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Influence of exercise and nutrition on sarcopenia in cardiovascular disease

A Scientific Statement of the European Association of Preventive Cardiology of the ESC

Veronique Cornelissen[1]

Henner Hanssen[2]

Christopher Hurst[3,4]

Raphael Knaier[2]

Elena Marques-Sule[5]

Trine Moholdt[6,7]

Daniel Neunhaeuserer[8]

Kristina Norman[9]

Roberto Pedretti[10,11]

Annett Salzwedel[12]

Kai Savonen[13]

T. Scott Bowen[14]

[1]Department of Rehabilitation Sciences, KU Leuven, Belgium

[2.]Department of Sport, Exercise and Health, Sports and Exercise Medicine; Faculty of Medicine, University of Basel, Basel, Switzerland

[3] AGE Research Group, Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK

[4] NIHR Newcastle Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust, Cumbria Northumberland Tyne and Wear NHS Foundation Trust and Faculty of Medical Sciences Newcastle University, Newcastle upon Tyne, UK

[5]Department of Physiotherapy, Faculty of Physiotherapy, University of Valencia, Valencia, Spain

[6]Department of Circulation and Medical Imaging, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway

[7]Department of Obstetrics and Gynaecology, St. Olav's Hospital, Trondheim, Norway

[8]Sports and Exercise Medicine Division, Department of Medicine, University of Padova, Padova, Italy

[9]Department of Nutrition and Gerontology, German Institute for Human Nutrition Potsdam Rehbruecke; and Department of Geriatrics and Medical Gerontology, Charite Universitätsmedizin Berlin, Berlin, Germany

[10]School of Medicine and Surgery, University of Milan Bicocca, Milan, Italy

[11]Cardiology Unit, Hospital of Erba, Erba (CO), Italy

[12]Department of Rehabilitation Medicine, Faculty of Health Sciences Brandenburg, University of Potsdam, Potsdam, Germany

[13]Foundation for Research in Health Exercise and Nutrition, Kuopio Research Institute of Exercise Medicine, Kuopio, Finland.

[14]School of Biomedical Sciences, Faculty of Biological Sciences, University of Leeds, Leeds, UK

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✉ **Corresponding Author Address:**

T Scott Bowen
School of Biomedical Sciences,
Faculty of Biological Sciences,
University of Leeds,
Leeds,
UK LS2 9JT
email: t.s.bowen@leeds.ac.uk
Tel: +44 113343 3834

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Abbreviations

ACE	Angiotensin-Converting Enzyme
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
CVD	Cardiovascular Disease
DXA	Dual Energy X-ray Absorptiometry
EWGSOP	European Working Group on Sarcopenia in Older People
ExT	Endurance Exercise Training
FITT	Frequency, Intensity, Time, and Type
GDF15	Growth Differentiation Factor 15
GLP1	Glucagon-Like Peptide-1
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HIIT	High-Intensity Interval Training
ICD10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
IGF1	Insulin-like Growth Factor 1
IL1β	Interleukin 1 beta
IL6	Interleukin 6
MuRF1	Muscle RING-Finger Protein-1
PGC1α	Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha
RAAS	Renin–Angiotensin–Aldosterone System
RM	Repetition Maximum
RxT	Resistance Exercise Training
SARC-F	Strength, Assistance, Rise, Climb, Falls Questionnaire
SARMs	Selective Androgen Receptor Modulators
SGLT2	Sodium-Glucose Cotransporter 2
SPPB	Short Physical Performance Battery
TNFα	Tumour Necrosis Factor alpha
TUG	Timed Up and Go
VO_2peak	Peak Pulmonary Oxygen Uptake

Abstract

This document aims to review current scientific evidence on exercise and nutrition as a treatment for sarcopenia in the context of cardiovascular disease (CVD). First, we introduce the topic of sarcopenia and its estimated prevalence in patients with CVD. Then, we critically analyse the available evidence to support the use of exercise and nutrition, both alone and combined, for treating sarcopenia in patients with CVD followed by discussing factors that may optimise management. We further discuss the relevance of how medications used in CVD impact sarcopenia and how they may negatively interact with exercise/nutritional interventions. Finally, we provide insights into the practical implications and future directions for managing sarcopenia in patients with CVD. In summary, optimised physical exercise interventions (dedicated resistance training in addition to endurance training and other modalities) together with adequate nutritional intake (avoiding malnutrition and ensuring sufficient protein consumption) is advised for the prevention and management of sarcopenia. However, there currently remains a lack of high-quality evidence to support these approaches in the context of CVD, where baseline sarcopenia status has typically not been evaluated. Future work, therefore, is required in CVD populations with confirmed sarcopenia to better understand what optimal exercise and nutritional strategies are required to further improve sarcopenia management.

1.0 Introduction

Cardiovascular disease (CVD) is a global contributor to morbidity and mortality, with rates projected to rise[1]. Many patients with CVD present with the co-morbidity sarcopenia, which is characterised by a loss of skeletal muscle mass and function[2,3]. Sarcopenia decreases mobility and increases frailty and risk of falls, which promote disease progression and low quality of life in patients with CVD[3]. Sarcopenia is associated with an increased risk of all-cause mortality in both those with[4-6] and without CVD[7,8], while further representing a key risk factor for the onset as well as progression of CVD[9,10]. Since 2016, sarcopenia has been recognised as a disease (ICD10-CM: M62.84)[11]. Combined, CVD and sarcopenia can be viewed as a perfect storm that worsen symptoms, functional independence, and clinical outcomes[2,12].

There is currently no document published by the European Society of Cardiology (ESC) dedicated to the topic of sarcopenia and its management in patients with CVD, which highlights a knowledge gap. A primary gap identified in general sarcopenia research is the identification and validation of tailored treatment interventions for the diverse group of patients with CVD[13]. Despite the global prevalence of sarcopenia rapidly increasing[3], evidence supporting the implementation of effective and targeted treatments remain limited. One important reason for that is the lack of screening for sarcopenia in clinical practice, precluding the provision of therapies addressing sarcopenia. As such, this manuscript creates awareness and informs the clinical field on the need to evaluate the presence of sarcopenia and adapt therapy accordingly. Interventions to combat sarcopenia include regular physical exercise and healthy nutrition, and while much evidence supports these approaches for improving general cardiovascular health and fitness in CVD populations[14,15], the evidence for and the optimal doses required, either independently or combined, that address poor skeletal muscle health (sarcopenia) in the diverse group of patients with CVD remains incompletely addressed[2].

This paper, therefore, aims to provide a scientific statement evaluating the current evidence to support the use of exercise and nutrition as treatments for sarcopenia in CVD. Specifically, in CVD populations we aimed to identify: i) current definition, criteria, and prevalence of sarcopenia; ii) what exercise training or nutritional interventions show greatest efficacy for treating sarcopenia; iii) if concurrent exercise-nutrition interventions are available that optimise sarcopenia treatment and underlying mechanisms; iv) the positive/negative interactions between medications and exercise/nutrition on sarcopenia management; v) practical implications and gaps in knowledge that require addressing. To support immediate clinical relevance, evidence is primarily sourced from human studies, and we focus on those studies in which sarcopenia was diagnosed to strengthen specificity.

2.0 Evidence Review

The document was prepared by a working group composed of contributors from the European Association of Preventive Cardiology (EAPC) of the ESC, as well as from other relevant invited healthcare professionals with expertise in the fields of sarcopenia, exercise physiology, physiotherapy, and nutrition. Members of the group were asked to perform a detailed literature search of the selected topic using electronic databases, and to select and critically evaluate relevant papers to provide a scientific statement.

3.0 Sarcopenia: definition and diagnosis

The 2021 ESC Guidelines on CVD prevention and management in clinical practice highlighted a need to screen and treat sarcopenia appropriately[16,17]. However, there remains a lack of knowledge on how to diagnose and manage sarcopenia in the CVD field. There is considerable overlap, but clear distinction, between sarcopenia and several other conditions that include frailty[18], cachexia[19], and malnutrition[12,20] (Figure 1) and each should be treated accordingly. Sarcopenia is defined as a progressive and generalised skeletal muscle disorder involving the accelerated loss of muscle mass and function that is associated with a range of adverse outcomes including falls, fractures, functional decline, and mortality[3,21]. Sarcopenia is defined '*primary*' or age-related when no other specific cause is evident, or '*secondary*' when causal factors other than ageing are present[13]. Secondary sarcopenia, where muscle loss is associated with specific disease(s), is particularly relevant for those living with CVD[22], with one small study (N=17-30) showing that > 50% of patients with advanced heart failure (HF) were diagnosed with sarcopenia despite being < 60 years of age[23]. However, caution is warranted when generalising smaller studies to the general CVD population. Sarcopenia can also be sub-categorised as being either acute or chronic[13], with differences in aetiology and prognostic implications. Acute sarcopenia, lasting <6 months, is typically related to acute illness, injury or hospitalisation[24], and is reversible if appropriate treatment (e.g., exercise, nutrition) is initiated in a timely manner. Acute sarcopenia is particularly relevant in patients with CVD, where hospitalizations due to invasive surgery or HF decompensation are high and linked to increased sarcopenia[2,16]. Chronic sarcopenia lasting >6 months on the other hand is associated with the presence of other chronic and progressive conditions.

Early efforts to conceptualise a definition of sarcopenia focused on the loss of muscle or lean mass[25]. However, muscle strength and function are now universally viewed as the central components of sarcopenia, because of stronger associations with adverse outcomes[7]. Several operational definitions of sarcopenia have been proposed, and revised, by working groups from around the world including Asia[26], Europe[13] and the USA[27] with ongoing work aiming to create a global consensus definition of sarcopenia[28]. The current European Working Group on Sarcopenia in Older People (EWGSOP2) definition is the most widely applied in research and clinical practice and characterises sarcopenia as a loss of muscle strength, mass, and function[13]. The EWGSOP2 uses an algorithm for identifying individuals with possible sarcopenia, diagnosis, and severity (Figure 1). The algorithm shows that clinical suspicion and/or the SARC-F questionnaire[29] should be used initially to identify individuals with probable sarcopenia. Low muscle strength can then be identified using either grip strength[30] or chair stand test[31]. Sarcopenia is confirmed by the presence of low muscle quantity or quality (e.g., by dual energy x-ray absorptiometry [DXA] or bioelectrical impedance analysis [BIA]). Finally, sarcopenia severity is thereafter assessed by the measurement of physical performance (e.g., gait speed, short physical performance battery [SPPB], timed up-and-go test [TUG], or 400-meter walk test [400MWT]).

More recently, increasing attention has been given to the concept of sarcopenic obesity, with considerable effort made to establish a consensus on definition and diagnostic criteria[32]. Characterised by a concurrent decline in muscle mass and function with increased adiposity, sarcopenic obesity is a growing concern because of its association with a range of adverse health outcomes[33]. The combination of sarcopenia and obesity may act synergistically to augment the consequences of either condition alone[34]. Sarcopenic obesity may have particular relevance for many patients with CVD, especially in HF with preserved ejection fraction (HFpEF), where it has been linked to greater exercise intolerance[35] and mortality[36] in large cohort studies. Moreover, although often overlooked, another key feature common in CVD[37] that is closely linked to greater symptoms and mortality is respiratory muscle weakness[38]. Testing for respiratory muscle sarcopenia could therefore provide a useful assessment in patients with CVD, although limitations currently include no established cut-off criteria.

- **Take home message**

  There needs to be a greater awareness in the CVD field of what sarcopenia is, how it is diagnosed, and the associated negative outcomes, as this will aid early detection and appropriate treatment. Current guidelines for sarcopenia management are based on evidence from the general population and do not account for the additional influence of CVD.

4.0. Prevalence of sarcopenia in CVD

The prevalence of sarcopenia varies widely between studies, likely influenced by the definition, methods, and cut-off criteria used[39]. Sarcopenia is estimated to influence around 5-10% of the general population, typically increasing with age[21]. A meta-analysis including different classifications and cut-off points reported high variability in sarcopenia incidence in the general population ranging from 10-27%, with rates of 2-9% for severe sarcopenia[39]. Similarly, substantial variation is reported for sarcopenic obesity with estimates of 5-15%[7,40], which is likely impacted by the definition lacking consensus[33]. Although sex differences have been reported, they remain inconsistent and show sensitivity to the classification criteria[39]. Compared with the general population, the prevalence of sarcopenia amongst patients with CVD is significantly higher at 35%, ranging from 10 to 69%[2,22]. However, these higher rates may be influenced by a potential bias compared with the general population due to CVD patients spending increased time in medical care. Sarcopenia is particularly common amongst patients with HF (both with reduced ejection fraction [HFrEF] and HFpEF), suggested to occur in at least 20-34% of patients based on large cohorts[22,41,42] and increasing up to ~50% at time of left ventricular assist device implantation[23] and ~60-70% in those hospitalized for acute decompensated HF in smaller studies[22,42]. Sarcopenia in HF is more prevalent in men compared with women[41,43] (but based on small female sample sizes of N=16-41), and in those who are older[41] (i.e., 31% and 25% in those above compared to below 65 years of age, respectively[44]). However, rates as high as 50% have been reported in those with HF aged between 40-50 years of age, albeit in small populations (N=30-55)[23,45]. Despite a systematic review and meta-analysis reporting a high incidence of sarcopenia in other CVD conditions[2,22] such as aortic stenosis (21-70%), coronary artery disease (12-25%), cardiac arrhythmia (30%), cardiac surgery (35%) and peripheral artery disease (35%), these other conditions have generally received less attention. Finally, sarcopenia can be further increased by existing and chronic comorbidities common to patients with CVD, such as chronic kidney disease, obesity, hypertension, respiratory diseases, diabetes, and cancer[12], further exacerbating symptoms and disease progression[12,21] (Graphical Abstract).

- **Take home message**

  The estimated prevalence of sarcopenia is higher in patients with CVD compared with the general population, and this is likely exacerbated by coexisting chronic comorbidities that further contribute towards greater symptoms and poorer clinical outcomes.

5.0 Aetiology and mechanisms of sarcopenia in CVD

An improved understanding of the biological mechanisms underpinning the onset of sarcopenia could help identify suitable therapeutic targets and improve treatment strategies. However, the mechanisms underlying sarcopenia are complex and multifactorial[12,46]. Briefly, proposed mechanisms include chronic low-grade inflammation, hormonal changes, neuromuscular impairments, mitochondrial dysfunction, changes in rates of protein turnover, oxidative stress, genetic/epigenetic factors, stem cell dysfunction, and cellular senescence[12,46]. Lifestyle factors likely contribute, such as inadequate nutrition[47] and physical inactivity[48], especially during periods of disuse associated with hospital (re)admissions, where recovery is known to be slower in old compared with young patients[49] and exacerbated by CVD[50]. Interestingly, lack of exercise training alone does not seem to be a sole mechanism, as small cohort studies (N=20-28) have shown that even lifelong exercise delays rather than eliminates signs of sarcopenia[48].

As noted in Section 4.0, the prevalence of acute and chronic sarcopenia are higher in CVD compared with the general population, which is likely due to additional CVD-specific mechanisms promoting the onset and progression of secondary sarcopenia above and beyond that associated with ageing (i.e. primary sarcopenia). These mechanisms may include crosstalk with primary organ dysfunction, reduced peripheral perfusion (hypoxia), increased systemic inflammation, iron deficiency, insulin resistance, neurohormonal disturbances (increased sympathetic activity), and endothelial dysfunction. Also, additional comorbidities (e.g. kidney disease, cancer, diabetes), disease-related malnutrition, physical inactivity, increased hospital readmissions, and side effects of medications may play a role[51]. Moreover, sex differences in sarcopenia prevalence are reported in CVD[41] and recent evidence suggests sex-specific biological mechanisms may contribute[43]. Underlying changes to muscle characteristics in patients with CVD include a shift in fibre-type composition and metabolism (from oxidative and fatigue-resistant Type I to the more glycolytic and fatigable Type II), increased mitochondrial dysfunction, fibre atrophy (predominantly Type II) and apoptosis, fibre contractile weakness, increased fibrosis and fat infiltration, and reduced muscle capillarity[51,52]. Importantly, however, mechanisms of secondary sarcopenia specific to CVD remain incompletely understood. Although many studies have investigated the underlying mechanisms of muscle pathology in populations with CVD[2], especially in HF[52,53], most of these studies did not make any diagnosis of sarcopenia, which may explain variability between past studies[54-56]. Together, therefore, most knowledge is based on evidence drawn from CVD populations that likely included those with and without diagnosed sarcopenia, meaning current biological understanding remains vague.

- **Take home message**

  The underlying biological mechanisms causing sarcopenia are complex and remain incompletely understood, with most of our understanding derived from patients without CVD.

6.0. Principles of exercise training in CVD

Lifestyle interventions are important tools to prevent and overcome the sarcopenia-related health burden in patients with CVD, of which exercise training forms a cornerstone[57,58]. The practical basics of an exercise prescription should address the components included in the so-called FITT principles: frequency, intensity, time, and type.[59] Frequency is how often exercise is performed each week, intensity is how hard the exercise is, time is the exercise duration, and type is the mode of exercise (typically endurance or resistance, but also flexibility and balance exercises). The American College of Sports Medicine (ACSM) advises adding volume (the total amount of exercise) and progression (how the programme advances), when designing an individualised exercise prescription (FITT-VP)[59]. Exercise volume is the product of exercise frequency, intensity, and duration of each exercise session. The suggested rate of progression in an exercise programme depends on the health status, physical fitness, training responses, and goals of each individual[59]. Progression implies increasing any of the components of the FITT principle, as tolerated by the individual. Specification of all FITT components is important for an optimal personalised exercise prescription as outlined in detail previously[14,60]. Nevertheless, in clinical practice substantial variability exists amongst CV patients in both clinical characteristics and their responses to exercise therapy[61]. This underscores that the principle of one size fits all will not be sufficiently effective and that individual adjustments should be made according to the patient's underlying disease(s), risk profile, and individual needs to maximize its effectiveness on the health outcome for the patient. Given the increasing incidence of sarcopenia there is a need to inform on more specific and professional advice for exercise training that will also target improvements in muscle health in patients with CVD.

6.1 Evidence for resistance exercise training as a treatment targeting sarcopenia in CVD

Strength or resistance exercise training (RxT) is currently recognised as a primary treatment to manage sarcopenia[62]. The International Clinical Practice Guidelines for Sarcopenia advise RxT for improving muscle mass, muscle strength, and physical performance[63]. RxT involves working against applied forces such as resistance machines, free weights, bodyweight exercises, or resistance bands. These exercises can be individualised based on the FITT principles[59], or aligned to RxT programming variables[62]. The current suggestions for RxT in CVD populations includes 30-60 min of weekly training with 8-10 different exercises per session, with each set containing 8-12 repetitions at 40-60% one repetition maximum (1RM) at least twice weekly[58]. Further advice includes having an interval of at least 48 hours between training sessions of the same muscle groups[58]. Note, however, these guidelines are generalised to the CVD population. As such, a more gradual and tailored approach is likely required for those with diagnosed sarcopenia, significant frailty, or mobility issues (e.g., arthritis), whereby use of the modified repetition maximum (RM) approach may be required (e.g., the highest weight that can be lifted over a defined number of repetitions; 10RM)[62].

Solid evidence in older patients shows that RxT can increase muscle strength and physical performance, and to a lesser extent muscle mass, as reported in systematic (umbrella) reviews[64-67]. However, for those diagnosed with sarcopenia, less high-quality evidence is available[66,68]. A recent network meta-analysis from 42 randomized controlled trials provided moderate-high evidence to support the utility of RxT as a treatment for sarcopenia, which included a majority of studies meeting baseline characteristics for sarcopenia diagnosis (3728 patients; 73% female)[69]. Moreover, a randomized controlled study in older patients with sarcopenia (~85 years of age) recovering from acute illness showed improved handgrip strength, physical performance, and mobility after a RxT intervention for 12 weeks (2 x per week, 20 min sessions with 3 sets of 8-12 reps of multiple strength exercise at 70-80% 1RM)[70]. Although similar findings have been reported in other studies using RxT protocols in patients diagnosed with sarcopenia[71,72], these were confounded by a post acute care study setting, lack of muscle mass measures, and low samples sizes, highlighting the need for more well-controlled studies to show complete efficacy of RxT in sarcopenia treatment.

Among patients with CVD, the benefits of RxT on muscle strength are well supported[49,73,74] (Table 1; Figure 2). For example, a systematic review and meta-analysis in patients with HF concluded that RxT improves muscle strength and physical function, without adverse effects on cardiac measures[73]. A systematic review included studies on patients with peripheral arterial disease and found RxT was likely the best treatment[75]. In HFrEF and coronary heart disease, multiple studies have shown benefits for RxT on muscle strength and physical function[73,76]. A small, randomized RxT study showed that muscle strength was improved by ~50% in females with HFrEF compared with controls[77]. This study also found that exercise capacity was increased following 10 weeks of high-intensity progressive RxT, although without significant changes in muscle mass[77]. Similar changes

related to muscle strength have also been reported in other randomized studies on RxT in HFrEF including benefits to quality of life and clinical status[78-80], but large-scale clinical studies on RxT in HFrEF are currently missing. Although most studies have performed low-to-moderate load RxT(< 40% 1RM), utilising high-load RxT (70-80% 1-RM) may provide greater strength gains in patients with coronary artery disease or HF[81-83] and excellent guidelines are available to direct this in CVD populations[81-83]. Similarly, in peripheral arterial disease, high-intensity progressive RxT (4-6 months for 3 x per week) showed beneficial effects on muscle strength, muscle mass, walking time, and quality of life scores[84]. Although high-load RxT shows few adverse effects in patients with CVD[85], large randomized controlled trials are still required to support efficacy and feasibility in the frailest patients. Less is known about the effects of RxT on muscle function in other CVDs, such as HFpEF or valvular heart disease[86]. A recent randomized controlled study in a small, predominately male cohort of older patients with HFpEF, reported that RxT for ~12 weeks was safe and improved muscle strength and physical performance[87]. However, almost all knowledge to date on the effect of RxT on muscle strength and mass in patients with CVD derives from studies in populations without sarcopenia diagnosed at baseline (Table 1; Figure 2). An ongoing randomised controlled trial that includes patients with HFpEF diagnosed with sarcopenia will determine whether home-based RxT (2 x per week, 2 sets of 10 reps at 60%–70% 1RM) can attenuate sarcopenia[88]. As such, current evidence for the specific effects of RxT on sarcopenia-related outcomes in patients with CVD is uncertain (Figure 2), whereas it remains unclear in the long-term whether sarcopenia returns to pre-training levels if or once patients cease RxT.

- **Take home message**

  Resistance training is advised as a safe add-on treatment for patients with CVD and concomitant sarcopenia, primarily for improving muscle strength and physical performance. Emerging evidence supports the gradual (starting low) and progressive implementation of higher-load resistance training when feasible. However, there is still limited high-quality evidence regarding the specific optimal frequency, intensity, time, and type parameters of resistance training that yield the greatest benefits for patients with CVD diagnosed with sarcopenia.

6.2 Evidence for endurance and high-intensity interval exercise training in treating sarcopenia in CVD

For sarcopenia management, less attention has been directed towards the effects of endurance exercise training (ExT; also termed aerobic training) compared with RxT in patients with and without CVD. Current guidelines for ExT in patients with CVD advise at least 150 min per week of moderate-intensity exercise over 5 days, or at least 75 min per week of vigorous-intensity exercise over 3 days (typically termed high-intensity training that may or may not include intervals; HIIT) or a combination[89]. Although ExT does not generally promote muscle hypertrophy, it is safe and promotes muscle health, cardiorespiratory fitness, and quality of life scores in patients with CVD[89,90]. Even low to moderate-intensity cycling may help preserve muscle mass and strength in CVD patients due to the low loading components required. The key mechanisms for how ExT increases muscle health in patients with CVD include improved mitochondrial function, a shift in muscle fibre-type composition and metabolism (glycolytic to oxidative), increased muscle capillarity, enhanced anti-inflammatory capacity, and also anti-atrophy effects related to a downregulation in molecular catabolic signalling (e.g. MuRF1, myostatin)[52,57]. Together these changes contribute towards increasing exercise capacity (e.g., peak pulmonary oxygen uptake; VO_{2peak}) and may further benefit muscle mass and function in patients with CVD[52,57] (Table 1).

In patients with sarcopenia but no CVD, a recent network meta-analysis supported the beneficial effects of ExT on muscle strength and physical performance, but not muscle mass[91]. However, other reports have been conflicting[69]. To date, most studies on the effects of ExT in patients with CVD failed to specify those diagnosed with sarcopenia or include sarcopenia assessments, limiting current understanding (Table 1). For example, patients with coronary artery disease who completed 3 months of ExT-based cardiac rehabilitation improved knee extensor muscular endurance, which was the strongest predictor for changes in VO_{2peak}[92]. However, in a subsample of this population in the SAINTEX-study, no significant effect could be observed on isometric handgrip strength or isokinetic quadriceps strength after 12 weeks of 3 weekly sessions of HIIT or ExT.[93] These differences between studies are most likely due to the method used to evaluate muscle strength, which focussed more on isometric rather than dynamic strength. Interestingly, some randomised controlled trials in patients with HFrEF have shown that ExT may confer anti-atrophic effects and even restore baseline muscle mass. For instance, 24 weeks of daily ExT containing 20 min sessions cycling at 70% VO_{2peak} attenuated muscle atrophy in patients with HFrEF[94] and these findings were repeated in another study that was performed for just 12 weeks[95]. Moreover, these anti-atrophic effects were age-independent and observed in both those < 55 or > 65 years of age in patients with HFrEF[96]. Similarly, 6 weeks of HIIT in heart transplant recipients resulted in a 5% increase in quadriceps muscle cross-sectional area[97]. These findings are in line with a recent review in healthy older adults documenting improvements in muscle mass and strength following HIIT, albeit with the caveat of a high risk of bias and low number of studies[98]. However, recent landmark studies in the

field of HF have reported that ExT (moderate-intensity or HIIT) show similar benefits to exercise capacity and muscle (cellular/molecular) adaptations after 12 weeks[99,100]. Again, the lack of sarcopenia diagnosis, as well as incomplete measures of muscle mass, strength, and physical performance, limit interpretation (Table 1; Figure 2) and indicate the need for further research.

- **Take home message**

  Endurance training increases exercise capacity in patients with CVD and these benefits extend to promoting muscle function and reducing muscle atrophy. However, the specific effects of endurance training in patients with CVD diagnosed with sarcopenia remain unclear.

6.3 Additional factors influencing the response to resistance and endurance exercise training

The complex and multifactorial aetiology of sarcopenia in patients with CVD[51,101] presents a challenge in identifying specific exercise modalities to combat the decline in muscle health. Most evidence points towards RxT combined with ExT as offering the greatest benefits to reduce sarcopenia in CVD[52,102] (Figure 2). For example, HIIT supplemented with RxT in HFrEF showed additional benefits for muscle strength compared with HIIT alone following 36 sessions[103]. In addition, concurrent RxT and ExT performed in older adults with sarcopenia resulted in higher muscle strength and gait speed when combined with balance training as shown from a meta-analysis[104]. In a large-scale longitudinal study, high flexibility was associated with reduced risk of sarcopenia in adults over 50 years of age[105]. As such, every 1 cm increase in flexibility was associated with a 4% reduced incident of low muscle mass and handgrip strength[105]. More data from randomised controlled trials are still required to strengthen evidence concerning the effects of different training modalities on sarcopenia in CVD. Sex-specific differences in the response to exercise training should also be an important consideration in the treatment of sarcopenia in CVD. In healthy older adults, a meta-analysis that included 36 randomized controlled trials of RxT demonstrated that the effects sizes for absolute and relative change in muscle strength differed between males and females[109]. Given the sex differences in skeletal muscle biology[43] and sarcopenia incidence[41] in CVD populations, more research is needed to understand how sex interacts with the exercise response to influence sarcopenia (Figure 2).

- **Take home message**

  Combining different modes of exercise training, particularly resistance and endurance training, will likely improve sarcopenia management in CVD and optimise the muscle response.

7.0. A role for nutrition in the management of CVD and sarcopenia

Nutrition is an important and modifiable factor for sarcopenia in older patients[110], but the evidence in patients with CVD remains scarce[111]. Malnutrition is a key predictor of survival in patients with and without CVD, increasing the risk of complications and mortality, and closely associated with incident sarcopenia[20,112,113]. However, malnutrition is frequently overlooked in patients with CVD despite its high prevalence, affecting up to 50% of patients with HF[20,112,113]. The pathophysiology of malnutrition includes changes in appetite, dietary intake, and malabsorption, which can promote sarcopenia[111]. Assessment of nutritional status alongside physical activity levels are therefore crucial to estimate energy requirements and avoiding over- or under-nutrition (which themselves are forms of malnutrition; Fig. 1)[111]. Establishing healthy dietary habits should thus constitute a central step in the treatment of CVD, which is unanimously advocated by major guidelines and offers an alternative treatment than pharmacotherapy alone[15,114]. Critically, the interaction between nutrition and pharmacotherapy is complex, which likely impacts sarcopenia incidence even further.

7.1 Optimising nutrition as a treatment for sarcopenia in CVD

Adequate protein intake is important in the management of sarcopenia. Protein requirements vary according to age and health status[115]. While 0.8 g/kg body mass per day is an appropriate protein intake in young to middle-aged adults, older adults require > 1 g/kg body mass per day and up to 1.2-1.5 g/kg body mass per day in under-nutrition or catabolic states[111]. Protein intake is especially important due to malnutrition being common in individuals with HF[113] or undergoing cardiac surgery[116]. However, protein intake is frequently insufficient in community-dwelling older adults according to a recent meta-analysis, which showed that 14-30% consumed less than 0.8 g protein/kg body mass daily[117]. Low protein intake may contribute to sarcopenia by decreasing muscle protein synthesis[118], although this mechanism remains debated[47].

For optimal muscle protein synthesis, animal proteins provide all essential amino acids (i.e., complete proteins), although recent evidence supports the efficacy of plant-based proteins[119]. In particular, leucine (an essential branched-chain amino acid) stimulates muscle protein synthesis even if protein intake is otherwise low[120]. The threshold for leucine content per meal has been estimated to be between 2.2-4.0 g/meal to adequately stimulate muscle protein synthesis[121,122]. Whey protein, a protein rich in leucine, is therefore frequently used in muscle growth studies and has been shown to increase lean mass, strength, and physical function in sarcopenic adults, but not in healthy older people, according to a meta-analysis[123]. One randomised controlled trial in patients with HF demonstrated that whey protein led to improvements in body composition, including skeletal muscle, but did not affect strength[124]. While the role of high protein intake on CVD risk remains controversial[125,126], the type of dietary protein may explain some of the discrepant results[127]. A network meta-analysis addressing the role of high versus low protein intake as well as protein type (animal vs plant) also showed that high-protein, high-carbohydrate, low-fat diet and plant-protein rich diets were associated with favourable outcomes[128]. Therefore, if protein intake is not met in patients with CVD, increasing protein intake from plant sources as well as from fish[129] or lean poultry[130] is reported safe and may be helpful to prevent sarcopenia. Overall, however, in people with CVD there remains limited evidence to support that protein supplementation alone reduces sarcopenia, and although some evidence supports potential improvements to lean mass and physical function[131] (Table 1), the wide variability in protein type and dose used in CVD patients is a key limitation[131].

Interestingly, in older people, improvements in muscle mass and function were also increased by co-supplementing whey protein with vitamin D[123]. However, the evidence for vitamin D supplementation alone is less clear. While vitamin D deficiency is linked to lower muscle mass, function, and homeostasis[132,133], a meta-analysis of 10 clinical trials concluded that supplementation with vitamin D as a monotherapy did not improve hand grip strength, lean mass, or muscle function in older adults[134]. Few studies have investigated the effect of vitamin D supplementation on sarcopenia in CVD patients, with one study showing no benefits after 20 weeks of treatment in

HFrEF[135]. Other nutrients studied include high-dose polyunsaturated fatty acid (PUFA) supplementation (>2.5 g/d) in patients with HFrEF, which was associated with greater gains in muscle strength of upper and lower extremities in older adults[136] and, when supplemented with amino acids, increased lean mass (but not muscle strength or physical function) (Table 1). However, caution is warranted using PUFAs in patients with CVD due to higher risk of arrhythmias[137]. A summary of nutritional interventions relevant for sarcopenia in CVD are presented in Table 1 and Figure 2.

- **Take home message**

  Adequate nutritional intake with sufficient protein may prevent sarcopenia in older people, but little evidence is currently available in the context of CVD. If protein intake is insufficient, fish and lean poultry, as well as whey protein supplementation, may serve as suitable sources of high-quality protein without affecting risk of CVD.

7.2. Consideration of additional factors influencing nutritional benefits

There is an increasing recognition that more diverse and healthy dietary patterns[138,139] are more important than focusing on single nutrients[47], and alongside more personalised nutritional interventions[114], could help optimise sarcopenia management in patients with CVD. Traditionally, diets advised for CVD prevention are plant-based[114,140]. Plant-based diets consist of whole grains, legumes, vegetables, fruit, nuts, seeds and unsaturated vegetable oils, and, when optimised, are suggested to provide adequate protein content[119]. The Mediterranean diet, which is also largely plant-based but includes protein from fish, eggs, dairy, and lean meat, has been suggested as a suitable diet both in CVD[15] and sarcopenia management[141,142], especially due to antioxidant and anti-inflammatory properties[143]. While observational studies show positive associations between Mediterranean diet and body composition and muscle function[144,145], an association with changes in sarcopenia requires further research[145]. Although clinical trials on the effect of a Mediterranean diet on sarcopenia-related measures are scarce, a sub-analysis of the PREMID study showed that a Mediterranean diet combined with physical activity attenuated loss of lean mass in adults > 60 years of age with metabolic syndrome[146].

Antioxidant nutrients such as carotenoids, polyphenols, and certain vitamins (which act as an exogenous defence against oxidative damage) have also gained attention, but the interpretation of current findings is hampered by different study methodologies. There is observational evidence that both higher dietary intake and serum levels of carotenoids are associated with better muscle function and strength[147,148] as well as reduced decline of physical function (gait speed) over time in older adults[149-151]. A recent meta-analysis, which aggregated findings from observational studies and randomised controlled trials on antioxidant-rich food intake and supplementation of antioxidants (vitamin E and magnesium), showed associations with better grip strength and muscle function in old-young adults[152]. Iron supplementation may offer another promising treatment for sarcopenia in patients with CVD, especially in those with iron deficiency[153]. Iron deficiency is associated with muscle dysfunction in patients with HFrEF[154] but this can be reduced following short-term iron supplementation[155].

While beneficial for CVD prevention[156], caloric restriction and fasting should be cautiously prescribed in older adults due to the potential loss of muscle mass[157], although duration seems critical. For example, data show short-term caloric restriction may benefit muscle/physical performance in obesity[157], including those with HFpEF[158,159] (Figure 2). There is not yet sufficient data on time-restricted eating, but this approach may constitute an option if weight loss is needed, as it still allows adequate-per-meal protein intake and can be combined with exercise training to counteract potential muscle loss[160]. In this regard, the time-of-day for meals has been implicated in the management of sarcopenia, with some data reporting that the distribution of protein intake (~30 g/meal) is important in older patients[161,162] and potentially a higher intake in the evening is associated with higher

BMI[163,164], whereas glucose tolerance, insulin secretion[165], and satiety[166] may be improved when meals are consumed earlier in the day. To date, high quality studies on the effect of meal timing on muscle health are missing in the setting of CVD and sarcopenia, which is also similar for other emerging and related areas implicated as potential future therapeutic targets including the muscle-gut microbiome axis[167,168,169].

- **Take home message**

  Various factors influence how nutrition impacts sarcopenia, including the amount of energy, composition, delivery, and timing of the diet. Dietary patterns may overall be more important than single nutrients in the prevention of sarcopenia. How to tailor these nutritional factors to optimally manage sarcopenia in the context of CVD remains unclear.

8.0. Interaction between exercise and nutrition to optimise sarcopenia management in CVD

Although potential benefits in sarcopenia management may be achieved via independent exercise or nutritional strategies, a combination of these approaches may prove most effective[91,170]. This is likely due to both interventions impacting a wide range of underlying mechanisms linked to poor muscle health in both CVD and ageing, as reviewed in detail elsewhere[52,57]. Briefly, these may include improved neurohormonal status alongside reduced systemic/local inflammation (IL6, IL1β, TNFα), reactive oxygen species, hypoxia, and insulin resistance. These changes help normalise anabolic/catabolic signalling (e.g. IGF1-Akt, MuRF1, myostatin) to increase protein turnover alongside improving myofilament, intracellular calcium, and neuromuscular homeostasis to impact both fibre size and function[52,57]. Further mechanisms also involve improved mitochondrial function/signalling (e.g., via PGC1α) and reversal of abnormal fibre type shifts, which benefit energy metabolism to decrease muscle fatigue[52,57].

In this regard, when in a state of negative energy balance, evidence favours that coupling a high-protein diet with RxT potentiates muscle mass gains[2]. The underlying mechanism is linked to changes in the dynamic balance between rates of muscle protein synthesis and muscle protein degradation. As both protein synthesis and breakdown increase after RxT, the careful timing of protein intake following exercise can help increase protein synthesis further to promote muscle protein balance and maximise muscle adaptations[161,171]. Research into the effects of protein supplementation when combined with RxT remains a dynamic field[2]. A systematic review and meta-analysis showed that protein supplementation in conjunction with RxT provides greater improvements in muscle mass in older individuals compared with RxT alone[172]. In general, however, improvements in muscle mass following concurrent RxT and protein supplementation across the lifecourse remain conflicting[172,173], as are findings combining RxT with multi-ingredient supplements (e.g. creatine, vitamin D)[174]. This evidence supports that other potential mechanisms could be limiting muscle adaptations following RxT, which could offer future therapeutic targets (see *Section 9.0*).

Critically, many populations included in past studies that investigated concurrent exercise and nutrition interventions were not diagnosed with sarcopenia. In this regard, some of the strongest evidence to date comes from the combined exercise/nutritional SPRINTT study, a multicentre randomised control trial including 16 clinical sites[175]. This study included > 1000 older (> 70 years of age) community-dwelling males and females diagnosed with sarcopenia and physical frailty[175]. Participants were randomised to either control (receiving healthy ageing lifestyle education) or multicomponent intervention (combining regular RxT, ExT, balance and flexibility exercises, alongside dietary assessments and personalised plans including a protein intake of 1-1.2 g/kg body mass per day) for up to 3 years[175]. Overall, those assigned to multicomponent interventions showed reduced incidence of sarcopenia for the primary outcome measure of physical performance (SPPB), with less frailty and immobility. However, only females showed improved indices of muscle mass

and strength, highlighting the importance of sex differences[175]. The SPRINTT trial is one of the few well-controlled studies investigating how the interaction of exercise and nutrition can be used to effectively manage sarcopenia. These findings have been supported by multiple network meta-analyses in patients with diagnosed sarcopenia from 26-46 randomised controlled trials. Such studies concluded that RxT combined with mixed exercise modalities (ExT, balance) was the most effective for increasing muscle mass, strength, and physical performance, whereas nutritional supplementations promoted specific gains in strength and physical performance[69,91,176]. In this regard, another important investigation includes the FrOST study (n=43)[177-179], which specifically used a time- and cost-efficient, low-volume/high-intensity dynamic RxT protocol (2 x per week over 12-18 months) in older men with osteosarcopenia. Specifically, this study supplemented osteosarcopenia patients with adequate whey protein, vitamin D, and calcium to confirm that supervised RxT increased muscle mass and strength compared with untrained controls alongside decreasing cardiometabolic risk factors, thus showing particular relevance for CVD populations.

Unfortunately, in patients with CVD there remain few high-quality studies and little evidence to support concurrent exercise and nutritional interventions enhance sarcopenia treatment[102] (Table 1; Figure 2). For example, a randomized clinical trial in patients with HFrEF showed that after 3 months those performing RxT with or without branch chain amino-acids supplementation (10 g per day) had similar improvements in muscle strength and body composition[180]. Moreover, a pilot study in patients with congenital heart disease diagnosed with sarcopenia found increased muscle mass after 2 months of RxT combined with amino acid supplementation (leucine), however, a control group performing RxT alone was not included[181]. Interestingly, a randomised controlled trial in older obese HFpEF patients combining caloric restriction with ExT and RxT for 20 weeks showed greater muscle strength, physical performance, and quality of life scores, although muscle loss was an adverse effect[158,159]. Ongoing trials are currently underway in patients with HFpEF diagnosed with sarcopenia, which will shed further light into whether RxT combined with protein supplementation is beneficial[88]. Moving forwards, more studies should address the effectiveness of combined exercise and nutritional interventions in sarcopenia management specific to CVD populations, carefully accounting for mitigating factors that include participant profiles (age, sex, health status), diversity of protein supplements (type, quantity, duration), exercise training protocols (FITT), and assessment tools[2]. Beyond protein intake, RxT combined with vs. without creatine supplementation (3-6 months at ~5-20 g/d) is also reported to maximise gains in muscle strength, lean mass, and physical performance in older adults[182]. This approach could be relevant for patients with CVD given that smaller studies reported short-term creatine supplementation (20 g/d) for up to 6 weeks improved muscle strength, endurance, and body weight in HFrEF patients[183,184]. However, larger studies are still required to confirm efficacy and safety of creatine across varying treatment doses and durations, especially as some studies suggest lower doses in conjunction with exercise may provide no additional benefits to muscle health in patients with CVD[185].

- **Take home message**

  Evidence suggests that multicomponent interventions (mixed exercises with nutritional support) likely provide the most effective approach to attenuate sarcopenia, however, there is a lack of high-quality evidence to confirm if this is similar in CVD populations.

9.0. What limits optimal muscle gains in patients with CVD for treating sarcopenia?

Compared with younger adults, older adults may show lower increases in muscle mass following exercise or nutritional stimuli, which is termed anabolic resistance[171]. Blunted muscle adaptations following RxT are also observed in patients with CVD independent of age[186,187]. Collectively, CVD may exacerbate limitations in muscle growth with RxT compared with age-matched controls, without impacting functional gains in strength and physical function. However, whether muscle improvements in response to exercise are limited in patients with CVD diagnosed with sarcopenia remains poorly explored. The mechanisms that underlie anabolic resistance in ageing remain an active research area, however, most evidence points towards a limitation in the ability to increase rates of protein synthesis appropriately[171]. Although more controversial[188,189], another mechanism may include the inability to activate and recruit resident muscle stem (satellite) cells, which was recently linked to CVD[100,190]. As such, optimising protein intake to overcome limitations in anabolic signalling during RxT[186] could help manage sarcopenia more effectively in patients with CVD.

Other potential mechanisms limiting the treatment of sarcopenia in CVD include reduced muscle blood flow/capillarity[191] and mitochondrial dysfunction[192,193]. Given that CVD is associated with lower endothelial function, muscle capillarity, and mitochondrial function[194-197], specific interventions that target these mechanisms (e.g., low-load blood flow restriction exercise) may enhance muscle blood flow and oxidative capacity to promote muscle gains. For example, small pilot studies without sarcopenia diagnosed showed muscle functional improvements in patients after cardiac surgery[198] or with HFrEF[187] following low-load blood flow restriction exercise for 6 weeks, or in protocols that combined both RxT with ExT for 6 months in HFrEF[199]. However, it remains questionable how practical such protocols are to implement in patients with CVD and sarcopenia. A more feasible approach for managing sarcopenia in CVD may include respiratory (inspiratory) muscle training. For example, data from large-randomised studies in HFrEF reported that combining inspiratory muscle training with ExT and RxT over 12 weeks showed greater improvements in physical function and quality of life than ExT alone[200,201]. Taken together, concurrent RxT and ExT will likely optimise gains in muscle mass, strength, and physical performance in patients with CVD and sarcopenia, especially when combined with other exercise modalities such as balance, flexibility, and/or inspiratory muscle training (Figure 2). Finally, other mechanisms that may influence the interaction between sarcopenia, CVD, exercise, and nutrition, but require further study in humans, include epigenetic modifications[202,203], but also the promising area related to muscle-secreted hormones/factors called myokines (e.g. irisin, apelin, musclin)[204,205]. Although some myokines have been linked to increased risk and progression of CVD[205,206], other myokines released in response to exercise (termed exerkines) have cardioprotective and anti-sarcopenic properties[204], highlighting another future avenue to exploit in the management of sarcopenia in CVD.

- ***Take home message***

  Ageing and CVD can both attenuate muscle growth in response to resistance training, yet improvements in muscle strength remain achievable in most patients. Different modes of exercise combined with adequate nutrition may be appropriate to overcome limiting mechanisms and optimise sarcopenia management.

10.0. Influence of pharmacological and device therapies on sarcopenia in CVD

The high prevalence and wide range of medications taken by patients with CVD could have a positive or negative impact on exercise-nutritional outcomes and therefore affect overall sarcopenia treatment. For example, some medications may negatively impact exercise training outcomes[207]. As such, the impact of medications on sarcopenia *per se* and their interaction with exercise and nutritional strategies in patients with CVD should be carefully evaluated. To date, there remains no established drug agent approved for treating sarcopenia, whereas the interactions of various CVD medications with exercise-nutritional responses remains poorly investigated. However, promising studies in older patients have suggested that certain drugs could be effective for sarcopenia management (Table 2). These include myostatin inhibitors, which increase muscle mass in older patients but without parallel improvements in muscle function or physical performance[208,209]. These findings underscore the challenge and complexity of using drug agents alone to treat sarcopenia, pointing towards a combined approach integrating exercise and nutrition to optimise outcomes – a point highlighted by a study that showed combined exercise training with vs. without the anabolic agent testosterone induced greater improvements in muscle strength and clinical outcomes in HF patients[210]. However, apart from hormonal drug agents such as testosterone, growth hormone, and ghrelin (Table 2), that in themselves may pose significant health risks in patients with CVD, many candidate sarcopenic drug agents remain untested in CVD. These include selective androgen receptor modulators (SARMs), which may have less adverse effects compared with traditional anabolic agents despite providing similar anti-sarcopenic benefits[211] (Table 2). Nevertheless, there is evidence to support that various guideline-directed medical therapies prescribed in CVD such as angiotensin-converting enzyme inhibitors and beta-blockers benefit muscle mass and function in patients with[212-214] but not without CVD[215-217], whereas other recent evidence shows that sodium glucose cotransporter 2 (SGLT2) inhibitors are associated with decreased muscle atrophy in HFrEF[218] and frailty in HFpEF[219].

It is important to recognise that some drug agents with beneficial clinical outcomes may exacerbate sarcopenia, inducing potential muscle pathology related to atrophy, mitochondrial dysfunction, and necrosis, such as traditional loop diuretics[220,221], metformin[222], statins[223,224], and immunosuppressants (e.g., corticosteroids, cyclosporine[225]), and these may even have negative effects on exercise training outcomes. For example, 14 weeks of RxT combined with taking metformin in older adults was shown to blunt increases in muscle mass[222], whereas statins have been reported to blunt standard muscle adaptations to exercise training[207]. Moreover, although the clinical benefits of glucagon-like peptide-1 (GLP1) analogues in patients with obesity and HFpEF have been positive[226], it remains unclear whether this weight-loss approach promotes sarcopenia and under-nutrition[227,228] or if GLP1 analogues influence outcomes following exercise-nutrition interventions. Moreover, cardio-oncology studies have outlined the balance between using chemotherapy agents to promote lifespan but at the cost of accelerating sarcopenia[229]. Collectively,

therefore, careful consideration should be given to medications being prescribed to patients with CVD as they may have an impact on the progression and severity of sarcopenia. Noteworthy, almost all studies showing beneficial effects of drug agents in CVD on skeletal muscle were limited by low sample sizes, did not control for the potential confounding factor of physical inactivity or diagnose baseline sarcopenia, whereas many have not investigated if medications have beneficial or detrimental effects to exercise and nutritional interventions. Further work is therefore required to clarify these issues in addition to investigating other emerging pathways of interest (e.g. GDF15)[230]. In addition to drug agents, other studies have investigated the effects of devices (e.g. left ventricular assist devices[23,231] or cardiac resynchronization therapy[232]), muscle stimulation protocols (e.g. via neuromuscular electrical stimulation[233-236]), and supplemental oxygen to impact the muscle microenvironment[237] on indices of sarcopenia, but with conflicting findings (Table 2).

- ***Take home message***

  Various medications and devices prescribed as a primary treatment for CVD may attenuate sarcopenia progression (e.g., ACE inhibitors, beta-blockers), however, some drug agents may conversely promote sarcopenia (e.g. GLP1 analogues) and potentially inhibit muscle adaptations in response to exercise (e.g. metformin, statins). Future studies should investigate which type of medications can positively or negatively impact exercise-nutritional interventions, and how they help or interfere with sarcopenia management in CVD.

11.0 Practical implications for treating sarcopenia in clinic settings

Although a main goal in CVD management is to improve or prevent deterioration of cardiac function and limit disease progression[16,17], treating other systemic pathological conditions such as sarcopenia is critical for reducing symptoms and improving quality of life. Sarcopenia represents a viable therapeutic target that shows a degree of reversibility, which is closely linked to clinical outcomes in CVD[2]. Thus, a key aim should be to integrate sarcopenia screening and diagnosis into the routine clinical management and follow-up of patients with CVD. This approach would allow early interventions including tailored exercise and nutritional strategies to effectively manage sarcopenia (Figure 2). Assessing and diagnosing sarcopenia alongside related conditions such as frailty, cachexia, and malnutrition (e.g. via nutritional assessments)[20,238], should become a priority and targeted as early as possible in patients with CVD (Graphical Abstract). Rapid screening can be implemented during annual consultations, hospitalisations (phase I) and at entry of an ambulatory programme, based on clinical suspicion or by administering the SARC-F questionnaire. In cases where sarcopenia is suspected, this should then be followed by relatively straightforward assessments of muscle strength such as handgrip or chair-stand test to confirm probable sarcopenia. The subsequent diagnostic confirmation through evaluation of muscle mass and assessment of severity via physical performance tests can be carried out by physiotherapists or cardiac nurses working in the outpatient clinics, inpatient units or ambulatory care settings. The management of sarcopenia should then be incorporated within cardiac rehabilitation or facilitated by appropriate referral of the patients to physiotherapists and dieticians, following a holistic individualised approach[14] including optimising exercise and nutritional strategies to manage sarcopenia (Figure 2; Figure 3).

There is preliminary evidence that cardiac rehabilitation is beneficial for managing sarcopenia, as shown in a large study conducted in males and females with HF that reported reduced sarcopenia following 3-5 months of out-patient cardiac rehabilitation (combined ExT and RxT 5 x per week)[239]. Interestingly, those failing to decrease their sarcopenia status showed higher mortality[239], providing a strong argument for treating sarcopenia as a central component of cardiac rehabilitation. This may be especially true in older patients with CVD who are hospitalised with acute events, in whom rates of sarcopenia are high and recovery low[240] and where risk of acute sarcopenia is high[24]. For example, early and tailored physical rehabilitation focusing on strength, balance, mobility and endurance (36 sessions, 60 min each, over 3 months) in an elderly predominantly frail population of hospitalised patients with acute decompensated HF improved physical performance and outcomes compared with usual care in a large multicentre randomized controlled REHAB-HF trial (n=326), although nutritional support was not addressed[240]. A secondary analysis of the REHAB-HF trial further compared patients diagnosed with vs. without baseline sarcopenia (handgrip strength/gait speed) following rehabilitation[241]. The findings revealed that even hospitalised patients with sarcopenia could improve a range of physical performance indices compared with patients without

sarcopenia[241]. Given the high incidence of acute hospitalisation in patients with CVD and increased risk of acute sarcopenia during this time frame[24], these findings suggest treating sarcopenia early in hospitalised patients with CVD via physical exercise, but with further tailored nutritional interventions, would attenuate acute sarcopenia and its subsequent progression. As evidence shows that females with CVD have less improvements in physical performance compared with males following cardiac rehabilitation[242] despite showing less signs of muscle pathology[43], sex differences should also be accounted for during cardiac rehabilitation and treating sarcopenia in CVD patients.

In summary, the treatment of sarcopenia in patients with CVD should involve multi-component cardiac rehabilitation and a multi-disciplinary team including clinicians, exercise professionals, physiotherapists, dietitians, and social workers according to recent standards and guidelines[14,16,243]. It is critical patients meet target exercise intensity thresholds during cardiac rehabilitation programmes otherwise the training may be insufficient to produce tangible benefits on reducing sarcopenia[14,83]. Integration of all aspects relevant to the individual patient should be contemplated, including personal and environmental context factors (e.g. living status, collaboration with care providers) as outlined by the International Classification of Functioning, Disability and Health[243].

- ***Take home message***

  Integrating sarcopenia diagnosis and management during outpatient consultations, hospitalisation (phase I), and at entry of an ambulatory cardiac rehabilitation programme (phase II) will help detect and treat this condition early, with tailored exercise and nutritional approaches optimising functional outcomes. Figure 3 provides an infograph for healthcare professionals to aid sarcopenia management in CVD.

12.0 Future directions and conclusions

Research on the pathological mechanisms and optimal treatments of sarcopenia in patients with CVD remains in its infancy (Figure 2; Table 1). Future studies should include patients with CVD who have been diagnosed with sarcopenia to optimise exercise and nutritional strategies. Nevertheless, current limitations related to different sarcopenia definitions are slowing progress in identifying mechanisms and effective treatments[244]. Cardiac rehabilitation offers an excellent opportunity to diagnose sarcopenia early, monitor its progression, and optimise its management[14]. Optimising exercise and nutritional interventions, including combined modes of exercise alongside adequate protein intake and early treatment of malnutrition, are critical considerations in patients with CVD and sarcopenia. Addressing determinants of a non-responsive muscle micro-environment could also be relevant. Importantly, patients with severe- rather than moderate-sarcopenia may require a more nuanced approach, for instance greater emphasis on multicomponent interventions[175], whereas specific considerations may be needed in relation to sex differences[43]. Given the large prevalence of obesity in patients with CVD (e.g. HFpEF), sarcopenic obesity likely represents an important area of future research, as does the alternative therapeutic target of respiratory (diaphragm) sarcopenia in CVD[38]. In conclusion, reducing sarcopenia in patients with CVD will increase engagement in more physical activity and promote functional independence, which will ultimately improve quality of life and long-term outcomes.

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Author contributions

VC and TSB contributed to the conception and design of the work. VC, HH, CH, RK, EMS, TM, DN, KN, RP, AS, KS, TSB drafted and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Figures legends

Graphical Abstract. Optimising the management of sarcopenia in cardiovascular disease (CVD) by implementing early screening/diagnosis followed by combined exercise with nutritional interventions. A reciprocal relationship exists between CVD and sarcopenia. Various CVDs promote the onset and progression of sarcopenia (bubble size indicates relative prevalence in each condition, with the highest in heart failure), which is commonly exacerbated by additional comorbidities including chronic kidney disease (CKD) and type 2 diabetes (T2D). Sarcopenia is characterised by loss of skeletal muscle mass and strength, and decreased physical performance. Assessing and diagnosing sarcopenia should be done as early as possible and integrated into standard clinical practice and cardiac rehabilitation (CR). Current evidence suggests that the most effective approach for reducing sarcopenia in CVD is likely via resistance training combined with other exercise modalities such as endurance training, alongside minimising malnutrition and attaining adequate protein intake. Personalising the selected interventions to the individual with CVD is key to attaining the greatest benefits to reduce sarcopenia, including accounting for current medications.

Figure 1. Operational definition of sarcopenia and screening algorithm for case finding, diagnosis and quantifying severity, based on current European Working Group on Sarcopenia in Older Patients (EWGSOP)[13], presented alongside the closely related but distinct conditions of cachexia[19], the physical phenotype of frailty[245], and malnutrition (based on the Global Leader Initiative on Malnutrition (GLIM) criteria)[246]. Probable sarcopenia is identified by Criterion #1. Diagnosis is confirmed by additional documentation of Criterion #2. If Criteria 1, 2 and 3 are all met, sarcopenia is defined as severe. *Abbreviations: ASM, appendicular skeletal muscle mass derived by DXA or BIA; BIA, bioelectrical impedance analysis; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; MRI, magnetic resonance imaging; SPPB, short physical performance battery; TUG, timed up and go.*

Figure 2. Summary of the potential benefits of exercise training and nutritional interventions in the management of sarcopenia in patients with cardiovascular disease (CVD), with current knowledge gaps in the field presented (detailed explanation in main). Evidence favours that different modes of exercise training can primarily increase muscle strength and physical performance, whereas nutritional supplementation potentially benefits muscle mass. There is sparse evidence to confirm whether combined exercise and nutritional interventions provide the most effective approach to reducing sarcopenia in patients with CVD. An important caveat is that most evidence is drawn from patients with CVD where sarcopenia was not diagnosed or from older adults without CVD, which limits current understanding. *Abbreviations: AA, amino acids; CVD, cardiovascular disease; PUFA, polyunsaturated fatty acids; Vit, vitamin.*

Figure 3. Proposed “speedy” check list for diagnosing and managing sarcopenia in patients with cardiovascular disease

Tables

Table 1. Selected studies investigating exercise, nutritional, and their combined effects on sarcopenia status in patients with cardiovascular disease

Intervention	Study details	Population	Baseline sarcopenia diagnosed?	Sarcopenia outcomes (and others)	References
Resistance training	Randomised controlled trial 10 weeks, 3 x per week, 60 min session dynamic muscle group exercises at 80% 1RM for 3 sets x 8 reps	N=16 HFrEF (16 females) 77±6 y	No	↑ Muscle strength ↑ Physical performance (6MWT distance) ↔ Muscle mass (↑ Muscle endurance, ↔ cardiac function)	Pu et al. 2001[77]
	18 weeks, 3 sets of 8 reps @ 80% 1RM for 7 dynamic exercises	N=10 HFrEF/HFpEF (7 males) 73±2 y	No	↑ Muscle strength, ↑ Physical function ↔ Lean mass, (↔ Exercise capacity, ↔ cardiac function)	Savage et al. 2011[78]
	Randomised controlled trial 3-4 months, 2-3 x per week, 3 sets at high-load (6-8 repetitions @ 80% 1RM) or low-load (12-16 repetitions @ 40% 1RM)	N=59 Coronary artery disease (44 males) 62±8 y	No	↑ Muscle strength (↑ Exercise capacity)	Kambic et al. 2022[82]
	Randomised controlled trial 3 months, 3 sessions per week, 2 sets of multiple exercise 8-12 repetitions @ at 60% 1RM	N=9 HFpEF (8 males) 70±7 y	No	↑ Muscle strength ↔ lean mass (↑ Exercise capacity, ↓ fat mass)	Sharif et al. 2024[87]
	Randomised controlled trial 8 weeks, 3 x per week, 1 h, 2 sets, 25 repetitions per major muscle groups (resistance band)	N=16 HFrEF (8 males) 63±9 y	No	↑ Physical performance (gait speed, 6MWT distance) (↑ Exercise capacity, ↑ QoL)	Tyni-Lenne et al. 2001[247]
	Randomised controlled trial 6 weeks, interval training, 3 x per week, 9 x 5 min bouts (intervals) @ ventilatory	N=12 Heart transplant recipients (11 males) 54±2 y	No	↔ Muscle mass (↑ Mitochondria indices, ↔ muscle capillarity)	Lampert et al. 1998[97]

Endurance Training	threshold and 90% peak power, cycle ergometry.				
	Randomised controlled trial 6 months, 4-6 x per week, 20 minutes @ 70% VO_{2peak}, cycle ergometry	N=20 HFrEF (20 males) 54±2 y	No	↑ Exercise capacity (VO2peak) (↓ Muscle inflammation)	Gielen et al. 2003[94]
	3 months, moderate continuous training, 2 x per week, 45 min session @ 80% HRpeak	N=260 with coronary artery disease (223 males) 61±10 y	No	↑ Muscle strength	Thomaes et al. 2012[92]
	3 months, 3 x per week of intervals (4 x 4 bouts of 4 min high intensity @ 85-95% HRpeak, with 3 min bouts of recovery @ 50-70% of HRpeak) or moderate continuous training (37 minutes @ 60-70% of HRpeak)	N=200 coronary artery disease (180 males) 58±9 y	No	↔ Muscle strength	Pattyn et al. 2017[93]
	Randomised controlled trial; 3 months of HIIT (3 x per week, 4 x 4 bouts of 4 min @ 80–90% HRR with 3 min recovery bouts @ 35-50%HRR) or moderate continuous training (5 x per week, 40 minutes per session @ 35-50% of HRR); Cycle ergometry	N=41 HFpEF (12 males) 72 y	No	↑ Exercise capacity (↓ Muscle atrophy markers in HIIT. ↑ Mitochondrial function in HIIT)	Winzer et al. 2022[100]
	Randomised controlled trial 3 months, 7 x per week with 20-30 min sessions @ 60%VO_{2peak}; Cycle ergometry	n=37 advanced HFrEF (37 males) 61±2 y	No	↑ Muscle mass (↓ Muscle catabolic markers)	Hollriegel et al. 2013[95]
	Randomised controlled trial 6 weeks of a high caloric (600 kcal/d) protein rich (20 g/d) supplement	n=29 HFrEF (24 males) 63±11 y	No	↑ Physical performance (6MWT distance) ↑ Lean mass, (↑ Body mass, ↑ QoL)	Rozentryt et al. 2010[248]

Nutrition	Randomised controlled trial 8 weeks of essential amino acids supplementation (8g/d)	n=38 HFrEF (27 male) 74±4 y	No	↑ Physical performance (6MWT distance, VO_{2peak})	Aquilani et al. 2008; Lombardi et al. 2014[249,250]
	Randomised controlled trial 12 weeks of fish oil (6.5 g/d) and l-alanyl-l-glutamine (8g/d)	n=31 HFrEF (26 male) 59±2 y	No	↑ Lean mass ↔ Muscle strength (and function), ↔ Physical performance (6MWT distance, VO_{2peak}) (↑ QoL, ↔ heart function)	Wu et al., 2015[251]
	Randomised controlled trial 12 months of individualized nutrition high protein	n=86 HFrEF (NA)	No	↑ 6MWT distance	Ortiz Cortes et al. 2024[252]
	Randomised controlled trial 24 weeks of a high protein (7.4g/d), high energy (141 kcal/d) supplementation	n=38 HFrEF (27 males) 68±2 y	Yes	↑ Lean mass ↑ Physical performance (6MWT distance) (↑ QoL in both control and intervention groups)	Herrera-Martinez et al. 2023[253]
Concurrent exercise and nutrition	Randomised controlled trial 20 weeks of ExT (3 x per week) + caloric restriction (350 kcal/d)	n=100 obese HFpEF (81 females) 67±5 y	No	↑ Physical performance (6MWT distance, VO_{2peak}) ↓ Muscle mass (↑ QoL, ↓ Cardiac mass, ↓ Body mass)	Sahni et al. 2021[145]
	Randomised controlled trial 20 weeks of RxT + ExT (3 x per week) + caloric restriction (350 kcal/d)	n=88 Obese HFpEF (75 females) 68±5 y	No	↑ Muscle strength, ↑ Physical performance (6MWT distance, VO_{2peak}) ↓ Muscle mass (↑ QoL)	Lauretani et al. 2008[146]
	Randomised controlled trial 36 months of RxT+ExT+balance+flexibility training with dietary assessments and personalised plans.	n=1519 Community-dwelling older adults (1088 females) 79±6 y	Yes	↑ Muscle strength, ↑ Physical performance ↑ Muscle mass (females) (↓ Mobility disability, ↓ Physical frailty)	Bernabei et al. 2022[175]
	Randomised controlled trial 12 weeks of RxT with branched-chain amino acid supplementation (10 g/d)	N=66 HFrEF (39 male) 73 (62-80) y	No	↑ Muscle strength (↑ VO_{2peak}, ↓ Symptoms, ↓ Fatigue; ↔ in RxT group alone)	Xiao et al. 2019[160]

Abbreviations: ExT, Endurance exercise training; HFrEF or HFpEF, heart failure with reduced or preserved ejection fraction; HRR, heart rate reserve; HIIT, High-intensity interval training; QoL, quality of life; RxT, resistance exercise training; 1RM; 1 repetition maximum; 6MWT, 6 minute walk test;

Table 2. Selected pharmacological, device, and stimulation interventions with potential for influencing sarcopenia in patients with cardiovascular disease

Treatment	Agent	Population	Baseline sarcopenia diagnosed?	Sarcopenia outcomes (and others)	References
Anabolic stimulants	Testosterone	HFrEF	No	↑ muscle strength, ↑ physical performance (↔cardiac function)	Toma et al. 2012; Caminiti et al. 2009[254,255]
	Human growth hormone	HFrEF	No	↔ physical performance (no muscle measurements)	Osterziel et al. 1998[256]
	Selective androgen receptor modulators (SARMs)	Older adults	No	↑ Lean mass. ↑ physical performance	Wen et al. 2025; Dalton et al. 2011[211,257]
		Older adults	Yes	↑ Lean mass. ↔ physical performance	Papanicolaou et al. 2013[258]
Myostatin inhibitors	Bimagrumab	Older adults	Yes	↑ Lean mass ↔ physical performance, ↔ muscle function	Rooks et al. 2020[209]
		Older hip fracture adults	Yes	↑ Lean mass ↔ physical performance,	Hofbauer et al. 2021[208]
		Type 2 diabetes + obesity	No	↑ Lean mass. (↑ metabolic markers)	Heymsfield et al. 2021[259]
Anti-GDF-15 therapy:	Ponsegromab	Cancer cachexia	No	↑ Physical activity (↑ weight, ↑ appetite)	Groarke et al. 2024[230]
Ghrelin	Anamorelin, Macimorelin.	HFrEF	No	↑ muscle mass, ↑ physical performance (↑ cardiac function).	Nagaya et al. 2024[260]
		Non-small-cell lung cancer	Yes	↑ lean mass, ↔ muscle strength.	Temel et al. 2016[261]
	β2-adrenergic receptor agonist	HFrEF	No	↑ muscle mass, ↑muscle strength ↔ physical performance (adverse cardiac effects)	Kamalakkannan et al. 2008[262]
	β-blockers	HFrEF	No	↓ cachexia	Clark et al. 2017[214]

Guideline-directed medications	ACE inhibitor	Hypertension/HFrEF	No	↑muscle strength ↑muscle atrophy ↑ physical performance (↓ cachexia)	Schaufelberger et al. 1996; Anker et al. 2003; Vescovo et al. 1998 [212,263,264]
	SGLT2i	HFrEF	No	↓ muscle atrophy (↑ anti-inflammatory and muscle metabolism)	Wood et al. 2024[218]
Cardiac devices	Ventricular Assist Device	Advanced HFrEF	Yes	↑ Muscle mass, ↑ Physical performance. ↔ Muscle strength (↑ quality of life)	Vest et al. 2022[23]
		Advanced HFrEF	No	↓ Muscle atrophy. ↑ Muscle strength. physical performance unassessed	Khawaja et al. 2014[231]
	Cardiac resynchronization therapy	HFrEF	No	↔ muscle atrophy ↑ Physical performance (↔ inflammation)	Larsen et al. 2013[232]
Muscle stimulation	Vibration therapy	Older adults	Yes	↑ muscle strength ↑ physical performance.	Wu et al. 2020[265]
	Neuromuscular electrical stimulation	HFrEF, cardiac surgery	No	↑ physical performance ↑ muscle strength (↑ quality of life)	Poltavskaya et al. 2022; Banerjee et al. 2009[236,266]
	Pulsed electromagnetic fields	Older adults	No	↑ physical performance, ↑ muscle mass.	Venugobal et al. 2023[235]

Abbreviations: HFrEF or HFpEF, Heart failure with reduced or preserved ejection fraction;

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