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The Impact of Frailty on Disease-Specific Health Status in Cardiovascular Disease.

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Abstract

Frailty is a syndrome of older age that reflects an impaired physiologic reserve and decreased ability to recover from medical stressors. While the impact of frailty on mortality in cardiovascular disease has been well described, its impact on cardiovascular disease-specific health status—cardiac symptoms, physical functioning, and quality of life—has been less well-studied. In this review, we summarize the impact of frailty on health status outcomes across different cardiovascular conditions. In heart failure, frail patients have markedly impaired disease-specific health status and are at risk for subsequent health status deteriorations. However, frail patients have similar or even greater health status improvements with interventions for heart failure, such as cardiac rehabilitation or guideline-directed medical therapy. In valvular heart disease, the impact of frailty on disease-specific health status is of even greater concern, since management involves physiologically taxing procedures that can worsen health status. Frailty increases the risk of poor health status outcomes after transcatheter aortic valve intervention or surgical aortic valve replacement for aortic stenosis, but there is no evidence that frail patients benefit more from one procedure versus another. In both heart failure and valvular heart disease, health status improvements may reverse frailty, highlighting the overlap between cardiovascular disease and frailty and emphasizing that treatment should typically not be withheld based on the presence of frailty alone. Meanwhile, data are limited on the impact of frailty on health status outcomes in the treatment of coronary artery disease, peripheral artery disease, and atrial fibrillation and requires further research.

INTRODUCTION

Frailty is an aging-related syndrome of impaired reserve across multiple physiologic systems that results in increased vulnerability and an impaired ability to recover from acute medical stressors. A diagnosis of frailty increases the risk of morbidity and mortality after nearly any intervention or clinical insult, from acute illnesses to elective surgeries (cardiac and noncardiac). Frailty also increases the risk of failure to regain physical and mental function after an illness or surgery, which are vital to preventing dependence and social isolation.

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While the impacts of frailty on physical function, generic quality of life, and mortality in persons with cardiovascular disease are well established, how frailty impacts cardiovascular disease-specific health status has been less studied. Disease-specific health status assesses the symptoms, functional limitations, and quality of life associated with a particular disease process. For example, a heart failure-specific health status measure asks the patient to quantify their burden of oedema and dyspnoea, how these specific symptoms impair their physical and social functioning, and how heart failure-related symptoms and functional limitations impact their quality of life. Disease-specific health status outcomes are the best indicators of the patient's symptomatic response to cardiovascular treatments, are often the target of the intervention (e.g., coronary stenting for stable angina), and are prioritized by patients who are older and with comorbidities.[1] It is therefore essential to understand the effect of frailty on disease-specific health status and, even more importantly, the impact of frailty on improvement in health status after cardiovascular treatments and interventions.

In this review, we discuss the cross-sectional and longitudinal associations of frailty with disease-specific health status in different forms of cardiovascular disease (Table 1, Supplemental Table) and highlight some of the gaps in knowledge. Notably, this review does not detail the logistics of assessing frailty (other than to highlight the overlap of frailty measures with some of the symptoms of cardiovascular diseases), the prevalence of frailty in patients with cardiovascular conditions,[2–4] or the impact of frailty on clinical outcomes or mortality—each of these topics has been covered more than adequately in several prior studies, meta-analyses, and reviews. Instead, we focus on how frailty affects the specific symptoms of cardiovascular disease—e.g., chest pain, palpitations, oedema—and its impact on treatments designed to target these symptoms.

Overlap between frailty measures and symptomatic cardiovascular disease.

Frailty and cardiovascular disease share similar risk factors, such as older age, lack of exercise, poor diet, and smoking. Cardiovascular disease itself increases the risk for frailty due to physical deconditioning, polypharmacy, and other mechanisms. Similarly, a treatment that improves cardiovascular symptoms can reduce functional limitations and consequently prevent, improve, or even reverse frailty. When assessing frailty in patients with cardiovascular disease, it is important to recognize that there is substantial overlap between the measures of frailty and the symptoms and functional limitations of cardiovascular disease (Figure, **panel A**). For example, weakness, fatigue, and slow gait speed are all key markers of frailty; however, a person may have these symptoms due entirely to heart failure or valvular heart disease without underlying frailty (Figure, **panel B**). As such, it can be challenging to discern true frailty from symptomatic cardiovascular disease, which will improve with interventions to treat the underlying cardiovascular disease. For example, after transcatheter aortic valve implantation (TAVI), a patient often has less fatigue and a faster gait speed. This has been termed "reversible frailty" and is important to distinguish from irreversible frailty, where cardiovascular interventions may have limited benefit and potentially create an acute insult from which the patient does not recover.

In situations where the disease process impacts the assessment of frailty, it may be useful to focus more on measures of physiological impairment that are less impacted by the disease process (e.g., unintentional weight loss, grip strength), measures that are not predominantly comprised of functional assessments, measures of chronic disease (e.g., low albumin or haemoglobin levels), or higher thresholds for measures (e.g., very slow gait speed or wheelchair bound, activities of daily living dependence) to identify irreversible frailty. Further work in these clinical settings is needed to identify those patients with positive markers for frailty but who will improve with treatment.

Frailty measures.

There has been increasing awareness of the concept of frailty in cardiology and cardiac surgery as a major risk factor for increased morbidity and mortality and the need to evaluate frailty prior to invasive procedures. This assessment has been traditionally based on an "eyeball" test from a single physician, which is limited by personal biases and low reproducibility.[5] However, even with objective assessments of frailty, there is no consensus about specific clinical or laboratory measures that should be included.[6,7] As such, numerous tools exist to quantify frailty (Table 2),[8] and estimates of the prevalence of frailty among individuals with cardiovascular disease vary widely depending on the method used.

Several commonly used frailty measures focus only on physical attributes, such as the Short Physical Performance Battery (SPPB)[9] and the timed up-and-go test (TUG),[10] or use single-item measures of physical functioning, such as the 5-meter walk[11] and handgrip strength.[12] The Fried frailty phenotype is the most commonly used frailty measure and combines slow gait speed, weakness, unintentional weight loss, low physical activity, and self-reported exhaustion.[13] A different conceptual model for frailty is the accumulation of deficits Frailty Index[14], where between 30 and 70 anthropomorphic measures, comorbidities, laboratory values, and health status data are integrated into an index, under the principle that the more deficits an individual has, the more likely they are to be frail.[15] Although health status and survey measures increase the accuracy of the frailty index, it can be constructed using entirely claims-based data.[6,7] While this diagnostic strategy has clear limitations, being more centred on comorbidity burden than physical function, it can be useful for estimating frailty in existing studies without explicit prospectively-collected frailty measurements.

Both strategies for assessing frailty in cardiovascular disease have limitations: frailty measures focused on physical functioning can be impacted by cardiovascular-specific symptoms and the accumulation of deficits measure is heavily impacted by comorbidity burden and the severity of the underlying cardiovascular disease. Understanding the overlap between symptomatic cardiovascular disease and the frailty assessment used in a particular study is essential for determining the impact of frailty on outcomes. Given this overlap, it is also imperative to recognize that meeting criteria for frailty should not solely determine a lack of eligibility for a cardiovascular treatment, particularly if this treatment is focused on improving cardiovascular symptoms. Patients with the highest burden of cardiovascular symptoms and limitations due to those symptoms often have the greatest potential to benefit from these treatments, although perhaps a less-invasive approach could be considered in these cases.

Impact of frailty on health status

Heart failure.—There is substantial overlap in the pathophysiology of the frailty syndrome with heart failure,[16] where hemodynamic abnormalities lead to global tissue hypoxia, cellular apoptosis, skeletal muscle dysfunction, and systemic inflammation. Similarly, frailty is characterized by systemic inflammation and neurohormonal dysfunction (particularly insulin resistance), resulting in muscle infiltration with adipose tissue and mitochondrial dysfunction.[17,18] Both pathophysiologic pathways result in sarcopenia, sustained declines in functional status, and diminished physiologic reserve. Cross-sectionally, frailty is associated with a greater burden and longer duration of heart failure symptoms and poorer health status in patients with ambulatory heart failure and reduced ejection fraction[19–22], heart failure and preserved ejection fraction[23,24], and recent heart failure decompensation.[25] Longitudinally, frail patients are also at greater risk of experiencing health status declines than non-frail patients. A secondary analysis of two large trials of patients with heart failure and reduced ejection fraction (PARADIGM-HF and ATMOSPHERE) showed that frailty was associated with a 60% greater odds of experiencing a clinically significant deterioration in health status at 1 year.[20]

Given the substantial overlap in pathophysiology between heart failure and frailty, therapies that target the adverse hemodynamic sequelae of heart failure (and therefore improve disease-specific health status) may play an important role in reversing frailty. In a multicentre study of 29 frail patients with advanced heart failure, the average number of Fried frailty criteria decreased from 3.9 ± 0.9 at baseline to 2.8 ± 1.4 at 6 months after left ventricular assist device implantation. Moreover, patients who were no longer frail had substantially larger improvements in heart failure disease-specific health status compared with those who still met criteria for frailty, further highlighting the close relationship between these two conditions.[26] The impact of frailty on the effects of guideline-directed medical therapy (GDMT) on health status can be more complicated. Titration of medical therapy to trial-proven doses can improve heart failure disease-specific health status[27,28], but frail patients are less likely achieve optimal doses of GDMT due to increased susceptibility of adverse side effects.[29] In patients with heart failure and reduced ejection fraction (PARADIGM-HF), sacubitril-valsartan showed similar benefits in frail and non-frail patients for heart failure hospitalization and cardiovascular death, although the effect of frailty on health status outcomes was not examined.[20] In patients with preserved ejection fraction (PARAGON-HF), sacubitril-valsartan reduced heart failure hospitalizations to a greater degree as frailty increased, but there were no differential effects of sacubitril-valsartan on death or health status outcomes.[23] Notably, in both trials, frail patients had a greater risk of falls and study drug discontinuation due to adverse events than non-frail patients. In contrast, SGLT-2 inhibitors appear to be well-tolerated in frail patients, without additional adverse effects. In patients with either reduced ejection fraction (DAPA-HF)[21] or preserved ejection fraction (DELIVER),[24] there was a greater differential treatment benefit with dapagliflozin versus placebo in improving heart failure symptoms, functional limitations, and quality of life as the degree of frailty increased.

Beyond heart failure-specific interventions, physical rehabilitation can be of particular benefit to patients with heart failure and frailty, improving heart failure disease-specific health status, exercise tolerance, and functional mobility. In a secondary analysis of HF-ACTION, frail patients with heart failure and reduced ejection fraction had similar improvements in diseasespecific health status with aerobic exercise program compared with non-frail patients.[22] In the REHAB-HF trial of patients with recent heart failure decompensation, a tailored physical therapy program that targeted strength, balance, mobility, and endurance improved both frailty markers and health status at 3 months, as compared with usual post-hospital care.[30]

Valvular heart disease.—Like heart failure, valvular heart disease has substantial overlap with frailty due to the cascade of abnormal cardiac filling pressures leading to systemic inflammation, musculoskeletal dysfunction, and sarcopenia. However, due to the higher average age of valve patients, the prevalence of frailty is generally higher in the valve population versus those with heart failure. Furthermore, concerns about any interaction of frailty with treatment benefit in valvular heart disease is even greater, as the treatment options in valvular heart disease are often invasive and thus could have a greater negative impact in patients with frailty. In the setting of severe aortic stenosis, frail patients have poorer health status at baseline[31,32] and follow-up with TAVI[33] or surgical aortic valve replacement (SAVR)[32] compared with non-frail or pre-frail patients. Importantly, frailty is an important predictor of death and persistently poor health status after TAVI.[34–36] However, frailty may also be potentially reversible after valve replacement, and improvements in frailty may be strongly driven by improvements in health status.[37] Due to increased vulnerability to physiologic stressors and slower recovery, it has been postulated that patients who are frail may benefit more from a less invasive/transcatheter approach to valve replacement. However, in separate analyses from the PARTNER and CoreValve trials of patients with severe aortic stenosis, frailty was not associated with a differential treatment benefit of TAVI versus SAVR for death, heart failure hospitalization, or health status outcomes.[38,39] Therefore, while frailty is an important predictor of poor outcomes, including persistently poor health status after valve replacement, there is no evidence that frail patients benefit more from TAVI versus SAVR.

The impact of frailty on health status after mitral valve intervention has been less studied. In a single centre study of patients undergoing mitral valve transcatheter edge-to-edge repair who were deemed prohibitive risk for valve surgery, surviving patients who were frail had greater improvement in health status over follow-up compared with non-frail patients.[40] However, much of this was driven by the fact that frail patients were more symptomatic and had substantially worse quality of life before the procedure and therefore had more to gain from mitral valve repair.[41]

Coronary artery disease.—Although not as intricately linked as with heart failure or valve disease, the relationship between frailty and coronary artery disease (CAD) is also likely bidirectional and may be explained in part by an overlapping risk factor milieu (e.g., renal insufficiency, obesity, and elevated inflammatory biomarkers).[42–44] The functional impairments caused by the frailty syndrome may increase sedentary behaviour, further increasing risk of development or progression of CAD.[45]

Among patients with CAD, frailty is associated with worse CAD disease-specific health status as compared with non-frail patients. In a cross-sectional study of 629 patients who underwent percutaneous coronary intervention (PCI), patients who were frail had a similar burden of angina symptoms but markedly worse CAD-related physical functioning and quality of life, as compared with non-frail and pre-frail patients.[46] This disparity between angina burden and degree of angina-related physical impairment suggests that frail patients may be required to limit their physical activity more to maintain acceptable levels of angina. Given the existing mobility impairment in patients who are frail, any insult to functional ability, such as angina, will have greater negative impact on quality of life. The impact of frailty on the benefits of treatments, such as anti-anginal drugs, PCI, or coronary artery bypass grafting, on health status outcomes has not been studied but warrants further investigation.

Peripheral artery disease.—Peripheral artery disease (PAD) results in skeletal muscle apoptosis and atrophy through ischemia-mediated tissue injury,[47] leading to exercise intolerance, exertional limb symptoms, and progressive functional decline. Frailty likely further exacerbates this functional decline, though the impact of frailty on disease-specific health status in patients PAD has been only minimally studied. In a cross-sectional study of 216 patients with symptomatic PAD, frail patients reported more health status impairment than non-frail patients.[48] However, health status was examined in this study with the Walking Impairment Questionnaire, which is a single-domain instrument that captures health status related to physical functioning and thus has substantial overlap with frailty itself. The effect of frailty on PAD disease-specific health status measures, such as the Peripheral Artery Questionnaire[49], has not been examined. As such, the impact of claudication on functional impairment and quality of life in frail versus non-frail patients is unknown. Moreover, the impact of frailty on health status outcomes with guideline-recommended therapies, such as supervised exercise therapy and surgical or endovascular revascularization, is also unknown. These unanswered questions should be prioritized given the substantial overlap in functional limitations between PAD and frailty (perhaps even more so than those seen in heart failure or valve disease) and the potential to improve frailty with PAD-specific treatments.

Atrial fibrillation.—The relationship between frailty and health status in patients with atrial fibrillation is poorly defined. This is partly due to the more diverse cohort of patients with atrial fibrillation, while some is also due to a lack of well-validated disease-specific health status measures. In a cross-sectional analysis of 1165 patients in the SAGE-AF registry[50], frail patients were 1.3-times more likely to have impaired disease-specific health status as compared with non-frail patients, but this difference was no longer significant after adjusting for comorbidity burden. Another cross-sectional study of 158 patients showed that frailty was associated with a greater burden of atrial fibrillation symptoms and poorer quality of life.[51] Whether frailty alters the health status outcomes of different treatments for atrial fibrillation has not been studied.

Conclusion and future directions.

Frailty is common in patients with cardiovascular disease and can have a substantial impact on patients' functional capacity and quality of life. Importantly, frailty and cardiovascular disease-specific health status are intricately linked, with shared risk factors and pathophysiology. Treatments that reduce cardiovascular symptoms and the resultant functional limitations can also improve frailty status or even prevent frailty among those with marginal reserve. Thus, we need to be cautious not to empirically withhold these types of treatments solely based on an assessment of frailty. However, cardiovascular interventions that are more invasive or have a higher risk of complications could be potentially harmful in these patients, who have an impaired ability to recover acute stressors. Therefore, understanding the role of frailty in the outcomes after cardiovascular interventions is critically important for knowing which treatments to target to which patients. Given the importance of health status outcomes in maintaining autonomy and functional independence in older patients with frailty, examining the differential impact of frailty on disease-specific health status outcomes with one treatment versus another must be a priority in future studies. This knowledge, in addition to better understanding how to readily identify vulnerable patients in routine clinical care, will be critical for shared decision-making, informing patient selection, and improving the health and well-being of older patients with cardiovascular diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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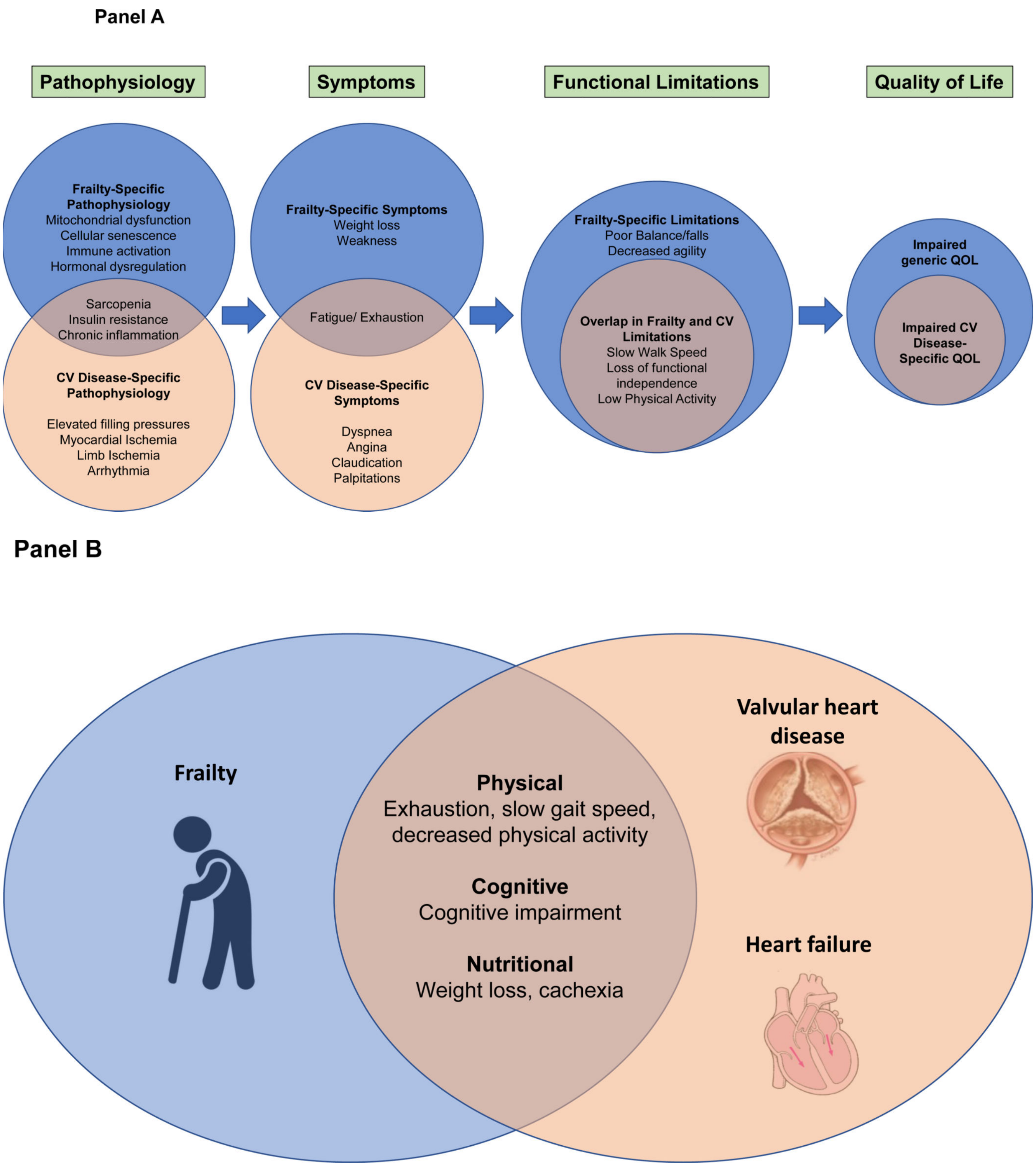

FIGURE:

A. Overlap between cardiovascular disease and frailty in pathophysiology, symptoms, functional limitations, and quality of life. Frailty can increase the burden of disease-specific symptoms, as in heart failure or valvular heart disease, or exacerbate the functional limitations due to a cardiovascular disease process, as in peripheral artery disease. Frailty widens the discrepancy between observed versus desired symptom burden and physical functioning, leading to an even greater impairment in quality of life.

B. Overlap of heart failure and valvular heart disease with frailty. Because of similar pathophysiologic mechanisms, there is substantial overlap between frailty and the symptoms of heart failure and valvular heart disease. Elevated filling pressures and pulmonary congestion result in exhaustion, slow gait speed due to dyspnoea, and decreased physical activity due to deconditioning. Decreased cerebral blood flow may also result in cognitive impairment. Gut oedema leads to early satiety and unintentional weight loss. Abbreviations: CV, cardiovascular; QOL, quality of life.

Table 1.

Summary of the impact of frailty on health status outcomes in cardiovascular disease.

Cardiovascular condition	Common health status measures	Impact of frailty on cross-sectional health status	Impact of frailty on longitudinal health status	Impact of frailty on health status treatment outcomes
Heart failure	Kansas City Cardiomyopathy Questionnaire Minnesota Living with Heart Failure Questionnaire	Worse health status[19–25]	Greater likelihood of clinically significant health status deterioration[20]	LVAD: potentially reverses frailty. Patients no longer frail after LVAD derive larger health status benefits compared with those still frail[26] Sacubitril-valsartan: similar health status improvements in frail versus non-frail patients with HFpEF.[23] Not yet studied in HFrEF SGLT2 inhibitors: greater health status improvements as degree of frailty increases in HFrEF and HFpEF[21,24] Exercise therapy: improves frailty markers and health status, [30] similar health status improvements in frail versus non-frail patients[22]
Valvular heart disease	Kansas City Cardiomyopathy Questionnaire	Worse health status[31, 32]	Persistently poor health status after TAVI[34–36]	No differential treatment benefit with TAVI versus SAVR[38,39] Greater health status benefit in frail versus non-frail patients with M-TEER[40]
Coronary artery disease	Seattle Angina Questionnaire	Similar angina burden[46] More related limitations Worse related quality of life	Not yet studied	Not yet studied
Peripheral artery disease	Walking Impairment Questionnaire Peripheral Artery Questionnaire	Worse physical function[48] Unknown impact on symptoms and quality of life	Not yet studied	Not yet studied
Atrial fibrillation	Atrial Fibrillation Effect on Quality of Life Questionnaire	Possibly worse health status[50,51]	Not yet studied	Not yet studied

Abbreviations: LVAD, left ventricular assist device; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; SGLT2, sodium-glucose cotransporter 2; TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; M-TEER, mitral transcatheter edge-to-edge repair.

Table 2.

Commonly used frailty measures and their use in cardiovascular disease.

Frailty Measure	Criteria	Advantages	Disadvantages
Fried Frailty Phenotype	1. Unintentional weight loss ≥10 pounds or ≥5% body weight in prior year 2. Weak grip strength Men: ≤29.0 kg if BMI ≤24 kg/m^2 ≤30.0 kg if BMI 24–26 kg/m^2 ≤31.0 kg if BMI 26–28 kg/m^2 ≤32.0 kg if BMI >28 kg/m^2 Women: ≤17.0 kg if BMI ≤23 kg/m^2 ≤17.3 kg if BMI 23–26 kg/m^2 ≤18.0 kg if BMI 26–29 kg/m^2 ≤21.0 kg if BMI >29 kg/m^2 3. Low activity Men <128 kCal expended /week Women <90 kCal expended/ week 4. Exhaustion: self-reported tiredness or weakness “all of the time” or most of the time” 5. Slowness, based on 5-m walk speed Men: ≤0.65 m/s if ≤173 cm tall, ≤0.76 m/s if >173 cm tall. Women: ≤0.65 m/s if ≤159 cm tall, ≤0.76 m/s if >159 cm tall Presence of 1–2 markers indicates pre-frailty, ≥3 indicates frailty	Most widely cited and commonly used in clinical research Easy to administer in clinical setting	Comprised of functional assessments that overlap with CVD symptoms
Rockwood Frailty Index (FI)	Between 30–70 deficits, including comorbidities, anthropomorphic measures, labs, self-reported health, and functional status—are summed to create an index FI expressed as a ratio of number of deficits present divided by number of deficits evaluated Deficits can be expressed as binary (0 or 1) or multi-level (0, 0.25, 0.50, 0.75, 1.0) FI of ≥0.21 indicate frailty	Can be used to estimate frailty without the need for functional measures Can be used to estimate frailty retrospectively (i.e., claims-based data)	Requires multiple variables to construct Requires electronic health record infrastructure to collect in clinical setting FI developed in one population may not be generalizable to another More reflective of comorbidity burden than functional status Depending on number of patient-reported outcome measures used, may overlap with symptoms of CVD
Short Physical Performance Battery	Points assigned for performance in balance (standing, semi-tandem, and tandem stance), chair raises, and 4-m walk speed 0–3 points: very low performance	Objectively assesses multiple domains of physical functioning: balance, strength, agility, and speed	Only includes physical elements of frailty; may not fully represent frailty as a construct

Frailty Measure	Criteria	Advantages	Disadvantages
	4–6 points: low performance 7–9 points: moderate performance 10–12 points: high performance		Impractical to administer during clinical visit
Timed Up-and-Go	Patient sits up from chair, walks 3m, turns around and walks back to chair, then sits. Time of ≥16s suggestive has 96% specificity for frailty	Easy to administer during clinical visit Multiple dimensions of physical function incorporated into single test	Only includes physical elements of frailty; may not fully represent frailty as a construct Overlaps with CVD symptoms
Essential Frailty Toolkit	1. Complete 5 chair raises: ≥15s (1 point) Unable to complete (2 points) 2. MMSE <24 (1 point) 3. Low hemoglobin (1 point) Men: <13mg/dL Women: <12mg/dL 4. Albumin <3.5g/dL (1 point) Scoring: 0 points = robust 1–2 points = pre-frail ≥3 points = frail	Outperforms other tests in predicting mortality and disability Easy to administer during clinical visit Multiple domains of frailty assessed Does not overlap significantly with CVD symptoms	Recently developed and not as commonly used in cardiovascular research.
Clinical Frailty Scale	Clinician-assigned frailty assessment; ranges from 1 (“very fit”) to 9 (“terminally ill”).	Easiest measure to administer	Low reproducibility, high risk of bias since it is based on individual clinician’s subjective assessment.
FRAIL scale	Five-item patient-reported outcome assessing fatigue, difficulty walking stairs, difficulty walking on flat ground, comorbidity burden, weight loss. 0 points = robust 1–2 points= pre-frail ≥3 points = frail	Patient-reported outcome Easy to administer during clinical visit	No objective functional measures Predominantly comprised of physical function measures that overlap with CVD symptoms

Abbreviations: CVD, cardiovascular disease.