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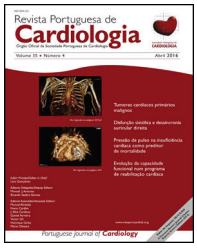

REVIEW ARTICLE

Frailty in cardiovascular disease: Screening tools

Ana Zão[a,*], **Sandra Magalhães**[a], **Mário Santos**[b,c]

[a] *Serviço de Medicina Física e de Reabilitação, Centro Hospitalar do Porto, Porto, Portugal*
[b] *Serviço de Cardiologia, Centro Hospitalar do Porto, Porto, Portugal*
[c] *Departamento de Fisiologia e Cirurgia Cardiotorácica, Faculdade de Medicina da Universidade do Porto, Porto, Portugal*

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Abstract Cardiovascular disease (CVD) is the leading cause of death in developed countries and disproportionately affects older adults. Frailty is a complex clinical syndrome with multiple causes and contributing factors in which there is increased vulnerability when exposed to a minor stressor and increased risk for adverse outcomes, such as disability, hospitalization and mortality. Frailty is an important prognostic factor in patients with CVD, and so identifying this feature when assessing these patients may help to individually tailor cardiovascular treatment. The first step is to identify frailty. Several tools have been validated as screening methods for frailty. However, they diverge with regard to complexity, nature, feasibility and the outcome they can predict. The aim of this review is to describe the available screening tools for frailty and to examine their usefulness in patients with CVD.

PALAVRAS-CHAVE
Fragilidade;
Doenças cardiovasculares;
Avaliação;
Rastreio

Fragilidade nas doenças cardiovasculares: instrumentos de rastreio

Resumo As doenças cardiovasculares (DCV) constituem a principal causa de morte nos países desenvolvidos e afetam desproporcionalmente os indivíduos idosos. A fragilidade é definida como uma síndrome clínica complexa com múltiplos fatores predisponentes e caraterizada por um aumento da vulnerabilidade e maior risco de desfechos adversos, nomeadamente, incapacidade, institucionalização e/ou mortalidade. Parece ser um fator prognóstico importante em doentes com DCV, pelo que o reconhecimento dos doentes com fragilidade pode permitir identificar os doentes com maior risco e assim orientar a estratégia terapêutica cardiovascular mais segura e eficaz. Assim, primeiramente é fundamental identificar a fragilidade. Vários

* Corresponding author.
E-mail address: anazaomfr@gmail.com (A. Zão).

instrumentos foram validados como métodos de rastreio de fragilidade. No entanto, eles divergem quanto à complexidade, natureza, viabilidade e resultados que podem prever. O objetivo desta revisão é descrever as ferramentas disponíveis para rastreio de fragilidade e avaliar as suas diferenças e utilidade nos doentes com DCV.

List of abbreviations

ACS	acute coronary syndrome
BADL	basic activities of daily living
CABG	coronary artery bypass grafting
CAF	Comprehensive Assessment of Frailty
CFS	Clinical Frailty Scale
CHS	Cardiovascular Health Study
CSHA	Canadian Study of Health and Aging
CVD	cardiovascular disease
EFS	Edmonton Frail Scale
EFT	Essential Frailty Toolset
EuroSCORE	European System for Cardiac Operative Risk Evaluation
GFI	Groningen Frailty Indicator
GFST	Gérontopôle Frailty Screening Tool
LVAD	left ventricular assist device
MACCE	major adverse cardiovascular and cerebrovascular events
MMSE	Mini-Mental State Exam
MNA	Mini Nutritional Assessment
MPI	Multidimensional Prognostic Instrument
MSSA	MacArthur Study of Successful Aging
STS	Society of Thoracic Surgeons
TAVI	transcatheter aortic valve implantation
TFI	Tilburg Frailty Indicator
TUG	Timed Up and Go

Introduction

Cardiovascular disease (CVD) is the leading cause of death in developed countries and disproportionately affects older adults.[1] Age by itself is a strong predictor of adverse events in acute coronary syndrome (ACS) and other CVD. Most prognostic models consider age, but do not take into account other related factors, such as frailty, health status, disability and cognition.[2] Patients who have lower physiological reserve and functional capacity are at higher risk for homeostatic disruption when facing a stressful event.[3] Identification of patients at increased risk of frailty and a better understanding of the impact of this variable on CVD outcomes may improve the quality of healthcare.

The aim of this review is to define frailty and to describe the available screening tools that can help to identify frailty among patients with CVD. We discuss the advantages and limitations of each tool, as well as the potential impact of their use in clinical practice.

Frailty

Definition and epidemiology

Frailty is a complex clinical syndrome with multiple causes and contributing factors in which there is increased vulnerability when exposed to a minor stressor and increased risk for adverse outcomes, such as disability, hospitalization and/or mortality.[4,5] This is often manifested by maladaptive response to stressors, leading to a vicious cycle toward functional decline and other serious adverse health outcomes. It is characterized by diminished strength, endurance and physiological reserve across the neuromuscular, metabolic and immune systems.[6] It is important to note that old age itself does not define frailty, because some patients remain vigorous despite advanced age, while others can have functional decline in the absent of apparent stress factors or failure to rebound following hospitalization or illness.[5] Thus, it is important to note the difference between biological age and chronological age.[7]

The prevalence of frailty ranges from 4% to 17%, and is higher among women (almost double that in men), increasing significantly in patients older than 80 years of age.[8,9] Pre-frailty (which describes patients at risk for frailty who fulfill some, but not all, criteria for frailty) has been also been the subject of various studies, which show a prevalence around 28-44%.[9] Several factors are thought to contribute to the development of frailty, including poor nutrition, reduced exercise tolerance, aging, chronic inflammation and immunological decline.[7] Thus, it can potentially be prevented or treated with specific modalities, such as exercise, protein-calorie and vitamin D supplementation, and reduction of polypharmacy.[6] However, a common feature of frail persons is mild cognitive impairment, which hampers the application of therapeutic regimens, especially exercise programs.

Pathophysiology

Frailty is a multifactorial condition. The literature shows that certain changes in physiological systems are associated with an increased risk for frailty, including a

proinflammatory state and elevated markers of blood clotting,[10] sarcopenia,[7] anemia,[11] anabolic hormone deficiencies,[12,13] insulin resistance,[14] significant immune system alterations,[15] and oxidative stress.[16]

The importance of diagnosing frailty in patients with cardiovascular disease

The aging of populations is increasing the number of frail patients with CVD. Thus, identifying frailty has important implications for clinical care. Frailty worsens prognosis in patients with CVD (Table 1) and of patients undergoing cardiac surgery and other cardiovascular interventions, and can reduce the net benefits of some cardiac interventions because of competing risks.[17,18] Frailty also increases the risk of cardiovascular and non-cardiovascular mortality and the need for rehabilitation and institutional care.[2,19,20] In the large TRILOGY ACS trial, which included 4671 patients older than 65 years with ACS, 25% were considered pre-frail and 5% frail (according to the Fried score).[21] Frail patients were more likely to suffer stroke or cardiovascular death after adjusting for the Global Registry of Acute Coronary Events (GRACE) score. Frailty is also a strong independent predictor of mortality in heart failure patients. One study found a population-attributable risk associated with frailty for emergency department visits of 35% and for hospitalizations of 19% among patients with heart failure.[22] Kang et al. found that frailty was strongly and independently associated with short-term outcomes for elderly patients with ACS.[23] In a study by Ekerstad et al. frailty was strongly and independently associated with in-hospital mortality, one-month mortality, prolonged hospital care, and the primary composite outcome in patients with non-ST-segment elevation myocardial infarction.[24] Ricci et al. also found that frail and pre-frail older individuals accounted for a substantial proportion of those with more cardiovascular risk factors, especially diabetes, highlighting the need for preventive strategies in order to avoid the co-occurrence of CVD and frailty.[25]

Similarly, frailty is associated with higher mortality and morbidity and greater need for health care in patients with valvular disease undergoing cardiac surgery.[20,26]

The number of elderly patients undergoing cardiac surgery is increasing. Frailty screening may be useful to identify patients with increased risk of adverse outcomes. Sundermann et al. found that patients who died within one year had a median Comprehensive Assessment of Frailty (CAF) score of 16 [5;33] compared to 11 [3;33] in one-year survivors (p=0.001), proving the prognostic value of frailty in cardiac surgery.[20] Afilalo et al. also demonstrated the association between frailty and mortality or major morbidity after coronary artery bypass grafting (CABG) and/or valve surgery (odds ratio [OR] 2.63; 95% confidence interval [CI] 1.17-5.90).[28] In a study by Jung et al., frailty was associated with a 3- to 8-fold increase in risk of postoperative delirium. According to these authors, 'frail' and 'fit' may be considered two ends of a continuum, and the risk of postoperative delirium grows as one becomes increasingly frail.[29] There has also been interest in understanding whether preoperative frailty is associated with worse outcomes after implantation of a left ventricular assist device (LVAD) as destination therapy. A study by Dunlay et al. using a deficit index to assess frailty found that patients who were intermediate frail (adjusted HR 1.70, 95% CI 0.71-4.31) and frail (HR 3.08, 95% CI 1.40-7.48) were at increased risk for death (p=0.004 for trend). The mean number of days alive out of hospital the first year after LVAD implantation was higher for patients who were not frail.[30] Schoenenberger et al. studied elderly patients undergoing transcatheter aortic valve implantation (TAVI) and showed that all the components of their geriatric baseline examination helped predict functional decline after intervention (OR: 3.31; 95% CI 1.21-9.03).[26] Stortecky et al. found that frailty was associated with increased all-cause mortality (OR: 3.68; 95% CI 1.21-11.19), and with increased major adverse cardiovascular and cerebrovascular events (MACCE) (OR: 4.89; 95% CI 1.64-14.60) one year after TAVI (OR: 3.68; 95% CI 1.21-11.19).[31]

Pre-frailty, which is a potentially reversible state, also appears to have some prognostic value. The findings of Sergi et al. suggest that pre-frailty is independently associated with a higher risk of older adults developing CVD. Among the physical domains of pre-frailty, low gait speed seems to be the best predictor of future CVD.[32]

Assessment of frailty may lead to patients being reclassified to different clinical risk categories, suggesting it signals risk not captured by currently used risk assessment scores.[2,32]

How to screen for frailty

An ideal frailty screening tool should (1) be able to accurately identify frailty; (2) predict the response of frail patients to potential therapies; and (3) be simple and easy to apply and have low cost.[33] Simple and rapid screening tests have been developed and validated to enable the objective recognition of frail persons. They differ mainly in the nature and number of deficits they measure, in line with two contrasting conceptual models: the frailty phenotype, or physical frailty, and the frailty index or deficit accumulation.[34] The phenotype concept considers frailty as a syndrome, consisting of a small number of highly specific deficits in health, such as unintentional weight loss, exhaustion, slowness, low physical activity and impaired grip strength. Further specific health deficits, such as cognitive deficits, have been proposed as part of a frailty phenotype scale. By contrast, frailty indices are based on the concept of cumulative deficit, assessing frailty through a larger number of unspecified age-associated health deficits (usually at least 30). The most commonly used are the FRAIL Questionnaire screening tool,[35–38] the Cardiovascular Health Study Frailty Screening Scale (Fried criteria),[9] the Clinical Frailty Scale (CFS),[39] frailty indices,[40,41] and the Edmonton Frail Scale[42] (Table 2).

The FRAIL Questionnaire screening tool

The FRAIL Questionnaire screening tool considers deficits accumulated in five domains, forming its acronym: **F**atigue (self-reported), **R**esistance, **A**mbulation (slow walking speed), Illnesses, and **L**oss of weight (5% or more in the past year). The five domains are weighted equally. Individuals

Table 1 Studies of frailty in cardiovascular disease.

Study	CVD and population	Screening tools for frailty	Other tools	Results
Kang et al.[23]	ACS 352 patients, age >65 years	CFS	CGA CAD-specific index	CFS was useful in evaluation of elderly patients with ACS. Frailty was strongly and independently associated with short-term outcomes for elderly patients with ACS.
Uchmanowicz et al.[50]	ACS	TFI	CGA	Significant correlations were demonstrated between the values of the TFI and other scales.
Ekerstad et al.[24]	ACS 307 patients, age >75 years	CFS	CAD-specific index	Frailty was strongly and independently associated with in-hospital mortality, 1-month mortality, prolonged hospital care and the primary composite outcome. The combined use of frailty and comorbidity may constitute a novel risk prediction concept in regard to cardiovascular patients with complex needs.
Boxer et al.[17]	Heart failure	CHS	6 MW	Both tools were associated with mortality (p=0.005) and highly correlated. The 6 MW may be useful as a measure of frailty.
Invasive cardiac interventions				
Afilalo et al.[51]	TAVI and valve surgery 1020 patients, median age 82 years	EFT CHS Fried+[a]	CFS PPB Bern Scale Columbia Scale	Frailty is a risk factor for death and disability following TAVI and valve surgery. The EFT outperformed other frailty scales and is recommended for use in this setting.
Jung et al.[29]	Elective cardiac surgery, 133 patients	MFC 35-item Frailty Index SPPB	SPBB EuroSCORE II	Frailty results in a 3- to 8-fold increase in risk of postoperative delirium, independent of the EuroSCORE II. The addition of frailty improves the ability of the EuroSCORE II to predict postoperative delirium, pointing to opportunities for improved prevention and management.
Dunlay et al.[30]	LVAD	31-item Frailty Index	-	Frailty before destination LVAD implantation is associated with increased risk of death and may represent a significant patient selection consideration.
Schoenenberger et al.[26]	TAVI	Geriatric baseline examination	EuroSCORE STS	The geriatric baseline examination, but not established risk scores, was predictive of functional decline.
Green et al.[53]	TAVI	MFC		Frailty was associated with increased 1-year mortality after TAVI.
Stortecky et al.[31]	TAVI	MGA	EuroSCORE STS MACCE	Risk prediction can be improved by adding multidimensional geriatric assessment-based information to global risk scores.
Afilalo et al.[28]	CABG and/or valve surgery	Simplified Fried criteria (5-item) Fried criteria (7-item) MSSA Five-meter gait speed test	Disability scales[b] Surgical risk scores[c]	Clinicians should use an integrative approach combining frailty, disability, and risk scores to better characterize elderly patients referred for cardiac surgery and identify those that are at increased risk.

Table 1 (*Continued*)

Study	CVD and population	Screening tools for frailty	Other tools	Results
Sundermann et al.[20]	CABG (25%) vs. valve surgery (35%) vs. combined procedures (26%)	CAF	EuroSCORE STS	CAF is an additional tool to assess prognosis of elderly patients before cardiac surgical interventions. The CAF score facilitates prediction of 30-day outcome of high-risk elderly patients.

6 MW: six-minute walk test; ACS: acute coronary syndrome; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CAF: Comprehensive Assessment of Frailty score; CFS: Clinical Frailty Scale; CGA: Comprehensive Geriatric Assessment; CHS: Cardiovascular Health Study scale; CVD: cardiovascular disease; EFT: Essential Frailty Toolset; EuroSCORE: European System for Cardiac Operative Risk Evaluation; LVAD: left ventricular assist device; MACCE: major adverse cardiovascular and cerebral events; MFC: Modified Fried Criteria; MSSA: 4-item MacArthur Study of Successful Aging frailty scale; MGA: Multidimensional Geriatric Assessment; PPB: Physical Performance Battery; SPPB: Short Physical Performance Battery; STS: Society of Thoracic Surgeons risk score; TAVI: Transcatheter aortic valve implantation; TFI: Tilburg Frailty Indicator.

[a] Fried+: Fried criteria+cognition and mood assessment.

[b] Disability scales: 6-item Katz Activities of Daily Living scale; 7-item Older Americans Research and Services Instrumental Activities of Daily Living scale; 7-item Nagi scale.

[c] Surgical risk scores: the Society of Thoracic Surgeons Predicted Risk of Mortality, the Society of Thoracic Surgeons Predicted Risk of Mortality or Major Morbidity; EuroSCORE; revised Parsonnet score; Age-Creatinine-Ejection Fraction score.

with two deficits are considered pre-frail, and those with three or more deficits are classified as frail.

Fried criteria for frailty

The Fried criteria for frailty (also known as the Cardiovascular Health Study Frailty Screening Scale, the Physical Frailty Phenotype and the Hopkins Frailty Phenotype) was first developed in the Cardiovascular Health Study.[9] It assesses physical characteristics or phenotype, which include five domains: unintentional weight loss (4.5 kg or more in the last year), exhaustion (self-reported), low physical activity, weakness (low grip strength), and walking speed.[9,43] Low physical activity is assessed through the frequency of moderate intensity activities, such as gardening or household chores. Similarly to the previous scale, individuals with two deficits are considered pre-frail, and those with three or more deficits are classified as frail.[29]

Clinical Frailty Scale

The CFS is a global clinical assessment of frailty based on physical function and level of independence with activities of daily living proposed by Rockwood et al.[39] Each point on its scale has a visual chart and a written description of frailty to assist the classification process. Scoring is based on clinical judgment and ranges from 1 (very fit) to 9 (terminally ill).[39]

Frailty indices

Frailty indices are based on the deficit accumulation approach to measuring frailty, and are commonly used tools to assess frailty in order to estimate the related risk for adverse health outcomes, such as mortality.[44] A frailty index is based on the concept that frailty is a consequence of interacting physical, psychological, and social factors. As deficits accumulate, people become increasingly vulnerable to adverse outcomes. The subject answers 20 or more questions related to medical and functional issues. The tool can be adapted to information available in the medical record and does not require a patient interview or exam to assess frailty. The 70 items of the original version are not to be considered a fixed set of variables (Table 3). It has been reported that estimates of risk are stronger when a minimum of 50 items are considered, but shorter versions (as few as 20 items) have also been studied.[39–41] Rockwood and Mitnitski[44] proposed a deficit accumulation-based frailty index using a comprehensive geriatric assessment (FI-CGA). This involves the accumulation of 30 or more comorbidities, symptoms, diseases, disabilities and other health deficits and is expressed as a ratio calculated as the number of deficits in an individual divided by the number of total deficits measured; the greater the number of deficits, the higher the score. The comprehensive geriatric assessment (CGA) includes medical, nutritional, functional and psychological assessments by a multidimensional team. The FI-CGA was initially developed as a ten-domain index with 14 CGA components and was later expanded to include 52 CGA components.[33]

Edmonton Frail Scale

The Edmonton Frail Scale (EFS) was developed to be practical and usable in the community setting or at the bedside. It is scored out of 17 and contains the following components: cognition, general health status, self-reported health, functional independence, social support, nutrition, mood, continence, and functional performance. The component scores are summed and the following cut-offs are used to classify frailty severity: not frail (0-5), apparently vulnerable (6-7), mildly frail (8-9), moderately frail (10-11) and severely frail (12-17).

Table 2 Characteristics of the most commonly used frailty scales.

Screening tool	Measurement method	Criteria for frailty
Simple FRAIL Questionnaire	1. Fatigue: are you fatigued? 2. Resistance: cannot walk up 1 flight of stairs? 3. Aerobic: cannot walk 1 block? 4. Illnesses: do you have more than 5 illnesses? 5. Loss of weight: Have you lost more than 5% of your weight in the past 6 months?	Frail: ≥3 Pre-frail: 1 or 2
Cardiovascular Health Study Frailty Screening Scale	1. Weight loss – loss of 10 pounds unintentionally in past year or weight at age 60-weight at exam ≥10% of age 60 weight. 2. Exhaustion – self-report of fatigue or felt unusually tired or weak in the past month. 3. Low activity – frequency and duration of physical activities (walking, doing strenuous household chores, doing strenuous outdoor chores, dancing, bowling, exercise). - Men: <383 kcal/week=1 - Women: <270 kcal/week=1 4. Slowness: - Men: walking 4 m ≥7 s if height ≤173 cm or ≥6 s if height ≥173 cm=1 - Women: walking 4 m ≥7 s if height ≤159 cm or ≥6 s if height ≥159 cm=1 5. Weakness – grip strength (kg) for body mass index (kg/m^2)[a]	Frail: ≥3 Pre-frail: 1 or 2
Clinical Frailty Scale	1. Very fit – people who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age. 2. Well – people who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally. 3. Managing well – people whose medical problems are well controlled, but are not regularly active beyond routine walking. 4. Vulnerable – while not dependent on others for daily help, often symptoms limit activities. A common complaint is being ''slowed up'', and/or being tired during the day. 5. Mildly frail – these people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework. 6. Moderately frail – people need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing. 7. Severely frail – completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~6 months). 8. Very severely frail – completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness. 9. Terminally ill - approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail. Scoring frailty in people with dementia: - The degree of frailty corresponds to the degree of dementia. - Common symptoms in mild dementia include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal. - In moderate dementia, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting. - In severe dementia, they cannot do personal care without help.	
Edmonton Frail Scale	Cognition Please imagine that this pre-drawn circle is a clock. I would like you to place the numbers in the correct positions then place the hands to indicate a time of 'ten after eleven' No errors=0; Minor spacing errors=1; Other errors=2	0-5=Not frail 6-7=Vulnerable 8-9=Mild frailty 10-11=Moderate frailty 12-17=Severe frailty

Table 2 (*Continued*)

Screening tool	Measurement method	Criteria for frailty
	General health status - In the past year, how many times have you been admitted to a hospital? - 0 times=0; 1-2 times=1; >2 times=2- In general, how would you describe your health? Excellent, very good, good=0; Fair=1; Poor=2 Functional independence With how many of the following activities do you require help? (meal preparation, shopping, transportation, telephone, housekeeping, laundry, managing money, taking medications) 0-1 activities=0; 2-4 activities=1; 5-8 activities=2 Social support When you need help, can you count on someone who is willing and able to meet your needs? Always=0; Sometimes=1; Never=2 Medication use - Do you use five or more different prescriptions on a regular basis? No=0; Yes=1 - At times do you forget to take your prescription medication? No=0; Yes=1 Nutrition Have you recently lost weight such that your clothing has become looser? No=0; Yes=1 Mood Do you often feel sad or depressed? No=0; Yes=1 Continence Do you have a problem with losing control of urine when you don't want to? No=0; Yes=1 Functional performance I would like you to sit in this chair with your back and arms resting. Then, when I say 'GO,' please stand up and walk at a safe and comfortable pace to the mark on the floor (approximately 3 m away), return to the chair and sit down 0-10 s=0; 11-20 s=1; >20 s or patient unwilling, or requires assistance=2	

IADLs: instrumental activities of daily living.

[a] Men: Body mass index (BMI) $\leq$24 and grip strength $\leq$29 kg=1; BMI 24.1-26 and grip strength $\leq$30 kg=1; BMI 26.1-28 kg and grip strength $\leq$30 kg=1; BMI >28 and strength $\leq$32 kg=1; women: BMI $\leq$23 and grip strength $\leq$17 kg=1; BMI 23.1-26 and grip strength $\leq$17.3 kg=1; BMI 26.1-29 and grip strength $\leq$18 kg=1; BMI >29 and grip strength $\leq$21 kg=1.

Other screening tools

The scales described above are those most commonly used to assess frailty. However, other frailty scales are available, as listed below.

The Groningen Frailty Indicator (GFI) considers 15 dichotomous self-reported deficits in four domains: physical, cognitive, social, and psychological.[45]

The Tilburg Frailty Indicator contains 15 self-reported items in physical, psychological, and social domains.[46]

The Gérontopôle Frailty Screening Tool (GFST) comprises two steps: an initial questionnaire (containing six components: living alone, involuntary weight loss, fatigability, mobility, memory complaints and slow gait speed) followed by the clinician's judgment of frailty status.[47]

PRISMA-7 contains seven self-reported components: older than 85 years; male; health problems which limit activities; health problems requiring staying at home; support of another person needed; social support; and use of a cane or walker or wheelchair. Frailty is defined by a score of 3 or more.[48]

The Multidimensional Prognostic Instrument (MPI) is a multidimensional prognostic tool used for hospitalized older patients. It includes eight CGA components: ADL, instrumental ADL, risk of developing pressure sores, comorbidity, medication number, nutritional status, cognitive status, and living status.[49]

Frailty assessment tools used in cardiovascular disease

Some frailty assessment tools have been designed to be used specifically in the setting of CVD (Table 4). Some of the tools described above are also used for this purpose.[23,24,50]

Kang et al. used the CFS, which was useful in assessment of elderly patients with ACS, predicting all-cause

Table 3 List of variables used by the Canadian Study of Health and Aging (CSHA) to construct the 70-item CSHA Frailty Index.[39]

Changes in everyday activities	Problems going out alone	Poor limb coordination
Head and neck problems	Impaired mobility	Poor coordination, trunk
Facial bradykinesia	Musculoskeletal problems	Poor standing posture
Poor muscle tone in neck	Bradykinesia of the limbs	Irregular gait pattern
Problems getting dressed	Poor muscle tone in limbs	Falls
Problems with bathing	Impaired vibration	Mood problems
Problems carrying out personal grooming	Tremor at rest	Feeling sad, blue, depressed
Urinary incontinence	Postural tremor	History of depressed mood
Toileting problems	Intention tremor	Tiredness all the time
Bulk difficulties	History of Parkinson's disease	Depression (clinical impression)
Rectal problems	Family history of degenerative disease	Sleep changes
Gastrointestinal problems	Seizures, partial complex	Restlessness
Problems cooking	Seizures, generalized	Memory changes
Sucking problems	Syncope or blackouts	Short-term memory impairment
Skin problems	Peripheral pulses	Long-term memory impairment
Malignant disease	Cardiac problems	Changes in general mental functioning
Breast problems	Myocardial infarction	Onset of cognitive symptoms
Abdominal problems	Arrhythmia	Clouding or delirium
Presence of snout reflex	Congestive heart failure	Paranoid features
Presence of the palmomental reflex	Lung problems	History relevant to cognitive impairment or loss
History of thyroid disease	Respiratory problems	Family history relevant to cognitive impairment or loss
Thyroid problems	History of diabetes	Headache
History of stroke	Arterial hypertension	Cerebrovascular problems
Other medical history		

mortality, unscheduled return visit, and in-hospital and recurrent major adverse cardiovascular events.[23]

Ekerstad et al. used frailty as measured by the CFS to assess short-term outcomes for elderly patients with non-ST-segment elevation myocardial infarction, and showed that the combined use of frailty and other comorbidity tools (such as the coronary artery disease-specific index) may constitute a novel risk prediction concept in regard to cardiovascular patients with complex needs.[24]

Uchmanowicz et al. investigated the correlation of a scale for assessing frailty – the Tilburg Frailty Indicator and its mental and physical domains – with other screening tools commonly used for CGA in patients with ACS. Significant correlations were demonstrated between the values of the TFI and other scales.[50]

Boxer et al. also found that the six-minute walk and the five-item Cardiovascular Health Study were independently predictive of mortality in older adults with heart failure, with hazard ratio (HR) 0.82 (95% CI 0.72-0.94) and 1.64 (95% CI 1.19-2.26), respectively, and both could be useful as a measure of frailty.[17]

In a prospective observational study by Jung et al. in elective cardiac surgery patients, frailty was defined using the seven-item Cardiovascular Health Study score, the Short Physical Performance Battery (SPPB) and a 35-item frailty index. They found that the addition of frailty improved the ability of the EuroSCORE II to predict postoperative delirium, pointing to opportunities for improved prevention and management.[29]

The CAF is a tool created by Sundermann et al.[20] to assess the prognosis of elderly patients before cardiac surgical interventions and accurately predicts mortality. It comprises grip strength, walking speed, balance, and ability to pick up a pen from the floor, rise from a chair three times and put on and remove a jacket, thus combining characteristics of the CHS criteria[9] of patient phenotype, physical performance, and laboratory results. According to the authors, a combination of the CAF and traditional scoring systems may facilitate more accurate risk scoring in elderly high-risk patients scheduled for conventional cardiac surgery or transcatheter aortic valve replacement.[27] The CAF was preoperatively applied to 400 patients aged $\geq$74 years admitted to a cardiac surgical department between September 2008 and January 2010. For 213 of these patients one-year follow-up was assessed by telephone interview until April 2010. One hundred and ten male and 103 female patients were included. Twenty-five percent underwent isolated coronary revascularization, 35% isolated valve procedures and 26% underwent combined procedures. One-year mortality was 12.2%. Patients who died within one year had a median frailty score of 16 [5;33] compared to 11 [3;33] in one-year survivors (p=0.001).[20] Sundermann et al. showed that the CAF score facilitates prediction of mid-term outcome of high-risk elderly patients and the modified CAF score showed a promising ability to predict one-year mortality in patients undergoing cardiac surgery.[20,27]

The study by Dunlay et al. assessed the association between preoperative frailty and worse outcomes after implantation of an LVAD. Patients undergoing LVAD implantation as destination therapy at the Mayo Clinic, Rochester, MN between February 2007 and June 2012 were included in this study. Frailty was assessed using a deficit index (including 31 impairments, disabilities and comorbidities) and defined as the proportion of deficits present. Patients were then divided based on tertiles of the deficit index (>0.32=frail, 0.23 to 0.32=intermediate frail, <0.23=not frail). The authors concluded that frailty before destination LVAD implantation, as assessed by their deficit index, is associated with increased risk of death and may represent a significant patient selection consideration.[30]

Some tools have also been applied to patients undergoing TAVI. Stortecky et al. assessed the Multidimensional Geriatric Assessment (MGA) as a predictor of mortality and MACCE after TAVI. This prospective cohort comprised 100 consecutive patients aged ≥70 years undergoing TAVI. Global risk scores (Society of Thoracic Surgeons [STS] score, EuroSCORE) and MGA-based scores (cognition, nutrition, mobility, activities of daily living [ADL], and frailty index) were assessed as predictors of all-cause mortality and MACCE 30 days and one year after TAVI. This study provides evidence that risk prediction can be improved by adding MGA-based information to global risk scores.[31]

Schoenenberger et al. used the EuroSCORE, the STS score, and a geriatric baseline examination (based on assessment of cognition, mobility, nutrition, instrumental and basic activities of daily living) to predict functional decline in elderly patients undergoing TAVI. Overall predictive performance was best for the geriatric baseline examination and low for the EuroSCORE and STS score. In univariate analysis, all components of the geriatric baseline examination helped predict functional decline. The

Table 4 Tools used to assess frailty in cardiovascular disease.

Study	Tool	Measurement method	Criteria for frailty
Sundermann et al.[20]	CAF	• Patient is asked to get up and down from a chair 3 times and time is measured • Self-reported weakness • Patient is asked to climb as many stairs as they are able • Two physicians (one a cardiac surgeon) conduct the CFS from the CSHA Serum creatinine level	Results from the CAF scores are tabulated into a scale from 1 to 35 points as outlined by the supplementary CAF Test Sheet. Scores between 1 and 10 are deemed not frail, between 11 and 25 are deemed moderately frail, and between 26 and 36 are deemed severely frail
Green et al.[53]	Modified Fried frailty criteria	• Slow 15-m gait speed • Weak dominant handgrip strength • Assistance required in any of Katz Index of Independence in Activities of Daily Living criteria • Serum albumin as a measurement of malnutrition	Frailty defined as a score >5 on a scale from 0-12 where a higher score equates to more frail For gait speed, grip strength, and serum albumin, based on which quartile a patient was in, a value of 0-3 was given for each quartile in descending order. For activities of daily living, 0 points were given for independent and 3 for dependent
Afilalo et al.[28]	4 scales used: • 5-item Modified Fried Criteria • 7-item expanded Modified Fried Criteria • 4-item MSSA • Five-Meter Gait Speed Test	• 5-item Modified Fried Criteria: gait speed, handgrip strength, inactivity, exhaustion, and weight loss • 7-item Modified Fried Criteria: the above as well as cognitive impairment and depressed mood • 4-item MSSA used gait speed, handgrip strength, inactivity, and cognitive impairment • prolonged time for gait speed test (>6 s to walk 5 m)	Defined as frail if any of the 4 scales deemed patient as frail
Stortecky et al.[31]	Multidimensional Geriatric Assessment	• MMSE showing cognitive impairment MNA shows malnutrition • TUG showing limitation of mobility • BADL and instrumental activities of daily living showed an activity with limitation • Preclinical mobility disability defined as decreased frequency of walking 200 m and/or climbing stairs in preceding 6 months	Defined frailty as ≥3 points, 2 points if MMSE <21, 1 point if MMSE ≥21 and <27, MNA <12, TUG ≥20 s, BADL with at least 1 limited activity, instrumental activities of daily living with at least 1 limited activity, preclinical mobility disability
Schoenenberger et al.[26]	Geriatric baseline examination	• MMSE showing cognitive impairment • MNA shows malnutrition • TUG showing limitation of mobility • BADL and instrumental activities of daily living showed an activity with limitation • Preclinical mobility disability defined as decreased frequency of walking 200 m and/or climbing stairs in preceding 6 months	Defined frailty as ≥3 points, 2 points if MMSE <21, 1 point if MMSE ≥21, and <27, MNA <12, TUG ≥20 s, BADL with at least 1 limited activity, instrumental activities of daily living with at least 1 limited activity, preclinical mobility disability

Table 4 (*Continued*)

Study	Tool	Measurement method	Criteria for frailty
Jung et al.[29]	Modified Fried Frailty Criteria definition of frailty	Slowness – After two trials of a 5 m walk, average time >6 s Weakness – After three grip strength measurements with each hand, maximum value ≤30 kg if male or ≤20 kg if female Weight loss – Self-reported weight loss >4.5 kg (10 lbs) or >5% body weight in past 12 months Exhaustion – Two-item CES-D scale ≥1 out of 2 Depression – 5-GDS ≥2 out of 5 Low physical activity – Paffenbarger Physical Activity Index <383 kcal per week if male or <270 kcal per week if female Cognitive impairment – MoCA score <26 out of 30	Patient was deemed frail if at least 3 of the 7 criteria were present
	35-item Frailty Index	(i) Comorbidities – Angina – Arthritis – Asthma – Cerebrovascular disease – Cognitive impairment – COPD – Dyslipidemia – Gastrointestinal disease – Hearing impairment – Hypertension – Myocardial infarction – Pacemaker – Peripheral vascular disease – Pre-operative atrial flutter or fibrillation – Prior angioplasty or stent – Pulmonary hypertension – Solid tumor – Visual impairment (ii) Physical and emotional measures – Decline in food intake – Depression based on the 5-GDS – Exhaustion based on the two-item CES-D – Falls in past year – Inability to complete repeated chair stand test – Low physical activity based on Paffenbarger Physical Activity Index – Poor balance – Self-rating of health – TUG – Unintentional weight loss in past 3 months – Unintentional weight loss >4.5 kg (10 lbs) – Weak grip (iii) Functional measures – Banking, inability to perform – Cleaning, inability to perform – Cooking, inability to perform – Driving, inability to perform – Shopping, inability to perform	Frailty Index score=individual's total number of deficits/35 Deficits: each counted as present or absent

Table 4 (*Continued*)

Study	Tool	Measurement method	Criteria for frailty
	SPPB	(i) 5-m gait speed measurement – After two trials, average time: ≤6.5 s: 4 points; 6.6-8.3 s: 3 points; 8.4-11.6 s: 2 points; ≥11.7 s: 1 point; unable: 0 points (ii) Balance tests – Side-by-side stand time ≥10 s: 1 point; <10 s: 0 points; – Semi-tandem stand ≥10 s: 1 point; <10 s: 0 points – Tandem stand ≥10 s: 2 points; 3-9.99 s: 1 point; <3 s: 0 points (iii) Repeated chair stand test – Time to stand up from chair 5 times ≤11.19 s: 4 points; 11.20-13.69 s: 3 points; 13.70-16.69 s: 2 points; 16.70-59.99 s: 1 point; ≥60 s or unable: 0 points	Patient was deemed frail if composite score ≥9 points
Uchmanowicz et al.[50]	TFI	First part: Sociodemographic characteristics of a participant: gender, age, marital status, country of origin, educational level, and monthly income Potential determinants of frailty. Second part: Components of frailty (15 self-reported questions, divided into three domains): - Physical domain (0-8 points): eight questions related to physical health, unexplained weight loss, difficulty in walking, balance problems, hearing problems, vision problems, strength in hands, and physical tiredness. - Psychological domain (0-4 points): four items related to cognition, depressive symptoms, anxiety, and coping. - Social domain (0-3 points): three questions related to living alone, social relations, and social support.	Eleven items from part two of the TFI have two response categories (''yes'' and ''no''), while the other items have three (''yes'', ''no,'' and ''sometimes''). ''Yes'' or ''sometimes'' responses are scored 1 point each, while ''no'' responses are scored 0. The instrument's total score may range from 0 to 15: the higher the score, the higher one's frailty. Frailty is diagnosed when the total TFI score is >5.

Table 4 (*Continued*)

Study	Tool	Measurement method	Criteria for frailty
Dunlay et al.[30]	31-item deficit index	Need help preparing meals	Yes=1, No=0
		Need help feeding yourself	Yes=1, No=0
		Need help dressing yourself	Yes=1, No=0
		Need help using the toilet	Yes=1, No=0
		Need help with housekeeping	Yes=1, No=0
		Need help climbing stairs	Yes=1, No=0
		Need help bathing	Yes=1, No=0
		Need help walking	Yes=1, No=0
		Need help using transportation	Yes=1, No=0
		Need help getting in and out of bed	Yes=1, No=0
		Need help managing medications	Yes=1, No=0
		Depend on assistive devices (walker, cane, etc.) or other people to perform activities of daily life	Yes=1, No=0
		Dependent on a device for normal breathing	Yes=1, No=0
		Climb 2 flights of stairs without rest	No, cannot do at all=1; Yes, with difficulty=0.5; Yes with no difficulty=0
		Myocardial infarction	Yes=1, No=0
		Diabetes	Yes=1, No=0
		Peripheral vascular disease	Yes=1, No=0
		Cerebrovascular disease	Yes=1, No=0
		COPD	Yes=1, No=0
		Ulcer	Yes=1, No=0
		Hemiplegia	Yes=1, No=0
		Moderate/severe renal insufficiency	Yes=1, No=0
		History of liver disease	Yes=1, No=0
		Rheumatologic disease	Yes=1, No=0
		History of malignancy	Yes=1, No=0
		History of dementia	Yes=1, No=0
		Hypertension	Yes=1, No=0
		Hyperlipidemia	Yes=1, No=0
		Body mass index	Underweight or obese=1; overweight=0.5; normal=0
		Depression	Yes=1, No=0
		Anemia	Yes=1, No=0
			Yes=1, No=0
			Yes=1, No=0
			Patients were divided into tertiles of the deficit index: Lowest tertile=not frail; middle tertile=intermediate frail; highest tertile=frail
Afilalo et al.[51]	Essential Frailty Toolset	(i) Time to stand 5 times from a seated position without using arms: <15 s=0 points; ≥15 s=1 point; unable to complete=2 points (ii) Cognition: MMSE ≥24: 0 points; MMSE <24: 1 point (iii) Hemoglobin: ≥13 g/dl (in men) or ≥12 g/dl (in women): 0 points; <13 g/dl (in men) or <12 g/dl (in women): 1 point (iv) Serum albumin: ≥3.5 g/dl: 0 points; <3.5 g/dl: 1 point	Composite score: 0-5

5-GDS: five-item Geriatric Depression Scale; BADL: basic activities of daily living; CAF: Comprehensive Assessment of Frailty score; CES-D: Center for Epidemiologic Studies Depression scale; CFS: Clinical Frailty Scale; COPD: chronic obstructive pulmonary disease; CSHA: Canadian Study of Health and Aging; MMSE: Mini Mental State Exam; MNA: Mini Nutritional Assessment; MoCA: Montreal Cognitive Assessment score; MSSA: 4-item MacArthur Study of Successful Aging frailty scale; SPPB: Short Physical Performance Battery; TFI: Tilburg Frailty Indicator; TUG: Timed Up and Go test.

authors concluded that the geriatric baseline examination, but not established risk scores, was predictive of functional decline.[26]

In the 2012 study by Afilalo et al., a total of 152 patients were enrolled in a prospective, multicenter cohort study of elderly patients (>70 years) undergoing CABG and/or valve surgery in the US and Canada. Four different frailty scales, three disability scales, and five cardiac surgery risk scores were measured in all patients. The primary outcome was the STS composite endpoint of in-hospital postoperative mortality or major morbidity. The four frailty scales examined in this study are described in Table 4. The authors concluded that clinicians should use an integrative approach combining frailty, disability, and risk scores to better characterize elderly patients referred for cardiac surgery and identify those that are at increased risk.[28]

The same author, in a recent study (2017),[51] compared the incremental predictive value of seven different frailty scales to predict poor outcomes following TAVI and valve surgery: the Fried criteria (described above),[9] Fried+(the Fried criteria plus cognition assessed by the Mini Mental State Exam [MMSE] and mood assessed by the Short-form Geriatric Depression Scale), the Rockwood CFS,[39] the SPPB (three physical tests, with each scored 0 to 4 for a composite score of 0 to 12: gait speed, time to stand five times from a seated position without using arms and the ability to stand 10 s with the feet in tandem or side-by-side positions),[52] the Bern Scale (six items for a composite score of 0 to 7: gait speed, mobility, cognition, nutrition and disability in activities of daily living and instrumental activities),[26,31] the Columbia Scale (four items, with each scored 0 to 3 for a composite score of 0 to 12: gait speed, grip strength, serum albumin and disability),[53] and the Essential Frailty Toolset (EFT) (four items for a composite score of 0 to 5: time to stand five times from a seated position without using arms (1 point if $\geq$15 s, 2 points if unable to complete), cognition (1 point if MMSE <24), hemoglobin (1 point if <13 g/dl in men or <12 g/dl in women), and serum albumin (1 point if <3.5 g/dl).[51] Frailty as measured by the EFT was the strongest predictor of death at one year ($p<0.001$) and of worsening disability at 1 year (adjusted OR:2.13; 95% CI:1.57 to 2.87) and death at 30 days (adjusted OR: 3.29; 95% CI: 1.73 to 6.26).

Some authors, instead of validating existing frailty screening tools, used certain parameters to derive their own frailty score. Green et al. used a modification of the Fried frailty criteria that included gait speed, grip strength, serum albumin, and activities of daily living status to derive a frailty score among older adults with severe aortic stenosis who underwent TAVI. In this study frailty was not associated with increased periprocedural complications in patients selected as candidates to undergo TAVR, but was associated with increased one-year mortality after TAVR.[53]

Screening tools: critical analysis

We have described individual multiple frailty measurement scales. There have been various studies comparing the most commonly used screening tools, but agreement on which has the best ability to predict prognosis and all-cause mortality is lacking. While some studies found similar prognostic performance in some of these tools,[54,55] other studies found significant differences.[56] In 2013, a consensus conference identified some of these tools as allowing physicians to objectively recognize frail persons.[6] However, they range from short, fast and crude screening tools to sophisticated and time-consuming scales. A source of concern is the fact that many frailty scales have been modified somewhat from their original and validated version, leading to significant differences in frailty classification.[33]

Table 5 Comparison of the frailty phenotype and frailty indices.[57]

Frailty phenotype	Frailty indices
Performance on five variables	Deficit count or proportion of potential deficits that a person has accumulated
Signs, symptoms	Diseases, activities of daily living, results of a clinical evaluation
Possible before a clinical assessment	Doable only after a comprehensive clinical assessment
Categorical variable	Continuous variable
Predefined set of criteria	Unspecified set of criteria
Frailty as a pre-disability syndrome	Frailty as an accumulation of deficits
Meaningful results potentially restricted to non-disabled older persons	Meaningful results in every individual, independently of functional status or age
Advantages: - performance-based - easy to apply	Advantages: - simple approach - robust indicator of frailty
Disadvantages: - floor effect for some variables (immobile patients)	Disadvantages: - cumbersome in clinical setting

Since the frailty phenotype and frailty indices are based on different concepts, it is inappropriate to consider them as alternatives and/or interchangeable.[57] Table 5 describes the main characteristics of these two different instruments.

The FRAIL screening tool is clinically advantageous due to its simple nature and ability to be obtained from data already included in a CGA.[2] It has been found to be predictive of mortality in specific populations, such as patients with CVD.[43]

The CHS scale (Fried criteria) is a widely used scale applied in multiple epidemiological studies, and has good predictive value for adverse clinical outcomes, including mortality. However, a major factor precluding its clinical application is the inclusion of measurements not routinely used for patient assessment (such as grip strength measured by a dynamometer). Another important limitation of this

scale is that it does not include psychosocial components of frailty.[9]

The CFS has been validated as a predictor of adverse outcomes in hospitalized older people, such as all-cause, in-hospital mortality, one-month mortality and prolonged hospital care.[23,24,33]

Deficit accumulation-based frailty indices are well validated and are better at predicting adverse clinical events than other frailty measurements in both hospital and community settings. They have been applied to multiple datasets, but can be time-consuming to calculate. The FI-CGA is used as a clinical standard for frailty assessment and has been found to predict patient response in multiple fields, including cardiology.[2]

The EFS is a valid and reliable measurement tool in the hospital setting and, since it has only nine components, it is much simpler to extract from CGAs than the FI-CGA.[42] In a community-based sample, even when administered by non-specialists with no formal training in geriatric care, the EFS compared favorably with the clinical assessment of geriatric specialists who completed a more comprehensive evaluation.[42]

Compared with other frailty assessment tools, the MPI appears to have greater ability to predict adverse outcomes. Nevertheless, additional research is needed to confirm these results.[33,49]

The GFI has moderate internal consistency and adequate discriminative ability, and shows good feasibility and reliability as a frailty measurement. Some authors have proposed that it should be used together with a frailty index as part of a two-step screening process.[58]

The TFI shows good reliability for identifying frailty in community-dwelling older people. However, although its physical components show good ability to predict adverse events, its social components appear to be weak predictors.[59,60]

The GFST, designed for early recognition of frailty in community-dwelling older people, appears to be a good frailty screening tool; however, it gives no specific guidance for clinicians on how to identify frailty and the clinician's judgment of frailty status is quite subjective.[33]

Although PRISMA-7 shows good accuracy in identifying frailty in community-dwelling older people, its ability as a screening tool is limited since it has a tendency to over-screen for frailty.[59]

Some of these tools have also been used in cardiovascular patients, such as the Fried frailty criteria,[17,23,24,29] frailty indices,[29,30] and the TFI.[50]

The geriatric baseline examination developed by Schoenenberger et al.,[26] the multidimensional geriatric assessment used by Stortecky et al.,[31] and the CAF,[20,27] developed by Sundermann et al., are three recent frailty tools which have been shown to be useful in predicting mortality and assessing prognosis of elderly patients with CVD or before cardiac surgical interventions.

Some authors, such as Afilalo et al., prefer to use an integrative approach combining frailty, disability, and risk scores to better characterize elderly patients referred for cardiac surgery, which has proved to be useful for identifying those at increased risk.[28]

The same author recently showed the superiority of the EFT compared to other frailty scales when predicting poor outcomes following TAVI and valve surgery, since it is a relatively simple tool that is neither particularly burdensome nor time-consuming and at the same time captures multiple domains of frailty. The authors suggested it had the highest predictive value for death and worsening disability at one year and recommended its use in this setting.[51]

Assessment of frailty as a preoperative surgical risk factor has been shown to be useful and may increase the number of elderly patients considered eligible for surgical interventions, since it enables prior screening for risk and prediction of surgical success and safety.

When selecting a screening tool, it is also important to take into account the ecology of its application, since some frailty measurements are more suitable for use in population health studies as screening, whereas others are appropriate in the clinical setting for screening or diagnosis of frailty.[42,55,57]

Conclusion

Frailty is an important prognostic factor in patients with CVD. It increases the risk of adverse events associated with cardiovascular therapeutic interventions, and therefore needs to be taken into account when considering whether to intervene. Frail patients may have more complications and fewer benefits because of the competing adverse event risk. The clinical relevance of frailty assessment will be even greater in the future because the number of frail patients with CVD is set to grow as populations age. Both successful treatment approaches for frail patients and the inclusion of frailty when assessing patients for CVD intervention require the systematic and routine identification of frailty. Simple and rapid screening tests have been developed and validated to enable the objective recognition of frail persons. There are significant differences between these scales in their nature, validity and feasibility. Further studies are needed to establish their significance regarding overall and cardiovascular mortality. In the CVD field, the two most commonly used and most robust frailty assessment tools for use by clinicians and researchers are the Fried criteria and frailty indices. Other new tools specifically designed for CVD have proved extremely useful for this propose. In line with previous studies, we suggest the use of one simple tool for frailty screening and a second one for a full assessment, and for these purposes we recommend the use of the Fried criteria and a frailty index, respectively. The impact of therapeutic strategies targeting frailty itself is still unclear. Nevertheless, routine screening and objective diagnosis of frailty is bound to improve the therapeutic decision-making process and prognostic assessment of patients with CVD.

Conflicts of interest

The authors have no conflicts of interest to declare.

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