Carlo Vigorito | Ana Abreu | Marco Ambrosetti
Romualdo Belardinelli | Ugo Corra | Margaret Cupples
Constantinos H. Davos | Stefan Hoefer | Marie-Christine Iliou
Jean-Paul Schmid | Heinz Voeller | Patrick Doherty

Frailty and cardiac rehabilitation: A call to action from the EAPC Cardiac Rehabilitation Section

Suggested citation referring to the original publication:
European Journal of Preventive Cardiology 24(6) (2017)
DOI https://doi.org/10.1177/2047487316682579
ISSN (print) 2047-4873
ISSN (online) 2047-4881

European Journal of Preventive Cardiology

EUROPEAN SOCIETY OF CARDIOLOGY®

Clinical practice

European Journal of Preventive Cardiology
2017, Vol. 24(6) 577–590

DOI: 10.1177/2047487316682579
journals.sagepub.com/home/ejpc

SAGE

Frailty and cardiac rehabilitation: A call to action from the EAPC Cardiac Rehabilitation Section

Carlo Vigorito[1], Ana Abreu[2], Marco Ambrosetti[3], Romualdo Belardinelli[4], Ugo Corrà[5], Margaret Cupples[6], Constantinos H Davos[7], Stefan Hoefer[8], Marie-Christine Iliou[9], Jean-Paul Schmid[10], Heinz Voeller[11] and Patrick Doherty[12]

Abstract

Frailty is a geriatric syndrome characterised by a vulnerability status associated with declining function of multiple physiological systems and loss of physiological reserves. Two main models of frailty have been advanced: the phenotypic model (primary frailty) or deficits accumulation model (secondary frailty), and different instruments have been proposed and validated to measure frailty. However measured, frailty correlates to medical outcomes in the elderly, and has been shown to have prognostic value for patients in different clinical settings, such as in patients with coronary artery disease, after cardiac surgery or transvalvular aortic valve replacement, in patients with chronic heart failure or after left ventricular assist device implantation.

The prevalence, clinical and prognostic relevance of frailty in a cardiac rehabilitation setting has not yet been well characterised, despite the increasing frequency of elderly patients in cardiac rehabilitation, where frailty is likely to influence the onset, type and intensity of the exercise training programme and the design of tailored rehabilitative interventions for these patients.

Therefore, we need to start looking for frailty in elderly patients entering cardiac rehabilitation programmes and become more familiar with some of the tools to recognise and evaluate the severity of this condition. Furthermore, we need to better understand whether exercise-based cardiac rehabilitation may change the course and the prognosis of frailty in cardiovascular patients.

Keywords

Frailty, cardiac rehabilitation, elderly

Received 11 August 2016; accepted 12 November 2016

[1]Department of Translational Medical Sciences, University of Naples Federico II, Italy
[2]Cardiology Department Hospital Santa Marta, Centro Hospitalar Lisboa Central, Portugal
[3]Cardiovascular Rehabilitation Unit, Le Terrazze Clinic, Cunardo, Italy
[4]Cardiologia Riabilitativa Lancisi, AOR Ancona, Italy
[5]Department of Cardiac Rehabilitation, Salvatore Maugeri Foundation, Veruno, Italy
[6]Department of General Practice, UKCRC Centre of Excellence for Public Health Research (NI), Northern Ireland, Queens University, Belfast
[7]Cardiovascular Research Laboratory, Biomedical Research Foundation Academy of Athens, Greece
[8]Medical University Innsbruck, Austria
[9]Cardiac Rehabilitation Department, Hopital Corentin Celton-Assistance Publique Hôpitaux de Paris, France
[10]Cardiology Clinic, Tiefenau Hospital and University of Bern, Switzerland
[11]Center of Rehabilitation Research, University of Potsdam, Germany; Department of Cardiology, Klinic am See, Rudersdorf
[12]Department of Health Sciences, University of York, UK

Corresponding author:
Carlo Vigorito, University of Naples Federico II, School of Medicine, Via S. Pansini 5, Naples, 80131, Italy.
Email: vigorito@unina.it

Introduction

We belong to an ageing world where people are living longer. In 2030, progressive population ageing will lead to an increase in the proportion of people aged over 65 years from 17.4% to 25.6%, and the population of elderly people will almost double in Europe from 87.5 million in 2010 to 152.6 million in 2060.[1] Progressive ageing is associated with geriatric syndromes (particularly frailty) that pose a severe burden on health systems. Therefore, there is a need to understand these syndromes better, with particular attention to the relevance of frailty in the context of care of older cardiac patients, including cardiac rehabilitation (CR).

Frailty and its relationship with disability and comorbidity

Frailty is characterised by impairment in many domains (e.g. physical, psychological and social) with consequent effects on mortality, hospitalisation, dependence, disability and significant healthcare cost.[2] Although varying definitions exist, there is a common thread in that frailty is a dynamic age-related vulnerability[3] characterised by declining function, associated with a loss of physiological reserves of multiple organs or systems, and an increased risk of negative outcomes, such as institutionalisation and death.[4,5] The pathophysiological mechanisms underlying the development or progress of a frailty status are multifactorial, and include inflammatory mechanisms, the hypothalamic–hypophysary axis, and anabolic–catabolic hormone imbalance.[5] Studies show that frailty, independently of how it is measured, is significantly and independently correlated to medical outcomes.[6,7] Despite the relevance of frailty as a prognostic indicator, uncertainty remains regarding its definition, its measurement, the feasibility of its measurement in clinical practice and whether such measurements can be influenced by interventions or describe the progress or deterioration of health status. This is particularly true in the CR setting, where the increasing age of patients admitted to CR poses problems in individualising models of clinical evaluation and interventions.

The extent of frailty is not determined purely by the magnitude and frequency of comorbidity or disability, as patients with the same comorbidity or disability may present with different degrees of frailty or no frailty at all. On the other hand, a patient may be frail with few comorbidities or disabilities.[8] Based on data from the Cardiovascular Health Study, about 25% of older patients show signs of frailty without either multiple comorbidities or disabilities.[9] Disability may be a consequence of frailty but, alternatively, disability may be closely linked to the development or worsening of frailty status; in particular, so-called primary frailty, described in older patients without overt pathological conditions, and can lead to diseases or disability and to secondary frailty that in turn may worsen the phenotypic presentation of frailty.[10] The recognition and measurement of frailty and the possibility of modifying this status are important issues within and beyond modern geriatric medicine.

Frailty models

Two main models of frailty have been proposed. The phenotype model proposed by Fried et al. views frailty as a biological syndrome resulting from cumulative decline across multiple physiological systems.[4] The model advanced by Rockwood et al. views frailty as a multidimensional risk state that can be measured more by the quantity than by the nature of health problems.[11–13]

Primary frailty model: the phenotype model. According to Fried et al., a wealth of epidemiological or observational studies has described the presence of frailty in the general elderly population (physiological ageing). In this environment frailty has been defined as 'primary frailty', a phenotypic presentation involving decline in physical functioning and psychological status, without taking into consideration associated diseases or pathological conditions. Fried's phenotype frailty index[4] (PFI) has been widely adopted: it was derived from an analysis of five health domains: nutrition; physical exhaustion; low energy expenditure (or inactivity status); mobility; and muscular strength (Table 1). Deterioration of each of these domains was scored as 1 if present or 0 if absent, giving a potential score spanning from 0 to 5. The phenotype model classified three categories: robust (no deterioration); pre-frail (one or two function deterioration); or frail (three or more function deterioration). This categorisation was independently correlated with outcomes, such as survival, falls, disability and institutionalisation.[4]

Secondary frailty model: accumulation of deficit model. The conceptualisation of frailty proposed by Rockwood et al. considers the accumulation of multiple deficits such as symptoms, signs, disabilities, pathological conditions and abnormal laboratory values (secondary frailty).[11–14] In this model, a frailty index (FI) was measured as deficit accumulation (Table 2). Each deficit can be coded as binary (1 or 0) or ordinal (0, 0.5, 1). This FI is the sum of the deficit values divided by the total number of deficits listed (e.g. 10 deficits present out of 40 gives a FI ratio of $10/40 = 0.25$) and is significantly correlated with outcomes; for example, with each unit increase the hazard rate for mortality increases by 4%.[15]

Table 1. Phenotype frailty index.[4]

Domain	Criterion	Score
Nutritional status	Non-intentional weight loss of at least 4.5 kg in prior year	No: 0 Yes: 1
Physical exaustion	Self-reported exhaustion (two questions from the CES-D* depression scale)	No: 0 Yes:1
Low energy expenditure	Lower category of physical activity by a validated questionnaire (e.g. MLTAQ-short version)**	Kcals/week expended Men: <383 Kcal/week = 1 Women: <270 Kcals/week = 1
Mobility	Gait speed on a 4.5 meter walk, stratified by gender and height	Men height ≤173 cm and time ≥7 s = 1 Men height >173 cm and time ≥6 s = 1 Women height ≤159 cm and time ≥7 s = 1 Women height >159 cm and time ≥6 s = 1
Muscular strength	Lower category of muscular strength measured by hand handgrip, stratified by gender and BMI	Men BMI ≤24 and strength ≤29 = 1 Men BMI 24.1–26 and strength ≤30 = 1 Men BMI 26.1–28 and strength ≤30 = 1 Men BMI >28 and strength ≤32 = 1 Women BMI ≤23 and strength ≤17 = 1 Women BMI 23.1–26 and strength ≤17.3 = 1 Women BMI 26.1–29 and strength ≤18 = 1 Women BMI >29 and strength ≤21 = 1

BMI: body mass index.
*Orme J, Reis J and Herz E. Factorial and discriminate validity of the Center for Epidemiological Studies depression (CES-D) scale. *J Clin Psychol* 1986; 42: 28–33.
**Taylor HL, Jacobs DR, Schucker B, et al. Questionnaire for the assessment of leisure time physical activities. *J Chron Dis* 1978; 31: 741–755.

Frailty indices adopting the deficit accumulation model can be derived from different numbers and types of variables, provided certain criteria are fulfilled.[14] The number of deficits, rather than a single deficit, is related to adverse outcomes, as the final number reflects a global measure of vulnerability. A patient with a score of less than 0.2 would be considered not frail, an increasing score indicates an increased level of frailty. In order for a FI to be able to capture sufficient features or risk factors for frailty, it should include at least 40 items, covering several health domains, such as physical, cognitive, psychological and social.[14] It is important to note that frailty increase parallels ageing, independently of baseline frailty, and evaluation of interventions to reduce frailty must take into consideration a natural physiological increase in frailty with age.

Frailty assessment

Assessing instruments. An important issue in the clinical environment, and particularly in primary care, is that the measurement of frailty based on either the phenotypic or deficit accumulation model may be complex and time consuming. There are, however, alternative instruments to apply in clinical practice for screening and evaluating frailty in the general population (Table 3). Some follow the phenotypic model,[16–19] others consist of administered or self-administered questionnaires,[20,21] and some require clinical evaluation[22] or task performance and measurement such as the Edmonton frailty scale (EFS).[23] Some scales are designed to be screening instruments[18] and others to be more multifaceted tools requiring comprehensive geriatric assessment (CGA).[24] They are designed for use with different groups of individuals, and differ in their feasibility and prognostic ability.

Despite these differences, all scales were predictive of all-cause mortality or of relevant elderly outcomes, in most cases independently from other prognostic indices. A recent comparison of these scales in the SHARE survey[25] showed some differences in their prognostic predictive ability. Receiver operating characteristic (ROC) curves showed that FI derived from the deficit accumulation model, FI derived from CGA (FI-CGA) and EFS performed slightly better than other scales.

As CGA, consisting of a multidimensional assessment of several health domains, is the cornerstone of modern geriatric care,[26] FI-CGA may be considered as one of the best models to measure frailty. The FI-CGA, validated in the Canadian Study of Health and Aging (CSHA), a large population-based study,[24–27] explored 10 domains, assigning a score to each domain and constructing a frailty categorisation: mild (FI-GCA 0–7),

Table 2. Frailty index based on the deficit accumulation model.[14]

List of 40 variables included in the FI	Cut point				
Help bathing	Yes: 1	No: 0			
Help dressing	Yes: 1	No: 0			
Help getting in/out of chair	Yes: 1	No: 0			
Help walking around house	Yes: 1	No: 0			
Help eating	Yes: 1	No: 0			
Help groomirg	Yes: 1	No: 0			
Help using toilet	Yes: 1	No: 0			
Help up/down stairs	Yes: 1	No: 0			
Help lifting 10 lbs	Yes: 1	No: 0			
Help shopping	Yes: 1	No: 0			
Help with housework	Yes: 1	No: 0			
Help with meal preparations	Yes: 1	No: 0			
Help taking medications	Yes: 1	No: 0			
Help with finances	Yes: 1	No: 0			
Lost more than 10 lbs in last year	Yes: 1	No: 0			
Self-rating of health	Poor: 1	Fair: 0.75	Good: 0.5	V. good: 0.25	Excellent: 0
How health has changed in last year	Worse: 1	Better/same: 0			
Stayed in bed at least half of the day due to health (in the last month)	Yes: 1	No: 0			
Cut down on usual activity (in the last month)	Yes: 1	No: 0			
Walk outside	<3 days: 1	>3 days: 0			
Feel everything is an effort	Most of the time: 1	Some time: 0.5	Rarely: 0		
Feel depressed	Most of the time: 1	Some time: 0.5	Rarely: 0		
Feel happy	Most of the time: 1	Some time: 0.5	Rarely: 0		
Feel lonely	Most of the time: 1	Some time: 0.5	Rarely: 0		
Have trouble getting going	Most of the time: 1	Some time: 0.5	Rarely: 0		
High blood pressure	Yes: 1	Suspect: 0.5	No: 0		
Heart attack	Yes: 1	Suspect: 0.5	No: 0		
CHF	Yes: 1	Suspect: 0.5	No: 0		
Stroke	Yes: 1	Suspect: 0.5	No: 0		
Cancer	Yes: 1	Suspect: 0.5	No: 0		
Diabetes	Yes: 1	Suspect: 0.5	No: 0		
Arthritis	Yes: 1	Suspect: 0.5	No: 0		
Chronic lung disease	Yes: 1	Suspect: 0.5	No: 0		
MMSE	<10: 1	11–17: 0.75	18–20: 0.5	20–24: 0.25	>24: 0
Peak flow (l/min)	<340 (men); <310 (women)				
Body mass index (BMI)	<18, >30 (men); <18.5, >30 (women)				
Shoulder strength (kg)	<12 (men); <9 (women)				1 point awarded for each criterion
Grip strength (kg)	<29–32 (men); <17–21 (women)				
Rapid pace walk for 20 ft (s)	>10 (men and women)				
Usual pace walk for 20 ft (s)	>16 (men and women)				

moderate (FI-CGA 7–13) and severe (FI-CGA > 13) frailty.[24] The same data from CGA can be analysed by counting the deficit according to the deficit accumulation model,[3] and both types of measurements have been correlated to outcome.[27]

Extensive reports in the literature have shown that frailty can indeed be measured with relative ease even in hospital settings, for patients in general medical wards,[6,7,28–31] geriatric units,[32,33] survivors of intensive care units or emergency departments,[34,35] including

Table 3. Frailty instruments in general population.

Frailty tool	Instrument type	Details	Reference
Groningen frailty indicator	Multidimensional questionnaire	15 items, focusing on 4 functional domains: physical (9 items), cognitive (1 item), social (3 items), psychological (2 items). A score >4 (out of 15) can be considered frail.	Schuurmans et al. *J Gerontol A Biol Sci Med Sci* 2004; 59: M962–965.
Tilburg frailty indicator	Multidimensional self reported questionnaire	The 2d subscale evaluates 3 domains and 15 items about physical (8 items), social (3 items), and psychological factors (4 items), including 1 item on cognition. Scores range from 0 to 15. A score of >5 is associated with frailty.	Gobbens et al. *J Am Med Dir Assoc* 2010; 11: 344–355.
SHARE frailty instrument	Phenotypic model	5 Adapted phenotypic frailty items (grip strength and 4 self-reported items: fatigue, loss of appetite and/or eating less than usual, difficulties climbing stairs and/or walking 100 m, and low level of physical activity). Frailty categories: non-frail, pre-frail and frail.	Romero-Ortuno, *Geriatr Gerontol Int* 2013; 13: 497–504.
Study of osteop. fracture index (SOF)	Phenotypic model	3 Items: 1) unintentional weight loss; 2) inability to rise from a chair 5 times without the use of arms; 3) low energy level. Robust: 0 component; pre-frail: 1 component; frail: 2 or 3 components.	Ensrud, et al. *J Am Geriatr Soc* 2009; 57: 492–498.
FRAIL scale	Questionnaire (phenotypic model)	5 Item (fatigue, resistance, ambulation, illnesses, loss of weight). Pre-frail: 1–2 deficits Frail: 3 deficits or more	Abellan Van Kan, et al. *J Am Dir Assoc* 2008; 9: 71–72.
Gerontopole frailty screening	Questionnaire (phenotypic model)	6 Items: social, nutrition, exhaustion, mobility, cognition, physical activity. Plus GP opinion.	Subra. *J Nutr Health Aging* 2012; 16: 714–720.
Edmonton frailty scale	Multidimensional questionnaire and 2 tasks	17 Simple questions or tasks, assessing cognition, self-perceived health, dependence for ADL, social support, medication use, nutrition, mood, continence and functional performance. Each item is given from 0 to 2 points, and a frailty state is assigned to a global scores >8/17.	Rolfson, et al. *Age Ageing* 2006; 35: 526–529.
Clinical frailty scale	Multidimensional assessment based on history taking and clinical examination	Frailty assessment tool in the domains of mobility, energy, physical activity, and function. Scale ranging from a level of 1 (very fit) to 8 (very severely frail)	Rockwood, et al. *Can Med Assoc J* 2005; 173: 489–495.
FI-compr. geriatric assessment (FI-CGA)	Multidimensional geriatric-oriented assessment	Geriatric assessment of several domains: cognition, disability, mood and motivation, communication, mobility, balance, bowel/bladder function, nutrition, social resources and comorbidity. Can be reported as a continuous (deficit accumulation) or a categorical score.	Jones, et al. *J Am Geriatr Soc* 2004; 52: 1929–1933.

critical oncological[36] or dialysed patients[37] (Table 4). In these settings, frailty has been assessed by a variety of tools including the FI-CGA instrument,[28,30] the CSHA clinical frailty scale[6,7,31,34,37] and the phenotypic model.[29,35,36] Frailty varied from 20% to 82%, according to the scale and the population examined.

A direct comparison among some of these scales in hospitalised patients aged over 65 years was reported by Pilotto et al., who described an innovative frailty instrument based on a modified CGA (CGA-based multidimensional prognostic index – MPI).[38] The MPI integrated data from eight domains such as

Table 4. Frailty instruments in hospital environment.

Frailty tool	Setting	Patient numbers/age	Frailty	Reference
Frailty index based on a CGA (FI-CGA)	General medical ward	409 Patients mean age 81.8 years	Mean frailty 0.42 index (SD 0.11)	Hubbard, et al. *J Gen Intern Med* 2011; 26: 1471–1478.
Phenotype	General medical ward	90 Patients mean age 76 ± 6.4 years	20%	Stiffler, et al. *J Emerg Med* 2013; 45: 291–298.
Clinical frailty scale	Emergency department	5795 Patients >75 years	Not reported	Wallis, et al. *Q J Med* 2015; 108: 943–949.
Deficit accumulation FI	Acute geriatric rehabilitation ward	265 Patients mean age 82.6 ± 8.6 years	Mean frailty index 0.34 ± 0.09	Singh, et al. *Age Ageing* 2012; 41: 242–246.
Clinical frailty scale	General medical wards	421 critically ill adults aged > 50 years	32.8%	Bagshaw, et al. *CMAJ* 2014; 186: E95–102.
Phenotype	ICU survivors	22 Patients mean age 77 years	82%	Baldwin, et al. *J Crit Care* 2014; 29: 401–408.
Clinical frailty scale	General medical wards for acute illness	2125 Patients mean age 82.9 years	Not reported	Basic, et al. *J Aging Health* 2015; 27: 670–685.
Clinical frailty scale	Patients discharged from 7 medical wards	495 Patients mean age 64 years	33%	Kahlon, et al. *CMAJ* 2015; 187: 799–804.
CGA and phenotype	Oncologic patients (review of 20 studies)	2916 Participants 72–81 years	Frailty 42% Pre-frailty 43%	Handforth, et al. *Ann Oncol* 2015; 26: 1091–1101.
Clinical frailty scale	On dialysis	390 Patients	26% Mild–mod. 53% severe	Alfaadel, et al. *Clin J Am Soc Nephrol* 2015; 10: 832–840.
Frailty index based on a CGA (FI-CGA)	Medical ward	752 Patients aged 75+ years	Mean FI-CGA = 0.38	Evans, et al. *Age Ageing* 2014; 43: 127–132.
Multidimentional prognostic Index (MPI)	Geriatric units	2033 Patients mean age 79.8 years	Grade 2: 36.5% Grade 3: 21.6%	Pilotto, et al. *PLoS One* 2012; 7: e29090.

disability (basic and instrumental activities of daily life – BADL-IADL), cognitive, nutritional, comorbidities, drug use, risk of developing pressure sores and cohabitation status. ROC curve analysis for the endpoint of mortality showed good performance of MPI compared with FI and FI-CGA.

Value of frailty instruments in measuring outcome

Frailty depends on several interrelated factors and can change over time. As frailty is a dynamic process influenced by progressive aging,[39,40] it is uncertain whether it can be used as an outcome measure of an intervention.[41] Therefore, an evaluative outcome instrument to measure frailty with reliable clinimetric properties is needed.[9] A review of many commonly adopted frailty instruments in clinical practice has analysed their clinimetric properties (agreement, construct validity, responsiveness, interpretability, content validity, internal consistency, floor and ceiling effect).[42] Frailty instruments have mostly been validated as prognostic tools, but their ability for capturing intervention-induced changes in frailty over time is unclear. At the present time, and with caution, the FI calculated according to the deficit accumulation model[11,12] appears, from the clinimetric standpoint, the most suitable and reliable to capture changes in frailty over time. Using the frailty index as a tool to estimate the increase in healthcare resources required for different levels of frailty may help to identify the investment needed to reduce frailty in the community.[43,44]

Frailty in cardiology

With progressive population ageing, the burden of cardiovascular disease has become prevalent as a cause of mortality, morbidity and disability.[45] Therefore, there has been a recent surge of interest in evaluating frailty

in patients with cardiovascular conditions. Frailty has been assessed in patients affected by various cardiovascular diseases, and many of the instruments adopted have demonstrated prognostic value;[46–48] they may have value in defining guidelines for cardiac patients' management during hospitalisation and after discharge. Each of the instruments proposed has its own grade of complexity and prognostic information. In general, even as a sole prognostic indicator and with the above limitations, instruments describing a frailty status in several populations of cardiac patients have outscored other more usually adopted prognostic indicators.[46–48]

Frailty in elderly patients with acute coronary syndrome or percutaneous transluminal coronary angioplasty

Many studies have evaluated frailty in elderly patients after an acute coronary syndrome (ACS) or percutaneous transluminal coronary angioplasty (PTCA) by using several instruments, such as the phenotypic model (PFI),[4] the CSHA clinical frailty scale,[22] or the EFS.[23] In this setting frailty ranged from 10% to 48%, and higher levels of frailty were associated with worse outcomes (Table 5).[47,49–55]

These studies showed an independent added prognostic value of frailty assessment, and although larger studies are needed to refine risk prediction models, it is suggested that clinicians and researchers should consider how they can embed frailty measurement into clinical practice.

Frailty in elderly patients undergoing cardiac surgery

In the current era, the elderly represent the fastest growing group of patients referred for cardiac surgery, with the proportion of patients aged 75 years or older rising from 16% in 1990 to 25% in most recent estimates.[56] These complex and often frail patients are at increased risk of falls, prolonged hospitalisation and mortality after surgery.[56,57] For this reason, many groups have evaluated preoperative frailty to increase prognostic capability.[56,58,59]

Recently, Afilalo et al.[56] in a population of 152 elderly patients (>70 years) undergoing coronary artery bypass graft and/or valve surgery, evaluated the incremental prognostic value of four different frailty scales and of three disability scales compared with classic cardiac surgery risk scores. Frailty scales adopted in this study were the Fried frailty scale,[4] the expanded Fried frailty scale (addition of cognitive impairment and depressed mood),[60] the four-item MacArthur study of successful ageing frailty scale subdimensions (gait speed, handgrip strength, inactivity, cognitive impairment),[61] and gait speed alone. Compared with the Parsonnet score[62] or the Society of Thoracic Surgeons predicted risk of mortality or major morbidity score (STS-PROMM),[63] the addition of frailty and disability provided independent incremental value and improved model discrimination for in-hospital postoperative mortality or major morbidity. Thus, the integration of frailty, disability and risk scores should better characterise elderly patients referred for cardiac surgery and identify those who are at increased risk.

Transvalvular aortic valve replacement

Transvalvular aortic valve replacement (TAVR) is a successful intervention in elderly patients with aortic stenosis, and patients after TAVR benefit from CR despite their older age and clinical complexity and frailty.[64] Several studies have recently described the added prognostic value of frailty evaluation over standard criteria in elderly patients undergoing TAVR.

A modified Fried frailty score (gait speed, grip strength, serum albumin and activities of daily living) in very old patients was independently associated with increased one-year mortality after TAVR.[65] A frailty index based on the assessment of cognition, mobility, nutrition, BADL and IADL predicted functional decline after TAVR, suggesting that this index might identify elderly patients who could potentially benefit from additional geriatric interventions.[66] Another study reported that a multidimensional geriatric assessment-based score (including cognition, nutrition, mobility, BADL, plus a 'home-made' frailty index) predicted one-year mortality and major adverse cardiovascular and cerebral events (MACCE) after TAVR in patients aged over 70 years.[67] Recently, a PARTNER trial sub-study found that, in older recipients of TAVR, frailty, assessed using a modified frailty phenotype model (serum albumin, dominant handgrip strength, gait speed and activities of daily living), independently predicted all-cause mortality or poor outcome at one year.[68]

A recent review of six studies and 4756 patients undergoing cardiac surgery or TAVR concluded that frail elderly patients have a higher likelihood of mortality, morbidity, functional decline and MACCE following cardiac surgery or TAVR, regardless of the frailty assessment tool.[69]

All of the studies[65–69] have reported frailty measurement before surgery or intervention and utilised it as an added prognostic tool for later events, but none of these studies has evaluated frailty in the immediate postoperative period, which is usually unstable and therefore not well suited for measurements of frailty that require clinical stability.

Table 5. Frailty tools in acute coronary syndrome or percutaneous transluminal coronary angioplasty.

Author	Patient numbers/age	Diagnosis	Frailty criteria	Frailty %	Outcome (frail vs. non-frail)
Ekerstad, et al. *Circulation* 2011; 124: 2397–2404.	Patients aged 75 years or older	NSTEMI	CSHA clinical frailty scale >5	48.5%	Frailty was independently associated with 1-year mortality after adjusting for CV risk and comorbidity (HR 4.3, 95% CI 2.4–7.8)
Sanchis, et al. *Am Heart J* 2014; 168: 784–791.	342 Patients Mean age 77 years	ACS	Fried score >3 Green score >5/12	Fried: 34% Green: 48%	Green score was an independent outcome predictor (per point; mortality: HR 1.25, 95% CI 1.15–1.36, $P = 0001$)
Sujino, et al. *J Cardiol* 2015; 66: 263–268.	62 Patients aged >85 years	STEMI	CSHA clinical frailty scale >6	35.5%	CSHA-CFS >6 ($P = 0.002$, OR 16.69) was an independent predictor of failure of discharge to home
White.; TRILOGY ACS investigators. *Eur Heart J Acute Cardiovasc Care* 2016; 5: 231–242.	4996 Patients aged >65 years	ACS	Fried score Pre-frail (1–2 items) Frail (≥3 items)	Frail: 4.7% Pre-frail: 23.0%	After adjustment for covariates, frailty was independently associated with cardiovascular death, MI, or stroke: pre-frail vs. not-frail, HR: 1.33; 95% CI 1.15–1.54; $P < 0.001$; frail vs. not-frail, HR 1.52; 95% CI 1.18–1.98; $P = 0.002$
Graham, et al. *Can J Cardiol* 2013; 29: 1610–1615.	183 Patients aged 65 years	ACS	Edmonton frail scale score >7	30%	After adjusting for confounders, the HR for mortality for EFS >7 compared with EFS 0–3 was 3.49 (95% CI 1.08–7.61; $P < 0.002$)
Singh, et al. *Circ Cardiovasc Qual Outcomes* 2011; 4; 496–502.	628 Patients aged >65 years	PTCA	Fried score Intermediate frail (1–2 items) Frail (≥3 items)	Frail: 18.6% Intermediate frailty: 46%	Three-year mortality was 28% for frail patients, and 6% for non-frail patients. Frailty, comorbidities and SF-36 improved prediction of death and death/MI over Mayo Clinic risk score
Murali-Krishnan, et al. *Open Heart* 2015; 2: e000294.	745 Patients mean age 62 years	PTCA	CSHA clinical frailty scale ≥5	Frail: 10.8%	Frailty was associated with increased 30-day (HR 4.8, 95% CI 1.4–16.3, $P = 0.013$) and 1 year mortality (HR 5.9, 95% CI 2.5–13.8, $P < 0.001$)
Myers, et al. *Eur J Prev Cardiol* 2014; 21: 758–766.	1521 Patients aged >65 years	ACS	Rockwood deficit accumulation frailty index (0–1 continuous scale)	====	Frailest group (≥0.25) had twice the multivariable-adjusted mortality risk of those in the least frail group (<0.10) (HR 2.02, 95% CI 1.46–2.79)

Frailty in elderly patients with chronic heart failure/ left ventricular assist device

Frailty prevalence in chronic heart failure (CHF) patients ranges from 15% to 74%, depending on the population and assessment method. The FRAIL-HF study[70] reported that 70.2% of non-dependent older patients hospitalised for CHF are frail, as evaluated by the Fried criteria. In these patients a superimposition of primary frailty associated with progressive ageing and frailty secondary to CHF is difficult to disentangle, as both share similar physiopathological mechanisms, such as anabolic–catabolic and neurohormonal imbalance, systemic inflammation, increased oxidative stress or mitochondrial dysfunction.[71] In CHF frailty is consistently associated with poor outcome, quality of life, disability or hospitalisation.[72–80]

McNallan et al. reported that frailty, measured by the Fried criteria, was an independent predictor of hospitalisations in community patients with CHF.[72] Cacciatore et al., utilising the Lachs frailty staging score (based on sensorial compromise, cognitive impairment, urinary incontinence, poor social support and disability), found that the probability of death in patients with CHF and a frailty score of 3 was 100% as

Table 6. Recommended tools for frailty evaluation in cardiac rehabilitation.

Tool	Items	Reference
Edmonton frailty scale	17 Simple questions or tasks, assessing cognition, self-perceived health, dependence for ADL, social support, medication use, nutrition, mood, continence and functional performance. Each item is given from 0 to 2 points, and a frailty state is assigned to a global score >8/17.	23
Clinical frailty scale from the CSHA study	Frailty assessment tool in the domains of mobility, energy, physical activity and function. Scale ranging from a level of 1 (very fit) to 8 (very severely frail).	22

compared with 55% in patients with CHF and a frailty score of 1.[73] Lupon et al. found that a scale based on evaluation of BADL–IADL, cognitive function, psychological and social status, was independently correlated with quality of life, hospitalisation and mortality.[74,75]

Volpato et al.[76] and Chiarantini et al.,[77] utilising the short physical performance Battery (SPPB), a test measuring lower extremity physical performance by walking speed, balance test and ability to stand up from a chair,[78] found in patients hospitalised for CHF that poor SPPB scores at hospital discharge were predictive of a greater risk of rehospitalisation or death. Even single items such as low gait speed or low grip strength in community living CHF patients were correlated with hospitalisation at follow-up,[79] and the Barthel index of disability and cognitive compromise correlated with six months mortality in CHF patients admitted to hospital.[80]

Recently, Dunlay et al. found, in a small cohort study of advanced CHF patients undergoing left ventricular assist device (LVAD) implantation, that pre-intervention frailty was associated with increased mortality.[81] This suggests that frailty assessment may be relevant for identifying suitable candidates for this invasive procedure. There is evidence that LVAD intervention[82] and heart transplantation[83] improve some biological, structural and functional markers of frailty associated with CHF.

Frailty and CR

Despite the negative bias for referring very elderly patients with complex comorbidities and frailty to CR,[84] at present patients older than 75 years represent about one third of those referred to CR.[85] Thus frailty might be present in a substantial proportion of patients admitted to CR, and this condition needs specific consideration.

The prevalence of frailty and its clinical and prognostic relevance has not as yet been well characterised in the environment of CR, although many studies have reported the measurement of frailty in patients with coronary syndromes in intensive care units or in cardiology wards,[49–52] and others have underscored the close link between frailty and CHF.[71–80] As patients after ACS or CHF represent a considerable proportion of those participating in CR,[85,86] we may suggest that frailty measurement should be performed in CR, to help plan their management and estimate their prognosis.

Frailty complicates the management of elderly patients, because it may affect the type and timing of diagnostic procedures and pharmacological and non-pharmacological treatment. Baseline physical function evaluation should be tailored to their physical conditions, and the CR programme should be individualized on the basis of their functional compromise and disability.[87] Pharmacological treatment should be carefully weighted, balancing guideline recommendations with a prudent approach, because associated comorbidities may increase iatrogenic complications. In community living or institutionalised frail elderly patients tailored exercise training has improved to some degree their physical function and quality of life.[88–93] Individuals at higher risk of disability at baseline derive the most benefit from these types of interventions[90] by increasing gait speed, improving balance and performance in activities of daily life,[91] or SPPB.[92] However, it is still uncertain whether these positive results can be applied to CR patients. Particularly in patients with CHF, structured exercise training improves the neurohormonal, inflammatory and metabolic parameters of CHF-related frailty and has favourable effects on physical function, functional capacity and quality of life.[70] It is still uncertain whether therapeutic interventions (pharmacological and non-pharmacological) that have proved successful in younger CHF patients will be successful in elderly patients, because the majority of randomised clinical trials in CHF do not include very elderly patients with frailty. However, from a practical standpoint, exercise-based CR programmes should be implemented, with caution, aimed at obtaining improvement in physical mobility, functional capacity, fall prevention, disability prevention or decreased progression, and improvement in quality of life.

Nutrition is also a very important part of the multidimensional intervention in CR,[94] particularly in very elderly and frail or sarcopenic/cachectic patients, where a poor nutritional status is one of the main

pathophysiological mechanisms for frailty. Recent studies suggest that improving nutritional status may reduce the risk of frailty.[95,96] Furthermore, a recent review has shown that nutrition may improve the functional outcome of elderly and frail patients.[97]

Future directions

Step 1: Feasibility of frailty measurement in the setting of cardiac rehabilitation

Assessment of frailty in the CR requires additional time within routine clinical evaluation. While the addition of frailty tools to the management of the elderly patient holds promise, multiple topics should be clarified before recommending their widespread clinical application. These include identifying which of the many tools provides the best combination of performance and facility, with clear definition of standardised values.

A variety of instruments for measuring frailty could be tested in CR and compared regarding their practical feasibility, trying to achieve a compromise between simplicity of administration and completeness of frailty domain representation. It is important to stress that the proposed tools should be selected among those already validated in hospitalised patients with cardiovascular disease, and particularly in patients after an acute coronary event or with CHF, who are likely to be similar to those admitted to CR programmes. It is uncertain whether tools validated before the index event for CR or in other clinical settins may be applicable to patients after a cardiovascular acute event/intervention.

The EFS could be used as representative of a user-friendly but comprehensive instrument (see also Table 6).[23] The EFS is easy to administer, requiring less than 5 minutes to perform; it can be administered by any professional (nurse, technician) or student, and it has been validated in elderly patients after acute coronary syndromes,[49] where it was found to correlate with prognosis. It also includes two clinical performance items interrogating cognition (clock test) and functional performance (timed up and go – TUG test). Tools based on the deficit accumulation model, such as the 40-item FI adopted by Singh et al.[98] adopted in elderly patients in acute geriatric rehabilitation wards, could be used to assess prognosis or guide intervention planning, or for evaluating frailty changes with time; however, in the busy CR world tools based on the deficit accumulation model may be cumbersome to apply. Therefore, an easy-to-use tool based on a standardised subjective evaluation of frailty would be more easily accepted and adopted, such as the Canadian Study on Health and Ageing clinical frailty scale[22] (Table 6).

The authors, through the European Association of Preventive Cardiology (EAPC), seek to evaluate the feasibility of applying these or more tools in CR centres through a European registry study in all elderly patients aged over 75 years. This would have the advantage of familiarising the cardiologist working in CR with frailty instruments, while screening for the frequency of frail elderly patients enrolled in European cardiac rehabilitation centres.

Some practical points should be discussed, such as who carries out these measurements. It is the authors' opinion that, due to the simple nature of the data to be collected, any health professional (cardiologist, cardiologist in training, nurse, allied health professional or medical student) could perform a frailty measurement, provided a uniform method of data collection is agreed and shared within and between CR centres.

The timing of frailty assessment in CR is also relevant. It is the authors' opinion that frailty should be measured at admission to CR if the patient is already stable, or later as soon as clinical stability is reached in the course of the rehabilitative programme. We believe that this approach is more correct, because before the acute event or surgery a frailty status may be worsened by the severity of disease, and may improve after clinical stabilisation is reached in CR. On the other hand, in patients entering CR after cardiac surgery, surgical complications in addition to a pre-surgical disability may limit their function, and it would be wise to wait for a progressive improvement in physical function before screening patients for frailty.

Step 2: Frailty and prognosis

It is still uncertain whether the addition of any frailty score/index to routine assessments in elderly patients entering CR may increase the prognostic capacity in that setting.

Therefore, these instruments should be tested in the CR environment as prognostic indicators against clearly defined endpoints, such as hospitalisation length, quality of life, disability and compared to traditional prognostic indicators, such as left ventricular ejection fraction, myocardial ischemia, arrhytmias or functional capacity. In this regard, a prospective observational study could be proposed for CR centres in Europe to evaluate the prognostic ability of frailty tools. If this is successful, CR practitioners may acquire an added tool to improve the prediction of outcomes, and be able to tailor the type and intensity of interventions for frail patients better.

In conclusion, it is the opinion of the authors that lead CR practitioners should work together with geriatricians to become more familiar with frailty instruments and their application in the clinical

environment in very elderly patients, to improve their prognostic ability and to design specific tailored interventions in complex patients. Further large studies can then be undertaken, to determine if the use of frailty measurement improves outcomes for elderly and frail patients admitted to CR.

Key messages

- Frailty is a condition specifically present in the elderly population, characterised by declining function of multiple physiological systems associated with loss of physiological reserves.
- Two main models are proposed for frailty: the phenotypic model (primary frailty) or the deficits accumulation model (secondary frailty).
- Different instruments have been used to measure frailty.
- Frailty correlates to medical outcomes in the elderly, independently of how it is measured.
- Frailty has been shown to have prognostic value for patients with coronary artery disease, cardiac surgery, TAVR, CHF and LVAD.
- The prevalence, clinical and prognostic relevance of frailty in a CR environment has not yet been well characterized.
- The presence and severity of frailty may modulate the CR programme through tailored interventions.
- We need to understand better to what extent CR may change the course and the prognosis of frailty, especially in cardiovascular patients, because exercise training and nutrition are well-known cornerstones in the management of elderly cardiac patients.

Author contribution

CV, AA, RB, UC, MC, CD, MCI, JPS, HV, SH and PD contributed to conception or design of work. CV, AA, MA and PD contributed to acquisition, analysis, or interpretation for the work. CV and PD drafted the manuscript. CV, AA, MA, RB, UC, MC, CD, SH, MCI, JPS, HV and PD critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. European Commission, Directorate-General for Research and Innovation. Population ageing in Europe: facts, implications and policies. European Commission, Bruxelles, Belgium. ISBN 978-92-79-35063-4. doi: 10.2777/60452.
2. Morley JE, Perry HM III and Miller DK. Editorial. Something about frailty. *J Gerontol A Biol Sci Med Sci* 2002; 57: M698–704.
3. Rockwood K and Mitnitski A. Frailty defined by deficit accumulation and geriatric medicine defined by Frailty. *Clin Ger Med* 2011; 27: 17–26.
4. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; 56: M146–156.
5. Clegg A, Young J, Iliff S, et al. Frailty in elderly people. *Lancet* 2013; 381: 752–762.
6. Bagshaw SM, Stelfox HT, McDermid RC, et al. Association between frailty and short- and long-term outcomes among critically ill patients: a multicenter prospective cohort study. *CMAJ* 2014; 186: E95–102.
7. Basic D and Shanley C. Frailty in an older inpatient population: using the clinical frailty scale to predict patient outcomes. *J Aging Health* 2015; 27: 670–685.
8. Fried LP, Ferrucci L, Darer J, et al. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci* 2004; 59: 255–263.
9. De Lepeleire J, Iliffe S, Mann E, et al. Frailty: an emerging concept for general practice. *Br J Gen Pract* 2009; 59: e177–182.
10. Strindberg TE and Pitkala KH. Frailty in elderly people. *Lancet* 2007; 21: 1328–1329.
11. Rockwood K, Mitnitski A and Mac Knight C. Some mathematical models of frailty and their clinical implications. *Rev Clin Gerontol* 2002; 12: 109–117.
12. Rockwood K and Mitnitski. A frailty in relation to the accumulation of deficits. *J Gerontol A Biol Sci Med Sci* 2007; 62A: 722–727.
13. Kulminski A, Yashin A, Arbeev K, et al. Cumulative index of health disorders as an indicator of aging-associated processes in the elderly: results from analyses of the national long term care survey. *Mech Ageing Dev* 2007; 128: 250–258.
14. Searle SD, Mitnitski A, Gahbauer EA, et al. A standard procedure for creating a frailty index. *BMC Geriatrics* 2008; 8: 24.
15. Mitnitski A, Song X, Skoog I, et al. Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. *J Am Geriatr Soc* 2005; 53: 2184–2189.
16. Romero-Ortuno R. The SHARE frailty instrument for primary care predicts mortality similarly to a frailty index based on comprehensive geriatric assessment. *Geriatr Gerontol Int* 2013; 13: 497–504.
17. Ensrud KE, Ewing SK, Cawthon PM, et al. A comparison of frailty indexes for the prediction of falls, disability,

fractures, and mortality in older men. *J Am Geriatr Soc* 2009; 57: 492–498.
18. Abellan van Kan G, Rolland YM, Morley JE, et al. Frailty: towards a clinical definition. *J Am Dir Assoc* 2008; 9: 71–72.
19. Subra J, Gillette-Guyonnet S, Cesari M, et al.; Platform Team. The integration of frailty into clinical practice: preliminary results from the Gérontopôle. *J Nutr Health Aging* 2012; 16: 714–720.
20. Schuurmans H, Steverink N, Lindenberg S, et al. Old or frail: what tells us more? *J Gerontol A Biol Sci Med Sci* 2004; 59: M962–965.
21. Gobbens RJ, van Assen MA, Luijkx KG, et al. The Tilburg Frailty Indicator: psychometric properties. *J Am Med Dir Assoc* 2010; 11: 344–355.
22. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005; 173: 489–495.
23. Rolfson DB, Majumdar SR, Tsuyuki RT, et al. Validity and reliability of the Edmonton Frail Scale. *Age Ageing* 2006; 35: 526–529.
24. Jones DM, Song X and Rockwood K. Operationalizing a frailty index from a standardized comprehensive geriatric assessment. *J Am Geriatr Soc* 2004; 52: 1929–1933.
25. Theou O, Thomas D, Brothers TD, et al. Operationalization of frailty using eight commonly used scales and comparison of their ability to predict all-cause mortality. *J Am Geriatr Soc* 2013; 61: 1537–1551.
26. Ellis G, Whitehead MA, O'Neill D, et al. Comprehensive geriatric assessment for older adults admitted to hospital. *Cochrane Database Syst Rev* 2011; 7: CD006211.
27. Jones D, Song X, Mitnitski A, et al. Evaluation of a frailty index based on a comprehensive geriatric assessment in a population-based study of elderly Canadians. *Aging Clin Exp Res* 2005; 17: 465–471.
28. Hubbard RE, Eeles EM, Rockwood MR, et al. Assessing balance and mobility to track illness and recovery in older inpatients. *J Gen Intern Med* 2011; 26: 1471–1478.
29. Stiffler KA, Finley A, Midha S, et al. Frailty assessment in the emergency department. *J Emerg Med* 2013; 45: 291–298.
30. Evans SJ, Sayers M, Mitnitski A, et al. The risk of adverse outcomes in hospitalized older patients in relation to a frailty index based on a comprehensive geriatric assessment. *Age Ageing* 2014; 43: 127–132.
31. Kahlon S, Pederson J, Majumdaret SR, et al. Association between frailty and 30-day outcomes after discharge from hospital. *CMAJ* 2015; 187: 799–804.
32. Singh I, Gallacher J, Davis K, et al. Predictors of adverse outcomes on an acute geriatric rehabilitation ward. *Age Ageing* 2012; 41: 242–246.
33. Pilotto A, Rengo F, Marchionni N, et al. Comparing the prognostic accuracy for all-cause mortality of frailty instruments: a multicentre 1-year follow-up in hospitalized older patients. *PLoS One* 2012; 7: e29090.
34. Wallis SJ, Wall J, Biram RW, et al. Association of the clinical frailty scale with hospital outcomes. *Q J Med* 2015; 108: 943–949.
35. Baldwin MR, Reid MC, Westlake AA, et al. The feasibility of measuring frailty to predict disability and mortality in older medical intensive care unit survivors. *J Crit Care* 2014; 293: 401–408.
36. Handforth C, Clegg A, Young C, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. *Ann Oncol* 2015; 26: 1091–1101.
37. Alfaadel TA, Soroka SD, Kiberd BA, et al. Frailty and mortality in dialysis: evaluation of a clinical frailty scale. *Clin J Am Soc Nephrol* 2015; 10: 832–840.
38. Pilotto A, Ferrucci L, Franceschi M, et al. Development and validation of a multidimensional prognostic index for one year mortality from comprehensive geriatric assessment in hospitalized older patients. *Rejuvenation Res* 2008; 11: 151–161.
39. Peterson MJ, Giuliani C, Morey MC, et al. Physical activity as a preventative factor for frailty: the health, aging, and body composition study. *J Gerontol A Biol Sci Med Sci* 2009; 64: 61–68.
40. Chin A, Paw MJ, van Uffelen JG, et al. The functional effects of physical exercise training in frail older people: a systematic review. *Sports Med* 2008; 38: 781–793.
41. Hubbard RE, Fallah N, Searle SD, et al. Impact of exercise in community-dwelling older adults. *PLoS One* 2009; 4: e6174.
42. de Vries NM, Staal JB, van Ravensberg CD, et al. Outcome instruments to measure frailty: a systematic review. *Ageing Res Rev* 2011; 10: 104–114.
43. Comans TA, Peel NM, Hubbard RE, et al. The increase in healthcare costs associated with frailty in older people discharged to a post-acute transition care program. *Age Ageing* 2016; 45: 317–320.
44. Ekdahl AW, Alwin J, Eckerblad J, et al. Long-term evaluation of the ambulatory geriatric assessment: a frailty intervention trial (AGe-FIT): clinical outcomes and total costs after 36 months. *J Am Med Dir Assoc* 2016; 17: 263–268.
45. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics – 2015 update: a report from the American Heart Association. *Circulation* 2015; 131: e29–322.
46. Afilalo J, Alexander KP, Mack MJ, et al. Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol* 2014; 63: 747–762.
47. Sanchis J, Bonanad C, Ruiz V, et al. Frailty and other geriatric conditions for risk stratification of older patients with acute coronary syndrome. *Am Heart J* 2014; 168: 784–791.
48. Singh M, Stewart R and White H. Importance of frailty in patients with cardiovascular disease. *Eur Heart J* 2014; 35: 1726–1731.
49. Graham MM, Galbraith PD, O'Neill D, et al. Frailty and outcome in elderly patients with acute coronary syndrome. *Can J Cardiol* 2013; 29: 1610–1615.
50. Singh M, Rihal CS, Lennon RJ, et al. Influence of frailty and health status on outcomes in patients with coronary disease undergoing percutaneous revascularization. *Circ Cardiovasc Qual Outcomes* 2011; 4: 496–502.
51. Ekerstad N, Swahn E, Janzonet M, et al. Frailty is independently associated with 1-year mortality for elderly patients with non-ST-segment elevation myocardial infarction. *Eur J Prev Cardiol* 2014; 21: 1216–1224.

52. White HD, Westerhout CM, Alexander KP, et al.; TRILOGY ACS investigators. Frailty is associated with worse outcomes in non-ST-segment elevation acute coronary syndromes: insights from the TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medicallY manage Acute Coronary Syndromes (TRILOGY ACS) trial. *Eur Heart J Acute Cardiovasc Care* 2016; 5: 231–242.
53. Sujino Y, Tanno J, Nakano S, et al. Impact of hypoalbuminemia, frailty, and body mass index on early prognosis in older patients (≥85 years) with ST-elevation myocardial infarction. *J Cardiol* 2015; 66: 263–268.
54. Murali-Krishnan R, Iqbal J, Rowe R, et al. Impact of frailty on outcomes after percutaneous coronary intervention: a prospective cohort study. *Open Heart* 2015; 2: e000294.
55. Myers V, Drory Y and Gerber Y. Clinical relevance of frailty trajectory post myocardial infarction. *Eur J Prev Cardiol* 2014; 21: 758–766.
56. Afilalo J, Mottillo S, Eisenberg MJ, et al. Addition of frailty and disability to cardiac surgery risk scores identifies elderly patients at high risk of mortality or major morbidity. Methods and results. *Circ Cardiovasc Qual Outcomes* 2012; 5: 222–228.
57. Lee DH, Buth KJ, Martin BJ, et al. Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. *Circulation* 2010; 121: 973–978.
58. Simon H, Sündermanna SH, Dademaschb A, et al. Frailty is a predictor of short- and mid-term mortality after elective cardiac surgery independently of age. *Interact Cardiovasc Thorac Surg* 2014; 18: 580–585.
59. Robinson TN, Eiseman B, Wallace JI, et al. Redefining geriatric preoperative assessment using frailty, disability and co-morbidity. *Ann Surg* 2009; 250: 449–455.
60. Rothman MD, Leo-Summers L and Gill TM. Prognostic significance of potential frailty criteria. *J Am Geriatr Soc* 2008; 56: 2211–2116.
61. Sarkisian CA, Gruenewald TL, John Boscardin W, et al. Preliminary evidence for subdimensions of geriatric frailty: the Macarthur study of successful aging. *J Am Geriatr Soc* 2008; 56: 2292–2297.
62. Bernstein AD and Parsonnet V. Bedside estimation of risk as an aid for decision-making in cardiac surgery. *Ann Thorac Surg* 2000; 69: 823–828.
63. Shahian DM, O'Brien SM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models, part 1: coronary artery bypass grafting surgery. *Ann Thorac Surg* 2009; 88: S2–S22.
64. Völler H, Salzwedel A, Nitardy A, et al. Effect of cardiac rehabilitation on functional and emotional status in patients after transcatheter aortic-valve implantation. *Eur J Prev Cardiol* 2015; 22: 568–574.
65. Green P, Woglom AE, Genereux P, et al. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: a single-center experience. *J Am Coll Cardiol Interv* 2012; 5: 974–981.
66. Schoenenbergern AW, Stortecky S, Neumann S, et al. Predictors of functional decline in elderly patients undergoing transcatheter aortic valve implantation (TAVI). *Eur Heart J* 2013; 34: 684–692.
67. Stortecky S, Schoenenberger AW, Moser A, et al. Evaluation of multidimensional geriatric assessment as a predictor of mortality and cardiovascular events after transcatheter aortic valve implantation. *J Am Coll Cardiol Interv* 2012; 5: 489–496.
68. Green P, Arnold SV, Cohen DJ, et al. Relation of frailty to outcomes after transcatheter aortic valve replacement (from the PARTNER Trial). *Am J Cardiol* 2015; 116: 264–269.
69. Sepehri A, Beggs T, Hassan A, et al. The impact of frailty on outcomes after cardiac surgery: a systematic review. *J Thorac Cardiovasc Surg* 2014; 148: 3110–3117.
70. Vidan MT, Sanchez E, Fernandez-Aviles F, et al. FRAIL-HF, a study to evaluate the clinical complexity of heart failure in nondependent older patients: rationale, methods and baseline characteristics. *Clin Cardiol* 2014; 37: 725–732.
71. Goldwater DS and Pinney SP. Frailty in advanced heart failure: a consequence of aging or a separate entity? *Clin Med Insights Cardiol* 2015; 9(Suppl. 2): 39–46.
72. McNallan SM, Singh M, Chamberlain AM, et al. Frailty and healthcare utilization among patients with heart failure in the community. *JACC Heart Fail* 2013; 1: 135–141.
73. Cacciatore F, Abete P, Mazzella F, et al. Frailty predicts long-term mortality in elderly subjects with chronic heart failure. *Eur J Clin Invest* 2005; 35: 723–730.
74. McNallan SM, Chamberlain AM, Gerber Y, et al. Measuring frailty in heart failure: a community perspective. *Am Heart J* 2013; 166: 768–774.
75. Lupón J, González B, Santaeugenia S, et al. Prognostic implication of frailty and depressive symptoms in in an outpatient population with heart failure. *Rev Esp Cardiol* 2008; 61: 835–842.
76. Volpato S, Cavalieri M, Sioulis F, et al. Predictive value of the short physical performance battery following hospitalization in older patients. *J Gerontol A Biol Sci Med Sci* 2011; 66A: 89–96.
77. Chiarantini D, Volpato S, Sioulis F, et al. Lower extremity performance measures predict long-term prognosis in older patients hospitalized for heart failure. *J Card Fail* 2010; 16: 390–395.
78. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol* 1994; 49: M85–94.
79. Chaudhry SI, McAvay G, Chen S, et al. Risk factors for hospital admission among older persons with newly diagnosed heart failure: findings from the Cardiovascular Health Study. *J Am Coll Cardiol* 2013; 61: 635–642.
80. Rozzini R, Sabatini T, Frisoni GB, et al. Frailty is a strong modulator of heart failure-associated mortality. *Arch Intern Med* 2003; 163: 737–738.
81. Dunlay SM, Park SJ, Joyce LD, et al. Frailty and outcomes following implantation of left ventricular assist device as destination therapy. *J Heart Lung Transplant* 2014; 33: 359–365.

82. Khawaja T, Chokshi A, Ji R, et al. Ventricular assist device implantation improves skeletal muscle function, oxidative capacity, and growth hormone/insulin-like growth factor-1 axis signaling in patients with advanced heart failure. *J Cachexia Sarcopenia Muscle* 2014; 5: 297–305.
83. Habedank D, Ewert R, Hummel M, et al. Changes in exercise capacity, ventilation, and body and body weight following heart transplantation. *Eur J Heart Fail* 2007; 9: 310–316.
84. Brown TM, Hernandez AF, Bittner V, et al.; American Heart Association Get With The Guidelines Investigators. Predictors of cardiac rehabilitation referral in coronary artery disease patients: findings from the American Heart Association's Get With The Guidelines Program. *J Am Coll Cardiol* 2009; 54: 515–521.
85. Giallauria F, Vigorito C, Tramarin R, et al.; ISYDE-2008 Investigators of the Italian Association for Cardiovascular Prevention, Rehabilitation and Prevention. Cardiac rehabilitation in very old patients: data from the Italian Survey on Cardiac Rehabilitation-2008 (ISYDE-2008) – official report of the Italian Association for Cardiovascular Prevention, Rehabilitation, and Epidemiology. *J Gerontol A Biol Sci Med Sci* 2010; 65: 1353–1361.
86. Giallauria F, Fattirolli F, Tramarin R, et al.; ISYDE-2008 Investigators of the Italian Association for Cardiovascular Prevention and Rehabilitation (GICR-IACPR). Cardiac rehabilitation in chronic heart failure: data from the Italian SurveY on carDiac rEhabilitation (ISYDE-2008). *J Cardiovasc Med (Hagerstown)* 2014; 15: 155–163.
87. Vigorito C, Incalzi RA, Acanfora D, et al.; Gruppo Italiano di Cardiologia Riabilitativa e Preventiva. Recommendations for cardiovascular rehabilitation in the very elderly. *Monaldi Arch Chest Dis* 2003; 60: 25–39.
88. Faber MJ, Bosscher RJ, Chin A, et al. Effects of exercise programs on falls and mobility in frail and pre-frail older adults: a multicenter randomized controlled trial. *Arch Phys Med Rehabil* 2006; 87: 885–896.
89. Binder EF, Schechtman KB, Ehsani AA, et al. Effects of exercise training on frailty in community-dwelling older adults: results of a randomized, controlled trial. *J Am Geriatr Soc* 2002; 50: 1921–1928.
90. Cesari M, Vellas B, Hsu FC, et al.; LIFE Study Group. A physical activity intervention to treat the frailty syndrome in older persons – results from the LIFE-P study. *Gerontol A Biol Sci Med Sci* 2015; 70: 216–222.
91. Chou CH, Hwang CL and Wu YT. Effect of exercise on physical function, daily living activities, and quality of life in the frail older adults: a meta-analysis. *Arch Phys Med Rehabil* 2012; 93: 237–244.
92. Giné-Garriga M, Roqué-Fíguls M, Coll-Planas L, et al. Physical exercise interventions for improving performance-based measures of physical function in community-dwelling, frail older adults: a systematic review and meta-analysis. *Arch Phys Med Rehabil* 2014; 95: 753–769.
93. Weening-Dijksterhuis E, de Greef MH, Scherder EJ, et al. Frail institutionalized older persons: a comprehensive review on physical exercise, physical fitness, activities of daily living, and quality-of-life. *Am J Phys Med Rehabil* 2011; 90: 156–168.
94. Balady GJ, Williams MA, Ades PA, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. *Circulation* 2007; 115: 2675–2682.
95. Bonnefoy M, Berrut G, Lesourd B, et al. Frailty and nutrition: searching for evidence. *J Nutr Health Aging* 2015; 19: 250–257.
96. Smit E, Winters-Stone KM, Loprinzi PD, et al. Lower nutritional status and higher food insufficiency in frail older US adults. *Br J Nutr* 2013; 110: 172–178.
97. Bibas L, Levi M, Bendayan M, et al. Therapeutic interventions for frail elderly patients: part I. Published randomized trials. *Prog Cardiovasc Dis* 2014; 57: 134–143.
98. Singh I, Gallacher J and Davis K. Predictors of adverse outcomes on an acute geriatric rehabilitation ward. *Age Ageing* 2012; 41: 242–246.
99. Hamilton BB, Granger CV, Shervin FS, et al. A uniform national data system for medical rehabilitation. In: Further MJ (ed.) *Rehabilitation outcomes: Analysis and measurements*. Baltimore: Paul H. Brooks, 1987.