

## JACC WHITE PAPER

# Frailty Assessment in the Cardiovascular Care of Older Adults



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Due to the aging and increasingly complex nature of our patients, frailty has become a high-priority theme in cardiovascular medicine. Despite the recognition of frailty as a pivotal element in the evaluation of older adults with cardiovascular disease (CVD), there has yet to be a road map to facilitate its adoption in routine clinical practice. Thus, we sought to synthesize the existing body of evidence and offer a perspective on how to integrate frailty into clinical practice. Frailty is a biological syndrome that reflects a state of decreased physiological reserve and vulnerability to stressors. Upward of 20 frailty assessment tools have been developed, with most tools revolving around the core phenotypic domains of frailty—slow walking speed, weakness, inactivity, exhaustion, and shrinking—as measured by physical performance tests and questionnaires. The prevalence of frailty ranges from 10% to 60%, depending on the CVD burden, as well as the tool and cutoff chosen to define frailty. Epidemiological studies have consistently demonstrated that frailty carries a relative risk of  $>2$  for mortality and morbidity across a spectrum of stable CVD, acute coronary syndromes, heart failure, and surgical and transcatheter interventions. Frailty contributes valuable prognostic insights incremental to existing risk models and assists clinicians in defining optimal care pathways for their patients. Interventions designed to improve outcomes in frail elders with CVD such as multidisciplinary cardiac rehabilitation are being actively tested. Ultimately, frailty should not be viewed as a reason to withhold care but rather as a means of delivering it in a more patient-centered fashion.

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**Abbreviations and Acronyms**

- ADL** = activities of daily living
- AS** = aortic stenosis
- AVR** = aortic valve replacement
- CAD** = coronary artery disease
- CVD** = cardiovascular disease
- SPPB** = Short Physical Performance Battery
- TAVR** = transcatheter aortic valve replacement

Frailty, from the French *frêle* meaning of little resistance, is a biological syndrome that reflects a state of decreased physiological reserve and vulnerability to stressors (1). Stressors are broadly classified as acute or chronic illness (e.g., myocardial infarction) or iatrogenic (e.g., cardiac surgery). When exposed to such stressors, frail patients are at risk for marked and often disproportionate decompensation, adverse events, procedural complications, prolonged recovery, functional decline, disability, and mortality (2).

Frailty has become a high-priority theme in cardiovascular medicine due to the aging and increasingly complex nature of our patients (3). Evolving technical innovations have enabled clinicians to treat a wider array of patients with devices and procedures, many of whom were previously regarded as “ineligible” (4,5). Uncertainty regarding individual benefit from such treatments has been coupled with growing economic constraints on healthcare systems, such that the issue of appropriate patient selection has intensified. There is an unmet need to optimize resource allocation to prevent patients from receiving costly but futile interventions.

Assessment of frailty is instrumental to refine estimates of risk and guide patients toward personalized treatment plans that will maximize their likelihood of a positive outcome. For example, given 2 heart failure patients with similar chronological age and comorbidities, the presence of objectively-measured frailty alerts the clinician that 1 of the 2 patients has a substantially higher risk of mortality and major morbidity. Furthermore, the frail patient faces a higher risk from invasive procedures but also a potential benefit from interventions such as cardiac rehabilitation to counteract the physical weakness characteristic of frailty. A critical mass of clinicians, researchers, and policy makers have embraced the concept of frailty, yet the lack of a scientific road map to integrate frailty into practice has been a limiting factor.

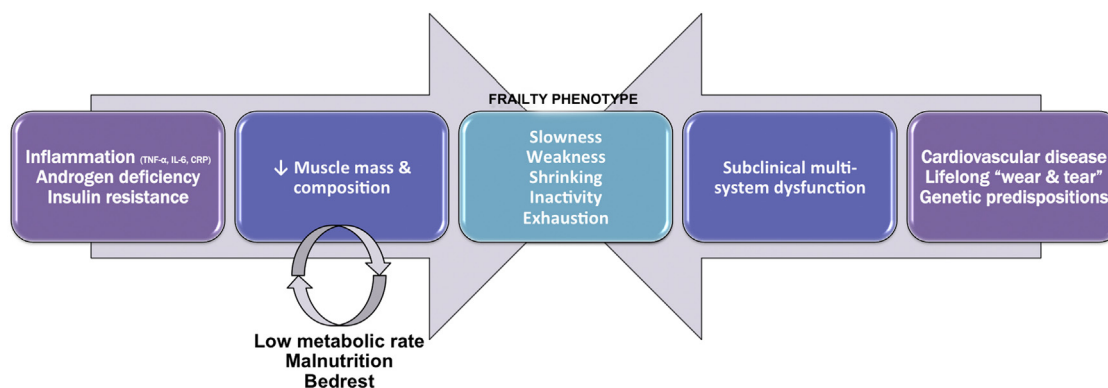
The objectives of this state-of-the-art paper are to: 1) summarize the existing body of evidence for frailty in patients with cardiovascular disease (CVD); 2) offer a perspective on integrating frailty into current clinical practice; and 3) point out the knowledge gaps for future research.

**Pathobiology of Frailty**

Frailty biology is a field of ongoing research and debate (6). Putative mechanisms revolve around dysregulation of the immune, hormonal, and endocrine systems (7)—notably, up-regulation of inflammatory cytokines (8–10), decreased

**Figure 1**

**Two of the Pathways Leading Toward the Phenotype of Frailty**



**(Left)** The age-associated activation of inflammatory cells and decline in androgen hormones upset the balance between catabolic and anabolic stimuli, respectively, leading to a decline in muscle mass and composition known as sarcopenia. This detrimental response is aggravated in patients with insulin resistance and metabolic syndrome. Addition of bed rest and malnutrition initiates a vicious cycle of further decline in muscle mass, limiting the necessary mobilization of amino acids in times of stress. **(Right)** The accumulation of subclinical impairments in multiple organ systems resulting from cardiovascular disease, lifelong “wear and tear,” and/or genetic predispositions lead to decreased homeostatic reserve and resiliency to stressors. Other pathophysiological pathways have been proposed. Biological pathways may manifest clinically as slow walking speed, weakness, weight loss, physical inactivity, and exhaustion—termed the phenotype of frailty. CRP = C-reactive protein; IL = interleukin; TNF = tumor necrosis factor.

testosterone levels (11,12), and insulin resistance (13). This leads to a catabolic milieu, in which muscle breakdown exceeds muscle building, leading to a progressive decline in muscle mass and strength (*sarcopenia*) (14). Under stressed conditions, subclinical impairments are unmasked, and a vicious cycle ensues with physical inactivity and malnutrition leading to further decline (15,16) (Fig. 1).

The pathobiology of frailty and CVD shares several commonalities, particularly a consistent correlation with the inflammatory biomarkers interleukin-6 and C-reactive protein. Just as immune cells and cytokines exert nefarious effects on the arterial wall to promote atherosclerosis, so too do they impact cellular senescence and body composition to promote frailty. Moreover, by causing impairments in multiple organ systems, subclinical CVD is one of the important contributors to frailty (17). This biological link frames the epidemiological data, showing that frailty and CVD coexist in a large number of individuals (18).

## Frailty Assessment Tools

Upward of 20 frailty tools have been developed to measure frailty (19); owing to a lack of consensus agreement, there is variability among studies and confusion on which tool to use. Most tools focus on 1 or more of the 5 core domains that define the frailty phenotype: slowness, weakness, low physical activity, exhaustion, and shrinking. Slowness is measured by a comfortable-pace gait speed test, weakness by a maximal handgrip strength test (using a dynamometer), and other domains by questionnaire or more specialized instruments. These domains may be considered individually or combined into a variety of scales (Table 1).

The Fried scale (20) encompasses slowness, weakness, low physical activity, exhaustion, and shrinking (unintentional weight loss), with  $\geq 3$  of 5 criteria required for a diagnosis of frailty. This is the most frequently cited frailty scale and has been demonstrated to predict mortality and disability in large cohorts of community-dwelling elders and patients with CVD. Whether cognition and mood should be considered as the sixth and seventh domains of frailty or as modulating factors (i.e., catalyzing the transition from frailty to overt disability) remains an area of discussion (1,21).

The Short Physical Performance Battery (SPPB) (22,23) encompasses slowness, weakness, and balance. This is measured by a series of 3 timed physical performance tests (gait speed, chair rises, and tandem balance), each is scored 0 to 4 and a total score  $\leq 5$  of 12 is required for a diagnosis of frailty.

In contrast to these multi-item frailty scales, 5-m gait speed, and to a lesser extent handgrip strength, has been advocated as a single-item measure of frailty (24–26) that often outperforms more elaborate and time-consuming

scales. The gait speed test has been shown to have excellent inter-rater reliability (intraclass coefficient 0.88 to 0.96) and test-retest reliability (intraclass coefficient 0.86 to 0.91) (27). It is responsive to change, with meaningful improvements in gait speed (estimated at 0.05 to 0.2 m/s [28,29]) predicting positive outcomes on a population level (30) but not necessarily an individual patient level (31). The walking distance has varied between 3 and 10 m, although the distance has little effect on measured speed (32). The 5-m distance has been adopted by large registries and is a good balance between allowing patients to achieve a steady walking speed without eliciting cardiopulmonary symptoms. The short distance and comfortable pace are well below cardiopulmonary limitations, making the focus of this test different than a typical stress test or 6-min walk test.

The aforementioned tools reflect the clinical phenotype of frailty; another school of thought reflects the accumulation of deficits (33). Deficits encompass an assortment of up to 70 symptoms, signs, comorbidities, disabilities, and frailty traits, which are counted and summed. A simplified bedside version has been developed (34). The International Academy on Nutrition and Aging Frailty Task Force (35) favored the clinical phenotype approach, stating that comorbidities and disabilities should be disentangled from frailty.

Disabilities, broadly defined as difficulty or dependency in carrying out activities of daily living (ADL) or instrumental ADL, are erroneously interchanged with “frailty” in many instances. However, disability is more correctly conceptualized as an adverse outcome associated with frailty (e.g., a frail patient becomes disabled after a myocardial infarction) or as a separate entity altogether (e.g., a nonfrail patient becomes disabled after a motor vehicle accident).

Patient heterogeneity precludes the use of a “one size fits all” scale and cutoff for frailty. There is a ceiling effect when physical performance scales such as the SPPB are administered to healthier individuals (more challenging versions are available) (36), and conversely there is a floor effect when the scales are administered to debilitated hospitalized patients (up to 30% have a score of 0). Certain scales may be effective to screen for frailty, whereas others may be required to focus on specific and potentially treatable domains. There is justifiable reason to consider various scales, more/less challenging variants of such scales, or different cutoffs to define frailty depending on the population being studied.

## Frailty in CVD: Current Body of Evidence

The prevalence of frailty in community-dwelling older adults is estimated to be 10% (37), and depending on the population studied and the frailty assessment tool used, rises

Table 1

## Recommended Frailty Assessment Tools

Domain	Tool(s)	Operational Definition	Common Cutoffs for Frailty
Slowness	5-m gait speed test	Patient is positioned behind start line and asked to walk at a comfortable pace past 5-m finish line; cue to trigger stopwatch is first footfall after start line and first footfall after finish line; repeated 3 times and averaged	Slow: <0.83 m/s (>6s) Very slow: <0.65 m/s (>7.7 s) Extremely slow: <0.50 m/s (>10 s)
Weakness	Handgrip strength test	Patient is asked to squeeze a handgrip dynamometer as hard as possible; repeated 3 times (once with each hand and then with strongest hand); maximum value is recorded	Men: <30 kg Women: <20 kg
	Knee extensor strength test	Patient is seated on the dynamometer machine and asked to extend his/her knee against resistance; maximum isotonic force is recorded	Frailty cutoffs not yet established
Low physical activity	Physical activity questionnaire	Many questionnaires have been validated; those that provide a measure of activity in kcal/week are recommended (e.g., Minnesota Leisure Time Activity, PASE, Paffenbarger Physical Activity Questionnaire)	Men: <383 kcal/week Women: <270 kcal/week
	Portable accelerometer	Patient is asked to wear a portable accelerometer for a period of 1 to 7 days; total kcal expenditure is recorded	Frailty cutoffs not yet established
Exhaustion	CES-D questionnaire	Patient is asked 2 questions: How often in the past week did you feel like everything you did was an effort?/like you could not get going? (often [i.e., ≥3 days] or not often [i.e., 0–2 days])	Positive if often is the answer to either question
	Anergia questionnaire	Patient is asked 7 questions pertaining to lack of energy over the past month	Positive if major criterion "sits around a lot for lack of energy" + any 2 of 6 minor criteria
Shrinking	Weight loss	Self-reported or measured unintentional weight change not due to dieting or exercise	≥10 lbs in past year
	Appendicular muscle mass	Measured muscle mass in arms and legs using a dual-energy x-ray absorptiometry scan	Frailty cutoffs not yet established; general cutoffs >2 SD from controls Men: ≤7.23 kg/height in m <sup>2</sup> Women: ≤5.67 kg/height in m <sup>2</sup>
	Serum albumin	Measured serum albumin	≤3.3 g/dl

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Table 1. Continued

Scale	Components	Operational Definition	Scoring
Short Physical Performance Battery	Balance test	Patient is asked to stand in semitandem position for 10 s; if patient is able, then he/she is asked to stand in full tandem position for 10 s; if patient is not able, then he/she is asked to stand in side-by-side position for 10 s	0 = side by side 0–9 s or unable 1 = side by side 10 s 2 = full tandem 0–2 s 3 = full tandem 3–9 s 4 = full tandem 10 s
	Chair rise test	Patient is seated on a straight-backed chair and asked to stand up 5 times as quickly as possible with arms folded across his/her chest; time to complete 5 chair rises is recorded (cue to stop stopwatch is when patient is standing after fifth chair rise)	0 = unable 1 = $\geq 16.7$ s 2 = 13.7–16.6 s 3 = 11.2–13.6 s 4 = $\leq 11.1$ s
	5-m gait speed test	As described above	0 = unable to walk 5 m 1 = $\geq 1.6$ s ( $\leq 0.43$ m/s) 2 = 8.3–11.5 s (0.44–0.60 m/s) 3 = 6.5–8.2 s (0.61–0.77 m/s) 4 = $\leq 6.4$ s ( $\geq 0.78$ m/s)
Fried scale	5-m gait speed test Handgrip strength test Physical activity questionnaire CES-D questionnaire Weight loss	As described above	Each item is scored 0–4 Frail if Composite score $\leq 5/12$ Each item is scored 0–1 Frail if Composite score $\geq 3/5$

CES-D = Center for Epidemiologic Studies Depression Scale; PASE = Physical Activity Scale for the Elderly.

to 10% to 60% in older adults with CVD (18). In CVD, frailty confers a 2-fold increase in mortality, an effect that persists even after adjustment for age and comorbidities. The relevance and impact of frailty has been demonstrated across a broad spectrum, including: 1) stable CVD; 2) subclinical CVD; 3) heart failure; 4) coronary syndromes; 5) cardiac surgery; and 6) transcatheter aortic valve replacement (TAVR). These studies are outlined in Table 2 and are discussed in the following text.

### Stable CVD in the Community

Beyond the cross-sectional association between frailty and CVD, the Women’s Health Initiative Study revealed that women with coronary artery disease (CAD) were more likely to develop de novo frailty over 6 years (12% vs. 5%) (38), and the Health ABC (Health, Aging, and Body Composition) study showed that older adults with objectively-measured frailty were more likely to develop CAD events (3.6% vs. 2.8% per year) (39). Furthermore, the 3C (Three-City) Study showed that slow gait speed was highly predictive of cardiovascular mortality (hazard ratio [HR]: 2.9) but not mortality from cancer or other causes (HR: 1.0) (25). The EPESE (Established Populations for Epidemiologic Studies of the Elderly) Study similarly showed that impaired mobility was predictive of CAD-related mortality (relative risk [RR]: 1.8 to 2.2), with the RR increase being equivalent in magnitude to diabetes (40). In 2 studies focusing on peripheral arterial disease, frailty predicted cardiovascular mortality (HR: 2.6 to 11.0) more so than all-cause mortality (HR: 1.9 to 2.9) (41,42).

Studenski et al. (43) performed a patient-level meta-analysis of 9 large prospective studies and found that for every 0.1 m/s increase in gait speed, there was a 10% improvement in survival. Short-distance gait speed was a robust yet simple “indicator of vitality that integrates known and unrecognized disturbances in multiple organ systems many of which affect survival.” Those who walked at a speed of 0.8 m/s were predicted to reach an average life expectancy, whereas those who walked  $>1.0$  m/s exceeded the average life expectancy (traffic signals at crosswalks are typically set at a pedestrian walking speed of 1.2 m/s, reflecting the expected lower limit for ambulatory citizens).

### Subclinical CVD

Before frail patients manifest clinical CVD, they tend to exhibit subclinical cardiovascular derangements. A seminal substudy from the Cardiovascular Health Study screened for subclinical CVD in 4,735 older adults and found that those who were frail had an increased prevalence of undiagnosed/subclinical lesions: myocardial injury on echocardiography,

Table 2

## Systematic Review of Frailty in Cardiovascular Disease

First Author, Year (Ref. #)	N	Design	Frailty Tool	% Frail	Main Outcome(s) for Frail vs. Nonfrail
Community dwelling					
Studenski, 2011 (43)	34,485	Meta-analysis of elderly in the community	Gait speed (2.4–6 m)	32%	12-yr mortality: HR: 0.90 (95% CI: 0.89–0.91) per 0.1-m/s increase in gait speed
Dumurgier, 2009 (25) (Three-City Study)	3,208	Prospective cohort of elderly in the community	Fast-pace gait speed (6 m)	Lowest third	5.1-yr mortality: 19% vs. 10%; HR: 1.4 (95% CI: 1.0–2.0) *HR: 2.92 for cardiovascular mortality vs. HR: 1.03 for cancer mortality
Corti, 1996 (40)	4,116	Prospective, multicenter cohort of elderly in the community	Inability to walk 0.5 miles or 1 flight of stairs	25%	4-yr CAD mortality: Men 3.5%/yr vs. 1.3%/yr; RR: 1.8 (95% CI: 1.1–3.0) Women 1.9%/yr vs. 0.6%/yr; RR: 2.2 (95% CI: 1.5–3.5) 4-yr incident CAD: Men 5.8% vs. 4.5% per yr; RR: 1.2 (95% CI: 0.7–2.1) Women 5.1% vs. 2.5% per yr; RR: 1.6 (95% CI: 1.3–2.1)
Chin A Paw, 1999 (103)	450	Prospective, multicenter cohort of elderly men in the community	Chin A Paw scale	13%	Prevalent CVD: 62% vs. 28% 3-yr mortality: 50% vs. 18%; OR: 4.1 (95% CI: 1.8–9.4)
Klein, 2005 (104)	2,515	Prospective, multicenter cohort of elderly and nonelderly in the community	Klein scale (level 1–4)	53–64 yrs: 0.7% 65–74 yrs: 5% 75–84 yrs: 22% ≥85 yrs: 53%	Prevalent CVD: Men: OR: 1.33 (95% CI: 1.06–1.67) per level Women: OR: 1.43 (95% CI: 1.13–1.82) per level 4-yr mortality: HR: 1.56 (95% CI: 1.27–1.92) per level
Woods, 2005 (38) (Women's Health Initiative Observational Study)	40,657	Prospective, multicenter cohort of elderly women in the community	Modified Fried scale ≥3	16%	Prevalent frailty with vs. without CAD: 17% vs. 7% Incident frailty with vs. without CAD: 12% vs. 5%; OR: 1.40 (95% CI: 1.11–1.76) 5.9-yr mortality: OR: 1.71 (95% CI: 1.48–1.97)
Chaves, 2005 (105) (Women's Health and Aging Studies I & II)	670	Prospective, multicenter cohort of elderly women in the community	Fried scale ≥3	14%	Prevalent CVD: 41% vs. 21%
Bandeem-Roche, 2006 (106) (Women's Health and Aging Studies I & II)	786	Prospective, multicenter cohort of elderly women in the community	Fried scale ≥3	11%	3-yr mortality: HR: 6.0 (95% CI: 3.0–12.1) 3-yr severe ADL disability: HR: 15.8 (95% CI: 5.8–42.8) 3-yr nursing home placement: HR: 24.0 (95% CI: 4.5–129.2)
Newman, 2006 (39) (Health ABC Study)	3,075	Prospective, multicenter cohort of elderly in the community	Gait speed (400 m)	N/A	Incident CVD: slowest Q 3.6%/yr vs. fastest Q 2.8%/yr; HR: 1.61 (95% CI: 1.05–2.45) 5-yr mortality: slowest Q 4.0%/yr vs. fastest Q 1.4%/yr; HR: 3.23 (95% CI: 2.11–4.94)

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Table 2 Continued

First Author, Year (Ref. #)	N	Design	Frailty Tool	% Frail	Main Outcome(s) for Frail vs. Nonfrail
Subclinical CVD					
Newman, 2001 (44) (Cardiovascular Health Study)	4,735	Cross-sectional study of elderly in the community	Fried scale $\geq 3$	6%	Prevalent clinical CVD: 38% vs. 17%; OR: 2.79 (95% CI: 2.12–3.67) Prevalent subclinical CVD: RWMA, LVH, pre-HTN, low ABI, carotid stenosis, silent CVA
Elbaz, 2005 (45)	2,572	Prospective, multicenter cohort of elderly and nonelderly in the community	Fast pace gait speed (6 m)	Lowest third	CIMT $>0.785$ mm: mean gait speed 1.47 m/s (vs. 1.61 m/s in CIMT $\leq 0.6$ mm); OR: 1.9 (95% CI: 1.4–2.8) Carotid plaques: mean gait speed 1.50 m/s (vs. 1.57 m/s in no plaque group); OR: 1.3 (95% CI: 1.0–1.7)
Singh, 2012 (41) (NHANES)	3,571	Prospective, multicenter cohort of elderly in the community, focus on those with PAD	Modified Fried scale $\geq 3$	6.4% all 17.5% ABI $<0.9$ (PAD)	Prevalent frailty with vs. without PAD: 18% vs. 5%; OR: 2.31 (95% CI: 1.08–4.94) 4.9-yr mortality in PAD patients: 52% vs. 21%; HR: 2.88 (95% CI: 1.40–5.96) 4.9-yr CVD mortality in PAD patients: 29% vs. 6%; HR: 11.02 (95% CI: 3.41–35.60)
McDermott, 2008 (42) (Walking and Leg Circulation Study)	444	Prospective multicenter cohort of patients with PAD (ABI $<0.9$ )	Gait speed $<0.76$ m/s (4 m); SPPB	Lowest quartile	4.8-yr mortality: HR: 1.87 (95% CI: 1.06–3.30) 4.8-yr CVD mortality: HR: 2.59 (95% CI: 1.04–6.44)
Cardiac surgery					
Afilalo, 2010 (63) (Frailty ABCs Study)	131	Prospective, multicenter cohort of elderly patients undergoing cardiac surgery	Gait speed $<0.83$ m/s (5 m) (i.e., $>6$ s to walk 5 m)	46%	In-hospital mortality/morbidity: 35% vs. 13%; OR: 3.05 (95% CI: 1.23–7.54) Discharge to facility: 46% vs. 20%; OR: 3.19 (95% CI: 1.40–8.41)
Afilalo, 2012 (67) (Frailty ABCs Study)	152	Prospective, multicenter cohort of elderly patients undergoing cardiac surgery	Gait speed $<0.83$ m/s (5 m) Fried scale $\geq 3$ Expanded Fried $\geq 3$ MSSA subdimensions	46% 20%	In-hospital mortality/morbidity: Gait speed: AUC 0.68 Fried: AUC 0.60 Expanded Fried: AUC 0.58 MSSA subdimensions: AUC 0.56
Lee, 2010 (64)	3,826	Retrospective cohort of elderly and nonelderly patients undergoing cardiac surgery	Ambulation dependence, ADL disability, or diagnosis of dementia	4%	In-hospital mortality: 15% vs. 5%; OR: 1.8 (95% CI: 1.1–3.0) 2-yr mortality: 30% vs. 11%; OR: 1.5 (95% CI: 1.1–2.2) Discharge to facility: 49% vs. 9%; OR: 6.3 (95% CI: 4.2–9.4)
Sündermann, 2011 (65)	400	Prospective cohort of elderly patients undergoing cardiac surgery	CAF score $\geq 11$	50% (43% moderate, 8% severe)	30-day mortality: 10% vs. 4%; AUC 0.71
Sündermann, 2011 (66)	213	Prospective cohort of elderly patients undergoing cardiac surgery	CAF score $\geq 11$	54% (45% moderate, 9% severe)	1-yr mortality: OR: 1.11 (95% CI: 1.04–1.16) per point
Robinson, 2011 (76)	223	Prospective cohort of elderly patients undergoing major surgery (34% cardiac surgery)	Timed up-and-go $\geq 15$ s	30%	Discharge to facility: 67% vs. 8%; OR: 13.0 (95% CI: 5.1–33.0)
Lee, 2011 (107)	262	Prospective cohort of elderly patients undergoing abdominal aortic aneurysm surgery	Cross-sectional area of psoas muscles at L4 by computed tomography	N/A	90-day mortality: HR: 0.33 (95% CI: 0.16–0.68) per 1,000-mm <sup>2</sup> increase in muscle area 1-yr mortality: 9% tertile 1 vs. 5% tertile 3 3-yr mortality: 21% tertile 1 vs. 13% tertile 3

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Table 2 Continued

First Author, Year (Ref. #)	N	Design	Frailty Tool	% Frail	Main Outcome(s) for Frail vs. Nonfrail
TAVR					
Rodés-Cabau, 2010 (70)	345	Retrospective, multicenter cohort of patients undergoing TAVR	Subjective judgment of treating physician	25%	Procedural complications: no differences except need for dialysis 7% vs. 1% (p = 0.009) 30-day mortality: 8% vs. 11% (p = 0.54) 8-month mortality: 22% vs. 22% (p = 1.00)
Ewe, 2011 (69)	147	Prospective, multicenter cohort of patients undergoing TAVR	Fried scale $\geq 3$	33%	9-month mortality/morbidity: HR: 4.2 (95% CI: 2.0–8.8)
Green, 2012 (71)	102	Cross-sectional study of TAVR (83%), high-risk AVR (11%), and medically managed AS (5%)	Gait speed <0.5 m/s (4.6 m)	63%	Prevalent ADL disability: OR: 1.52 (95% CI: 1.21–1.91) per 0.1 m/s; AUC 0.81
Green, 2012 (72)	159	Prospective cohort of patients undergoing TAVR	Modified Fried scale >median	50%	30-day mortality/morbidity: nonsignificant 1-yr mortality: 17% vs. 7%; HR: 3.51 (95% CI: 1.43–8.62)
Schoenenberger, 2012 (73)	119	Prospective cohort of patients undergoing TAVR	In-house scale $\geq 3/7$	50%	6-month ADL change $\geq 1$ : 31.3% vs. 12.1% (OR: 3.34 for functional decline; OR: 4.21 for functional decline or death, adjusted for STS) 6-month mortality: 18.6% vs. 3.3%
Stortecky, 2012 (74)	100	Prospective cohort of patients undergoing TAVR (same cohort as Schoenenberger)	In-house scale $\geq 3/7$	49%	1-yr mortality: OR: 2.93 (95% CI: 0.93–9.24) 1-yr major cardiovascular and cerebral events: OR: 4.89 (95% CI: 1.64–14.60); both adjusted for STS
Coronary disease					
Purser, 2006 (57)	309	Prospective cohort of elderly patients with severe CAD admitted to cardiac unit	Fried scale $\geq 3$ Rockwood scale $\geq 1$ Gait speed <0.65 m/s Grip strength <25 kg Chair rise <7/30 s	27% 63% 50% 50% 56%	6-month mortality: Fried: 12% vs. 8%; OR: 1.9 (95% CI: 0.6–6.0) Rockwood: 11% vs. 5%; OR: 1.4 (95% CI: 0.3–5.6) Gait speed: 14% vs. 4%; OR: 4.0 (95% CI: 1.1–13.8) Grip strength: 13% vs. 5%; OR: 2.7 (95% CI: 0.7–10.0) Chair rise: 12% vs. 5%; OR: 1.5 (95% CI: 0.4–5.0)
Ekerstad, 2011 (61)	307	Prospective, multicenter cohort of elderly patients with NSTEMI admitted to cardiac or medical unit	CSHA Clinical Frailty Scale $\geq 5$	49%	30-day mortality/morbidity: 46% vs. 27%; OR: 2.17 (95% CI: 2.8–3.67) 30-day mortality: 15% vs. 3%; OR: 4.7 (95% CI: 1.7–13.0)
Singh, 2011 (58)	629	Prospective, multicenter cohort of elderly patients post-PCI	Fried scale $\geq 3$	21%	3-yr mortality: 28% vs. 6%; HR: 2.74 (95% CI: 1.12–6.71)
Gharacholou, 2012 (60)	629	Cross-sectional analysis of elderly patients post-PCI (same cohort as Singh)	Fried scale $\geq 3$	21%	SAQ: more physical limitation and lower QOL (despite same angina frequency) SF-36: lower PCS and MCS scores
McNulty, 2011 (59)	101	Retrospective, multicenter cohort of elderly and nonelderly patients post-left main PCI	Subjective judgment of treating physician ("cachexia/frailty")	7%	1.5-yr mortality: unadjusted HR: 14.0 (95% CI: 5.4–36.0)

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Table 2 Continued

First Author, Year (Ref. #)	N	Design	Frailty Tool	% Frail	Main Outcome(s) for Frail vs. Nonfrail
Heart failure					
Cacciatore, 2005 (53)	120	Secondary analysis of cohort study of elderly patients with chronic heart failure	Lachs frailty staging system	15%	12-yr mortality: 94% vs. 69%; HR: 1.62 (95% CI: 1.08–2.45)
Altimir, 2005 (108)	360	Cross-sectional study of elderly patients with chronic heart failure referred to HF clinic	Altimir scale	42%	Prevalent frailty: 42%
Lupón, 2008 (49)	622	Prospective cohort of elderly patients with chronic heart failure referred to HF clinic	Altimir scale	40%	MLWHFQ: 39 vs. 19 (p < 0.001) HF hospitalization: 21% vs. 13% (p = 0.01) 1-yr mortality: 17% vs. 5%; HR: 2.09 (95% CI: 1.11–3.92)
Volpato, 2008 (54)	92	Prospective cohort of acute patients admitted to hospital (64% decompensated heart failure)	SPPB admission, discharge	N/A	Length of stay: +2.5–4 days for SPPB 0–4 on admission (+0.5 day for every SPPB point)
Volpato, 2011 (55)	87	Prospective cohort of acute patients admitted to hospital (64% decompensated heart failure)	SPPB admission, discharge, 1 month	N/A	Incident disability: +0.24 ADL limitations for SPPB 0–4 at discharge or SPPB decline at follow-up 1-yr mortality or hospitalization: 75% vs. 57%; OR: 5.38 (95% CI: 1.82–15.9) for SPPB 0–4 vs. 5–12; HR: 3.59 (95% CI: 1.20–10.0) for SPPB decline at follow-up
Chiarantini, 2010 (56)	157	Prospective, multicenter cohort of patients with decompensated heart failure discharged from cardiac unit	SPPB	51%	15-month mortality: SPPB 0: 62 per 100 PY; HR: 6.06 (95% CI: 2.19–16.76) SPPB 1–4: 29 per 100 PY; HR: 4.78 (95% CI: 1.63–14.02) SPPB 5–8: 17 per 100 PY; HR: 1.95 (95% CI: 0.67–5.70) SPPB 9–12: 9 per 100 PY; HR: 1 (referent)
Tjam, 2012 (109)	149	Secondary analysis of cohort study of elderly patients with chronic heart failure living in long-term care	RAI 2.0 scale	N/A	6-month mortality: AUC 0.87
Khan, 2013 (49) (Health ABC Study)	2,825	Prospective, multicenter cohort of elderly in the community without baseline heart failure	Modified SPPB $\leq 2$	31%	11-yr incident HF: HR: 1.30 (95% CI: 1.10–1.55) *Overall incidence 15.9% or 1.8 per 100 PY
Chaudhry, 2013 (110) (Cardiovascular Health Study)	758	Prospective, multicenter cohort of elderly in the community with newly diagnosed heart failure	Gait speed <0.8 m/s (4.6 m) Grip strength: men: <28.5 kg; women: <18.5 kg	42%	3.4-yr hospitalization: Gait speed: adjusted HR: 1.28 (95% CI: 1.06–1.55) Grip strength: adjusted HR: 1.19 (95% CI: 1.00–1.42)
Rozzini, 2003 (111)	995	Prospective cohort of acute patients admitted to cardiac unit	Barthel ADL <90 MMSE <18	20%	6-month mortality: 28% vs. 12% vs. 4% if both, either, or neither criteria present

ABI = ankle-brachial index; ADL = activities of daily living; AS = aortic stenosis; AUC = area under curve; AVR = aortic valve replacement; CAD = coronary artery disease; CAF = Comprehensive Assessment of Frailty; CIMT = carotid intima media thickness; CSHA = Canadian Study of Health and Aging; CVA = cerebrovascular accident; CVD = cardiovascular disease; Health ABC = Health, Aging, and Body Composition; HF = heart failure; HR = hazard ratio; HTN = hypertension; LVH = left ventricular hypertrophy; MCS = mental component summary; MLWHFQ = Minnesota Living With Heart Failure Questionnaire; MMSE = Mini-Mental Status Examination; MSSA = MacArthur Study of Successful Aging; NHANES = National Health and Nutrition Examination Survey; NSTEMI = non-ST-segment elevation myocardial infarction; OR = odds ratio; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; PCS = physical component summary; PY = person-years; QOL = quality of life; RAI = Resident Assessment Instrument; RR = relative risk; RWMA = regional wall motion abnormality; SAQ = Seattle Angina Questionnaire; SF-36 = Short-Form 36; SPPB = Short Physical Performance Battery; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement.

brain infarcts on magnetic resonance imaging, abnormal ankle-brachial index, carotid stenosis, pre-hypertension, and left ventricular hypertrophy (44). A subanalysis from the 3C Study showed that those who had slow gait speed were more likely to have carotid intimal-medial thickening and silent carotid plaques (45). Subclinical CVD predisposes to “unsuccessful aging” (46), often defined as impaired physical or cognitive functioning and development of clinically manifest disease (47).

### **Heart Failure**

Frailty is pertinent to the development, manifestations, and prognosis of heart failure. Frailty may be apparent at the myocardial organ level by predisposing patients to a greater extent of myocardial injury and, thus, clinical heart failure in response to stressors such as coronary ischemia or pressure or volume overload. Alternatively, frailty may be apparent at the global multisystem level by predisposing patients with heart failure to decompensate at a lower threshold and require more frequent hospitalizations. The person-years accrued for studies of frailty in the heart failure setting are greater than those for other cardiac conditions, involving approximately 2,300 patients with heart failure and up to 12 years of follow-up.

The Health ABC Study followed 2,825 older patients free of baseline heart failure over a period of 11 years and found that frailty (as measured by a modified SPPB) conferred a 30% higher risk of developing new heart failure (48). Excluding heart failure events in the first year did not alter the results, implying that frailty was not merely capturing undiagnosed/imminent cardiac dysfunction.

Although traditionally considered a geriatric condition, frailty was found by Lupón et al. (49) in one-third of younger patients with heart failure. Because chronic heart failure is known to perturb skeletal muscle and body composition (50,51) (giving rise to the phenotype of “cardiac cachexia” in extreme cases), it is not surprising to observe a large proportion of younger and older patients with heart failure exhibiting frailty traits.

Patients with chronic heart failure who were frail had a higher risk of mortality at 1 year (17% vs. 5%), heart failure hospitalizations (21% vs. 13%), and impaired quality of life (49). Chaudhry et al. (52) showed that slow gait speed was the most powerful predictor of hospitalizations, conferring a 30% increase; weak grip strength was also predictive, conferring a 16% increase. In a long-term study by Cacciatore et al. (53), patients with chronic heart failure who were frail had a substantially lower probability of surviving >10 years (6% vs. 31%).

Frailty is also relevant in acute decompensated heart failure. Volpato et al. (54,55) succeeded in administering the

SPPB to patients with recently decompensated heart failure at different time points (shortly after admission, at discharge, and 1 month after discharge). A low SPPB score on admission was associated with prolonged length of stay, whereas a low SPPB score at discharge was associated with a higher risk of ADL disability, mortality, or readmission (odds ratio [OR]: 5.4). In a similar study by Chiarantini et al. (56), the yearly mortality rates were 62%, 45%, 17%, and 9% for SPPB scores of 0, 1 to 4, 5 to 8, and 9 to 12, respectively. The SPPB was responsive to change, with 63% improving versus 20% worsening from admission to discharge and 50% improving versus 18% worsening from discharge to 1 month.

### **Acute Coronary Syndromes and Percutaneous Coronary Interventions**

In a seminal study of 309 elderly patients admitted to a coronary care unit and found to have multivessel CAD, Purser et al. (57) found that the prevalence of frailty varied considerably depending on the tool used: 27% with the Fried scale, 50% with gait speed <0.65 m/s, and 63% with the Rockwood scale. Each tool was associated with a trend toward increased 6-month mortality, yet only gait speed was statistically significant (OR: 4.0).

In a study of 629 elderly patients who underwent percutaneous coronary intervention at the Mayo Clinic, the prevalence of frailty was 21% with the Fried scale administered before discharge, conferring a significant increase in 3-year mortality (28% vs. 6%; OR: 2.74) (58). Similarly, “cachexia/frailty” was the most powerful predictor of 18-month mortality (HR: 14.0) (59) in a study of 111 patients undergoing percutaneous coronary intervention for unprotected left main disease in the Kaiser Permanente database.

Gharacholou et al. (60) further showed that, despite a similar severity of angina between frail and nonfrail patients, those who were frail had lower physical functioning and quality of life. Frailty exerted a greater impact on quality of life than comorbidities. Ekerstad et al. (61) explored the relationship between frailty and comorbidities in patients with non-ST-segment elevation myocardial infarction and showed that 79% of frail patients had at least 1 severe comorbidity. The OR for frailty to predict mortality was exponentially higher when the comorbidity burden was moderate to severe.

The studies of Ekerstad, Purser, and Lupón all showed that frail patients were less aggressively managed compared with their nonfrail counterparts; whether this is for better or for worse remains unclear. They were less likely to receive angiotensin-converting enzyme inhibitors (71% vs. 81%) and beta-blockers (63% vs. 80%), less likely to be admitted

to a coronary care unit (35% vs. 54%), and less likely to be referred for cardiac catheterization (15% vs. 46%) or coronary artery bypass surgery (9% vs. 16%).

### Cardiac Surgery

Cardiac surgery is an inherently relevant setting for frailty because surgery represents an iatrogenic physiological stressor to which the patient's resiliency will determine their post-operative course. Surgeons have been performing *de facto* clinical frailty assessments termed the "eyeball test" or the "end of the bed-o-gram" for quite some time. More recently, investigators have examined the role of objective frailty tools to predict post-operative outcomes, and even the lay media has been attracted by this prospect (62). The utility of frailty to prospectively guide surgical decisions and improve outcomes has yet to be explicitly tested.

The Frailty ABCs (Frailty Assessment Before Cardiac Surgery) prospective study showed that slow 5-m gait speed was associated with a 3-fold increase in post-operative mortality or major morbidity (OR: 3.1) (63). A walking time of 6 s or longer (<0.83 m/s) was selected as the optimal cutoff based on receiver-operating characteristic analysis. Importantly, gait speed contributed incremental value above the Society for Thoracic Surgeons risk score (area under the curve 0.70 for risk score alone vs. area under the curve 0.74 for risk score plus gait speed). Patients with slow gait speed and a high risk score had a 43% incidence of mortality/morbidity, whereas those with normal gait speed and a low to intermediate risk score had a 6% incidence. There was a trend toward interaction for female patients and those undergoing aortic valve replacement (AVR), both of which had a markedly greater RR when frailty was present.

Studies by Lee *et al.* (64) and Sündermann *et al.* (65,66) showed that pre-operative frailty was associated with post-operative mortality at 30 days and 1 to 2 years. These 2 studies differed in the frailty scales used, and as a result, in the reported prevalence of frailty. Lee *et al.* (64) retrospectively reviewed data from the Maritime Heart Center Cardiac Surgery Registry and defined frailty as ambulation dependence, ADL disability, or diagnosed dementia. This definition represented disability more than frailty and yielded a low 4% prevalence of frailty (mixed elderly and nonelderly cohort). Sündermann *et al.* (65,66) defined frailty as an aggregate of 35 criteria, which yielded a 50% prevalence of frailty. The data from Afilalo *et al.* (67) showed a 46% prevalence of frailty using gait speed versus 20% using the Fried scale and a low 5% prevalence of ADL disability; the single measure of gait speed outperformed other scales in predicting outcomes.

The presence of frank disability is infrequent in the general cardiac surgery population, in part because disabled

patients are less likely to be referred for such a surgery. Therefore, disability scales for basic ADL are insensitive to screen elderly patients in this context. Higher-level disability scales such as the Nagi scale are more sensitive and better predict outcomes. An interaction between frailty and disability has been reported, with the prognostic effect of frailty diminishing in patients who have progressed to the more advanced stage of disability (67).

In addition to predicting post-operative mortality and morbidity, 3 studies showed that frail patients were less likely to be discharged home and were more likely to require rehabilitation and/or institutionalization after cardiac surgery (OR: 3.2 to 13.0).

Thus, it is evident that frail patients who undergo cardiac surgery have higher rates of post-operative mortality, morbidity, prolonged length of stay, and need for discharge to facilities. It is not evident whether frail patients who undergo less invasive intervention (or no intervention) have improved outcomes, although this is at times extrapolated. For the time being, a more prudent extrapolation may be that the risks and benefits of cardiac surgery should be carefully weighed in frail patients, ideally with a multi-disciplinary heart team, and if indicated, should proceed with thorough pre-operative optimization and heightened post-operative surveillance.

### Transcatheter Aortic Valve Replacement

TAVR was initially developed for patients with severe aortic stenosis (AS) who were considered "too frail for surgery;" thus, the concept of frailty has been intimately linked to TAVR. Patients referred for TAVR typically have advanced age, multiple comorbidities, and a prevalence of frailty as high as 63%. Frailty is 1 of the "missing parameters" not captured by traditional risk scores (68) that are relied upon by clinicians as gatekeepers to TAVR. Few studies have been published in the past 2 years, limited to approximately 100 to 150 patients each, and larger studies are underway.

Although this was not the primary aim of their study, Ewe *et al.* (69) found that one-third of patients undergoing TAVR were frail according to the Fried scale and that frailty was among the most powerful predictors of death, myocardial infarction, stroke, or heart failure at 9 months (HR: 4.2). Frailty was not a significant predictor when defined according to the physician's subjective judgment in the earlier study by Rodés-Cabau *et al.* (70).

Green *et al.* (71,72) presented the experience at Columbia University and surprisingly showed that frailty was predictive of 1-year mortality (17% if frail vs. 7% if not frail; HR: 3.5) but not the composite of 30-day mortality or morbidity. The lack of 30-day event prediction was attributed to "adequacy of the standard selection process," although it should be noted

that there was no systematic frailty assessment on patients who had been screened out to substantiate the adequacy of the selection process and the absolute number of events was low. Furthermore, the trends toward greater risk in frail patients (especially for major bleeding, major vascular complications, and length of stay) were concerning. The increase in C-statistic from 0.73 to 0.77 and the net reclassification index of 0.24 were in the clinically meaningful range, yet confidence intervals were wide.

Between 19% and 35% of patients were unable to complete the short-distance gait speed test. This is a sizeable proportion of nonwalkers, larger than the <10% generally reported for other cardiac cohorts, which may reflect the heavy burden of comorbidity and disability in patients undergoing TAVR. Not being able to complete the gait speed test is an indicator of advanced frailty or perhaps even disability because nonwalkers have weaker grip strength, lower albumin levels, and more ADL disabilities. Low albumin levels and ADL disabilities were the strongest predictors in their TAVR cohort. A gait speed of 0.50 m/s was selected as the optimal cutoff based on receiver-operating characteristic analysis, slower than the 0.65 to 0.85 m/s cutoffs reported for other cardiac cohorts. The authors commented that >80% of their patients would have been considered frail if these traditional cutoffs had been used, supporting the notion that adapted cutoffs are required to achieve reasonable discrimination.

This is in slight contrast to the TAVR experience at Bern University (73,74), in which the vast majority of patients were able to complete the timed-up-and-go test (which requires standing up from a chair, walking 3 m, and turning around) and 61% of patients were able to do so faster than the usual cutoff of 20 s. Their frailty scale consisted of timed-up-and-go, mobility limitation, basic ADL disability, instrumental ADL disability, mini-mental status examination, and mini-nutritional assessment. Frailty was predictive of a 3- to 4-fold increase in functional decline at 6 months (measured by basic ADL disabilities) and major cardiac and cerebral adverse events at 1 year. There was a trend for frailty and all-cause mortality, which was stronger at 30 days compared with 1 year, although the number of events was small.

Synthesizing the evidence surrounding frailty in TAVR, 2 critical questions arise: first, are the standard frailty assessment tools (gait speed, even with adapted cutoffs, grip strength, and Fried scale) valid in this severely ill and often debilitated population or are these traits too ubiquitous, such that we should be relying on markers of more advanced frailty and frank disability (inability to walk, low albumin, ADL disability) to better discriminate risk? Second, does frailty increase the risk of short-term morbidity after TAVR (as it does in cardiac surgery) or does the less invasive nature

of the transcatheter procedure mitigate this risk? In both cardiac surgery and TAVR, the rate of technical success remains high and the risk of intraprocedural mortality low in frail patients.

## The Use of Frailty in Clinical Practice

There are many scenarios in day-to-day clinical practice in which frailty assessment can contribute valuable prognostic information and assist the clinicians in defining optimal care pathways for their patients. Ideally, frailty is not a reason to withhold care but rather a means of structuring care in a more patient-centered fashion.

A guiding principle is that frailty, disability, and comorbidity are inter-related but distinct entities (75). A second principle is that there is no definitive gold standard test for frailty, but rather an assortment of tools that reflect 1 or more domains of frailty. Multidomain tools do not necessarily provide incremental value above single-domain tools, and ease of implementation may be an important factor for adoption. A third principle is that frailty is a continuous spectrum, and specific cutoffs used to dichotomize frailty status in 1 group of patients may not be applicable in another group.

The tools recommended in Table 1 provide a (nonrestrictive) framework to improve consistency and comparability among studies. For investigators seeking to test new or modified tools, they are encouraged to also use 1 of the recommended tools as a comparator and to confirm the findings in a validation cohort before reporting.

### High-Yield Clinical Scenarios for Assessment of Frailty in Cardiovascular Medicine

*Consideration for cardiac surgery.* Frailty assessment tools should be employed in the pre-operative period; at a minimum, 5-m gait speed is a simple and powerful measure of frailty supported by prognostic data. However, it is premature to assume that frailty should determine eligibility for surgery at the individual patient level. Until data are available to prove a direct role for frailty in determining treatment, it is recommended to integrate frailty with other proven risk factors and risk models for decision making.

The timing of frailty assessment may be in the inpatient setting just before the surgery or in the outpatient setting, providing there is no intercurrent change or prolonged delay (arbitrarily >1 month) between the assessment and surgery. The choice of when to assess frailty tends to be logistically driven depending on feasibility and work flow at the given center.

Pre-operative optimization via a multidisciplinary approach is key to counteract the multiple physiological impairments (e.g., cardiac, neurological, muscular, respiratory, renal) that

lead to the decreased physiological reserve characteristic of frailty (76). Establishing a heart team and involving the appropriate consultants are instrumental in this regard. Prompt recognition and treatment of complications are primordial; deconditioning and delirium are 2 complications that merit special attention because of their insidious and devastating course. Cardiac rehabilitation may potentially improve frailty, and although this has yet to be proven, may ultimately serve to facilitate surgical recovery for frail elderly patients. Patients may benefit, for example, if cardiac rehabilitation is initiated before a planned procedure and then continued afterward, with aerobic and strength training alongside nutritional and educational components.

*Consideration for TAVR.* Because patient selection continues to be a central and often challenging issue, there is hope that frailty can be used to pre-select high-risk patients with AS who are best served by TAVR rather than surgical AVR. Proving this hypothesis has not been straightforward, particularly because the majority of patients referred for TAVR are frail and the usefulness of frailty (or any other risk factor) becomes limited when it is endemic. Moreover, because the TAVR procedure induces less physiologic stress compared with surgery, it is unclear whether frailty will predict post-procedural outcomes similarly in TAVR and surgery.

The role of frailty assessment in TAVR programs may ultimately prove to be in identifying who is *not* frail and thus appropriate for conventional AVR. At the other end of the spectrum, the role of frailty assessment may be in identifying who is extremely frail and/or disabled and thus appropriate for medical management without intervention. The latter patient typically exhibits 1 or more features of cachexia, severe weakness, inability to ambulate, dementia, and ADL dependencies. Anecdotally, balloon aortic valvuloplasty has been used to allow for rehabilitation and improvements in heart failure as a bridge to TAVR.

*Stable or recently stabilized heart failure or CAD.* Once identified in the inpatient or outpatient setting, frail patients may be excellent candidates for cardiac rehabilitation (targeting frail patients may be 1 strategy to overcome the underuse of cardiac rehabilitation in general), longitudinal heart function clinics, and comprehensive geriatric assessment (77). The latter may include evaluation by experts in nutrition, physical function, cognition, psychogeriatrics, and social support; each of which represents an area of potential vulnerability for frail patients and a blind spot for most cardiovascular practitioners who are not accustomed to dealing with these issues. This blind spot is increasingly being addressed at the educational level within cardiology curricula and continuing medical education programs.

## Controversies and Future Research Questions

Defining the optimal tool set to measure frailty is a high priority. We must first determine whether there is incremental value in using multi-item scales such as Fried as opposed to single-item measures such as 5-m gait speed (57,67,78,79). We must also determine the appropriate cutoff for each tool and patient group, particularly for gait speed (>10 cutoffs have been proposed ranging from 0.5 to 1.0 m/s). This underscores the need to validate frailty tools and cutoffs in the population of interest rather than extrapolating results from other studies.

The ongoing FRAILTY-AVR multicenter study (NCT01845207) is comparing different frailty tools to determine which is most predictive in high-risk patients with AS undergoing AVR and TAVR. The Society for Thoracic Surgeons Adult Cardiac Surgery Database is collecting 5-meter gait speed data to define its value across a broad sample of patients undergoing cardiac surgery. The CoreValve U.S. pivotal trial and PARTNER II (Placement of Aortic Transcatheter Valves) trial have integrated frailty assessment in all eligible patients. The SILVER-AMI Trial (NCT01755052) is evaluating the impact of frailty alongside other risk factors in older adults hospitalized with acute myocardial infarction. Many other CVD trials have begun considering frailty.

There is an impetus to develop more robust frailty tools. Existing tools are limited in the measurement of physical activity and energy expenditure (80,81); portable pedometers and actigraphy-based tools are being investigated for this purpose (82). Whereas most tools capture muscle strength, muscle mass is only indirectly measured by weight loss. Weight loss is a flawed measure of muscle mass because excess adiposity may mask low muscle mass—termed “sarcopenic obesity” (83,84). In a study of elderly patients with cancer, 7.5% of patients were found to be underweight, whereas 46.8% were sarcopenic (85). Muscle mass is a predictor of frailty and functional decline (86,87) and can be reliably measured by computed tomography, magnetic resonance, or dual-isotope x-ray absorptiometry (88).

Exciting translational research is seeking to gain mechanistic insights into the pathobiology of frailty and, in doing so, is fueling the development of frailty therapeutics and elusive frailty biomarkers. Biomarkers of senescence such as telomere length are not correlated with frailty (89). Other biomarkers have been correlated with frailty but remain nonspecific: C-reactive protein, interleukin 6, tumor necrosis factor alpha, neutrophil count, D-dimer, plasminogen activator inhibitor-1, testosterone, insulin-like growth factor-1, albumin, vitamin D, lymphocyte count, and memory/naive CD8 T-cell ratio. Thus, efforts to develop a specific

biomarker or panel of biomarkers for frailty have been unsuccessful to date (90).

With the accrual of diagnostic and prognostic data in CVD cohorts, we are now on the horizon of therapeutic trials to define how to best care for our frail cardiac patients (91,92). Interventions may be divided into those that: 1) direct frail patients toward less invasive therapeutic pathways; 2) monitor frail patients more closely to promptly detect and avert adverse events; 3) treat frail patients with therapies to improve their clinical or subclinical comorbidities; or 4) treat frail patients with therapies to reverse or reduce their intrinsic frailty.

A controversial question is to what extent a patient's frailty is intrinsic or related to a specific comorbidity that can be treated (so-called "reversible" comorbidity-related frailty) (93). Some suggest that when the degree of frailty is out of proportion to the burden of comorbidity, it is intrinsic and less likely to improve after removal of the comorbidity. This suggestion is an oversimplification because the manifestations of frailty are not only influenced by comorbidity but also by a host of other modulating factors (e.g., cognition, mood, compliance, and social support).

The most widely studied interventions to improve frailty are exercise training, nutritional supplementation, testosterone replacement, and comprehensive geriatric assessment/management (94–99). Testosterone levels are associated with frailty (100), and the benefits of testosterone replacement appear to be consistent across sexes (96). Other interventions are aimed at improving the delivery and coordination of care for frail elders (101). Ideally, frailty should be identified before a cardiac intervention is imminent. Regardless of the intervention, the treatment of frail patients should emphasize patient-centered outcomes such as functional status and quality of life (102).

## Conclusions

There is a substantial body of evidence to support the utility of frailty assessment in patients with diverse forms of CVD. The value of frailty as a prognostic marker is well demonstrated (with risk ratios that often exceed 2 and dwarf juxtaposed predictors in multivariable models). The value of frailty in guiding cardiovascular care and as a therapeutic target is beginning to emerge and should be expanded in future applications to improve patient outcomes. The frailty assessment tools outlined should facilitate this task by promoting a validated tool set that will allow us to compare and synthesize the results of different studies and provide a frame of reference when evaluating novel frailty markers.

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