ESC HEART FAILURE
ESC Heart Failure 2018; **5**: 1099–1107
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12387

REVIEW

Skeletal muscle wasting in chronic heart failure

Tsuyoshi Suzuki, Sandra Palus and Jochen Springer*

Department of Cardiology and Pneumology, University Medical Center Göttingen (UMG), Göttingen, Germany

Abstract

Patients suffering from chronic heart failure (CHF) show an increased prevalence (~20% in elderly CHF patients) of loss of muscle mass and muscle function (i.e. sarcopenia) compared with healthy elderly people. Sarcopenia, which can also occur in obese patients, is considered a strong predictor of frailty, disability, and mortality in older persons and is present in 5–13% of elderly persons aged 60–70 years and up to 50% of all octogenarians. In a CHF study, sarcopenia was associated with lower strength, reduced peak oxygen consumption (peak VO_2, 1173 ± 433 vs. 1622 ± 456 mL/min), and lower exercise time (7.7 ± 3.8 vs. 10.22 ± 3.0 min, both $P < 0.001$). Unfortunately, there are only very limited therapy options. Currently, the main intervention remains resistance exercise. Specialized nutritional support may aid the effects of resistance training. Testosterone has significant positive effects on muscle mass and function, and low endogenous testosterone has been described as an independent risk factor in CHF in a study with 618 men (hazard ratio 0.929, $P = 0.042$). However, the use of testosterone is controversial because of possible side effects. Selective androgen receptor modulators have been developed to overcome these side effects but are not yet available on the market. Further investigational drugs include growth hormone, insulin-like growth factor 1, and several compounds that target the myostatin pathway. The continuing development of new treatment strategies and compounds for sarcopenia, muscle wasting regardless of CHF, and cardiac cachexia makes this a stimulating research area.

Keywords Muscle wasting; Cardiac cachexia; Sarcopenia; Heart failure

Received: 5 November 2018; Accepted: 7 November 2018
**Correspondence to: Jochen Springer, Department of Cardiology and Pneumology, University Medical Center Göttingen, Robert-Koch-Strasse 40, Göttingen 37075, Germany. Email: jochen.springer@med.uni-goettingen.de*

Introduction

In the elderly population, cardiovascular diseases represent a highly prevalent group of disorders that include chronic heart failure (CHF), which leads to high morbidity and mortality.[1] The overall prevalence of cardiovascular disease in patients is ~2% of the population.[2] After 55 years of age, the rates of CHF increase strongly and double approximately every 10 years in male and every 7 years in female patients; thus, this patient population can be considered elderly to very old. With the rise in life expectancy, a rise in CHF patients' numbers will follow.[3–5] The symptom burden of patients is high, and it has been reported that 55–95% of patients experience shortness of breath and 63–93% experience tiredness.[6] However, public awareness about CHF aetiology and symptoms is unsatisfactory; particularly, knowledge about management, severity, and prognosis is lacking, which is critical for good self-care and adherence of patients.[7]

The CHF population can be divided into heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction, and of the two, HFpEF is the most common form.[8] The impaired myocardial relaxation in HFpEF is a robust and independent predictor of aerobic exercise capability,[9] and these patients also show a high prevalence of sarcopenic obesity.[10–12] Sarcopenia is mainly associated with the age-related loss of skeletal muscle[13] but is commonly observed in advanced stages of CHF leading to reduced exercise capacity and frailty,[14,15] which may represent a risk marker for adverse outcomes in CHF.[16] Cardiac troponin T contributes to the functional decline of the neuromuscular junction with ageing by interfering with protein kinase A signalling, which primarily affects the fast-twitch skeletal muscle.[17] Sarcopenia itself is a common

manifestation in the aged population[18–20] and is associated with increased mortality independently of age or other clinical and functional variables.[21–24] Low body mass index may be a risk factor for both current and future sarcopenia in the very old aged 85 and above, of whom 74.3% displayed either slow gait speed or weak grip strength.[25]

A large retrospective study showed that the prevalence of sarcopenia in the general population ranged from 12.6% (Poland) to 17.5% (India), and that of sarcopenic obesity ranged from 1.3% (India) to 11.0% (Spain).[13] Despite the high prevalence and profound negative impact, sarcopenia was given an ICD-10-code only recently.[26] Interestingly, in non-obese men, sarcopenia can be considered a risk factor for cardiovascular disease[27] and may predict adverse outcome in CHF.[16] However, using a combined lean mass and gait speed approach, sarcopenia was found in 36.5% subjects in a cohort of ~4400 with a mean age of 70 years, which was associated with an increased risk of cardiovascular-specific death for women, but not men.[22] Sarcopenia is also associated with standard R-CHOP chemotherapy intolerance in patients with malignancies[28] and worse survival of patients with ovarian cancer receiving neoadjuvant chemotherapy,[29] as well as rectal cancer[30] and haemodialysis patients.[31] Moreover, sarcopenia and myosteatosis are independently associated with a higher long-term mortality in liver cirrhosis.[32]

Chronic heart failure and muscle maintenance

Sarcopenia is considered to be a largely age-dependent syndrome, was originally defined as the age-related loss of skeletal muscle of the limbs two standard deviations below the mean of a healthy young reference group, and has been linked with to a range of adverse outcomes.[25,33] In contrast to cachexia, sarcopenia and muscle wasting cannot be identified by simply longitudinally determining the patients' body weight to detect involuntary weight loss.[34,35]

Sarcopenia affects 5–13% of elderly persons aged 60–70 years and up to 50% of all octogenarians.[36] The prevalence of sarcopenia in Asia ranges from 4.1% to 11.5% of the general older population.[37] The effects of sarcopenia are not only restricted to the loss of skeletal muscle mass but are also associated with muscle dysfunction and impaired physical performance, which may be exacerbated by chronic diseases.[38] In acute care wards, sarcopenia was an independent predictor of 3 year mortality (adjusted hazard ratio: 2.49; 95% confidential interval: 1.25–4.95) and readmission (adjusted hazard ratio: 1.81; 95% confidential interval: 1.17–2.80) after adjustment for age, sex, and other confounders.[39] Therefore, patients are in dire needs for a specialized sarcopenia therapy. Unfortunately, because of a lack of consensus on the definition of sarcopenia, there are problems with its definite detection.[35,40] This fact is exacerbated by the fact that no clinically validated biomarkers have been identified despite enormous research efforts both by academia and industry.[41–43] As a result, the definition of sarcopenia (two standard deviations of normal muscle mass) has been modified to contain measurements of impaired physical function, such as slow walking speed and low grip strength.[34] In addition, a sarcopenia-specific Quality of Life questionnaire has recently been introduced.[44] Despite this, there are still several definitions of sarcopenia with diverse cut-off values[45,46] that were all confirmed to be independent predictors of adverse outcomes.[47]

The prevalence of sarcopenia in CHF patients is higher at 20% compared with control subjects of the same age.[48] An even higher prevalence of sarcopenia (47%) has recently been suggested in patients below the age of 55 years suffering from dilated cardiomyopathy.[49] This particularly high incidence may be due to mitochondrial dysfunction combined with an abnormal energy metabolism and a transition of type I to type II myofibres.[50,51]

In CHF, divergent anti-oxidative and metabolic but similar catabolic responses, i.e. wasting of myofibrillar proteins, of the diaphragm and quadriceps muscles have been observed.[52] The increased catabolic stress in the skeletal muscle of CHF patients results in exercise intolerance, ventilatory inefficiency, and chronotropic incompetence, as well as insulin resistance, suggesting a significant contributing of the catabolic status mechanism to the patients' limited functional status.[53,54] Skeletal muscle density has been suggested to be an independent marker of clinical outcome.[55]

Continuous treatment with acetylated ghrelin was shown to normalize CHF-induced skeletal muscle mitochondrial dysfunction, pro-inflammatory changes, and reduced insulin signalling in a rat model.[34] Another contributing factor to sarcopenia is a variable degree of malnutrition[56] that may be caused by inflammatory cytokines,[57–59] which have been known to contribute to anorexia in chronic disease.[60–63] Malnutrition and sarcopenia are also common features of rehabilitation patients in whom the prevalence of malnutrition was 49–67% and that of sarcopenia 40–46.5%.[64] Malnutrition and sarcopenia have also been shown to be associated with early post-liver transplant morbidity/mortality, yet allocation indices do not include nutritional status.[65] Interestingly, premorbid obesity, but not exogenous macronutrients, attenuated muscle wasting in critical illness.[66] Low levels of testosterone or vitamin D were not prognostic for muscle mass and function in middle-aged and elderly men, while low insulin-like growth factor 1 (IGF-1) levels were found to predict alterations in gait speed in men aged $\geq$70 years.[67] A recent study has identified low testosterone in men as an independent risk factor in CHF.[68]

However, testosterone deprivation therapy due to prostate cancer selectively impairs lower-limb muscle function, primarily affecting muscles that support body weight,

mediate the forward movement the body during walking, and mediate balance.[69] On the other hand, supplementation of androgens such as dihydrotestosterone in mice reversed the reduction in protein synthesis and amino acid transporter expression observed in ageing animals.[70] In contrast to Gielen *et al.*,[67] a strong association between high vitamin D deficiency and an increased risk of heart failure in the elderly has been described.[71] Targeted medical nutrition including vitamin D supplementation has positive effects on blood pressure and plasma lipids.[72] In a Korean study, high serum vitamin D levels in mid-life and late-life were linked to reduced odds of various adverse effects on body composition, particularly in osteosarcopenic obesity, stressing the importance of maintaining adequate levels of vitamin D.[73] Vitamin D supplementation has also proven beneficial in improvement of muscle weakness in prostate cancer patients.[74] However, a recent systematic review finds not enough solid evidence for the use of minerals, vitamins, proteins, or other supplements in cancer.[74] Currently, there are only few therapy options for patients suffering from sarcopenia, which include (resistance) exercise,[75–77] nutritional approaches to increase consumption of proteins and micronutrients,[78,79] and finally, drug treatment, including testosterone,[80,81] growth hormone (GH), and IGF-1.[82] Resistance exercise is often used in combination with nutrition support, which increases muscle mass and muscle strength more than exercise alone.[46,83–85] Supplementation of a low-dose creatine in combination with resistance training improved lean mass in elderly over a period of 12 weeks.[86] A patient-centred exercise approach in frail elderly and older adults with mobility limitations physical activity was considered to improve effective quality of life and reduce frailty, while also being cost-effective.[87] An accelerometer-determined physical activity showed an independent, dose–response relationship with lean mass percentage and lower limb strength.[88] High-intensity training over a period of 6 months resulted in greater improvements of frailty and sarcopenia status among community-dwelling elders.[89] Interestingly, a significant plasticity of ageing skeletal muscle to adapt to resistance-type exercise training has been shown by transcriptomics after a 6 month training period including partial reversal of age-related changes in skeletal muscle gene expression.[90] Exercise training has been acknowledged as an evidence-based therapeutic approach with prognostic benefits in cardiovascular illness including CHF, as it improves risk factors such as hyperlipidaemia, hypertension, and coronary endothelial function.[91] Exercise training not only has cardio-protective effects and thereby attenuates the progression from cardiac dysfunction to CHF but also induces anti-catabolic signalling in skeletal muscle, possibly by stimulation of PGC1α.[92] In breast cancer patients undergoing adjuvant chemotherapy, a favourable effect of resistance exercise training was seen on sarcopenia and dynapenia.[93] However, in a meta-analysis on the effects of exercise, rehabilitation after intensive care unit discharge found no overall effect on functional exercise capacity and health-related quality of life.[94] A novel treatment option in CHF patients is neuromuscular electrical stimulation, which has been deemed safe to use. It has been shown to increase functional capacity, muscle strength, and quality of life more compared with conventional aerobic exercise.[95] However, in type II muscle fibres, baseline capillarization of the muscle may be a critical factor for permitting any muscle fibre hypertrophy in resistance exercise training in older men.[96]

Testosterone levels decline at the rate of 1% per year from 30 years of age leading to a reduction in muscle mass and strength,[97] The waning of testosterone appears to primarily decrease lower-limb muscle function,[69] making replacing it a seemingly perfect choice to treat sarcopenia. However, there is a fear that it will result in disproportionate side effects, predominantly an increased risk of prostate malignancies and cardiovascular events.[82] Interestingly, the administration method of testosterone appears to impact the cardiovascular risk. In a meta-analysis, oral testosterone significantly increased the risk of cardiovascular events, while no significant undesirable effects were observed, when testosterone was applied transdermally or by intramuscular injections.[98] Hence, studies focused on the testosterone application route are desirable, particularly in CHF patients. To circumvent the potential severe side effects of testosterone, selective androgen receptor modulators like enobosarm have been developed, which have similar anabolic effects to testosterone, but are believed to have fewer severe side effects.[99,100] However, a trial using the 4-aza steroidal drug MK0773 that has androgen gene selectivity and has been shown to increase IGF-1 levels and improve muscle function in women was terminated because of increased cardiovascular risk.[101] Recently, urolithin B, an ellagitannin-derived metabolite, has been observed to have beneficial effects on skeletal muscle growth by involving the androgen receptor in C2C12 myotubes and a mouse model of denervation.[102] Alternatives to stimulating the androgen receptor to induce muscle growth and strength are the use of GH and IGF-1, but of which are important in maintaining and building muscle mass.[103] However, a large meta-analysis showed that patients receiving GH were significantly more likely to experience side effects such as soft tissue oedema, arthralgias, carpal tunnel syndrome, and gynecomastia.[104] The GH/IGF-1 axis is controlled by several GH secretagogues that have been the subject of experimental therapies. Nasal application of growth hormone-releasing peptide-2, which is already in use for detection of GH secretion deficiency, has proven successful in anorexia.[105] Ghrelin, which is primarily produced in the fundus of the stomach, has been used in disease-related anorexia and conditions of muscle loss like sarcopenia and cachexia. In cancer cachexia patients, ghrelin improves food intake,[106,107] possibly by modulation of the central control of appetite dysregulation during cancer anorexia.[63] The small

molecule ghrelin-analogue anamorelin also increased muscle mass but had no effect on muscle strength.[108] However, ghrelin attenuated tumour-induced and cisplatin-induced muscle wasting in cancer cachexia mouse model.[109] A comparable effect was observed in a rat model of cisplatin-induced cachexia where the GH secretagogues hexarelin and JMV2894 improved calcium homeostasis in skeletal muscle.[110] Acetylated ghrelin normalized skeletal muscle mitochondrial oxidative capacity and Akt activation in rat CHF model.[34]

Myostatin (also known as GDF-8) is a negative regulator of muscle mass, which binds primarily to the activin II B receptor. A suppression of myostatin expression in knockout mice has shown significant increased muscle mass, an effect that can also be found in spontaneous, natural gene deletions in Belgian Blue cattle, whippets, and in a rare case, humans.[111] Human myocardium expressed myostatin in end-stage heart failure and the related signalling pathways in the myocardium seen to have a gender effect.[112] Myostatin released from the myocardium has been reported to be causal for skeletal muscle atrophy in a CHF mouse model.[113] In patients with liver cirrhosis, higher serum myostatin levels were associated with muscle mass loss, hyperammonemia, and impaired protein synthesis, as well as impaired survival.[114] Activation of activin II B receptor by activin A in the muscle has been described to induce muscle catabolism, which was dependent on p38beta MAPK-activated signalling pathway and resulted in the up-regulation of ubiquitin ligases MAFbx and UBR2 (E3alpha-II), as well as increases in LC3-II, a marker of autophagosome formation.[115] Circulating activin A levels have also been shown to be an independent predictor of survival in cancer patients.[116] Doxorubicin-induced cachexia was prevented by ACVR2B ligand blocking. Pretreatment with soluble ACVR2B-Fc had only minor impact in the heart while it had major effects in skeletal muscle at the transcriptome level.[117]

However, while neutralizing antibodies such as MYO-029, AMG 74, and LY2495655 or soluble receptor decoys such as ACE-11 and ACE-031 has significant beneficial effects on muscle mass and strength, they also exhibit several side effects including urticarial, aseptic meningitis, diarrhoea, confusion, fatigue, and unintentional muscle contractions.[82]

Other possibilities to induce muscle mass include β_2-adrenergic receptor agonists like salbutamol, clenbuterol, and formoterol. These compounds have beneficial effects on muscle mass and induction of protein synthesis in myocytes and simultaneously increased blood flow.[118] While clenbuterol has been observed to increase lean mass and maximal strength, the endurance and exercise duration was decreased.[119] Treatment of CHF patients with salbutamol resulted in detrimental ventricular arrhythmias.[120] However, formoterol treatment was cardio-protective aside from attenuating cachexia and improving survival in experimental cancer cachexia.[121] A combination treatment with formoterol and megestrol acetate has proven to be more effective in preventing muscle wasting than formoterol alone in the Yoshida hepatoma rat cancer cachexia model.[122] Megestrol acetate alone reduced autophagy in the heart and improved cardiac function in experimental cancer.[123]

Espindolol, the s-enantiomer of pindolol, is another multifactorial drug. It is a beta-1 receptor antagonist thereby reducing cellular stress and a partial beta-2 receptor agonist inducing muscle mass and also has 5-HT1A receptor activities leading to improvements in appetite and mood. Espindolol treatment in aged rats over the period of 1 month increased muscle mass considerably, while decreasing fat mass without negatively affecting cardiac function, making it an interesting candidate for sarcopenic obesity.[124] Importantly, espindolol lead to an increase in muscle mass and hand grip strength in Phase IIa cancer cachexia trial.[125,126] The beta blocker carvediolol has recently been shown to attenuate the development of cardiac cachexia and stimulate a partial reversal of cachexia in patients with severe CHF.[127]

Transition to cardiac cachexia

Sarcopenia in CHF may ultimately progress to cardiac cachexia,[128,129] which is associated with an exceptionally poor prognosis.[130] Earlier numbers showed a rate of up to 40% of CHF patients progressing to cardiac cachexia, which has significantly improved because of improved treatment of heart failure itself and is currently estimated to have a prevalence of 10%.[131] Other studies estimate a prevalence of cardiac cachexia of 5–15% in CHF. Mortality rates of cachectic patients range from 10–15% per year in chronic obstructive pulmonary disease to 20–30% per year in CHF and chronic kidney disease.[4] Cardiac cachexia has a dramatic prognostic impact with an 18 month mortality rate of up to 50%,[132] mortality is particularly high in obese cachectic CHF patients.[133] Patients with cardiac cachexia show higher rates of atrial fibrillation,[134] possibly contributing to the increased mortality.

Standard heart failure medication not only has remarkable beneficial effects on attenuating the progression to cardiac cachexia but also has shown to reduce cachexia and improve survival in experimental cancer cachexia, without affecting the tumour.[135]

While the majority of CHF patients has benefitted from heart failure medication, a subgroup of CHF patients seem to be unprotected from developing cachexia despite standard medication. Recently, several small molecule inhibitors of the E3-ligase muscle ring finger 1 have shown great potential in experimental cardiac cachexia by reducing muscle wasting and contractile dysfunction by inhibiting apoptosis and ubiquitin-proteasome-dependent proteolysis.[136] Additionally, microRNAs may also represent promising novel targets as potential biomarkers and as an interventions strategy in cardiac cachexia.[137]

In conclusion, while there have been stimulating and encouraging improvements in the field of muscle wasting, there are a number of crucial points that still have to be addressed in muscle wasting, sarcopenia, and cachexia in CHF: (i) the definition and discrimination of the different diseases states, (ii) robust biomarkers that aid tailor the anti-wasting therapy and allow monitoring of treatment success, and (iii) more research into exercise training in combination with existing drugs and/or investigational compounds.

Conflict of interest

None declared.

Funding

None.

References

1. Cattadori G, Segurini C, Picozzi A, Padeletti L, Anza C. Exercise and heart failure: an update. *ESC Heart Fail* 2018; **5**: 222–232.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**(27): 2129–2200.
3. Konishi M, Ishida J, Springer J, Anker SD, von Haehling S. Cachexia research in Japan: facts and numbers on prevalence, incidence and clinical impact. *J Cachexia Sarcopenia Muscle* 2016; **7**: 515–519.
4. Konishi M, Ishida J, Springer J, von Haehling S, Akashi YJ, Shimokawa H, Anker SD. Heart failure epidemiology and novel treatments in Japan: facts and numbers. *ESC Heart Fail* 2016; **3**: 145–151.
5. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jimenez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER, 3rd CS, Moy P, Muntner ME, Mussolino K, Nasir RW, Neumar G, Nichol L, Palaniappan DK, Pandey MJ, Reeves CJ, Rodriguez W, Rosamond PD, Sorlie J, Stein A, Towfighi TN, Turan SS, Virani D, Woo RW, Yeh MB. Turner, executive summary: Heart Disease and Stroke Statistics—2016 update: a report from the American Heart Association. *Circulation* 2016; **133**: 447–454.
6. Riley JP, Beattie JM. Palliative care in heart failure: facts and numbers. *ESC Heart Fail* 2017; **4**: 81–87.
7. Zelenak C, Radenovic S, Musial-Bright L, Tahirovic E, Sacirovic M, Lee CB, Jahandar-Lashki D, Inkrot S, Trippel TD, Busjahn A, Hashemi D, Wachter R, Pankuweit S, Stork S, Pieske B, Edelmann F, Dungen HD. Heart failure awareness survey in Germany: general knowledge on heart failure remains poor. *ESC Heart Fail* 2017; **4**: 224–231.
8. Edelmann F. Facts and numbers on epidemiology and pharmacological treatment of heart failure with preserved ejection fraction. *ESC Heart Fail* 2015; **2**: 41–45.
9. Trankle C, Canada JM, Buckley L, Carbone S, Dixon D, Arena R, Van Tassell B, Abbate A. Impaired myocardial relaxation with exercise determines peak aerobic exercise capacity in heart failure with preserved ejection fraction. *ESC Heart Fail* 2017; **4**: 351–355.
10. Sengul Aycicek G, Sumer F, Canbaz B, Kara O, Ulger Z. Sarcopenia evaluated by fat-free mass index in patients with chronic heart failure. *Eur J Intern Med* 2015; **26**: e34.
11. Bekfani T, Pellicori P, Morris DA, Ebner N, Valentova M, Steinbeck L, Wachter R, Elsner S, Sliziuk V, Schefold JC, Sandek A, Doehner W, Cleland JG, Lainscak M, Anker SD, von Haehling S. Sarcopenia in patients with heart failure with preserved ejection fraction: impact on muscle strength, exercise capacity and quality of life. *Int J Cardiol* 2016; **222**: 41–46.
12. Narumi T, Watanabe T, Kadowaki S, Takahashi T, Yokoyama M, Kinoshita D, Honda Y, Funayama A, Nishiyama S, Takahashi H, Arimoto T, Shishido T, Miyamoto T, Kubota I. Sarcopenia evaluated by fat-free mass index is an important prognostic factor in patients with chronic heart failure. *Eur J Intern Med* 2015; **26**: 118–122.
13. Tyrovolas S, Koyanagi A, Olaya B, Ayuso-Mateos JL, Miret M, Chatterji S, Tobiasz-Adamczyk B, Koskinen S, Leonardi M, Haro JM. Factors associated with skeletal muscle mass, sarcopenia, and sarcopenic obesity in older adults: a multi-continent study. *J Cachexia Sarcopenia Muscle* 2016; **7**: 312–321.
14. Uchmanowicz I, Loboz-Rudnicka M, Szelag P, Jankowska-Polanska B, Loboz-Grudzien K. Frailty in heart failure. *Curr Heart Fail Rep* 2014; **11**: 266–273.
15. Szulc P, Feyt C, Chapurlat R. High risk of fall, poor physical function, and low grip strength in men with fracture —the STRAMBO study. *J Cachexia Sarcopenia Muscle* 2016; **7**: 299–311.
16. Yamada S, Kamiya K, Kono Y. Frailty may be a risk marker for adverse outcome in patients with congestive heart failure. *ESC Heart Fail* 2015; **2**: 168–170.
17. Xu Z, Feng X, Dong J, Wang ZM, Lee J, Furdui C, Files DC, Beavers KM, Kritchevsky S, Milligan C, Jin JP, Delbono O, Zhang T. Cardiac troponin T and fast skeletal muscle denervation in ageing. *J Cachexia Sarcopenia Muscle* 2017.
18. Marty E, Liu Y, Samuel A, Or O, Lane J. A review of sarcopenia: Enhancing awareness of an increasingly prevalent disease. *Bone* 2017; **105**: 276–286.
19. Buckinx F, Reginster JY, Brunois T, Lenaerts C, Beaudart C, Croisier JL, Petermans J, Bruyere O. Prevalence of sarcopenia in a population of nursing home residents according to their frailty status: results of the SENIOR cohort. *J Musculoskelet Neuronal Interact* 2017; **17**: 209–217.
20. Ebner N, von Haehling S. Highlights from the 9th Cachexia Conference. *J Cachexia Sarcopenia Muscle* 2017; **8**: 508–511.
21. Harris R, Chang Y, Beavers K, Laddu-Patel D, Bea J, Johnson K, LeBoff M, Womack C, Wallace R, Li W, Crandall C, Cauley J. Risk of fracture in women with sarcopenia, low bone

mass, or both. *J Am Geriatr Soc* 2017; **65**: 2673–2678.
22. Brown JC, Harhay MO, Harhay MN. Sarcopenia and mortality among a population-based sample of community-dwelling older adults. *J Cachexia Sarcopenia Muscle* 2016; **7**: 290–298.
23. Ebner N, von Haehling S. Unlocking the wasting enigma: highlights from the 8th Cachexia Conference. *J Cachexia Sarcopenia Muscle* 2016; **7**: 90–94.
24. Tieland M, Trouwborst I, Clark BC. Skeletal muscle performance and ageing. *J Cachexia Sarcopenia Muscle* 2018; **9**: 3–19.
25. Dodds RM, Granic A, Davies K, Kirkwood TB, Jagger C, Sayer AA. Prevalence and incidence of sarcopenia in the very old: findings from the Newcastle 85+ Study. *J Cachexia Sarcopenia Muscle* 2017; **8**: 229–237.
26. Anker SD, Morley JE, von Haehling S. Welcome to the ICD-10 code for sarcopenia. *J Cachexia Sarcopenia Muscle* 2016; **7**: 512–514.
27. Abe T, Thiebaud RS, Loenneke JP, Bemben MG, Loftin M, Fukunaga T. Influence of severe sarcopenia on cardiovascular risk factors in nonobese men. *Metab Syndr Relat Disord* 2012; **10**: 407–412.
28. Go SI, Park MJ, Song HN, Kim HG, Kang MH, Lee HR, Kim Y, Kim RB, Lee SI, Lee GW. Prognostic impact of sarcopenia in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Cachexia Sarcopenia Muscle* 2016; **7**: 567–576.
29. Rutten IJ, van Dijk DP, Kruitwagen RF, Beets-Tan RG, Olde Damink SW, van Gorp T. Loss of skeletal muscle during neoadjuvant chemotherapy is related to decreased survival in ovarian cancer patients. *J Cachexia Sarcopenia Muscle* 2016; **7**: 458–466.
30. Choi MH, Oh SN, Lee IK, Oh ST, Won DD. Sarcopenia is negatively associated with long-term outcomes in locally advanced rectal cancer. *J Cachexia Sarcopenia Muscle* 2018; **9**: 53–59.
31. Kittiskulnam P, Carrero JJ, Chertow GM, Kaysen GA, Delgado C, Johansen KL. Sarcopenia among patients receiving hemodialysis: weighing the evidence. *J Cachexia Sarcopenia Muscle* 2017; **8**: 57–68.
32. Montano-Loza AJ, Angulo P, Meza-Junco J, Prado CM, Sawyer MB, Beaumont C, Esfandiari N, Ma M, Baracos VE. Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis. *J Cachexia Sarcopenia Muscle* 2016; **7**: 126–135.
33. Choi MH, Oh SN, Lee IK, Oh ST, Won DD. Sarcopenia is negatively associated with long-term outcomes in locally advanced rectal cancer. *J Cachexia Sarcopenia Muscle* 2017; **9**: 53–59.
34. Barazzoni R, Gortan Cappellari G, Palus S, Vinci P, Ruozi G, Zanetti M, Semolic A, Ebner N, von Haehling S, Sinagra G, Giacca M, Springer J. Acylated ghrelin treatment normalizes skeletal muscle mitochondrial oxidative capacity and AKT phosphorylation in rat chronic heart failure. *J Cachexia Sarcopenia Muscle* 2017; **8**: 991–998.
35. von Haehling S. Casting the net broader to confirm our imaginations: the long road to treating wasting disorders. *J Cachexia Sarcopenia Muscle* 2017; **8**: 870–880.
36. Morley JE, Anker SD, von Haehling S. Prevalence, incidence, and clinical impact of sarcopenia: facts, numbers, and epidemiology-update 2014. *J Cachexia Sarcopenia Muscle* 2014; **5**: 253–259.
37. Chen LK, Lee WJ, Peng LN, Liu LK, Arai H, Akishita M. Recent advances in sarcopenia research in Asia: 2016 update from the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc* 2016; **17**: 767,e1–7.
38. Dos Santos L, Cyrino ES, Antunes M, Santos DA, Sardinha LB. Sarcopenia and physical independence in older adults: the independent and synergic role of muscle mass and muscle function. *J Cachexia Sarcopenia Muscle* 2017; **8**: 245–250.
39. Yang M, Hu X, Wang H, Zhang L, Hao Q, Dong B. Sarcopenia predicts readmission and mortality in elderly patients in acute care wards: a prospective study. *J Cachexia Sarcopenia Muscle* 2017; **8**: 251–258.
40. Scherbakov N, Doehner W. Searching for a relevant definition of sarcopenia: results from the cross-sectional EPIDOS study. *J Cachexia Sarcopenia Muscle* 2016; **7**: 100–101.
41. Drescher C, Konishi M, Ebner N, Springer J. Loss of muscle mass: current developments in cachexia and sarcopenia focused on biomarkers and treatment. *J Cachexia Sarcopenia Muscle* 2015; **6**: 303–311.
42. Calvani R, Marini F, Cesari M, Tosato M, Anker SD, von Haehling S, Miller RR, Bernabei R, Landi F, Marzetti E. S. consortium, Biomarkers for physical frailty and sarcopenia: state of the science and future developments. *J Cachexia Sarcopenia Muscle* 2015; **6**: 278–286.
43. Nedergaard A, Dalgas U, Primdahl H, Johansen J, Overgaard J, Overgaard K, Henriksen K, Karsdal MA, Lonbro S. Collagen fragment biomarkers as serological biomarkers of lean body mass—a biomarker pilot study from the DAHANCA25B cohort and matched controls. *J Cachexia Sarcopenia Muscle* 2015; **6**: 335–342.
44. Beaudart C, Biver E, Reginster JY, Rizzoli R, Rolland Y, Bautmans I, Petermans J, Gillain S, Buckinx F, Dardenne N, Bruyere O. Validation of the SarQoL(R), a specific health-related quality of life questionnaire for Sarcopenia. *J Cachexia Sarcopenia Muscle* 2017; **8**: 238–244.
45. Morley JE, Cao L. Rapid screening for sarcopenia. *J Cachexia Sarcopenia Muscle* 2015; **6**: 312–314.
46. Malmstrom TK, Miller DK, Simonsick EM, Ferrucci L, Morley JE. SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. *J Cachexia Sarcopenia Muscle* 2016; **7**: 28–36.
47. von Haehling S. The wasting continuum in heart failure: from sarcopenia to cachexia. *Proc Nutr Soc* 2015; **74**: 367–377.
48. Fulster S, Tacke M, Sandek A, Ebner N, Tschope C, Doehner W, Anker SD, von Haehling S. Muscle wasting in patients with chronic heart failure: results from the studies investigating co-morbidities aggravating heart failure (SICA-HF). *Eur Heart J* 2013; **34**: 512–519.
49. Hajahmadi M, Shemshadi S, Khalilipur E, Amin A, Taghavi S, Maleki M, Malek H, Naderi N. Muscle wasting in young patients with dilated cardiomyopathy. *J Cachexia Sarcopenia Muscle* 2017; **8**: 542–548.
50. Kinugawa S, Takada S, Matsushima S, Okita K, Tsutsui H. Skeletal muscle abnormalities in heart failure. *Int Heart J* 2015; **56**: 475–484.
51. St-Jean-Pelletier F, Pion CH, Leduc-Gaudet JP, Sgarioto N, Zovile I, Barbat-Artigas S, Reynaud O, Alkaterji F, Lemieux FC, Grenon A, Gaudreau P, Hepple RT, Chevalier S, Belanger M, Morais JA, Aubertin-Leheudre M, Gouspillou G. The impact of ageing, physical activity, and pre-frailty on skeletal muscle phenotype, mitochondrial content, and intramyocellular lipids in men. *J Cachexia Sarcopenia Muscle* 2017; **8**: 213–228.
52. Mangner N, Weikert B, Bowen TS, Sandri M, Hollriegel R, Erbs S, Hambrecht R, Schuler G, Linke A, Gielen S, Adams V. Skeletal muscle alterations in chronic heart failure: differential effects on quadriceps and diaphragm. *J Cachexia Sarcopenia Muscle* 2015; **6**: 381–390.
53. Agapitou V, Dimopoulos S, Kapelios C, Karatzanos E, Manetos C, Georgantas A, Ntalianis A, Terrovitis J, Karga H, Nanas S. Hormonal imbalance in relation to exercise intolerance and ventilatory inefficiency in chronic heart failure. *J Heart Lung Transplant* 2013; **32**: 431–436.
54. Doehner W, Turhan G, Leyva F, Rauchhaus M, Sandek A, Jankowska EA, von Haehling S, Anker SD. Skeletal muscle weakness is related to insulin resistance in patients with chronic heart failure. *ESC Heart Fail* 2015; **2**: 85–89.
55. Chu MP, Lieffers J, Ghosh S, Belch A, Chua NS, Fontaine A, Sangha R, Turner RA, Baracos VE, Sawyer MB. Skeletal

muscle density is an independent predictor of diffuse large B-cell lymphoma outcomes treated with rituximab-based chemoimmunotherapy. *J Cachexia Sarcopenia Muscle* 2017; **8**: 298–304.
56. Morley JE. Anorexia of ageing: a key component in the pathogenesis of both sarcopenia and cachexia. *J Cachexia Sarcopenia Muscle* 2017; **8**: 523–526.
57. Iwakami N, Nagai T, Furukawa TA, Sugano Y, Honda S, Okada A, Asaumi Y, Aiba T, Noguchi T, Kusano K, Ogawa H, Yasuda S, Anzai T. Prognostic value of malnutrition assessed by Controlling Nutritional Status score for long-term mortality in patients with acute heart failure. *Int J Cardiol* 2017; **230**: 529–536.
58. Calvani R, Marini F, Cesari M, Buford TW, Manini TM, Pahor M, Leeuwenburgh C, Bernabei R, Landi F, Marzetti E. Systemic inflammation, body composition, and physical performance in old community-dwellers. *J Cachexia Sarcopenia Muscle* 2017; **8**: 69–77.
59. Saitoh M, Dos Santos MR, Emami A, Ishida J, Ebner N, Valentova M, Bekfani T, Sandek A, Lainscak M, Doehner W, Anker SD, von Haehling S. Anorexia, functional capacity, and clinical outcome in patients with chronic heart failure: results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). *ESC Heart Fail* 2017; **4**: 448–457.
60. Landi F, Liperoti R, Russo A, Giovannini S, Tosato M, Barillaro C, Capoluongo E, Bernabei R, Onder G. Association of anorexia with sarcopenia in a community-dwelling elderly population: results from the ilSIRENTE study. *Eur J Nutr* 2013; **52** 1261–1268.
61. Cooper C, Burden ST, Cheng H, Molassiotis A. Understanding and managing cancer-related weight loss and anorexia: insights from a systematic review of qualitative research. *J Cachexia Sarcopenia Muscle* 2015; **6**: 99–111.
62. Borner T, Arnold M, Ruud J, Breit SN, Langhans W, Lutz TA, Blomqvist A, Riediger T. Anorexia-cachexia syndrome in hepatoma tumour-bearing rats requires the area postrema but not vagal afferents and is paralleled by increased MIC-1/GDF15. *J Cachexia Sarcopenia Muscle* 2017; **8**: 417–427.
63. Molfino A, Iannace A, Colaiacomo MC, Farcomeni A, Emiliani A, Gualdi G, Laviano A, Rossi Fanelli F. Cancer anorexia: hypothalamic activity and its association with inflammation and appetite-regulating peptides in lung cancer. *J Cachexia Sarcopenia Muscle* 2017; **8**: 40–47.
64. Wakabayashi H, Sakuma K. Rehabilitation nutrition for sarcopenia with disability: a combination of both rehabilitation and nutrition care management. *J Cachexia Sarcopenia Muscle* 2014; **5**: 269–277.
65. Kalafateli M, Mantzoukis K, Choi Yau Y, Mohammad AO, Arora S, Rodrigues S, de Vos M, Papadimitriou K, Thorburn D, O'Beirne J, Patch D, Pinzani M, Morgan MY, Agarwal B, Yu D, Burroughs AK, Tsochatzis EA. Malnutrition and sarcopenia predict post-liver transplantation outcomes independently of the Model for End-stage Liver Disease score. *J Cachexia Sarcopenia Muscle* 2017; **8**: 113–121.
66. Goossens C, Marques MB, Derde S, Vander Perre S, Dufour T, Thiessen SE, Guiza F, Janssens T, Hermans G, Vanhorebeek I, De Bock K, Van den Berghe G, Langouche L. Premorbid obesity, but not nutrition, prevents critical illness-induced muscle wasting and weakness. *J Cachexia Sarcopenia Muscle* 2017; **8**: 89–101.
67. Gielen E, O'Neill TW, Pye SR, Adams JE, Wu FC, Laurent MR, Claessens F, Ward KA, Boonen S, Bouillon R, Vanderschueren D, Verschueren S. Endocrine determinants of incident sarcopenia in middle-aged and elderly European men. *J Cachexia Sarcopenia Muscle* 2015; **6**: 242–252.
68. Yoshihisa A, Suzuki S, Sato Y, Kanno Y, Abe S, Miyata M, Sato T, Oikawa M, Kobayashi A, Yamaki T, Kunii H, Nakazato K, Ishida T, Takeishi Y. Relation of testosterone levels to mortality in men with heart failure. *Am J Cardiol* 2018; **121**: 1321–1327.
69. Cheung AS, Gray H, Schache AG, Hoermann R, Lim Joon D, Zajac JD, Pandy MG, Grossmann M. Androgen deprivation causes selective deficits in the biomechanical leg muscle function of men during walking: a prospective case-control study. *J Cachexia Sarcopenia Muscle* 2017; **8**: 102–112.
70. Wendowski O, Redshaw Z, Mutungi G. Dihydrotestosterone treatment rescues the decline in protein synthesis as a result of sarcopenia in isolated mouse skeletal muscle fibres. *J Cachexia Sarcopenia Muscle* 2017; **8**: 48–56.
71. Porto CM, Silva VL, da Luz JSB, Filho BM, da Silveira VM. Association between vitamin D deficiency and heart failure risk in the elderly. *ESC Heart Fail* 2018; **5**: 63–74.
72. Calder PC, Laviano A, Lonnqvist F, Muscaritoli M, Ohlander M, Schols A. Targeted medical nutrition for cachexia in chronic obstructive pulmonary disease: a randomized, controlled trial. *J Cachexia Sarcopenia Muscle* 2018; **9**: 28–40.
73. Kim J, Lee Y, Kye S, Chung YS, Lee O. Association of serum vitamin D with osteosarcopenic obesity: Korea National Health and Nutrition Examination Survey 2008-2010. *J Cachexia Sarcopenia Muscle* 2017; **8**: 259–266.
74. Mochamat H, Cuhls M, Marinova S, Kaasa C, Stieber R, Conrad L, Radbruch M. Mucke, A systematic review on the role of vitamins, minerals, proteins, and other supplements for the treatment of cachexia in cancer: a European Palliative Care Research Centre cachexia project. *J Cachexia Sarcopenia Muscle* 2017; **8**: 25–39.
75. Landi F, Marzetti E, Martone AM, Bernabei R, Onder G. Exercise as a remedy for sarcopenia. *Curr Opin Clin Nutr Metab Care* 2014; **17**: 25–31.
76. Phu S, Boersma D, Duque G. Exercise and sarcopenia. *J Clin Densitom* 2015; **18**: 488–492.
77. Bowen TS, Schuler G, Adams V. Skeletal muscle wasting in cachexia and sarcopenia: molecular pathophysiology and impact of exercise training. *J Cachexia Sarcopenia Muscle* 2015; **6**: 197–207.
78. Rondanelli M, Klersy C, Terracol G, Talluri J, Maugeri R, Guido D, Faliva MA, Solerte BS, Fioravanti M, Lukaski H, Perna S. Whey protein, amino acids, and vitamin D supplementation with physical activity increases fat-free mass and strength, functionality, and quality of life and decreases inflammation in sarcopenic elderly. *Am J Clin Nutr* 2016; **103**: 830–840.
79. Santarpia L, Contaldo F, Pasanisi F. Dietary protein content for an optimal diet: a clinical view. *J Cachexia Sarcopenia Muscle* 2017; **8**: 345–348.
80. Urban RJ, Dillon EL, Choudhary S, Zhao Y, Horstman AM, Tilton RG, Sheffield-Moore M. Translational studies in older men using testosterone to treat sarcopenia. *Trans Am Clin Climatol Assoc* 2014; **125**: 27–42 discussion 42-4.
81. Vitale G, Cesari M, Mari D. Aging of the endocrine system and its potential impact on sarcopenia. *Eur J Intern Med* 2016; **35**: 10–15.
82. Morley JE. Pharmacologic options for the treatment of sarcopenia. *Calcif Tissue Int* 2016; **98**: 319–333.
83. Naseeb MA, Volpe SL. Protein and exercise in the prevention of sarcopenia and aging. *Nutrition research (New York, NY)* 2017; **40**: 1–20.
84. Daly RM. Exercise and nutritional approaches to prevent frail bones, falls and fractures: an update. *Climacteric: J Int Menopause Soc* 2017; **20**: 119–124.
85. Anker SD, Morley JE. Cachexia: a nutritional syndrome? *J Cachexia Sarcopenia Muscle* 2015; **6**: 269–271.
86. Pinto CL, Botelho PB, Carneiro JA, Mota JF. Impact of creatine supplementation in combination with resistance training on lean mass in the elderly. *J Cachexia Sarcopenia Muscle* 2016; **7**: 413–421.
87. de Vries NM, Staal JB, van der Wees PJ, Adang EM, Akkermans R, Olde Rikkert MG, Nijhuis-van der Sanden MW. Patient-centred physical therapy is (cost-) effective in increasing physical activity and reducing frailty in older

adults with mobility problems: a randomized controlled trial with 6 months follow-up. *J Cachexia Sarcopenia Muscle* 2016; **7**: 422–435.
88. Foong YC, Chherawala N, Aitken D, Scott D, Winzenberg T, Jones G. Accelerometer-determined physical activity, muscle mass, and leg strength in community-dwelling older adults. *J Cachexia Sarcopenia Muscle* 2016; **7**: 275–283.
89. Chan DD, Tsou HH, Chang CB, Yang RS, Tsauo JY, Chen CY, Hsiao CF, Hsu YT, Chen CH, Chang SF, Hsiung CA, Kuo KN. Integrated care for geriatric frailty and sarcopenia: a randomized control trial. *J Cachexia Sarcopenia Muscle* 2017; **8**: 78–88.
90. Hangelbroek RW, Fazelzadeh P, Tieland M, Boekschoten MV, Hooiveld GJ, van Duynhoven JP, Timmons JA, Verdijk LB, de Groot LC, van Loon LJ, Muller M. Expression of protocadherin gamma in skeletal muscle tissue is associated with age and muscle weakness. *J Cachexia Sarcopenia Muscle* 2016; **7**: 604–614.
91. Gielen S, Laughlin MH, O'Conner C, Duncker DJ. Exercise training in patients with heart disease: review of beneficial effects and clinical recommendations. *Prog Cardiovasc Dis* 2015; **57**: 347–355.
92. Souza RW, Piedade WP, Soares LC, Souza PA, Aguiar AF, Vechetti-Junior IJ, Campos DH, Fernandes AA, Okoshi K, Carvalho RF, Cicogna AC, Dal-Pai-Silva M. Aerobic exercise training prevents heart failure-induced skeletal muscle atrophy by anti-catabolic, but not anabolic actions. *PLoS One* 2014; **9**: e110020.
93. Adams SC, Segal RJ, McKenzie DC, Vallerand JR, Morielli AR, Mackey JR, Gelmon K, Friedenreich CM, Reid RD, Courneya KS. Impact of resistance and aerobic exercise on sarcopenia and dynapenia in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *Breast Cancer Res Treat* 2016; **158**: 497–507.
94. Connolly B, Salisbury L, O'Neill B, Geneen L, Douiri A, Grocott MP, Hart N, Walsh TS, Blackwood B. Exercise rehabilitation following intensive care unit discharge for recovery from critical illness: executive summary of a Cochrane Collaboration systematic review. *J Cachexia Sarcopenia Muscle* 2016; **7**: 520–526.
95. Saitoh M, Dos Santos MR, Anker M, Anker SD, von Haehling S, Springer J. Neuromuscular electrical stimulation for muscle wasting in heart failure patients. *Int J Cardiol* 2016; **225**: 200–205.
96. Snijders T, Nederveen JP, Joanisse S, Leenders M, Verdijk LB, van Loon LJ, Parise G. Muscle fibre capillarization is a critical factor in muscle fibre hypertrophy during resistance exercise training in older men. *J Cachexia Sarcopenia Muscle* 2017; **8**: 267–276.
97. Baumgartner RN, Waters DL, Gallagher D, Morley JE, Garry PJ. Predictors of skeletal muscle mass in elderly men and women. *Mech Ageing Dev* 1999; **107**: 123–136.
98. Borst SE, Shuster JJ, Zou B, Ye F, Jia H, Wokhlu A, Yarrow JF. Cardiovascular risks and elevation of serum DHT vary by route of testosterone administration: a systematic review and meta-analysis. *BMC Med* 2014; **12**: 211.
99. Srinath R, Dobs A. Enobosarm (GTx-024, S-22): a potential treatment for cachexia. *Future Oncol (London, England)* 2014; **10**: 187–194.
100. Dubois V, Simitsidellis I, Laurent MR, Jardi F, Saunders PT, Vanderschueren D, Claessens F. Enobosarm (GTx-024) modulates adult skeletal muscle mass independently of the androgen receptor in the satellite cell lineage. *Endocrinology* 2015; **156**: 4522–4533.
101. Papanicolaou DA, Ather SN, Zhu H, Zhou Y, Lutkiewicz J, Scott BB, Chandler J. A phase IIA randomized, placebo-controlled clinical trial to study the efficacy and safety of the selective androgen receptor modulator (SARM), MK-0773 in female participants with sarcopenia. *J Nutr Health Aging* 2013; **17**: 533–543.
102. Rodriguez J, Pierre N, Naslain D, Bontemps F, Ferreira D, Priem F, Deldicque L, Francaux M, Urolithin B. A newly identified regulator of skeletal muscle mass. *J Cachexia Sarcopenia Muscle* 2017; **8**: 583–597.
103. von Haehling S, Ebner N, Dos Santos MR, Springer J, Anker SD. Muscle wasting and cachexia in heart failure: mechanisms and therapies. *Nat Rev Cardiol* 2017; **14**: 323–341.
104. Liu H, Bravata DM, Olkin I, Nayak S, Roberts B, Garber AM, Hoffman AR. Systematic review: the safety and efficacy of growth hormone in the healthy elderly. *Ann Intern Med* 2007; **146**: 104–115.
105. Haruta I, Fuku Y, Kinoshita K, Yoneda K, Morinaga A, Amitani M, Amitani H, Asakawa A, Sugawara H, Takeda Y, Bowers CY, Inui A. One-year intranasal application of growth hormone releasing peptide-2 improves body weight and hypoglycemia in a severely emaciated anorexia nervosa patient. *J Cachexia Sarcopenia Muscle* 2015; **6**: 237–241.
106. Madeddu C, Mantovani G, Gramignano G, Maccio A. Advances in pharmacologic strategies for cancer cachexia. *Expert Opin Pharmacother* 2015; **16**: 2163–2177.
107. Hatanaka M, Konishi M, Ishida J, Saito M, Springer J. Novel mechanism of ghrelin therapy for cachexia. *J Cachexia Sarcopenia Muscle* 2015; **6**: 393.
108. Anker SD, Coats AJ, Morley JE. Evidence for partial pharmaceutical reversal of the cancer anorexia-cachexia syndrome: the case of anamorelin. *J Cachexia Sarcopenia Muscle* 2015; **6**: 275–277.
109. Chen JA, Splenser A, Guillory B, Luo J, Mendiratta M, Belinova B, Halder T, Zhang G, Li YP, Garcia JM. Ghrelin prevents tumour- and cisplatin-induced muscle wasting: characterization of multiple mechanisms involved. *J Cachexia Sarcopenia Muscle* 2015; **6**: 132–143.
110. Conte E, Camerino GM, Mele A, De Bellis M, Pierno S, Rana F, Fonzino A, Caloiero R, Rizzi L, Bresciani E, Ben Haj K, Salah JA, Fehrentz J, Martinez A, Giustino MA, Mariggio M, Coluccia D, Tricarico MD, Lograno A, De Luca A, Torsello D, Conte AL. Growth hormone secretagogues prevent dysregulation of skeletal muscle calcium homeostasis in a rat model of cisplatin-induced cachexia. *J Cachexia Sarcopenia Muscle* 2017; **8**: 386–404.
111. Elkina Y, von Haehling S, Anker SD, Springer J. The role of myostatin in muscle wasting: an overview. *J Cachexia Sarcopenia Muscle* 2011; **2**: 143–151.
112. Ishida J, Konishi M, Saitoh M, Anker M, Anker SD, Springer J. Myostatin signaling is up-regulated in female patients with advanced heart failure. *Int J Cardiol* 2017; **238**: 37–42.
113. Heineke J, Auger-Messier M, Xu J, Sargent M, York A, Welle S, Molkentin JD. Genetic deletion of myostatin from the heart prevents skeletal muscle atrophy in heart failure. *Circulation* 2010; **121**: 419–425.
114. Nishikawa H, Enomoto H, Ishii A, Iwata Y, Miyamoto Y, Ishii N, Yuri Y, Hasegawa K, Nakano C, Nishimura T, Yoh K, Aizawa N, Sakai Y, Ikeda N, Takashima T, Takata R, Iijima H, Nishiguchi S. Elevated serum myostatin level is associated with worse survival in patients with liver cirrhosis. *J Cachexia Sarcopenia Muscle* 2017; **8**: 915–925.
115. Ding H, Zhang G, Sin KW, Liu Z, Lin RK, Li M, Li YP. Activin A induces skeletal muscle catabolism via p38beta mitogen-activated protein kinase. *J Cachexia Sarcopenia Muscle* 2017; **8**: 202–212.
116. Loumaye A, de Barsy M, Nachit M, Lause P, van Maanen A, Trefois P, Gruson D, Thissen JP. Circulating activin A predicts survival in cancer patients. *J Cachexia Sarcopenia Muscle* 2017; **8**: 768–777.
117. Hulmi JJ, Nissinen TA, Rasanen M, Degerman J, Lautaoja JH, Hemanthakumar KA, Backman JT, Ritvos O, Silvennoinen M, Kivela R. Prevention of chemotherapy-induced cachexia by ACVR2B ligand blocking has different effects on heart and skeletal muscle. *J Cachexia Sarcopenia Muscle* 2018; **9**: 417–432.

118. Harrington D, Chua TP, Coats AJ. The effect of salbutamol on skeletal muscle in chronic heart failure. *Int J Cardiol* 2000; **73**: 257–265.
119. Kamalakkannan G, Petrilli CM, George I, LaManca J, McLaughlin BT, Shane E, Mancini DM, Maybaum S. Clenbuterol increases lean muscle mass but not endurance in patients with chronic heart failure. *J Heart Lung Transplant* 2008; **27**: 457–461.
120. Mettauer B, Rouleau JL, Burgess JH. Detrimental arrhythmogenic and sustained beneficial hemodynamic effects of oral salbutamol in patients with chronic congestive heart failure. *Am Heart J* 1985; **109**: 840–847.
121. Toledo M, Springer J, Busquets S, Tschirner A, Lopez-Soriano FJ, Anker SD, Argiles JM. Formoterol in the treatment of experimental cancer cachexia: effects on heart function. *J Cachexia Sarcopenia Muscle* 2014; **5**: 315–320.
122. Toledo M, Penna F, Oliva F, Luque M, Betancourt A, Marmonti E, Lopez-Soriano FJ, Argiles JM, Busquets S. A multifactorial anti-cachectic approach for cancer cachexia in a rat model undergoing chemotherapy. *J Cachexia Sarcopenia Muscle* 2016; **7**: 48–59.
123. Musolino V, Palus S, Tschirner A, Drescher C, Gliozzi M, Carresi C, Vitale C, Muscoli C, Doehner W, von Haehling S, Anker SD, Mollace V, Springer J. Megestrol acetate improves cardiac function in a model of cancer cachexia-induced cardiomyopathy by autophagic modulation. *J Cachexia Sarcopenia Muscle* 2016; **7**: 555–566.
124. Potsch MS, Tschirner A, Palus S, von Haehling S, Doehner W, Beadle J, Coats AJ, Anker SD, Springer J. The anabolic catabolic transforming agent (ACTA) espindolol increases muscle mass and decreases fat mass in old rats. *J Cachexia Sarcopenia Muscle* 2014; **5**: 149–158.
125. Lainscak M, Laviano A. ACT-ONE—ACTION at last on cancer cachexia by adapting a novel action beta-blocker. *J Cachexia Sarcopenia Muscle* 2016; **7**: 400–402.
126. Stewart Coats AJ, Ho GF, Prabhash K, von Haehling S, Tilson J, Brown R, Beadle J, Anker SD. for, A.C.T.O.N.E.s.g. on behalf of the, Espindolol for the treatment and prevention of cachexia in patients with stage III/IV non-small cell lung cancer or colorectal cancer: a randomized, double-blind, placebo-controlled, international multicentre phase II study (the ACT-ONE trial). *J Cachexia Sarcopenia Muscle* 2016; **7**: 355–365.
127. Clark AL, Coats AJS, Krum H, Katus HA, Mohacsi P, Salekin D, Schultz MK, Packer M, Anker SD. Effect of beta-adrenergic blockade with carvedilol on cachexia in severe chronic heart failure: results from the COPERNICUS trial. *J Cachexia Sarcopenia Muscle* 2017; **8**: 549–556.
128. Biolo G, Cederholm T, Muscaritoli M. Muscle contractile and metabolic dysfunction is a common feature of sarcopenia of aging and chronic diseases: from sarcopenic obesity to cachexia. *Clinical Nutrition (Edinburgh, Scotland)* 2014; **33**: 737–748.
129. Zamboni M, Rossi AP, Corzato F, Bambace C, Mazzali G, Fantin F. Sarcopenia, cachexia and congestive heart failure in the elderly. *Endocr Metab Immune Disord Drug Targets* 2013; **13**: 58–67.
130. Loncar G, Springer J, Anker M, Doehner W, Lainscak M. Cardiac cachexia: hic et nunc. *J Cachexia Sarcopenia Muscle* 2016; **7**: 246–260.
131. Christensen HM, Kistorp C, Schou M, Keller N, Zerahn B, Frystyk J, Schwarz P, Faber J. Prevalence of cachexia in chronic heart failure and characteristics of body composition and metabolic status. *Endocrine* 2013; **43**: 626–634.
132. Anker SD, Ponikowski P, Varney S, Chua TP, Clark AL, Webb-Peploe KM, Harrington D, Kox WJ, Poole-Wilson PA, Coats AJ. Wasting as independent risk factor for mortality in chronic heart failure. *Lancet (London, England)* 1997; **349**: 1050–1053.
133. Zamora E, Diez-Lopez C, Lupon J, de Antonio M, Domingo M, Santesmases J, Troya MI, Diez-Quevedo C, Altimir S, Bayes-Genis A. Weight loss in obese patients with heart failure. *J Am Heart Assoc* 2016; **5**: e002468.
134. Arambula-Garza E, Castillo-Martinez L, Gonzalez-Islas D, Orea-Tejeda A, Santellano-Juarez B, Keirns-Davies C, Pelaez-Hernandez V, Sanchez-Santillan R, Pineda-Juarez J, Cintora-Martinez C, Pablo-Santiago R. Association of cardiac cachexia and atrial fibrillation in heart failure patients. *Int J Cardiol* 2016; **223**: 863–866.
135. Springer J, Tschirner A, Haghikia A, von Haehling S, Lal H, Grzesiak A, Kaschina E, Palus S, Potsch M, von Websky K, Hocher B, Latouche C, Jaisser F, Morawietz L, Coats AJ, Beadle J, Argiles JM, Thum T, Foldes G, Doehner W, Hilfiker-Kleiner D, Force T, Anker SD. Prevention of liver cancer cachexia-induced cardiac wasting and heart failure. *Eur Heart J* 2014; **35**: 932–941.
136. Bowen TS, Adams V, Werner S, Fischer T, Vinke P, Brogger MN, Mangner N, Linke A, Sehr P, Lewis J, Labeit D, Gasch A, Labeit S. Small-molecule inhibition of MuRF1 attenuates skeletal muscle atrophy and dysfunction in cardiac cachexia. *J Cachexia Sarcopenia Muscle* 2017; **8**: 939–953.
137. Bei Y, Xiao J. MicroRNAs in muscle wasting and cachexia induced by heart failure. *Nat Rev Cardiol* 2017; **14**: 566.