

Clinical update

# Importance of frailty in patients with cardiovascular disease

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Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality. With the ageing population, the prognostic determinants among others include frailty, health status, disability, and cognition. These constructs are seldom measured and factored into clinical decision-making or evaluation of the prognosis of these at-risk older adults, especially as it relates to high-risk interventions. Addressing this need effectively requires increased awareness and their recognition by the treating cardiologists, their incorporation into risk prediction models when treating an elderly patient with underlying complex CVD, and timely referral for comprehensive geriatric management. Simple measures such as gait speed, the Fried score, or the Rockwood Clinical Frailty Scale can be used to assess frailty as part of routine care of elderly patients with CVD. This review examines the prevalence and outcomes associated with frailty with special emphasis in patients with CVD.

**Keywords** Frailty • Assessment • Prognosis • Cardiovascular disease

## Introduction

Cardiovascular diseases (CVDs) are the leading causes of death and hospitalization and represent an enormous clinical and public health burden which disproportionately affects older adults.<sup>1</sup> There has been a demonstrable shift in the burden of CVD towards older persons in the past two decades. During the same period, novel therapeutic approaches have improved their survival.<sup>2–4</sup> The overall health and prognosis of the older adults is influenced by frailty, comorbid conditions, and general health status as well as CVD. Current guidelines by the American College of Cardiology/American Heart Association (ACC/AHA) underscore the need to assess general health, comorbidity, cognitive status, and life expectancy,<sup>5,6</sup> but surprisingly do not mention frailty.

Despite their conceptual prognostic importance, these constructs are seldom formally evaluated in clinical practice and the treatment of CVD remains geared primarily towards the timely treatment of the underlying condition. A better understanding of the impact of these variables on outcomes may improve the care of patients with CVD. Identifying persons at increased risk among those with advanced chronologic age may foster care effectiveness by focusing on global health and by optimizing the use of finite healthcare resources. Addressing this need requires increased awareness and recognition by treating cardiologists, incorporation of frailty into

risk prediction models, and timely referral to manage frailty and other age-related problems. This review describes tools to assess frailty, and its relevance to the prognosis and clinical management of patients with CVD.

## Implications of cardiovascular disease in ageing populations

There are currently ~4.1 million deaths from CVD in Europe each year, with ~82% of these deaths in persons older than 65 years, and ~46% in persons older than 75 years.<sup>7</sup> The temporal declines in cardiovascular mortality, while varying widely between countries, have on average been similar for older (>65 years) compared with younger individuals within most European countries.<sup>7,8</sup> While age-specific cardiovascular mortality has been decreasing, in part because of lower case fatality rates, hospital admissions for CVD have continued to rise.<sup>7</sup> Improvements in life expectancy, more effective treatments and better outcomes are therefore changing the epidemiology of CVD, towards older persons who are more likely to be frail and to have greater comorbidity, creating enormous clinical, societal and economic challenges.<sup>9</sup>

Improved treatments and prevention of CVD are also increasing the proportion of patients who die from non-cardiac causes. In a

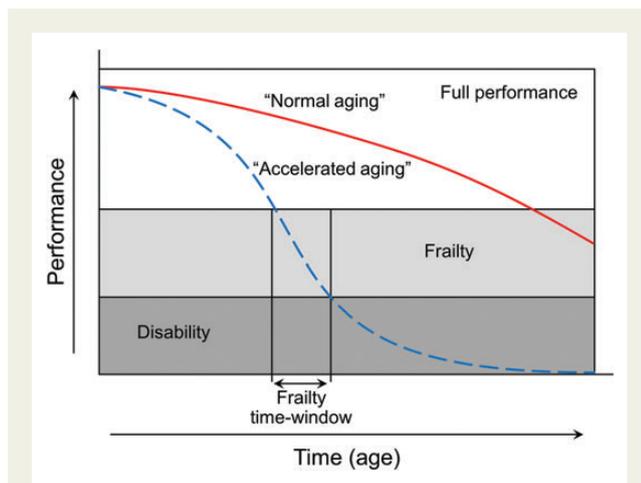
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large US cohort, there was a 33% decline in cardiac deaths at 5 years after hospital discharge following percutaneous coronary intervention (PCI), but a 57% increase in non-cardiac deaths.<sup>10</sup> Non-cardiac deaths also predominate in patients undergoing trans-catheter aortic valve replacement (TAVR) who, even after successful treatment, have high 1 year mortality, nearly 30% in the Placement of Aortic Transcatheter (PARTNER) Valve trial.<sup>11</sup> These observations emphasize the importance of considering non-cardiac predictors of death and quality of life in patients with CVD.

## Frailty

'Frailty' represents a complex clinical syndrome of increased vulnerability to stressors (Figure 1) which results from multiple impairments across different systems,<sup>12</sup> and accounts, at least in part, for the heterogeneity between biological and chronological age (Figure 2).<sup>13,14</sup> Individuals who have a lower functional capacity and fewer physiological reserves are at higher risk for homeostatic disruption with stress such as acute myocardial infarction (MI), heart failure, or cardiac surgery. Frailty has multiple contributors including age-related loss of muscle mass, reduced nutritional intake, low physical activity, as well as cardiovascular and non-CVD. Frailty has been associated with raised inflammatory markers including interleukin 6, C-reactive protein, low vitamin D, and low testosterone levels.<sup>15–19</sup>



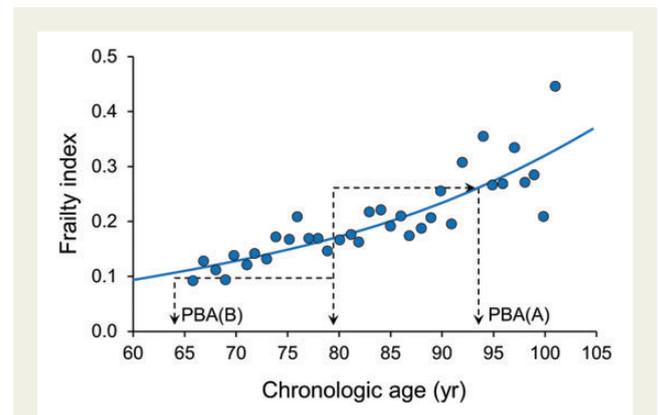
**Figure 1** Trajectories of health and functioning with ageing. On the 'Y' axis is the global measure of performance which may be physical, cognitive, social, or quality of life. Performance is divided into the meaningful levels. Individuals with full performance and high functional reserve can face environmental perturbations with ease. In contrast frail individuals have a high risk from homeostasis disruption and negative health outcomes including disability and death, due to exhaustion of functional reserve. With disability assistance is needed to function. The trajectory of decline with ageing varies widely between individuals. In some it is much steeper, and crosses the threshold of disability years before death. It may be precipitous after stroke, myocardial infarction, or fracture. Effective treatments of the presenting condition, avoiding complications and interventions which reduce frailty (arrow) may decrease the rate of decline or improve performance (modified from source).<sup>15</sup>

A clinically useful definition of frailty includes slowness, weakness, low physical activity, exhaustion, and weight loss (Supplementary material online, Figure S1). Frailty overlaps but is distinct from comorbidity, depression, poor quality of life, cognitive decline, and dependency in activities of daily living (Table 1).<sup>20,21</sup>

## Measuring frailty

Frailty is often assessed clinically from the 'end of the bed', using subjective approaches such as the 'eye ball test'. Lower body mass index values have been related to lower muscle mass.<sup>22</sup> These patients with sarcopenia are known to have adverse long-term outcomes.<sup>23</sup> However, this approach is unreliable and prone to bias. Simple, objective, and standardized methods provide quantitative estimates and reliable information on frailty to guide clinical decisions.

A number of simple tools are available to measure frailty using some or all of the key frailty criteria—by questionnaires or simple measurements.<sup>24</sup> Gait speed measured over 5–10 m, is easy to perform, reproducible, correlates with outcomes, is not confounded by fitness or cardiopulmonary symptoms.<sup>25,26</sup> Grip strength, measured by dynamometer (Jamar, Patterson Medical, IL, USA), is also easy to perform and predicts adverse outcomes.<sup>27</sup> The Short Physical Performance Battery and Up and Go test measures gait speed, chair rises, balance.<sup>28</sup> The Fried scale (Table 2) is based on the presence or absence of five frailty criteria—slowness assessed by walk speed, weakness assessed by hand grip strength, and self-reported low



**Figure 2** Relationship between frailty, age and the risk of death. This figure demonstrates a relationship between deficit accumulation as an estimate of biologic age and its correlation with the risk of death. Consider two people, A and B, of the same chronological age. At 78 years, the mean value of the frailty index is 0.16. Person A has a frailty index value of 0.26 that is higher than the mean value by 0.1 corresponding to the mean value of the frailty index at age 93 years. In essence, person A has the life expectancy of 93 years old; thus, although chronologically 78 years old, person A can be considered to be biologically 93 years old. In contrast, person B has a frailty index value of 0.1 that is lower than the mean value by 0.06 corresponding to the mean value of the frailty index at age 63 years. In essence, person B has the life expectancy of 63 years old; thus, although chronologically 78 years old, person B can be considered to be biologically 63 years old.<sup>14</sup>

**Table 1** Frailty and other multidimensional concepts which influence health, independence and quality of life in elderly patients with cardiovascular disease

|                               | Components   | Tools for measurement  |
|-------------------------------|--|--|
| Frailty                       | Exercise capacity<br>Muscle strength<br>Nutritional status   | Time to walk 4–10 m<br>Grip strength by dynamometer<br>Reported weight loss,<br>Frail screening tool<br>Fried criteria |
| Disability<br>Dependency      | Ability to undertake activities of daily living—shopping, finances, cleaning, cooking etc.<br>Dependent for basic cares—eating, toileting, washing, etc. | Nagi scale   |
| Cognitive function            | Memory and executive function<br>Mood  | Katz<br>MMSE, Montreal Cognitive Assessment Tool<br>Center for Epidemiological Studies Depression scale                |
| Physiological function        | Measures of organ system function  | Creatinine clearance, albumin, haemoglobin, forced expiratory volume in 1 s  |
| Comorbidity<br>Social support | Number and severity of chronic conditions<br>Family or community support<br>Financial resources  | Charlson index   |

**Table 2** Simplified Fried criteria for frailty<sup>99,100</sup>

|   |                           |  |
|---|---------------------------|--|
| 1 | Unintentional weight loss | >4.5 kg in the past year   |
| 2 | Exhaustion                | For at least 3 days during the last week 'I felt that everything I did was an effort' or 'I could not get going' |
| 3 | Physical activity         | No physical activity, spend most of the time sitting or rarely a short walk during the last year                 |
| 4 | Walk time                 | Time to walk 4 m >6 s  |
| 5 | Grip strength             | Grip strength by dynamometer   |

Frail = 3 or more criteria present, pre-frail = 1 or 2 criteria.

physical activity, exhaustion, and unintentional weight loss.<sup>29</sup> The few studies which compared frailty indices suggest that simple measures perform as well as the more complex multi-item tools.<sup>30,31</sup>

An alternative approach to assessing frailty is to quantify the accumulation of deficits.<sup>14,29</sup> The frailty index score calculates deficits based on symptoms, signs, disabilities, diseases, and laboratory measurements.<sup>14,32</sup> A standard Comprehensive Geriatric Assessment records ~40 items, some of which are self-reported (e.g. 'how would you rate your health'), while others are assessed by tests, (e.g. Mini-Mental State Examination), clinical evaluation (e.g. congestive heart failure) or laboratory measurement (diabetes mellitus).<sup>14,33</sup> A fraction is given for the deficits present to a limited extent (e.g. health as good = 0, fair = 0.5, poor = 1). The number of deficits is expressed as a proportion of the total possible. Research suggests cumulative deficits predict adverse outcomes more reliably than chronological age, and treatments which improve specific deficits may improve outcomes.<sup>34</sup>

**Table 3** The simple 'FRAIL' Questionnaire Screening Tool<sup>101</sup>

|  |
|--|
| <b>3 or greater = frailty; 1 or 2 = pre-frail</b>                      |
| Fatigue: are you fatigued?   |
| Resistance: cannot walk up one flight of stairs?                       |
| Aerobic: cannot walk one block   |
| Illness: do you have more than five illnesses?                         |
| Loss of weight: have you lost >5% of your weight in the past 6 months? |

A number of tools combine different components of physical function, cumulative deficits, and dependency. They include the FRAIL questionnaire<sup>35</sup> (Table 3), the Clinical Frailty Scale,<sup>36</sup> the Gérontopôle Frailty Screening Tool,<sup>37</sup> the Edmonton Frailty Scale,<sup>30,38</sup> and the Study of Osteoporotic Fracture index.<sup>30,39</sup> A global clinical assessment of frailty based on physical function and level of independence with activities of daily living has been proposed by Rockwood et al.<sup>36</sup> (Table 4).

In general, these assessments are easy to administer. While simpler tools may be limited by focusing on only a few aspects of a multidimensional problem, they are useful to identify individuals for a more comprehensive geriatric assessment. Screening for frailty has been recommended by a 2013 frailty consensus statement for all persons 70 years or older and those with significant (>5 lb; 2.3 kg) annual unintentional weight loss.<sup>40</sup> At present few large studies have compared different approaches,<sup>30,41</sup> and there is no clear consensus on which tools best inform clinical decisions. It is likely the optimal approach will vary depending on the clinical situation.

Even though tests to assess frailty are simple to administer, frailty measures are not included in most contemporary models of

**Table 4** A global clinical measure of fitness and frailty in elderly people

- 1 Very fit—robust, active, energetic, well-motivated and fit; these people commonly exercise regularly and are in the most fit group for their age
- 2 Well—without active disease, but less fit than people in category 1
- 3 Well, with treated comorbid disease—disease symptoms are well controlled compared with those in category 4
- 4 Apparently vulnerable—although not frankly dependent, these people commonly complain of being 'slowed up' or have disease symptoms
- 5 Mildly frail—with limited dependence on others for instrumental activities of daily living
- 6 Moderately frail—help is needed with both instrumental and non-instrumental activities of daily living
- 7 Severely frail—completely dependent on others for the activities of daily living, or terminally ill

outcome assessment. The reasons for the non-inclusion are not certain, but could relate to limited familiarity, concerns about the complexity of measurement, or to lack of widely accepted and standardized approaches. In addition some clinicians may not be aware of the importance of frailty, comorbidity, and quality of life as predictors of mortality and morbidity, or are uncertain of their relevance to clinical management.

We recommend using Fried criteria, the Rockwood clinical frailty scale or gait speed routinely in all patients with CVD who are 65 years or older. Gait speed, a component of Fried criteria cannot be measured in immobile or moribund patient and that is a limitation of the model. In these cases, deficit index can be calculated by the Rockwood clinical frailty scale.

## Prevalence of frailty

Varying degrees of frailty are common in elderly patients with CVD, but because different definitions and instruments are used, it is difficult to make simple comparisons of prevalence between studies and populations.<sup>42</sup> In a systematic review of 21 studies, the weighted prevalence of frailty in community dwellers older than 65 years was ~10% for 'physical frailty' and ~14% for a broader frailty phenotype.<sup>43</sup> In general, the prevalence of frailty increases with age, and is greater in females and in residents of long-term care facilities.<sup>29,44</sup> Frailty is about three times more prevalent among persons with compared with those without heart disease.<sup>45</sup> In the Cardiovascular Health Study, frail subjects were more likely to have subclinical CVD,<sup>46</sup> and subjects with subclinical CVD were more likely to have impaired physical or mental function during the follow-up.<sup>47</sup> Frailty has been reported in 20% of patients aged  $\geq 65$  years undergoing PCI,<sup>48,49</sup> and in 27% of patients aged  $\geq 70$  years with significant coronary artery disease at cardiac catheterization.<sup>31,48</sup> Frailty is particularly common in patients undergoing TAVR.<sup>11</sup> Frailty is also prevalent in patients with heart failure, which directly contributes to frailty by reducing exercise capacity and skeletal muscle function. Patients with congestive heart failure are more prone to falls and cognitive

**Table 5** Reasons for evaluating whether frailty is present in patients with cardiovascular diseases

- 1 Population ageing is increasing the number of frail patients with CVD
- 2 Eye ball or end of the bed assessments of frailty may not be reliable
- 3 Frailty increases the risks of cardiac surgery and other cardiovascular interventions
- 4 Frailty increases the risk of cardiovascular and non-cardiovascular mortality and the need for future institutional care
- 5 Frail patients may have more complications from medical treatments
- 6 The benefits of some cardiac interventions may be less in frail elderly patients because of competing risks. Non-cardiac deaths dominate following TAVR, PCI, and CABG

decline due to cerebral hypoperfusion, accelerating development of frailty and disability.<sup>50–52</sup>

## Frailty and prognosis

Frail patients with CVD have a worse prognosis than non-frail patients.<sup>46,47,53–58</sup> In 628 patients  $\geq 65$  years who underwent PCI at the Mayo Clinic, 3-year mortality was 28% for frail patients compared with 6% for non-frail patients using the Fried criteria.<sup>48</sup> Frailty, quality of life, and co-morbidity each improved prediction of mortality in addition to the conventional Mayo Clinic risk score. In 4671 patients aged  $>65$  years with an acute coronary syndrome managed medically who participated in the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY-ACS) trial,<sup>59</sup> 25% were pre-frail (one to two items) and 5% frail ( $\geq 3$  items) by a questionnaire based on the Fried frailty score.<sup>29</sup> Frail participants were more likely to suffer cardiovascular death, MI, or stroke after adjusting for the Global Registry of Acute Coronary Events (GRACE) score.

Frailty is a strong predictor of mortality in patients with chronic heart failure. In patients admitted to hospital with acute decompensated heart failure, simple measures of physical function have been associated with length of hospital stay, reduced activities of daily living, higher readmissions, and mortality.<sup>60</sup> In one community-based study, the attributable-risk associated with frailty in patients with heart failure was 35% for emergency department visits and 19% for hospitalizations.<sup>61</sup> In patients referred for cardiac surgery, frailty has been associated with postoperative mortality and morbidity, and greater need for rehabilitation and institutional care following the procedure.<sup>62,63</sup> In patients with severe symptomatic aortic stenosis treated by TAVR, frailty predicts need for institutional care and mortality 6–12 months after a successful procedure.<sup>64–66</sup>

## Relevance of frailty to clinical care

Identifying frailty has important implications for clinical care. The presence of frailty, worse health status, and more comorbid conditions identify a subset of elderly patients at higher risk of dying during the follow-up, even after a successful procedure (Table 5).<sup>67,68</sup> The magnitude of risk associated with the frailty,

comorbidity, and poor quality of life is greater than predicted from the risk models derived from conventional risk variables.<sup>65,67,68</sup> For example, in the study from the Mayo Clinic, the presence of frailty in a patient undergoing PCI increased the risk of mortality five-fold and mortality/MI ~2.5-fold compared with patients not determined frail at the time of the coronary intervention.<sup>48</sup> Frailty is also a strong, independent predictor of emergency department visits and hospitalizations in community dwellers with heart failure.<sup>61</sup> Identifying these conditions may be useful when counselling patients regarding their prognosis following a procedure. For example, if a patient is at moderate risk for long-term worse outcomes, they may decide against the procedure if they know the incremental risk from associated frailty and other age-associated determinants. Alternatively, a person at high risk estimated by conventional risk factors may be a better candidate if they are not frail and have good functional status. Assessment of frailty may therefore reclassify individuals to new and clinically meaningful risk categories. Identifying frailty can also prompt more comprehensive geriatric evaluation, and interventions to improve functional status. Reducing frailty is likely to both improve clinical outcomes and decrease healthcare utilization and costs.

## Management of patients diagnosed with frailty

In several observational studies, frail patients were less likely to receive cardiac catheterization or cardiac surgery (Figure 3).<sup>31,69</sup> Despite observed differences in care, there is currently limited evidence on how treatment and management should be altered for frail patients. Individualized approaches will be needed, depending on the patient and the treatment options. Treatment decisions may raise ethical dilemmas, particularly when it is uncertain how much benefit a frail patient will obtain from an intervention. It is important to distinguish frailty from futility, where attempts to improve prognosis are useless.<sup>11</sup> Frail patients may benefit greatly from treatments which reduce symptoms of limiting angina, and those related to heart failure or arrhythmia. Because frail patients have an increased risk of complications from procedures,<sup>67,68</sup> a less invasive strategy may be preferred, for example, trans-cutaneous rather than surgical

aortic valve replacement, or PCI rather than coronary artery bypass graft (CABG) for multi-vessel coronary artery disease. In some patients with a high mortality despite intervention, medical management may be more appropriate. In addition to frailty, quality of life, dependency, co-morbidity, dementia, and patient preference are relevant to these decisions.

The higher mortality of frail patients may reduce their ability to benefit from interventions when benefits accrue over time. Examples include elective repair of thoracic or abdominal aortic aneurysm, surgery for asymptomatic heart valve or coronary artery disease, and implantable cardioverter defibrillators. In a secondary analysis from the Surgical Treatment for Ischemic Heart Failure (STICH) trial which compared CABG with medical therapy in patients with ischaemic left ventricular dysfunction, patients with low exercise capacity, a marker of frailty, had a higher early mortality related to surgery if randomized to CABG, while mortality during ~5-year follow-up was similar by treatment. In contrast, patients with better exercise capacity had a lower risk from surgery and lower mortality during the follow-up if randomized to CABG compared with medical therapy.<sup>70</sup>

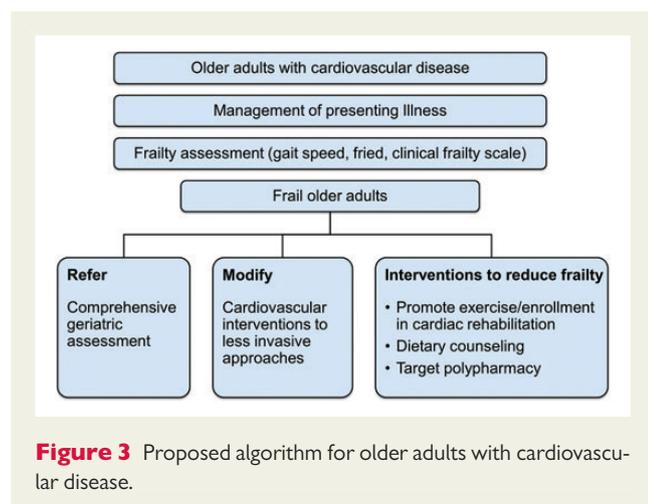
Recognizing frailty is also important for patient care. Closer attention may be needed to avoid complications related to dosing of medication, and to reduce the risk of falls when in unfamiliar environments. Planning of care can consider the likelihood of longer hospital admission and greater need for long-term support after discharge. For some elective procedures 'prehabilitation', which would include optimal treatment of medical conditions and interventions to reduce frailty, could reduce procedural risks. Clinical trials are needed to evaluate this approach.

## Interventions to reduce frailty

Frailty is dynamic and its earlier stages are potentially reversible.<sup>40</sup> Adverse outcomes are likely to be less in frail patients when treatment of the presenting cardiovascular and associated medical conditions is optimized, and complications avoided. In addition, a number of interventions have been proposed to reduce frailty. Two issues are important clinically: first, identification of the causes of frailty and its association with chronic inflammation and vascular disease; and second, establishment of the possibilities for prevention and their effectiveness.<sup>12</sup>

## Exercise prescription

The 2013 consensus statement on frailty focused on four interventions which have shown some efficacy in the treatment of frailty.<sup>40</sup> The most consistent benefit has been demonstrated with interventions related to exercise.<sup>71–73</sup> In a randomized trial, Singh et al.<sup>74</sup> demonstrated that exercise-based rehabilitation decreased hospitalization and nursing home placement following hip fractures in frail patients. Enrolment in cardiac rehabilitation improves outcomes of patients with CVD,<sup>75,76</sup> and may be particularly beneficial for frail patients. In addition to encouraging greater physical activity, specific deficits can be identified and prescription targeted to prevent and treat frailty. Patients with acute MI, stable angina, heart failure, cardiac transplant, or following major procedures such as PCI, CABG, or TAVR are eligible for cardiac rehabilitation. This facility, however, remains underutilized despite demonstration of



improvement in outcomes.<sup>77,78</sup> To improve outcomes of patients with CVD, cardiac rehabilitation services need to be optimally utilized and the protocols modified to cater for frail patients and to monitor their progress over the course of the treatment.

Dietary counselling may also be important. Nutritional supplements or a dietary plan that includes 25–30 g of high-quality protein per meal have been proposed to slow or prevent sarcopenic muscle loss.<sup>79</sup> Nutritional supplements can increase muscle mass, improve grip strength, and work synergistically with the benefits of resistance exercises in older adults.<sup>72,80–84</sup> Individual dietary prescription and supplements tailored to the needs of CVD patients with frailty presents the potential for an exciting new advance and current research efforts include the addition of branched amino acid leucine to resistance exercise in frail, older women (Clinical Trials, NCT 01922167).

Vitamin D supplements have been reported to improve muscle function, reduce falls,<sup>85</sup> and fractures,<sup>86</sup> and when combined with calcium to improve survival in elderly populations with vitamin D deficiency.<sup>87,88</sup> However, other meta-analyses suggest calcium supplements with or without vitamin D may increase the risk of MI.<sup>89</sup> There is currently uncertainty on whether vitamin D supplements benefit frail patients with CVD. The VITamin D and Omega-3 Trial (VITAL) which is currently enrolling 20 000 men and women in the USA to daily dietary supplements of vitamin D3 (2000 IU) or omega-3 fatty acids (Omacor<sup>®</sup> fish oil, 1 g) will provide more information on the role of vitamin D supplements.<sup>90</sup>

Polypharmacy or the use of multiple or duplicative medications increases the risk drug–drug and drug–disease interactions and contributes to adverse health outcomes. Reducing unnecessary medications can reduce costs and side effects.<sup>91–94</sup> In 30 136 patients with non-ST elevation MI in the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) registry, excessive dosing of unfractionated or low-molecular weight heparin or glycoprotein IIb/IIIa inhibitors occurred in 42% of subjects, and was associated with more bleeding, increased length of hospital stay and higher mortality.<sup>94</sup> Fifteen per cent of major bleeding was attributed to dosing errors which were more frequent in older subjects. Criteria proposed by Beers,<sup>95</sup> the Screening Tool of Older Persons Potentially Inappropriate Prescriptions, and Screening Tool to Alert Doctors to the Right Treatment (STOPP/START criteria),<sup>96,97</sup> can be used to guide reductions in poly-pharmacy.

Currently, evidence that interventions designed to improve frailty result in better outcomes in elderly patients with CVD is limited. Large randomised clinical trials are needed to evaluate the optimal management of these patients. The costs of care of the elderly are very high, and interventions which maintain independence of frail patients are more likely to be cost-effective. Evaluation of cost-effectiveness is an important aspect of future clinical trials.

## Conclusion

Improved life expectancy and population ageing are increasing the number of frail adults with CVD. Current evidence-based treatment guidelines do not usually account for frailty and other measures of overall health, and data on the efficacy and safety of evidence-based treatments in frail elderly patients are currently limited. Identifying

frailty is important because it is associated with an increased risk of both cardiovascular and non-cardiovascular morbidity and mortality, dependency, and complications from cardiovascular procedures and medical treatments. Including an objective assessment of frailty using simple tools will better inform the optimal care of older patients with CVD.

**Conflict of interest:** none declared.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

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