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INVITED EDITORIAL

Sarcopenia in heart failure: 'waste' the appropriate time and resources, not the muscles

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This editorial refers to 'Impact of sarcopenia on prognosis in patients with heart failure with reduced and preserved ejection fraction', by M. Konishi et al., doi:10.1093/eurjpc/zwaa117.

Sarcopenia is a predominantly age-related process that is a result of loss of skeletal muscle mass and function that leads to decreased physical ability. Sarcopenia's prevalence is 5–13% among patients aged 60–70 but can be as high as 50% in the >80-year-old age group.[1] For instance, in a multinational study of 18 000 elderly patients (≥65 years old) 12.6–17.5% of them were reported to be sarcopenic.[2] Identifying and diagnosing sarcopenia becomes extremely important as it has been linked to worsening functional status,[3] increased mortality,[4,5] and its prevalence is anticipated to increase in the coming years given the ageing of the global population.[6] Chronic cardiovascular diseases are also very common in the elderly, while heart failure (HF) has an estimated prevalence of 2% in this subgroup.[7,8] The prevalence of sarcopenia in the HF population is significantly higher compared to the general population, ranging from 19.5%[9] to 47.3%,[10] while an association with negative effects on functional status and prognosis has also been reported.[11–13]

Konishi *et al.*, evaluated in a retrospective fashion the impact of sarcopenia on mortality among 942 patients with heart failure with reduced ejection fraction (HFrEF) and heart failure[14] with preserved ejection fraction (HFpEF) patients from the FRAGILE HF registry ('Prevalence and prognostic value of physical and social frailty in geriatric patients hospitalized for heart failure'). FRAGILE HF was originally a prospectively designed multicentre study focused on the effect of frailty on hospitalized patients with HF.[15] The outcomes of interest were mortality and the composite endpoint of death and HF rehospitalization at 1 year. All of the participants were over the age of 65 and the patient population was similarly distributed between HFrEF ($n = 467$) and HFpEF ($n = 745$). Pertinent exclusion criteria included patients with prior transplant or left ventricular assist devises, patients on dialysis, and patients with low natriuretic peptide values (BNP <100 pg/mL or NT-proBNP <300 pg/mL). Sarcopenia assessment was conducted by specialized personnel prior to discharge and was based on the Asian Working Group for Sarcopenia (AWGS) criteria. In specific, patients were evaluated for (i) low muscle strength via assessment of handgrip strength (<26 kg for men and <18 kg for women was consistent with sarcopenia); (ii) decreased physical performance via performing a 4-min-walk test (speed <0.8 m/s was the cut-off for both men and women); and for concomitant decreased muscle mass via bioelectrical impedance analysis of the appendicular skeletal muscle mass.[2]

Patients with sarcopenia were older (82 ± 8 vs. 79 ± 8 years, $P < 0.001$), more likely to be of male sex (70.6% vs. 55.4%, $P < 0.001$) and with lower BMI (18.8 ± 3 vs. 22.1 ± 3.7 kg/m^2, $P < 0.001$) compared to patients without sarcopenia. Prevalence of sarcopenia was similar in the two HF groups (18.1% in HFrEF vs. 21.6% in HFpEF, $P = 0.191$) and slightly less in the HFpEF patients in the age-matched cohort (766 total patients, HFrEF: 23% vs. HFpEF: 17%, $P = 0.047$). Interestingly, patients with HFpEF were less likely to have decreased muscle mass by bioelectrical impedance analysis (22.1% vs. 31.0%, $P = 0.003$), but more likely to have low handgrip strength (67.8% vs 55.5%, $P < 0.001$) and slow gait speed (54.5% vs. 41.1%, $P < 0.001$) compared to their peers with HFrEF. Sarcopenic patients had higher unadjusted mortality rates in both HF groups (21.7% vs. 9.1% in HFpEF, and 22.0% vs. 9.1% in HFrEF, $P < 0.001$ for both). Sarcopenia maintained a significant association with 1-year mortality in all multivariable adjusted models. However, sarcopenia was not associated with higher rates of the 1-year combined endpoint (death or HF readmission), driven obviously by the absence of difference in the HF readmission rates.

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Konishi *et al.* should be praised for conducting such a meaningful study. Despite the fact that clinicians often associate sarcopenic patients with poor prognosis, the actual evidence behind that in the HF world is probably limited, especially when it comes to studies with analytic and appropriate sarcopenia assessment (the authors used tools such as bioelectrical impedance analysis to actually measure rather than calculate the skeletal body mass). The appropriate follow-up and relatively large sample are other strengths. However, a number of limitations may decrease our initial enthusiasm. First, the authors chose all-cause mortality as their primary endpoint, and data on cardiovascular mortality are not presented. Sarcopenia is known to be associated with worse prognosis in the general population and thus the association with worse 1-year mortality in HF patients is not surprising. To further support this argument, the absence of difference in readmission rates between sarcopenic and not sarcopenic HF patients is striking. Most of the risk factors for worse mortality in HF are usually associated with worse readmission rates as well and it is unclear why sarcopenia is an exception. Second, this was an Asian population and thus the generalizability to Caucasians, Blacks, and Hispanics is questionable. Third, the exclusion of patients with low NT-proBNP levels and patients undergoing dialysis might introduce attrition bias, with obese individuals excluded from the analysis. Fourth, even though bioelectrical impedance analysis can provide direct quantification of the skeletal muscle mass, is inherently prone to equipment variability, and thus might affect the reproducibility of the results. Fifth, it should be made clear that the attempt to dichotomize the sample based on the EF was not made in order to compare the—potentially different—effect of sarcopenia in HFrEF vs. HFpEF patients but rather in order to provide further insight about patient characteristics in the two subgroups. Future studies focused only on sarcopenic patients will be needed to determine whether one of the two HF phenotypes is exponentially worsening the outcomes of those patients.

The independent association of sarcopenia with mortality reminds us of the known obesity paradox in HF. It has been repeatedly shown that patients with HF seem to have favourable outcomes, including mortality, cardiovascular mortality, and hospitalization if they are overweight or mildly obese compared to their leaner peers.[16–19] Can the undiagnosed sarcopenia in the non-overweight/obese group be the explanation of those findings? Similar outcomes have been seen in other cardiovascular disease, including peripheral artery disease.[20] Unfortunately, BMI is incapable of differentiating between fat or fat free extra mass. This distinction becomes especially important in the elderly, who are predominantly affected by the age-related loss of muscle mass that has been linked with worse outcomes. Sarcopenic obesity, defined as decreased muscle strength and mass in the setting of coexisting obesity, has been linked to disability, worsening functional status, and cardiovascular outcomes.[21,22] The pathophysiology behind that may be related to the pattern of central and intramyocellular fat deposition, which leads to increased inflammation and frailty and has been repeatedly associated with worse outcomes in the HF population.[23–25]

How do the results of this study change the practice patterns of cardiologists and other practitioners involved in the care of HF patients? The main nuance of this study is that sarcopenia in patients with HF is independently associated with mortality and thus should no longer be viewed as a mere epiphenomenon of HF, but as a significant distinct entity with its own independent hazards.[11–13] It is of paramount importance for clinicians treating HF patients to maintain a low threshold for sarcopenia work-up when they encounter patients who may meet risk factors for muscle wasting (*Figure 1*). Assessment of basic muscle function in the outpatient setting is not time-consuming or expensive, and ancillary staff can perform testing for handgrip strength with a dynameter which costs approximately 200$ and should take no more than 3–5 min. Other standardized and validated tools for the assessment of sarcopenia, such as bioelectrical

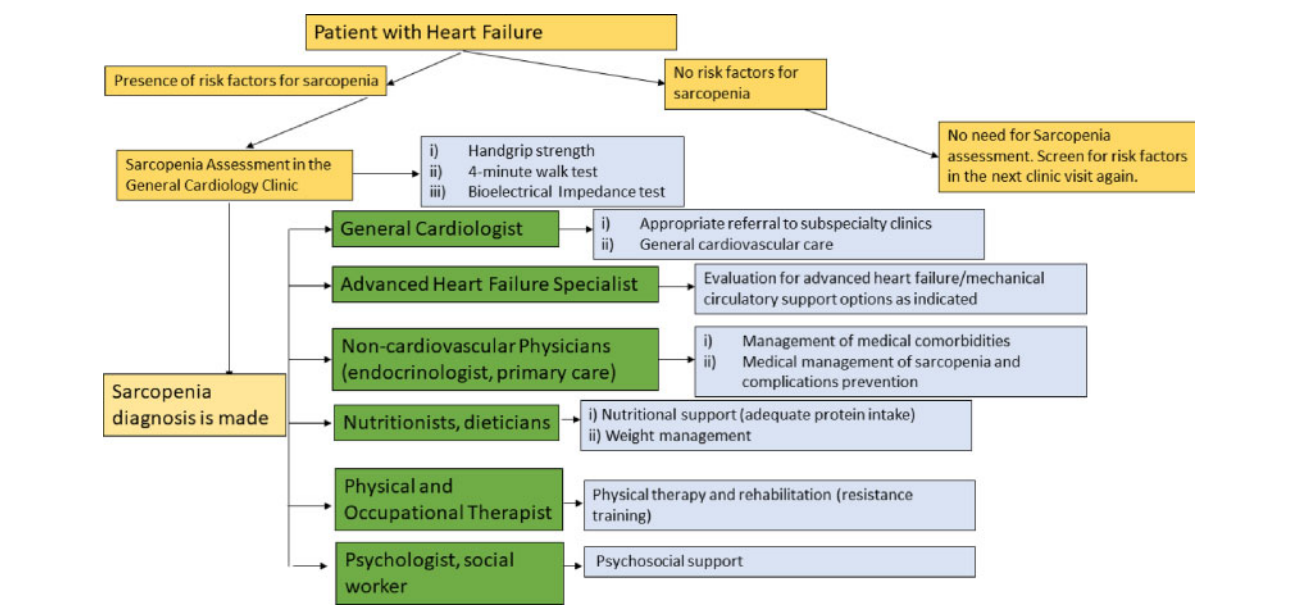

Figure 1 Sarcopenia assessment for patients with heart failure in the cardiology clinic.

impedance analysis can be incorporated in HF clinics to allow for reliable risk stratification of patients and reproducible research outcomes. Once sarcopenia diagnosis is made, cardiologists should refer their patients to the appropriate specialists in order to try to regain the lost muscle mass and avoiding further wasting. With nutritional protein intake that have proven benefit and are included in the official recommendations.[26]

In conclusion, the study by Konishi *et al*., substantially contributes to the existing literature on sarcopenia and HF. Sarcopenia is patients with HF has a significant prevalence and is associated with worse mortality. Cardiologists involved in HF care should deploy a multidisciplinary approach and collaborate with other specialists who can help frail and sarcopenic patients, including endocrinologists, nutritionists, dieticians, physical and occupational therapy specialists, and psychologists in order to achieve the best possible outcomes. In one sentence, it is worth 'wasting' the time and resources in order to treat muscle wasting and sarcopenia in patients with HF.

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References

1. 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.
2. 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 multicontinent study. *J Cachexia Sarcopenia Muscle* 2016;**7**:312–321.
3. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc* 2002;**50**:889–896.
4. Landi F, Cruz-Jentoft AJ, Liperoti R, Russo A, Giovannini S, Tosato M, Capoluongo E, Bernabei R, Onder G. Sarcopenia and mortality risk in frail older persons aged 80 years and older: results from ilSIRENTE study. *Age Ageing* 2013;**42**:203–209.
5. 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.
6. Ethgen O, Beaudart C, Buckinx F, Bruyère O, Reginster JY. The future prevalence of sarcopenia in europe: a claim for public health action. *Calcif Tissue Int* 2017;**100**:229–234.
7. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 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**:2129–2200.
8. Springer J, Springer J-I, Anker SD. Muscle wasting and sarcopenia in heart failure and beyond: update 2017. *ESC Heart Fail* 2017;**4**:492–498.
9. 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.
10. 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.
11. 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.
12. Kato A. Muscle wasting is associated with reduced exercise capacity and advanced disease in patients with chronic heart failure. *Future Cardiol* 2013;**9**:767–770.
13. 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.
14. Matsue Y, Kamiya K, Saito H, Saito K, Ogasahara Y, Maekawa E, Konishi1 M, Kagiyama N, Kamiya K, Saito H, Saito K, Ogasahara Y, Maekawa E, Misumi T, Kitai T, Iwata K, Jujo K, Wada H, Kasai T, Nagamatsu H, Ozawa T, Izawa K, Yamamoto S, Aizawa N, Makino A, Oka K, Momomura S-I, Matsue YImpact of sarcopenia on prognosis in patients with heart failure with reduced and preserved ejection fraction. *Eur J Prev Cardiol* 2020; doi:10.1093/eurjpc/zwaa117
15. Matsue Y, Kamiya K, Saito H, Saito K, Ogasahara Y, Maekawa E, Konishi, M., Kitai, T., Iwata, K., Jujo, K., Wada, H., Kasai, T., Nagamatsu, H., Ozawa, T., Izawa, K., Yamamoto, S., Aizawa, N., Yonezawa, R., Oka, K., Momomura, S.-i. and Kagiyama, N. Prevalence and prognostic impact of the coexistence of multiple frailty domains in elderly patients with heart failure: the FRAGILE-HF cohort study. *Eur J Heart Fail* 2020;**22**:2112–2119.
16. Güder G, Frantz S, Bauersachs J, Allolio B, Wanner C, Koller MT, Ertl G, Angermann CE, Störk S. Reverse epidemiology in systolic and nonsystolic heart failure: cumulative prognostic benefit of classical cardiovascular risk factors. *Circ Heart Fail* 2009;**2**:563–571.
17. Haass M, Kitzman DW, Anand IS, Miller A, Zile MR, Massie BM, Carson PE. Body mass index and adverse cardiovascular outcomes in heart failure patients with preserved ejection fraction: results from the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. *Circ Heart Fail* 2011;**4**:324–331.
18. Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. *JACC Heart Fail* 2013;**1**:93–102.
19. Papanastasiou CA, Giannakoulas G. Overweight and obesity: time to reconsider their role in heart failure. *Eur J Prev Cardiol* 2020;2047487320933738.
20. Kokkinidis DG, Armstrong EJ, Giri J. Balancing weight loss and sarcopenia in elderly patients with peripheral artery disease. *J Am Heart Assoc* 2019;**8**:e013200.
21. Baumgartner RN, Wayne SJ, Waters DL, Janssen I, Gallagher D, Morley JE. Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. *Obes Res* 2004;**12**:1995–2004.
22. Stephen WC, Janssen I. Sarcopenic-obesity and cardiovascular disease risk in the elderly. *J Nutr Health Aging* 2009;**13**:460–466.
23. Batsis JA, Villareal DT. Sarcopenic obesity in older adults: aetiology, epidemiology and treatment strategies. *Nat Rev Endocrinol* 2018;**14**:513–537.
24. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola V-P, Parissis J, Laroche C, Piepoli MF, Fonseca C, Mebazaa A, Lund L, Ambrosio GA, Coats AJ, Ferrari R, Ruschitzka F, Maggioni AP, Filippatos G. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017;**19**:1574–1585.
25. Sanders NA, Supiano MA, Lewis EF, Liu J, Claggett B, Pfeffer MA, Desai AS, Sweitzer NK, Solomon SD, Fang JC. The frailty syndrome and outcomes in the TOPCAT trial. *Eur J Heart Fail* 2018;**20**:1570–1577.
26. Bauer J, Morley JE, Schols AMWJ, Ferrucci L, Cruz-Jentoft AJ, Dent E, Baracos VE, Crawford JA, Doehner W, Heymsfield SB, Jatoi A, Kalantar-Zadeh K, Lainscak M, Landi F, Laviano A, Mancuso M, Muscaritoli M, Prado CM, Strasser F, Haehling S, Coats AJS, Anker SD. Sarcopenia: a time for action. An SCWD Position Paper. *J Cachexia Sarcopenia Muscle* 2019;**10**:956–961.