community-dwelling older men with low-normal baseline total testosterone levels	Continuous-scale physical functional performance Bilateral grip strength Leg extensor power Nottingham leg extensor power rig	No effect on functional performance but improved upper body strength
	Meta-analysis	β-hydroxy-β-methylbutyrate supplementation[83]	10 RCTs including 384 participants ≥50 y of age	Muscle strength (isokinetic knee flexion, extension, isometric knee extension, handgrip strength, bench press, leg press Physical performance (6MWD, SPPB, gait speed, get-up-and-go)	No or fairly low impact on improving muscle strength or physical performance

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incorporate objective measures routinely obtained in the inpatient settings, including laboratory and imaging techniques, which can best characterize older populations vulnerable to stressors as they relate to CVD.

REVERSIBILITY OF FRAILTY

A large longitudinal study of transitions of frailty among community-dwelling adults showed that frailty is in fact a dynamic process. In a 54-month

TABLE 3 Continued

Type of Intervention	Type of Study	Intervention	Subjects	Frailty Instrument Used	Outcomes
Nutrition	RCT	Nutritional supplement vs resistance training[86]	100 elderly nursing home residents	Muscle strength and size Gait velocity Stair-climbing power	High-intensity resistance exercise training improves muscle strength, but multinutrient supplementation has neither an independent nor an additive effect on these outcomes
	RCT	Diet, exercise, cognitive training, and vascular risk monitoring (FINGER trial)[96]	1,260 individuals 60-77 y of age with CAIDE dementia risk scores of ≥6 points and cognition at mean level or slightly lower than expected for age	Change in cognition measured through comprehensive NTB *z*-score	Greater improvement in NTB score in the intervention group
	Prospective cohort study	Mediterranean-style diet[93]	690 community-living persons (≥65 y of age)	Frailty defined as ≥2 of the following criteria: poor muscle strength, feeling of exhaustion, low walking speed, and low physical activity	Higher adherence to a Mediterranean-style diet was associated with lower odds of developing frailty compared with those with lower adherence
	Meta-analysis	Mediterranean diet[94]	Analysis of 4 studies including a total 5,789 community-dwelling older adults with a mean age of >60 y	Frailty	Greater adherence to a Mediterranean diet is associated with significantly lower risk for incident frailty in community-dwelling older people
	RCT	Protein-energy supplementation for 12 weeks[90]	87 frail older adults	Change of physical functioning SPPB Gait speed TUG test Handgrip strength One-legged stance	Physical functioning increased and SPPB remained stable with the intervention, although it decreased in the control group
	RCT	Cosupplementation with creatine and protein supplementation combined with resistance training (from the Pro-Elderly study)[87]	18 subjects	Handgrip strength TUG test Timed-stand test	Whey protein plus creatine and whey protein alone were similarly effective in improving muscle function
	RCT	Whey protein supplementation[88]	47 frail, hospitalized elderly patients	Grip strength Knee extensor force	Improvements in grip strength and knee extensor force
	RCT	Vitamin D and leucine-enriched whey protein nutritional supplement for 13 wk (PROVIDE study)[89]	380 sarcopenic primarily independent-living older adults with SPPB scores between 4 and 9 and low skeletal muscle mass index	Handgrip strength SPPB score Chair-stand test Gait speed Balance score Appendicular muscle mass	Improvement in muscle mass and lower-extremity function
	Prospective cohort study	"Prudent" dietary pattern characterized by high intake of olive oil and vegetables vs a "westernized" pattern with high intake of refined bread, whole dairy products, and red and processed meat[111]	1,872 non-institutionalized individuals ≥60 y of age	Fried criteria	A prudent dietary pattern showed an inverse dose-response relationship with the risk of frailty, while a westernized pattern had a direct relationship with slow walking speed and weight loss
	Meta-analysis	Alcohol consumption[112]	4 studies on 44,051 subjects ≥55 y of age	Frailty	Heavier alcohol consumption is associated with lower incident frailty compared with no alcohol consumption among community-dwelling middle-aged and older people
	Prospective cohort study	Dairy products[95]	1,871 community-dwelling adults ≥60 y of age	Modified version of the Fried criteria	Increased use of low-fat milk or yogurt was associated with a lower risk for frailty, but consumption of whole-milk dairy or cheese did not affect frailty status

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TABLE 3 Continued

Type of Intervention	Type of Study	Intervention	Subjects	Frailty Instrument Used	Outcomes
Cognitive	RCT	Cognitive stimulation and physical exercise (MIND&GAIT project)[99]	Older adults ≥65 y of age who are supported by the consortium end-user organizations who are frail or at risk of developing frailty	Barthel index	In process
	RCT	Nutritional supplementation vs cognitive training vs physical training vs combination treatment[97]	246 community-dwelling prefrail and frail old adults with a mean age of 70 y	Fried criteria	Combination training resulted in the greatest frailty reduction, followed by physical, and then cognitive and nutritional interventions
	RCT	Multicomponent physical exercise, cognitive training, dietary counseling, and promotion of psychosocial support (WE-RISE trial)[98]	Community-dwelling older adults ≥60 y of age with cognitive frailty	Cognitive frailty status as proposed by IANA/IAGG	In process
Social	RCT	Physical training and nutritional intervention program vs social support intervention that included cognitive training[100]	80 community-dwelling prefrail and frail adults ≥65 y of age	Frailty status (SHARE-FI)	Decreased frailty with both interventions; social support alone also resulted in improvement in frailty

6MWD = 6-min walk distance; ACS = acute coronary syndromes; ACTIVE-EMS = Effects of Acute Phase Intensive Electrical Muscle Stimulation in Frail Elderly Patients With AHF; ADHF = acute decompensated heart failure; AHF = acute heart failure; CABG = coronary artery bypass graft; CHAMPS = Community Health Activities Model Program for Seniors; CICU = cardiac intensive care unit; CRATUS = Allogeneic Human Mesenchymal Stem Cells (hMSC) in Patients With Aging Frailty via Intravenous Delivery; FINGER = Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; FITNESS = Frailty Interventions Trial in Elderly Subjects; HF= Heart Failure; HULK; Physical Activity Intervention for Patients With Reduced Physical Performance After Acute Coronary Syndrome; LIFE = Lifestyle Interventions and Independence for Elders; MOS = Medical Outcomes Study; mTOR = mechanistic target of rapamycin; NTB = neuropsychological test battery; OPTIMISE = Optimising Treatment for Mild Systolic Hypertension in the Elderly; PREHAB = Pre-Operative Rehabilitation for Reduction of Hospitalization After Coronary Bypass and Valvular Surgery; PREQUEL = Prehabilitation for Improving Quality of Recovery After Elective Cardiac Surgery; RCT = randomized controlled trial; RECOVER-TAVR = Does Cardiac Rehabilitation Improve Functional, Independence, Frailty and Emotional Outcomes Following Trans Catheter Aortic Valve Replacement?; REHAB-HF = Rehabilitation and Exercise Training After Hospitalization; SAVR = surgical aortic valve repair; SHARE-FI = Frailty Instrument for Primary Care of the Survey of Health, Ageing and Retirement in Europe; SPPB = Short Physical Performance Battery; TAVR = transcatheter aortic valve replacement; other abbreviations as in Tables 1 and 2.

follow-up period, more than one-half of the participants had transitions between frailty states, and although the majority of those transitions were to states of greater frailty, some patients transitioned to states of less frailty, indicating that frailty is a reversible process.[44] Xue et al[45] conducted a study using the NHATS cohort that measured the Fried physical frailty phenotype at different intervals over time and evaluated its association with mortality. The investigators showed that frailty is a dynamic process and about 60% of participants had either increases or decreases in frailty scores over time. The results also showed that a score of 5 was associated with a mortality rate more than 3 times higher than that of scores of 3 and 4. High scores, 4 and 5, were also associated with a decreased likelihood of complete reversibility of frailty to a score of 0. Although these results suggest that there is a point of irreversibility, they also indicate that implementing measures to intervene on frailty syndrome early rather than late may be beneficial.

FRAILTY AS AN OUTCOME

Because frailty is potentially a reversable state, it is necessary to study frailty as an outcome and to examine the underlying risk factors of frailty so that at-risk patients can be identified early and clinical interventions, including risk mitigation, can be implemented to prevent or delay the onset of frailty in the context of CVD prevention. Studies have shown that obesity, tobacco use, heavy alcohol use, low socioeconomic status, female sex, minimum physical activity, lower level of education attained, polypharmacy, falls, multimorbidity, social isolation, impaired cognitive function, depression, and spouse's depression are associated with an increased risk for frailty development.[46-48] Treatment of underlying risk factors for frailty can potentially delay or prevent frailty, which in turn is a precursor of CVD outcomes.

OVERVIEW OF FRAILTY INTERVENTIONS

Various interventions have been proposed to influence frailty status (**Table 3, Central Illustration**). Some interventions, such as cardiac rehabilitation, are already a part of CVD management, but other interventions, such as resistance and balance training, are not routinely prescribed. Although most of the attention has focused on physical frailty, interventions targeting other domains of frailty exist, including cognitive, nutritional, and psychosocial. Some pharmacologic interventions targeting systemic inflammation have been proposed. Numerous trials are ongoing, and we reviewed the results from these studies, which we present herein.

PHYSICAL INTERVENTIONS. As frailty leads to poor postoperative outcomes, there is growing interest in alleviating frailty prior to surgery through preoperative rehabilitation or prehabilitation. Waite et al[49] conducted a small prospective pilot study with 22 frail patients who had been listed for CABG or valve surgery. The intervention was a home program that consisted of balance and strength-training exercises and resulted in reduction of frailty in 18% of patients, along with improvement in 6-minute walk distance (6MWD), walking speed, and SPPB score. In Canada, the PREHAB (Pre-Operative Rehabilitation for Reduction of Hospitalization After Coronary Bypass and Valvular Surgery) study is enrolling older patients with CFS scores of ≥4 and <7.[50] The intervention consists of an 8-week comprehensive exercise therapy and education program targeting physical, psychological, social, and cognitive aspects of cardiac disease and frailty. The intervention is personalized on the basis of an intake of health status assessment and requires a minimum of 2 sessions of supervised structured exercise sessions per week and 4 educational sessions on topics including risk factor reduction, medication use, cardiovascular physiology, smoking cessation, and healthy eating. Frailty outcomes are measured using the modified Fried criteria and 6MWD. The PREQUEL (Prehabilitation for Improving Quality of Recovery After Elective Cardiac Surgery) study is currently enrolling adults undergoing elective cardiac surgery with CFS scores of 4 to 6.[51] The intervention is composed of structured 6- to 10-week exercise training. The frailty outcomes studied include CFS score, gait speed, and EFT score.

A large retrospective study of a physical intervention during hospitalization was conducted by Harada et al,[52] who studied the impact of a comprehensive cardiac rehabilitation program on inpatients with CVD and/or those who had undergone cardiovascular surgery. The intervention consisted of exercise training starting the day of admission. Patients who underwent in-hospital cardiac rehabilitation had decreased weight and skeletal muscle index, but significant improvements were observed in gait speed and muscle strength assessed by handgrip and leg weight bearing index. The Barthel index of activities of daily living was enhanced, indicating an improvement in overall physical function. Opasich et al[53] studied the impact of an in-hospital personalized physical therapy program based on each individual's frailty level compared with a traditional physiotherapy program for older patients after cardiac surgery. Frailty measures, assessed using the get-up-and-go test, chair stand, arm curl, and 6MWD, improved in the intervention group, and no participant in the intervention group went home severely frail. Among cardiac intensive care unit patients, Goldfarb et al[54] showed that physical intervention with early mobilization resulted in improved levels of function in both frail and nonfrail patients.

Multiple studies of cardiac rehabilitation postprocedure and posthospitalization have shown improvements in frailty measures. Eichler et al[55] evaluated a 3-week multicomponent inpatient cardiac rehabilitation program consisting of patient education, dietary counseling, psychological support, risk factor management, and individualized physical training after elective transcatheter aortic valve replacement (TAVR). The intervention resulted in improved 6MWD, a reduction in the proportion of frail patients, and an average decrease in the frailty index. Another study that evaluated the effects of multidimensional cardiac rehabilitation after TAVR demonstrated improvement in frailty (measured by 6MWD and Barthel index) at the end of cardiac rehabilitation, which persisted in the majority of patients at mid-term follow-up.[56] A pilot study for the RECOVER-TAVI (Does Cardiac Rehabilitation Improve Functional, Independence, Frailty and Emotional Outcomes Following Trans Catheter Aortic Valve Replacement?) trial showed that cardiac rehabilitation after TAVR resulted in improvement in frailty, measured using multiple frailty scores including Fried and Edmonton.[57] In a study on the addition of resistance and balance training to cardiac rehabilitation, patients were randomized to an intervention group consisting of 3 sessions per week of specially tailored resistance and balance training incorporated in 3 weeks of standard inpatient cardiac rehabilitation or a control group that participated in standard cardiac rehabilitation alone.[58] There was no statistically significant difference in frailty improvement as measured by 6MWD and SPPB between the groups at the end of the intervention, although at mid-term follow-up, the patients who had undergone the resistance and balance training had significantly lower frailty levels. Daily resistance and balance training in cardiac rehabilitation has also been studied in patients who underwent CABG, and results showed that resistance and balance training led to greater improvement in physical frailty compared with conventional cardiac rehabilitation as measured using 6MWD and the Timed Up and Go (TUG) test.[59]

Cardiac rehabilitation has also proved to reduce frailty in patients with HF. The REHAB-HF (Rehabilitation and Exercise Training After Hospitalization) trial assessed whether a progressive physical rehabilitation intervention that began during admission for acute decompensated HF and continued for 3 months postdischarge would improve frailty outcomes.[60] Among the 349 patients who were randomized, greater improvements in physical function, 6MWD, and quality of life along with reductions in frailty and depression were all associated with the early, transitional, tailored progressive rehabilitation group compared with "usual care."[61]

There is additional evidence showing that improvements in cognitive and psychosocial domains of frailty are related to cardiac rehabilitation. One retrospective study showed that patients who underwent surgical aortic valve replacement had reductions in both anxiety and depression scores after cardiac rehabilitation.[62] Another study showed reduced depression and improved cognitive functioning in all patients who underwent comprehensive cardiac rehabilitation consisting of an individualized multidisciplinary program.[63] The pilot study for the RECOVER-TAVI trial showed reductions in anxiety and depression scores after cardiac rehabilitation.[57] These studies show not only that cardiac rehabilitation diminishes physical frailty but that benefits extend to cognitive and psychosocial frailty.

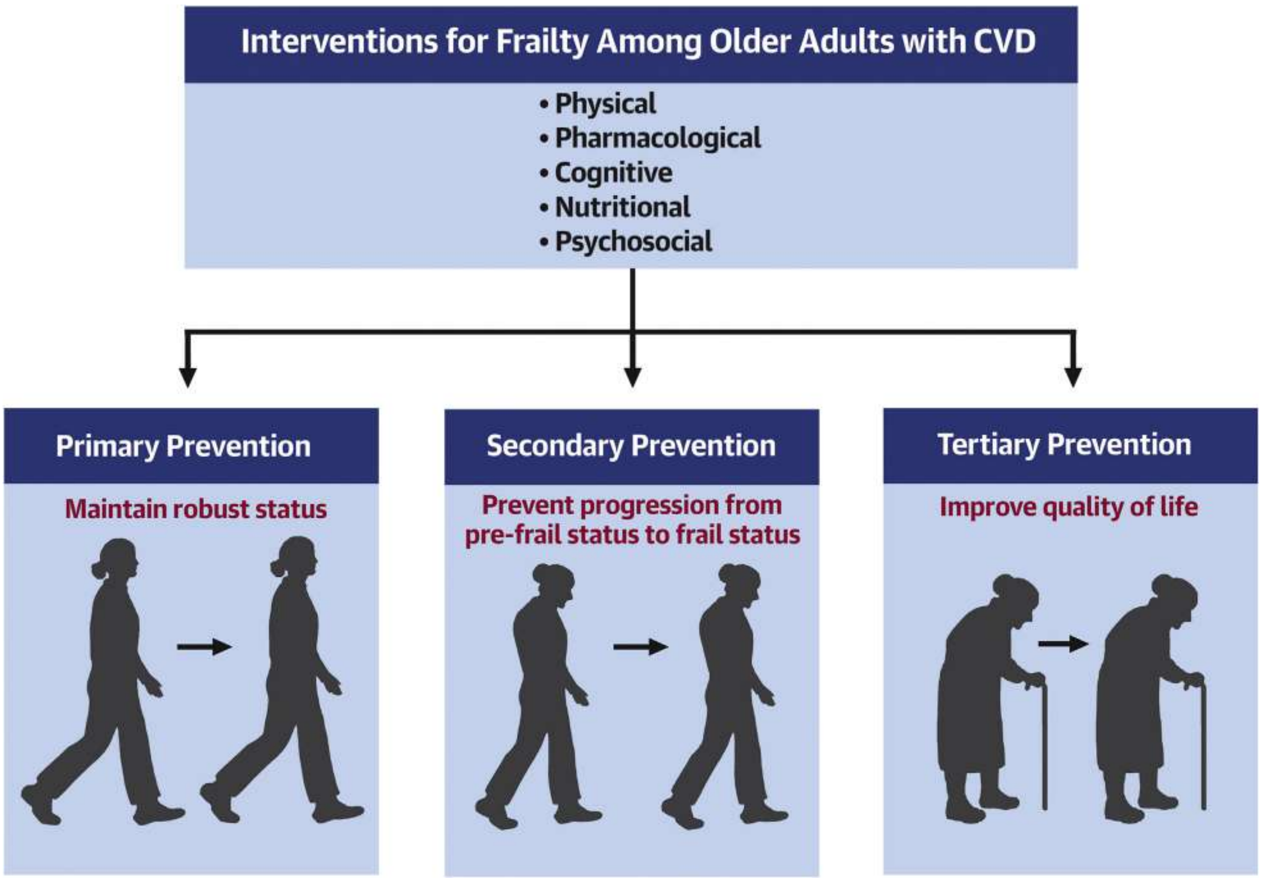
Benefits of cardiac rehabilitation extend to patients with pre-existing frailty. Lutz et al[64] studied 243 patients referred for 2 to 6 weeks of phase 2 cardiac rehabilitation, and the results showed a reduction in frailty measured by gait speed, TUG test, handgrip strength, and 6MWD in intermediately frail and severely frail patients. In fact, the frail group experienced greater percentage improvements from baseline in gait speed, TUG time, and 6MWD. The long-term effects of cardiac rehabilitation may persist after cardiac illness. Macchi et al[65] found that 65% of patients who adhered to at least light physical activity after cardiac rehabilitation and the degree of physical activity were directly correlated with 6MWD 1 year after rehabilitation. This supports the notion that there may be some lifestyle changes associated with cardiac rehabilitation that have long-term effects on preventing or reversing frailty (**Central Illustration**).

Because of the positive outcomes from the LIFE-P (Lifestyle Interventions and Independence for Elders Pilot) study,[66] in which an outpatient physical activity intervention was evaluated among the general frail older adult population, a similar intervention was studied in the CVD population that remained frail after cardiac rehabilitation. The study showed that the 1-year outpatient physical activity intervention reduced frailty as measured by the SPPB.[67] Ushijima et al[68] examined patients with CVD ≥65 years of age and showed that a 3-month outpatient cardiac rehabilitation program resulted in improvement in frailty status in 87% of patients to either prefrail (57%) or robust (30%), and all the nonfrail patients remained nonfrail during follow-up.

Van Dam van Isselt et al[69] studied geriatric rehabilitation, a term coined by the Boston working group referring to "evaluative, diagnostic, and therapeutic interventions whose purpose is to restore functional ability or enhance residual functional capability in older people with disabling impairments."[70] The intervention addressed body structure and function, functional status, and self-management and was studied in patients with CVD who were discharged to a skilled nursing facility. The results showed a reduction in physical frailty as measured by 6MWD and Barthel index. Subgroup analysis in patients with HF showed improvements in the same outcomes. The data show that early initiation of physical function programs, whether through geriatric rehabilitation or cardiac rehabilitation, may reverse frailty in patients with CVD. Other physical interventions that are under investigation include electric muscle stimulation during resting hours, as an adjunct to cardiac rehabilitation, to stimulate and potentially strengthen the skeletal muscles. This can potentially turn periods of immobility associated with functional decline into a productive time and may ultimately influence frailty status.[71]

PHARMACOLOGIC INTERVENTIONS. Several pharmacologic interventions to influence frailty have been studied, targeting different underlying physiological mechanisms of multisystem dysregulation. As changes in muscular structure and sarcopenia are

CENTRAL ILLUSTRATION Interventions Aimed at Preventing or Reversing Frailty in Patients With Cardiovascular Disease



Ijaz, N. et al. J Am Coll Cardiol. 2022;79(5):482–503.

Physical, pharmacologic, cognitive, nutritional, and psychosocial interventions or a combination thereof have the potential to prevent the onset of frailty (primary prevention), reverse frailty (secondary prevention), or improve the quality of life in older patients with pre-existing frailty (tertiary prevention).

associated with frailty, the effect of hormones on frailty is an area of active investigation. Among older patients with HF, the effect of vitamin D_3 supplementation on physical frailty as measured by 6MWD and the knee isokinetic muscle strength test was evaluated, but no significant change in frailty status was associated with vitamin D supplementation during follow-up.[72-74] Treatment with testosterone replacement therapy in older men results in an increase in lean mass and a decrease in fat mass, but testosterone supplementation did not result in any significant improvement in physical function, measured by the physical function performance test. However, there was an improvement in measurements of upper body strength, including grip strength, bench press, incline press, and average upper body strength compared with placebo.[75] A clinical trial designed to evaluate the effect of perioperative testosterone injections on frailty outcomes after rehabilitation among older patients undergoing CABG surgery is under way.[76]

As cognitive impairment has been described as a risk factor for the development of frailty, there has been interest in pharmacotherapy that may slow cognitive decline in preventing or improving frailty. There is a weak evidence that the omega-3 polyunsaturated fatty acids docosahexaenoic acid and eicosapentaenoic acid may be neuroprotective and reduce the risk for cognitive impairment. A pilot study was conducted to evaluate the impact of Efalex Active 50+ supplement, which contains 1 g docosahexaenoic acid and 160 mg eicosapentaenoic acid in addition to *Ginkgo biloba*, phosphatidylserine, alpha-tocopherol, folic acid, and vitamin B_{12}, among patients older than 60 years.[77] Although these are weak associations, the patients in the intervention group had mild improvement in some measures of mobility and cognition (motor screening task latency and verbal recognition memory recall). The protective role of these supplementation is yet to be studied in a larger trial.

As frailty and CVD have a bidirectional association, pharmacotherapy that targets systemic inflammation can potentially influence both disease processes. A large proportion of patients with CVD have diabetes, and metformin, which is widely used as a treatment for diabetes, also has anti-inflammatory and antioxidant effects. A few observation studies have reported an association between metformin therapy and improvement in frailty status, but these results were obtained from nonrandomized retrospective experiments.[78] A randomized controlled trial is currently under way to examine the effects of metformin on frailty status in older patients with prediabetes.[79] Finally, the association between impaired endogenous stem cell repair and frailty status is undergoing preliminary examination by Golpanian et al[80] using allogeneic human mesenchymal stem cells. A phase 1 study showed that allogeneic human mesenchymal stem cells are safe and well tolerated in older participants. Although the results remain exploratory because of the small sample size ($n = 15$), improvement in frailty status, 6MWD, and cognitive frailty status as measured by the MMSE were reported, and a phase 2 is under way.[81]

The mechanistic target of rapamycin (mTOR) signaling pathway has been proposed to influence frailty. mTOR is an enzyme that is activated by nutrients and is involved in protein synthesis and cell growth. Insulin and insulin-like growth factor 1 activate mTOR, and low levels of both factors are associated with longevity, indicating that inhibition of mTOR can result in a longer life span.[82] In contrast, stimulation of the pathway can lead to muscle anabolism and skeletal muscle growth. Therefore, pharmacotherapy on both stimulation and inhibition of the pathway has been studied. Beta-hydroxy beta-methylbutyrate (HMB) is a molecule that exerts downstream effects activating mTOR, and several studies have evaluated the impact of HMB supplementation on frailty. A meta-analysis of 7 of those studies showed that HMB supplementation in addition to physical exercise had no or low impact on muscle strength and physical performance in older subjects compared with exercise alone.[83] Rapamycin is an inhibitor of mTOR and was studied by Singh et al[84] in an observational study of 13 patients 60 years of age and older with coronary artery disease who were eligible for cardiac rehabilitation. The intervention consisted solely of rapamycin administration, and frailty was assessed by gait speed. Although there was no significant association between rapamycin and frailty status, there remains the question of whether rapamycin may improve physical function if studied in a population with a higher burden of frailty over a longer follow-up period.

Relevant to pharmacologic interventions, polypharmacy has been associated with frailty. A recent large trial studied the effects of antihypertensive medication reduction on frailty as a secondary outcome.[85] Medication reduction was noninferior to usual care with respect to blood pressure control, and contrary to expectation, there was no statistically significant difference between the groups in frailty status measured by the frailty index, the Morley FRAIL scale, and the Electronic Frailty Index. Further study of the association between polypharmacy and physical frailty is needed in the context of guideline directed medical therapy for CVD.

DIETARY INTERVENTIONS. The nutritional domain of frailty has also been widely studied, although most nutritional interventions have been in combination with physical interventions. The Boston FICSIT (Frailty and Injuries: Cooperative Studies of Intervention Techniques) study was a randomized, placebo-controlled, 10-week clinical trial comparing lower-extremity resistance training, nutritional supplement, both treatments, or a placebo activity and supplement.[86] Results showed that the resistance training improved muscle strength and mobility, but nutritional supplementation, consisting of a 360-kcal combination of carbohydrate, fat, soy-based protein, vitamins, and minerals to augment caloric intake by 20%, did not have any effect on outcomes. However, few studies that evaluated protein supplementation have shown that whey protein supplementation with[87] and without[88] resistance training may improve frailty domains by measures of muscle strength.

Several studies have investigated the effect of protein supplementation on frailty status, as reduced dietary protein intake is one factor that leads to sarcopenia. The PROVIDE study enrolled 380 older adults with mild to moderate limitations in physical function and low skeletal muscle mass index, who were randomized to a protein-rich supplement with vitamins or an isocaloric control product without protein or micronutrients (ie, only carbohydrates and fat).[89] Frailty was measured by handgrip strength, SPPB, gait speed, chair stand test, and balance. Results showed that after 13 weeks, there was no significant difference in handgrip strength or SPPB score, but there was a significant gain in muscle mass as measured by appendicular muscle mass and improvement in chair-stand ability. Similarly, multiple nutritional interventions did not result in a significant improvement in frailty status. Kim et al[90] designed a trial to study whether protein supplementation might be more beneficial in frail individuals of low socioeconomic status.[90] Frailty was measured by functional performance, SPPB, TUG test, one-legged stance, and maximal handgrip strength. The study found improvement in multiple areas, suggesting that a nutritional intervention in "at-risk older patients" may reduce the progression of frailty.

The association between certain dietary patterns and frailty was investigated, but significant confounding and selection bias existed. The Mediterranean diet is of great interest, as it has been associated with a decreased likelihood of cognitive decline[91] and CVD,[92] possibly because of a higher composition of antioxidants such as beta-carotene equivalents, vitamin C, and vitamin E, which through their anti-inflammatory effects may also prevent frailty. In the Invecchiare in Chianti study of aging, Talegawkar et al[93] conducted a longitudinal analysis in which they found that greater adherence to a Mediterranean diet was associated with a lower odds of frailty as defined by the Fried criteria, along with a lower odds of having low physical activity and walking speed during follow-up. A systematic review and meta-analysis of 4 large prospective cohort studies showed that greater adherence to a Mediterranean diet was associated with a significantly lower incident frailty, as assessed by modified versions of the Fried frailty criteria or the FRAIL scale.[94]

Studying dairy consumption, Lana et al[95] conducted a prospective cohort study based on data from Seniors-ENRICA (Study on Nutrition and Cardiovascular Risk in Spain), showing that over a follow-up period of 3.5 years, those who had greater consumption of low-fat dairy products had a lower risk for frailty development. It is difficult to ascertain any causal associations between nutritional interventions and frailty status because of significant confounding and selection bias, but certain nutritional interventions (eg, the Mediterranean diet, protein supplementation combined with physical intervention) may have an impact on frailty in at-risk patients with CVD.

COGNITIVE INTERVENTIONS. Cognitive interventions have generally been studied in combination with physical interventions to prevent or delay frailty. One of the largest randomized controlled trials studying the effects of a multicomponent intervention on cognitive frailty was reported by Ngandu et al.[96] The FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) trial enrolled a total of 1,260 older patients 60 to 77 years of age at risk for dementia and followed them over a 2-year period. The intervention group consisted of 4 components, including nutritional therapy consisting of dietary education, a physical exercise training program, cognitive training, and social activities. The intervention resulted in significant improvement in cognitive frailty status, the neuropsychiatric test battery, along with secondary outcomes of executive functioning and processing speed. Additionally, the intervention resulted in favorable effects on cardiovascular risk factors such as body mass index, dietary habits, and physical activity.

The Singapore Frailty Intervention Trial compared different types of interventions that target underlying domains of frailty.[97] The study was a randomized controlled trial in which 246 participants were randomly assigned to 12 weeks of nutritional supplementation, cognitive training, physical training, combination treatment, and usual-care control. The cognitive training consisted of 2-hour weekly sessions of cognitive-enhancing activities. Frailty was measured using Fried's operational definition. Results showed that the combination intervention was associated with the highest odds of frailty reduction, followed by the physical intervention, and then cognitive and nutritional interventions. The WE-RISE (Warga Emas-Resilient Mind and Muscle Exercise) trial is an ongoing single-blinded, randomized controlled trial whose aim is to examine a multidomain intervention to reverse cognitive frailty.[98] It consists of a multicomponent exercise program, an in-person cognitive intervention consisting of "pen-to-paper" tasks such as "spot-the-difference," mazes, matrix reasoning, and jigsaw puzzles. The nutritional intervention consists of dietary counseling and psychosocial intervention consisting of group-based activity. The primary outcome studied in this trial is cognitive frailty using the Fried criteria and a clinical dementia rating scale. The aim of the MIND&GAIT project is to promote independent living for frail older adults in Europe through a combined intervention using technology and traditional resources to develop and test a cognitive stimulation program, physical exercise program, and fall reduction plan.[99] More data on cognitive interventions and reversal of

TABLE 4 Clinical Pearls and Take-Home Points for Clinical Practice and Future Research

Identification of the frailty syndrome in older adults with cardiovascular disease is critical, and integrating interventions to reduce frailty should be part of comprehensive cardiac management for the expanding older adult population.
The frailty syndrome in older patients with cardiovascular disease can be measured objectively using the Essential Frailty Toolset.
Frail and prefrail patients should be referred for interventions such as tailored cardiac rehabilitation program to improve frailty status and influence cardiovascular outcomes.
Randomized experiments in cardiovascular aging are needed using consistent frailty tools to evaluate the efficacy and safety of frailty interventions.

cognitive frailty are expected to become available in the coming years.

PSYCHOSOCIAL INTERVENTIONS. Acknowledging the importance of social supports in maintaining healthy habits, Luger et al[100] conducted a study of nonprofessional, volunteer-administered interventions, comparing physical training and nutrition intervention with a social support group in which participants were visited twice a week by acquaintances over the 12-week duration of the study. The results showed that frailty, as measured using the frailty instrument of the Survey of Health, Ageing and Retirement in Europe, was reduced in both groups. Social support, such as a buddy system, may potentially play a role in addressing social determinants of frailty.

GAPS IN KNOWLEDGE

There is a lack of consensus on the definition of frailty that presents many challenges for research. Additionally, the abundance of tools used to measure frailty has resulted in heterogeneity in research output that limits consistency and reproducibility. The ideal frailty assessment tool should be a simple, quantitative, objective, and a universally accepted method, capable of providing a consistent, valid, and reproducible definition that can then be used in real time by clinicians to determine a well-defined either presence or absence of the phenotype, much like hypertension or diabetes. The EFT is a promising instrument that is simple, quantitative, and objective and easy to administer, but its use to date is limited to cardiovascular medicine, and its applicability to other fields is not known.

Most studies of frailty interventions use tools that measure 1 component of physical frailty (eg, the 6-minute walk test) because of ease of administration. Although 6MWD is correlated with the frailty syndrome in cardiac patients,[101] there are more comprehensive, validated tools and instruments available to measure the frailty syndrome (Figure 2). Future trials should study whether interventions show reductions in the global measure termed “frailty syndrome.”

Although there are data to suggest that frailty can be reversed, whether reversal in frailty influences the development and progression of CVD remains unknown. Further studies are needed on interventions that reverse frailty and the impacts thereof on long-term cardiovascular outcomes. Future prospective clinical trial data in older adult populations are needed to better outline the exact interactions among frailty status, CVD risk factors, and potential downstream consequences, using prespecified and robust frailty assessment methods. Although there is a strong association between CVD and frailty,[8,9] a direct “causal” association between frailty and CVD is not yet elucidated, as frailty can theoretically be an epiphenomenon of the aging process itself, which can result in higher oxidative stress levels and contribute to CVD.[10] However, basic research on the biologic underpinning of frailty has shown that there is underlying inflammation, metabolic dysregulation, and coagulopathy, which are significantly associated with the development of CVD.[11] If there is a “causal association” between frailty and CVD, then we need therapies that actively target the frailty syndrome as a stand-alone entity (Table 4).

CONCLUSIONS

Frailty is a syndrome that is relevant to the practice of cardiovascular medicine because each disease process can predispose to physical impairments that ultimately cause worsening of cardiovascular illness. Because of its multifactorial etiology, multiple underlying frailty domains exist, including physical, cognitive, nutritional, and psychosocial, that constitute the frailty construct. Multidimensional interventions targeting these domains have been proposed to prevent or reverse frailty. There is no compelling study demonstrating a successful intervention to improve a global measure of frailty. Emerging data from patients with HF indicate that interventions associated with positive outcomes on frailty and physical function are multidimensional and include tailored cardiac rehabilitation. Systematic efforts to integrate frailty assessment in cardiovascular practice are needed to improve the overall health and well-being of older patients, but clinical trials to evaluate frailty interventions in specific cardiac populations should further help optimize cardiovascular care in older adults.

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