Consensus statement

Nutrition, Obesity, and Cachexia in Patients With Heart Failure: A Consensus Statement from the Heart Failure Society of America Scientific Statements Committee

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ABSTRACT

Dietary guidance for patients with heart failure (HF) has traditionally focused on sodium and fluid intake restriction, but dietary quality is frequently poor in patients with HF and may contribute to morbidity and mortality. Restrictive diets can lead to inadequate intake of macronutrients and micronutrients by patients with HF, with the potential for deficiencies of calcium, magnesium, zinc, iron, thiamine, vitamins D, E, and K, and folate. Although inadequate intake and low plasma levels of micronutrients have been associated with adverse clinical outcomes, evidence supporting therapeutic repletion is limited. Intravenous iron, thiamine, and coenzyme Q10 have the most clinical trial data for supplementation. There is also limited evidence supporting protein intake goals. Obesity is a risk factor for incident HF, and weight loss is an established approach for preventing HF, with a role for bariatric surgery in patients with severe obesity. However weight loss for patients with existing HF and obesity is a more controversial topic owing to an obesity survival paradox. Dietary interventions and pharmacologic weight loss therapies are understudied in HF populations. There are also limited data for optimal strategies to identify and address cachexia and sarcopenia in patients with HF, with at least 10%−20% of patients with ambulatory systolic HF developing clinically significant wasting. Gaps in our knowledge about nutrition status in patients with HF are outlined in this Statement, and strategies to address the most clinically relevant questions are proposed. (*J Cardiac Fail 2019;25:380−400*)
Key Words: Heart failure, nutrition, obesity, cachexia, metabolism.

Lifestyle factors, including changes in dietary patterns, have contributed to rising secular trends in the incidence of diabetes mellitus (DM) and obesity, which in turn contribute to the heightened prevalence of heart failure (HF) in the United States and worldwide.[1] Among patients with established HF, dietary quality is frequently poor and may amplify morbidity and mortality. Current HF management guidelines emphasize the role of dietary sodium restriction and address specific micronutrient supplements but offer little additional guidance regarding appropriate dietary composition, or optimal nutritional counseling to improve clinical outcomes. Although there is some evidence supporting dietary modifications for HF prevention, there have been few rigorous studies of specific nutritional interventions in patients with established disease.

Obesity is acknowledged to have important implications for HF prevention, but few dietary, pharmacologic, or interventional strategies for obesity management have been systematically evaluated in patients with established HF. On the other

extreme, cardiac cachexia is associated with increased mortality, but there are few data to guide clinicians in management strategies for this condition. In light of continued clinical uncertainty about the optimal nutritional guidance for HF prevention and management, the present Heart Failure Society of America (HFSA) Consensus Statement aims to synthesize the available evidence regarding dietary quality, micronutrient supplementation, and management of obesity or cachexia, provide consensus recommendations for clinical practice, and outline key areas for future investigation.

Current Heart Failure Dietary Guidelines and Practice

Dietary guidance for patients with HF has traditionally focused on sodium and fluid intake restriction, despite the absence of robust data supporting improved clinical outcomes with these measures. None of the existing HF guidelines offer detailed recommendations for the management of obesity or cardiac cachexia (Table 1). Cardiology society guidelines generally endorse a 2−3 g/d sodium intake for most patients with HF and <2 L/d fluid restriction for those with advanced HF and hyponatremia. Despite broad application of these recommendations, they are based on limited scientific evidence (Table 1).[2−5] Ongoing randomized clinical trials (including NCT02467296, NCT02012179, and NCT02689635) are anticipated to clarify optimal guidance regarding sodium intake.

Recent guideline updates support intravenous iron replacement in patients with New York Heart Association (NYHA) functional class II−III HF and iron deficiency to improve functional status and quality of life (QoL; class IIB recommendation).[5] Routine use of nutritional supplements is generally discouraged owing to the lack of efficacy data, concerns about supplement purity and regulation, and the potential for pharmacologic interactions, although n-3 polyunsaturated fatty acids receive a weak endorsement.[2,5] The 2017 Academy of Nutrition and Dietetics (AND) heart failure evidence-based nutritional practice guideline offers practice recommendations and highlights the role of the registered dietitian nutritionist (RDN).[6]

However, it is acknowledged that reimbursement often limits access to an RDN in the United States, because the Centers for Medicare and Medicaid Services (CMS) cover RDN services only for patients with type 1 or 2 DM, chronic kidney disease (CKD), or a renal transplantation within the previous 36 months. Nutritional consultation may alternatively be accessed by some patients who are eligible for referral to a cardiac rehabilitation program. Therefore, it is important that other HF health professionals develop expertise in clinical nutrition to improve patient access to dietary counseling (Fig. 1). Using appropriate billing codes to document malnutrition may help to support such efforts (Supplemental Table S1).[7]

Dietary Composition and Counseling

The high reliance on prepared and processed foods in the United States means that sodium restrictions are often achieved by reducing overall food intake. In addition to restricting sodium, patients are often counseled to restrict vitamin K intake if receiving warfarin for anticoagulation, saturated fats if coronary artery disease (CAD) is present, and refined sugars if DM is present. Thus, restrictive dietary counseling has the potential to result in macronutrient and micronutrient deficiencies and place the patient at risk of malnutrition and cachexia. One small study targeting <2 g/d sodium intake for a week resulted in a significant reduction in caloric (from $2,467 \pm 748$ to $1,931 \pm 388$ kcal/d; $P = .016$), carbohydrate, calcium, thiamine, and folate intake.[8] In contrast, a trial of the Dietary Approaches to Stop Hypertension (DASH) diet for 6 months demonstrated that low-sodium diets can be nutritionally adequate for patients with HF with careful nutritional counseling.[9]

Dietary Strategies in Heart Failure

There are no comprehensive dietary counseling guidelines for patients with HF. However, nutrition professionals generally endorse the eating patterns recommended for patients with DM and CKD as appropriate for the majority of patients with HF. The American Diabetes Association recommends eating patterns based on DASH, Mediterranean, and plant-based diets.[10] The National Kidney Foundation also recommends the DASH diet, with appropriate adjustments for severely decreased renal function (eg, glomerular filtration rate <25 mL·min^{-1}·1.73 m^{-2}).[11] The DASH diet has the advantages of limiting sodium intake, being rich in plant-based foods and antioxidants, and decreasing dietary confusion because it is compatible with comorbid DM or CKD. Small clinical trials in patients with heart failure with preserved ejection fraction (HFpEF) show an association between the DASH diet and improved left ventricular (LV) diastolic function, blood pressure, arterial stiffness, markers of oxidative stress, and metabolic profile.[12−14] In an observational study of postmenopausal women with HF, higher DASH diet scores were associated with modestly lower mortality,[15] and a clinical trial of a home-delivered DASH diet program for 4 weeks after HF hospitalization was associated with a trend toward fewer readmissions.[16] Higher reported Mediterranean diet scores were associated with a lower rate of 1-year HF hospitalization for Spanish patients with an acute HF episode, but no difference in mortality.[17] Adherence to DASH or other recommended diets is not easily accomplished without counseling and support, which should ideally be provided by RDNs.

Nutritional Inadequacies and Deficiencies in Heart Failure

The prevalence of malnutrition in HF is highly dependent on the diagnostic tool used, ranging from 8% with the use of the Prognostic Nutritional Index to 54% with the use of the Controlling Nutritional Status (CONUT) tool in one contemporary community HF cohort.[18] There are multiple additional malnutrition screening tools in routine clinical use, including the Short Nutritional Assessment Questionnaire (SNAQ), Malnutrition Universal Screening Tool, Mini Nutritional Assessment (MNA), Nutrition Risk in the

Table 1. Summary of Heart Failure (HF) Nutritional Recommendations From Society Guidelines

Target	HFSA 2010[2]	ACC/AHA 2013,[3] ACC/AHA/HFSA 2017[5]	ESC 2016[4]	AND 2017[6]
Sodium	2−3 g/d (or <2 g if refractory hypervolemia) *strength of evidence = C*	<3 g/d *(class IIa) strength of evidence = C*	Avoid excessive salt intake (>6 g/d), without a specific recommendation	2−3 g/d *strength of evidence = Fair*
Fluid	<2 L/d for serum sodium <130 mEq/L or diuretic resistance *strength of evidence = C*	1.5−2 L/d in stage D HF, especially with hyponatremia *(class IIa) strength of evidence = C*	1.5−2 L/d may be considered in patients with severe HF, without a specific recommendation	1−2 L/d *strength of evidence = Fair*
Energy	No specific recommendation	No specific recommendation	No specific recommendation	Recommend 22 kcal/kg actual body weight nourished or 24 kcal/kg malnourished, or base on REE *strength of evidence = Fair*
Protein	No specific recommendation	No specific recommendation	No specific recommendation	Individualized, but ≥1.1 g/kg *strength of evidence = Fair*
Folate, vitamin B6, and vitamin B12 supplements	Consider daily multivitamin and mineral supplementation for those on diuretic therapy and restricted diets *strength of evidence = C*	Not recommended	NA	Not recommended for routine care *strength of evidence = Weak*
Thiamine supplements	NA	Not recommended	NA	Not recommended for routine care *strength of evidence = Weak*
Vitamin D supplements	NA	Not recommended	NA	Not recommended for routine care *strength of evidence = Weak*
Nutritional supplements	Not recommended for routine care *strength of evidence = B*	Not recommended *(class III) strength of evidence = B*	NA	Not recommended for routine care *strength of evidence = Weak*
Iron	Intravenous iron can be considered for documented deficiency	2017 update: intravenous iron reasonable in NYHA II−III HF and iron deficiency (ferritin <100 ng/mL or 100 to 300 ng/mL if transferrin saturation <20%) *(class IIb) strength of evidence = B*	Intravenous ferric carboxymaltose for symptomatic HFrEF patients and iron deficiency (ferritin <100 ng/mL or 100−299 ng/mL if transferrin saturation <20%) *(class IIa) strength of evidence = A*	Not recommended for routine care *strength of evidence = Weak*
n-3 polyunsaturated fatty acid supplements	Reasonable as adjuvant therapy for HFrEF NYHA II−IV *strength of evidence = B*	Reasonable as adjuvant therapy for HFrEF or HFpEF NYHA II−IV *(class IIa) strength of evidence = B*	May be considered in symptomatic patients *(class IIb) strength of evidence = B*	Not recommended for routine care *strength of evidence = Weak*
Coenzyme Q10	NA	Not recommended	NA	Not recommended for routine care *strength of evidence = Weak*
Cachexia	Provide caloric supplementation; anabolic steroids not recommended *strength of evidence = C*	No recommendations; importance as a component of advanced HF emphasized	No specific recommendations	Provide ≥1.1 g/d protein per kg actual body weight to prevent catabolism *strength of evidence = Fair*
Obesity	Provide specific weight loss diet instructions *strength of evidence = B*	No specific recommendation	Weight loss may be considered to manage symptoms if BMI 35−45 kg/m², without a specific recommendation	Weight loss for stage B and C HF with obesity *strength of evidence = Weak*

ACC, American College of Cardiology; AHA, American Heart Association; AND, Academy of Nutrition and Dietetics; BMI, body mass index; ESC, European Society of Cardiology; HFpEF, heart failure with preserved ejection fraction; HFSA, Heart Failure Society of America; HFrEF, heart failure with reduced ejection fraction; NA, not addressed; NYHA, New York Heart Association functional class; REE, resting energy expenditure.
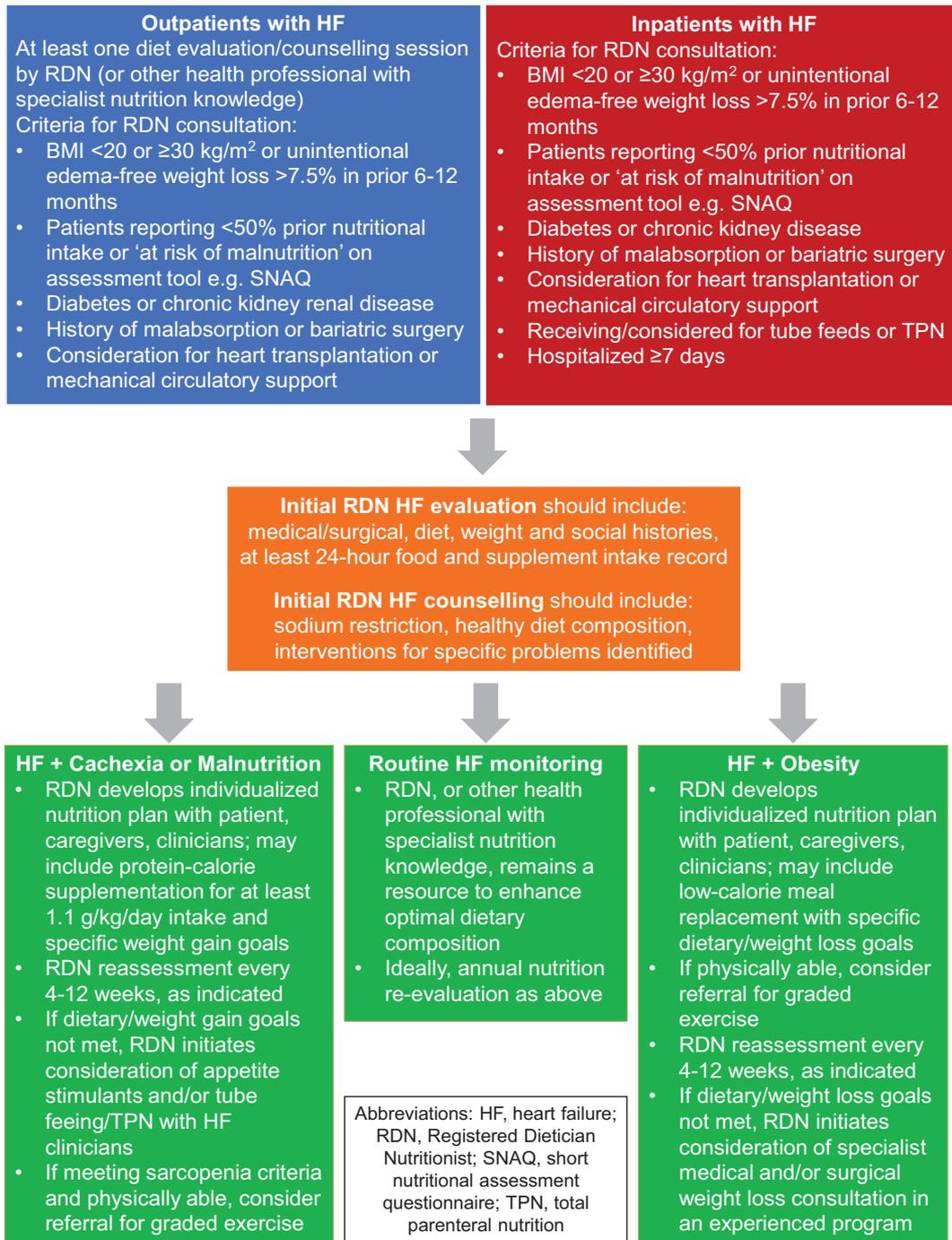
Outpatients with HF
At least one diet evaluation/counselling session by RDN (or other health professional with specialist nutrition knowledge)
Criteria for RDN consultation:
- BMI <20 or ≥30 kg/m² or unintentional edema-free weight loss >7.5% in prior 6-12 months
- Patients reporting <50% prior nutritional intake or 'at risk of malnutrition' on assessment tool e.g. SNAQ
- Diabetes or chronic kidney renal disease
- History of malabsorption or bariatric surgery
- Consideration for heart transplantation or mechanical circulatory support

Inpatients with HF
Criteria for RDN consultation:
- BMI <20 or ≥30 kg/m² or unintentional edema-free weight loss >7.5% in prior 6-12 months
- Patients reporting <50% prior nutritional intake or 'at risk of malnutrition' on assessment tool e.g. SNAQ
- Diabetes or chronic kidney disease
- History of malabsorption or bariatric surgery
- Consideration for heart transplantation or mechanical circulatory support
- Receiving/considered for tube feeds or TPN
- Hospitalized ≥7 days

Initial RDN HF evaluation should include: medical/surgical, diet, weight and social histories, at least 24-hour food and supplement intake record

Initial RDN HF counselling should include: sodium restriction, healthy diet composition, interventions for specific problems identified

HF + Cachexia or Malnutrition
- RDN develops individualized nutrition plan with patient, caregivers, clinicians; may include protein-calorie supplementation for at least 1.1 g/kg/day intake and specific weight gain goals
- RDN reassessment every 4-12 weeks, as indicated
- If dietary/weight gain goals not met, RDN initiates consideration of appetite stimulants and/or tube feeing/TPN with HF clinicians
- If meeting sarcopenia criteria and physically able, consider referral for graded exercise

Routine HF monitoring
- RDN, or other health professional with specialist nutrition knowledge, remains a resource to enhance optimal dietary composition
- Ideally, annual nutrition re-evaluation as above

Abbreviations: HF, heart failure; RDN, Registered Dietician Nutritionist; SNAQ, short nutritional assessment questionnaire; TPN, total parenteral nutrition

HF + Obesity
- RDN develops individualized nutrition plan with patient, caregivers, clinicians; may include low-calorie meal replacement with specific dietary/weight loss goals
- If physically able, consider referral for graded exercise
- RDN reassessment every 4-12 weeks, as indicated
- If dietary/weight loss goals not met, RDN initiates consideration of specialist medical and/or surgical weight loss consultation in an experienced program

Fig. 1. A proposed pathway for nutritional evaluation and counseling for patients with heart failure (HF). This is a consensus proposal for the structure of a nutritional evaluation and counseling pathway that can be adapted to patients with HF in the outpatient or inpatient settings. The pathway can be led by either a registered dietitian nutritionist (RDN) or another health professional with specialist nutrition knowledge, such as a nurse, advanced practice provider, or physician. SNAQ, Short Nutritional Assessment Questionnaire.

Critically Ill score, and Subjective Global Assessment. None have been validated specifically in HF, but the SNAQ score has some practical advantages (Table 2). Inadequate dietary intake of nutrients should be distinguished from low plasma concentrations, as well as from nutrient deficiencies, with the latter requiring a clinical or subclinical disease state. A suggested approach to screening for nutritional inadequacy or deficiency is outlined in Table 2.

Dietary protein intake has been estimated to be adequate for most patients with HF across multiple observational studies based on the current general population protein recommendation of 0.8 g/kg per day. Results from a 57-patient nitrogen balance study in nonobese patients with HF, compared with 49 control subjects, suggested that a higher protein goal of 1.1 g/kg or greater may be necessary,[19] which is consistent with recommendations from the Academy of

Table 2. Suggestions for HF Clinicians When Screening for Nutritional Inadequacies and Deficiencies

Target	Metrics	Tools and Resources	Macronutrients	Micronutrients
History	Medical history and disease chronicity can indicate the likelihood of malnutrition and inflammation	Identify malabsorption history: previous gastrointestinal surgery, including bariatric surgery or bowel resection, gastrointestinal symptoms, including ageusia (loss of taste), dysgeusia (distorted taste), or anorexia (loss of appetite), nausea, vomiting, diarrhea, constipation, dysphagia; dental health; history of aspiration events; history of diabetes and gastroparesis; medication history, including allergies, herbs, and supplements; social history, including food insecurity due to finances, assistance required with activities of daily living (shopping, cooking, eating), ethnic or social dietary preferences, substance abuse	Fat malabsorption, overall low calorie intake	Fat-soluble vitamins (A, D, E, K), B12, and minerals including copper, calcium, iron, zinc and selenium
Physical examination	Wasting of subcutaneous fat and/or skeletal muscle; physical signs specific to micronutrient deficiencies	Table 3 in: Esper DH. Utilization of nutrition-focused physical assessment in identifying micronutrient deficiencies. Nutr Clin Pract 2015;30:194−202 *Nutrition examination training workshops:* https://www.eatrightpro.org/practice/professional-development/face-to-face-learning/nfpe-workshop	Cachexia: loss of subcutaneous fat in orbital, triceps regions and overlying the ribs; cachexia/sarcopenia: loss of temporalis, pectoralis, deltoids, interosseous muscles, latissimus dorsi, trapezius, quadriceps, gastrocnemius muscle mass; Muehrcke lines in nails suggest hypoalbuminemia, alopecia associated with protein deficiency, and scaling of scalp with essential fatty acid deficiency	Nail, hair, and skin changes characteristic of vitamins A, B (any), C, or K, zinc, or iron deficiencies
Anthropometric data	Body mass index (kg/m^2)	Calculator: https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm—use dry weight for patients with volume overload	May reflect inadequate or excessive calorie intake	
	Percentage weight change: ((usual weight − current weight)/usual weight) × 100	Calculator: https://www.fitwatch.com/calculator/weight-loss-percentage/—review with patient to determine if weight loss is unintentional and whether diuresis contributed. See also Supplemental Table S1 for diagnostic criteria for malnutrition.	5%, 7.5%, 10%, or 20% unintentional weight loss thresholds feature in malnutrition diagnostic criteria	
Laboratory data	Screening for inflammation, prognostic markers, markers of iron deficiency	Scores incorporating laboratory data may aid in malnutrition identification: Geriatric Nutritional Risk Index, using albumin, weight, and height: http://touchcalc.com/calculators/gnri—a simple tool with some data for prognostic utility in HF cohorts (Kaneko 2015) *Controlling Nutritional Status Nutrition Risk in the Critically Ill Prognostic Nutritional Index —less established in HF cohorts* Sze S, Pellicori P, Kazmi S, Rigby A, Cleland JGF, Wong K, Clark AL. Prevalence and	Albumin and prealbumin: these biomarkers have prognostic utility in HF, but though related to nutritional status, there is insufficient evidence that they change in response to nutritional interventions; C-reactive protein or neutrophil-lymphocyte ratio for inflammatory state assessment	Hemoglobin, % iron saturation, and ferritin to screen for intravenous iron eligibility; United States Preventative Services Task force recommends against screening for vitamin D deficiency in asymptomatic adults

Table 2 (*Continued*)

Target	Metrics	Tools and Resources	Macronutrients	Micronutrients
		prognostic significance of malnutrition using 3 scoring systems among outpatients with heart failure: a comparison with body mass index. JACC Heart Fail 2018;6:476−86.		
Dietary assessment	Nutritional risk assessment tools	Short Nutritional Assessment Questionnaire: http://www.fightmalnutrition.eu/wp-content/uploads/2017/04/SNAQ_Engels.jpg—quick screening tool incorporating weight change, appetite, and supplementation; unlike MUST and MNA (below), does not incorporate medical diagnoses or inpatient status *Malnutrition Universal Screening Tool (MUST):* https://www.bapen.org.uk/screening-and-must/must-calculator *Mini Nutritional Assessment (MNA):* https://www.mna-elderly.com/mna_forms.html		
	Assessment of dietary intake	Patient dietary intake self-collection and analysis can be performed on a mobile-health application such as MyFitnessPal for food record *Predominantly research tools:* *inpatient nutrient intake analysis,* *daily food record or diary (typically at least 3−4 days),* *food frequency questionnaire:* https://sharedresources.fredhutch.org/content/ffq-sample-booklets *24-hour recall* https://epi.grants.cancer.gov/asa24/	Consult Institute of Medicine macronutrient (total calories, protein, carbohydrates, and fat) and micronutrient reference intakes for adequacy: https://ods.od.nih.gov/Health_Information/Dietary_Reference_Intakes.aspx	
Functional assessment	Handgrip strength	Handgrip thresholds <27 kg men, <16 kg women (European Working Group on Sarcopenia in Older People 2; Supplemental Table S6) *Subjective global assessment—weight change, intake change, gastrointestinal symptoms, functional status, metabolic demand, and physical examination*	Low handgrip strength is not a direct indicator of nutritional status but may be associated with insufficient calorie/protein intake or abnormalities of nutrient absorption/assimilation	

This list is not exhaustive but summarizes the most clinically useful tools for clinicians. Resources in addition to those that are recommended are presented in italics.

Nutrition and Dietetics[6] for patients with any stage of HF and from PROT-AGE (an international study group on dietary protein needs with aging).[20] However, this protein goal may not be appropriate for patients with severe CKD and is based on limited evidence. There are also concerns that high dietary protein intake, particularly from red meats, may increase the risk of CAD and HF incidence.[21,22] However 1.1 g/kg is well below the range of a high-protein diet, and functional status was superior in middle- and older-age Framingham participants with ≥1.2 versus <0.8 g/kg intake.[23]

A range of inadequate micronutrient intakes have been identified in geographically diverse HF cohorts, including calcium, magnesium, zinc, iron, thiamine, vitamins D, E, and K, and folate (Supplemental Table S2),[24] although evidence that these cause clinically relevant deficiencies is currently sparse.[25−27] Among patients with HF living in the United States (n = 246; 67% male, 73% white), 44% of participants with inadequate intake of ≥7 micronutrients experienced hospitalization or death within 1 year, versus 25% with <7 inadequacies (P = .0065).[27] The association remained significant after adjustment for comorbidities and medications resulting in nearly double the risk of hospitalization or death for patients in the high inadequacies group. Participants were equally likely to have micronutrient inadequacies across each body mass index (BMI) category, suggesting that patients with HF should be assessed for potential dietary insufficiency regardless of BMI.

Rarely, HF is the result of excess alcohol intake or a trace element deficiency, such as selenium or thiamine (vitamin B1), in which case addressing the underlying etiology would be expected to improve cardiac function. Serum electrolyte abnormalities are common in HF. Close laboratory monitoring is standard practice after initiation or dose changes of renin-angiotensin-aldosterone system antagonists because of the potential for hyperkalemia and of loop/thiazide diuretics because of the potential for hypokalemia and hypomagnesemia. Patients with elevated serum potassium should observe a low-potassium diet as part of a multicomponent approach that may also include potassium-binding medications. Low potassium or magnesium may be addressed with electrolyte supplementation or by augmenting intake of foods rich in these electrolytes, including avocados, spinach, potatoes, tomatoes, beans, and fruits (eg, bananas) for potassium and many vegetables and nuts—especially pumpkin seeds—for magnesium.

Micronutrient Supplementation in Heart Failure

Micronutrient supplementation may be provided either through a whole food approach or by supplementing single micronutrients. Although clinical trial logistics and finances favor the study of supplementation strategies, provision of a nutritionally complete diet that is rich in commonly inadequate micronutrients may be expected to have a larger impact on clinical outcomes owing to broader antioxidant and antiinflammatory actions. Micronutrient

supplementation in HF has been investigated in several small studies, but few large randomized trials (Supplemental Table S3).[28]

Three supplementation strategies have positive findings in randomized clinical trials and warrant specific attention: iron, thiamine, and coenzyme Q10 (CoQ10). Intravenous, but not oral, iron supplementation is now an established intervention for correcting iron deficiency (ferritin <100 ng/mL or 100−300 ng/mL if transferrin saturation <20%) and improving HF functional status and QoL. Although clinical trials were conducted in heart failure with reduced ejection fraction (HFrEF), the American College of Cardiology/American Heart Association/HFSA recommendation for intravenous iron repletion does not specify an ejection fraction criterion.[5] There has been a longstanding concern that high-dose diuretics may encourage thiamine (vitamin B1) deficiency owing to its water solubility and poor reabsorption during renal depletion of hydrogen ions with the use of diuresis, although definitive evidence is lacking.[29] In a 9-study meta-analysis, low thiamine levels were more common in patients with HF than in control subjects; some small (n<150) observational and randomized studies have suggested an association between thiamine repletion and improved LVEF, although higher-quality evidence would be necessary to make any clinical recommendations.[29]

Coenzyme Q10 doses ranging from 60 to 300 mg/d have been studied in HF, with some small trials suggesting improvements in NYHA functional class, LVEF, exercise capacity, QoL, and even mortality, but others being neutral.[30] Q-SYMBIO was a randomized controlled trial of 300 mg/d CoQ10 in NYHA III−IV HFrEF or HFpEF (n = 420), powered to address major clinical end points.[31] There were no changes in NYHA functional class, 6-minute walk test, or N-terminal pro−B-type natriuretic peptide (NT-proBNP) at 16 weeks. However, the incidence of the primary composite end point of major adverse cardiovascular events at 2 years was significantly reduced with the use of CoQ10 supplementation (hazard ratio 0.50, 95% CI 0.32−0.80; P = .003). Despite these findings, concerns about slow recruitment in this trial, which may limit the generalizability of results, have tempered enthusiasm for CoQ10 supplementation in clinical practice. Overall there is sparse data on which to make firm recommendations regarding micronutrition supplementation for patients with HF, and additional empirical research is required to adequately inform future clinical practice.

Recommendations for Dietary Composition and Counseling

- All patients with HF should be offered at least 1 evaluation and counseling session as an outpatient or inpatient from an RDN or other health professional with specialist nutrition knowledge.
- Clinical teams should use a consistent malnutrition screening tool (or combination of tools) in their HF

population, with simplicity and applicability favoring the SNAQ score, although no score has been proven to be superior in patients with HF.

- Patients who are identified with malnutrition (or at high risk of malnutrition), cachexia or obesity should have access to RDN consultation.
- Although data guiding optimal dietary composition are lacking, the DASH and Mediterranean diets both appear to be reasonable to recommend for normal-weight patients at risk of HF or with established HF.
- Protein intake should be individualized, but patients with HF should aim for the general population minimum of 0.8 g/kg per day protein intake to prevent cachexia, and ≥1.1 g/kg per day is reasonable if malnutrition or cachexia is present (per PROT-AGE and Academy of Nutrition and Dietetics recommendations).
- Other than in patients who are deficient in iron or other specific micronutrients, there is no clear role for routine micronutrient supplementation as a component HF management.
- Future trials of nutritional strategies in HF should be randomized, be adequately powered, distinguish between HFrEF and HFpEF, be of sufficient duration, and use clinically relevant HF end points.

Obesity

Obesity and Incident Heart Failure

Large observational studies have established obesity as a key risk factor for incident HF across multiple populations, with a meta-analysis showing a 41% increase in HF per 5-unit increment in BMI and a threshold of risk at $23-24$ kg/m^2.[32] The dose-response relationship between BMI and incident HF appears to be stronger for HFpEF than for HFrEF.[33] Conversely, maintenance of normal weight and physical activity during adult life have been associated with lower incident HF.[34] Adjusting for obesity-related comorbidities such as hypertension, DM, and low cardiorespiratory fitness, attenuated the association between obesity and HF in some cohorts.[33,35,36] Mechanisms linking obesity to HF include inflammation, insulin resistance, and hypertension, although obesity has a direct effect on LV mass independently from blood pressure.[37,38] Adipokines and gut hormones may mediate this relationship, with greater metabolic derangements increasing the risk of LV hypertrophy, diastolic dysfunction, and HF onset.[39]

Weight Loss for Heart Failure Prevention

For patients with obesity, a sustained $5\%-10\%$ weight loss can positively affect atrial fibrillation, insulin resistance, and LV hypertrophy and therefore could be expected to prevent HF.[40,41] Unfortunately, even when this degree of weight loss is achieved, it is challenging to maintain, particularly in severely obese individuals who would benefit the most.[42] Food intake rich in whole grains and vegetables and DASH dietary patterns are associated with lower incident

HF in observational cohorts,[43-45] but in the only large prospective clinical trial evaluating the Mediterranean diet, there was no between-group difference in HF incidence versus a low-fat diet.[46] But these were not weight-loss diets nor obese patient cohorts; there have been no clinical trials specifically examining calorie-restricted diets to attain weight loss for HF prevention. A prospective trial of an intensive lifestyle intervention combining a calorie-restricted diet and exercise program in patients with type 2 DM and BMI ≥25 kg/m^2 showed a nonsignificant trend toward lower incident HF.[47] There is not one superior dietary strategy for weight loss efficacy and the most important feature is probably patient adherence[48,49]; one barrier to weight loss maintenance is the reduction in energy expenditure that occurs with dieting, which may be less pronounced when a lower-carbohydrate diet is used.[42,50,51] Meal replacement programs, eg, with high-protein shakes, may help to support short- and medium-term weight loss.[52] Cardiovascular obesity management guidelines recommend a diet of $1200-1500$ kcal/d for women and $1500-1800$ kcal/d for men without endorsing any specific dietary strategies, but they do recommend a personalized approach and professional nutrition counseling.[40]

Weight loss pharmacotherapy is indicated when lifestyle modifications alone are unsuccessful with BMI ≥30 kg/m^2 or with ≥27 kg/m^2 and one or more obesity-associated comorbidities; if there is <5% weight loss at 3 months, an alternate therapy should be sought.[53] Orlistat and lorcaserin are associated with modest reductions in blood pressure as well as only modest weight reductions, whereas greater weight loss efficacy is seen with combination medications (Table 3). Liraglutide is specifically approved for weight loss at the 3 mg dose[54] with good efficacy. A reduction in major adverse cardiovascular events was observed in a DM population receiving 1.8 mg liraglutide, although the HF end point was neutral.[55] The cardiovascular safety study of naltrexone-bupropion did not report HF outcomes, and the lorcaserin safety study showed a neutral outcome for HF at 40 months of follow-up.[56]

Bariatric surgery has emerged as an effective and durable strategy for achieving large degrees of weight loss[57] in eligible candidates.[58] Bariatric surgery is associated with reduced inflammation and metabolic dysfunction, as well as improvements in myocardial structure and function.[59-61] Three large retrospective studies have each recently demonstrated that the risk of incident HF is halved at a median of 4 years in patients who pursue surgical weight loss compared with control patients with obesity or participants in a low-calorie diet program.[62-64]

Recommendations for Obesity in HF Prevention

- Maintenance of normal body weight throughout life through a combination of dietary and physical activity choices is associated with reduced incident HF and should be actively promoted across the entire lifespan.

Table 3. Weight Loss Medications and Considerations for Use in Heart Failure (HF)

Medication (FDA Approval), Mechanism	1-yr Placebo-Adjusted Weight Loss	Potential Benefits in HF Prevention or Management	Potential Risks in HF
Orlistat (1999) Gastrointestinal lipase inhibitor, decreased fat absorption	−2.5 kg with 60 mg −3.4 kg with 120 mg	Modest reductions in systolic blood pressure; modest reductions in blood glucose for patients with diabetes; no sympathetic stimulation or known adverse cardiac events and has been studied in a HF cohort (Beck-da-Silva, 2015)	Fat-soluble vitamin malabsorption; monitor renal function in patients at risk of renal insufficiency; potential for warfarin and amiodarone interactions
Lorcaserin (2012) Selective serotonergic 5-HT_{2C} receptor agonist	−3.2 kg	Modest reductions in systolic blood pressure	Possible association with regurgitant valvular disease development; $5HT_{2B}$ may be overexpressed in HF and therefore lorcaserin has not been studied in the HF population and should be used with caution; adverse effects include bradycardia
Phentermine (1959) Appetite suppressant, TAAR-1 agonist	−3.6 kg		Potential for heart rate and blood pressure elevations; considered to be contraindicated in patients with heart disease, including HF, as well as with arrhythmias, coronary artery disease and uncontrolled hypertension; associated with primary pulmonary hypertension, regurgitant cardiac valvular disease, and palpitations/tachyarrhythmias
Phentermine/topiramate extended release (2012) Amine anorectic + possible increased GABA activity	−6.7 kg with 7.5/46 mg −8.9 kg with 15/92 mg	Modest reductions in systolic blood pressure; minor improvements in blood glucose for patients with diabetes	Minor increases in heart rate; potential association with palpitations/tachyarrhythmias (see above); requires monitoring of serum chemistries and renal function
Bupropion/naltrexone (2014) Inhibits dopamine/norepinephrine reuptake + opioid antagonist	−6.2 kg	Minor improvements in blood glucose for patients with diabetes	Minor increases in blood pressure and heart rate; potential association with palpitations/tachyarrhythmias
Liraglutide 3 mg (2014) GLP-1 agonist	−6.2 kg −5.4 kg (SCALE trial)	Modest reductions in systolic blood pressure; improvements in blood glucose for patients with diabetes and decreased development of diabetes; reductions in major adverse cardiovascular events	Minor increases in heart rate; may not be appropriate for patients with advanced systolic heart failure, per FIGHT study results (Margulies 2016)

See Supplemental Table S4 for full details of adverse effects and study references.

- A target weight loss of at least 5%−10% is recommended for individuals with BMI ≥25 kg/m^2.
- No specific weight loss diet is recommended, but counseling with an RDN is advised; it is usual to recommend a negative energy balance of 500−750 kcal/d or absolute intake of 1200−1500 kcal/d diet for women and 1500−1800 kcal/d for men, aiming for a loss of 1−2 lb/wk.
- There are currently no data demonstrating HF prevention with the use of weight loss pharmacotherapy for patients with BMI ≥30 kg/m^2 or ≥27 kg/m^2 with 1 or more obesity-associated comorbidities, but 3 mg liraglutide daily is an attractive option given its weight loss efficacy and prevention of other cardiovascular events.
- For patients with BMI ≥40 kg/m^2, BMI ≥35 kg/m^2 and 1 or more obesity-related comorbidities, or BMI ≥30 kg/m^2 and type 2 DM with inadequate glycemic control despite optimal medical therapies, bariatric surgery is a reasonable approach to prevent incident HF and cardiovascular mortality.

Obesity in Patients With Heart Failure

Recent HF clinical trials have typically included ≥50% of patients who are classified as obese by BMI criteria (≥30 kg/m^2).[65] However, the diagnosis of HF can be challenging in obese individuals and may affect the design and interpretation of weight loss studies. Even without underlying HF, patients with obesity commonly experience exertional dyspnea, orthopnea, and lower-extremity edema. Both the physical examination and echocardiography may be harder to interpret when obesity is present. Most studies related to obesity and HF rely on BMI to measure adiposity, with the inherent limitation of BMI being unable to distinguish fat mass, lean mass, and fluid compartments or central versus peripheral obesity.

Patients with obesity have lower levels of circulating natriuretic peptides than normal-weight patients with similar degrees of HF.[66] However there is no consensus regarding the utility of BMI-adjusted BNP or NT-proBNP values. One post hoc analysis proposed a BNP threshold of 54 pg/mL for patients with BMI ≥35 kg/m^2, versus 110 pg/mL for BMI 25−34.9 kg/m^2 and 170 pg/mL for BMI <25 kg/m^2, to achieve 90% sensitivity for the diagnosis of HF.[67] The prognostic power of NT-proBNP in chronic HF appears to be consistent among BMI strata.[68]

Obesity Paradox and Weight Loss in Heart Failure

Unlike the use of weight loss for prevention of HF, the presence of an "obesity survival paradox" complicates the case for routinely recommending weight loss in established HF. Multiple analyses suggest that, despite being a risk factor for developing HF, higher BMI is associated with more favorable outcomes in patients with established HF.[69] A meta-analysis of 14 observational HF studies concluded that an obesity survival paradox was present with both HFrEF and HFpEF.[70] It has been suggested that the obesity paradox is a statistical aberration due to residual confounding or presentation of patents with obesity at younger ages

or with less severe cardiac disease.[71,72] It may also partly reflect the adverse effects of unintentional weight loss due to cachexia in the lower-BMI groups.

Despite the theoretic concerns related to the obesity survival paradox, there are several potential benefits of weight loss in patients with HF and moderate-to-severe obesity. These include resolution of comorbid conditions or symptom drivers (such as atrial fibrillation, hypertension, and obstructive sleep apnea) and reductions in insulin resistance and systemic inflammation. Importantly, weight loss may increase access to heart transplantation or mechanical support in advanced systolic HF, because the International Society of Heart and Lung Transplantation lists BMI >35 kg/m^2 as a contraindication to transplantation.[73]

Weight Loss for Heart Failure Management

Small clinical trials of diet and exercise offer some preliminary support for functional capacity improvements with weight loss for patients with HF, although only 2 such studies actually achieved significant weight loss (Table 4). Because weight reduction may confer metabolic and functional benefits, it is reasonable to recommend weight loss for selected patients, especially if young, functionally limited by obesity, and severely obese (eg, BMI ≥35 kg/m^2). However, weight loss may be especially challenging for patients and caregivers already managing chronic HF. The ability to exercise may be limited by cardiac symptoms or financial restrictions associated with poor health, and changes in excess adiposity versus fluid are impossible to discern on the scales.

As above for HF prevention, no specific diet weight loss diet can be recommended, but counseling with an RDN is advised to target 1200−1500 kcal/d for women and 1500−1800 kcal/d for men, aiming at a loss of 1−2 lb/wk.[40] Ketogenic and very-low-calorie diets (VLCD), which provide ≤800 kcal/d, have shown rapid metabolic and weight loss effects in the general population, but would require very close medical supervision in a patient with cardiac disease. Nutritional ketosis is associated with adverse gastrointestinal effects and could provoke a ketoacidosis crisis with comorbid DM. VLCDs are associated with gallstone formation, hypokalemia, and hypomagnesemia, which in the setting of a cardiomyopathy and diuretics could result in arrhythmias. Intermittent fasting has gained some favor as an effective weight loss strategy,[74] but the safety and efficacy for patients with HF remains undefined.

Six pharmacologic weight loss agents are currently available in the United States (Table 3),[75] but pharmacologic weight loss has not been studied in HF apart from one small study of orlistat. Orlistat is an inhibitor of pancreatic lipase and has demonstrated weight loss efficacy for patients with HF in a pilot trial.[76] Despite a good safety profile, the placebo-adjusted weight loss was relatively low compared with other approved medications, and gastrointestinal intolerance was common. Many anorectic drugs have theoretic concerns in HF (Supplemental Table S4), although the risks

Table 4. Summary of Diet and Exercise Weight Loss Studies in HF Cohorts

Study	Subjects	Intervention	Weight Loss Outcomes	Secondary Outcomes
Evangelista et al 2009[117]	14, HFrEF with NYHA II−III and BMI >27 kg/m² with noninsulin-treated type 2 DM	12 wk randomized to high protein hypoenergetic diet (40% total energy from carbohydrates, 30% from protein, 30% from fat) vs standard protein diet (55% total energy from carbohydrates, 15% from protein, 30% from fat) vs conventional diet	High protein group had greater weight loss vs standard protein or conventional diet groups (−9.9 vs −5.5 kg vs 1.51 kg, respectively; $P < .001$)	All 3 groups had significant improvements in hemoglobin A1c and QoL Between-group differences in percent body fat, 6MWT, peak VO2, cholesterol, triglyceride, HDL, LDL No differences in lean mass
O'Connor et al 2009 and Horwich et al 2011, HF-ACTION[118,119]	2331, HFrEF, 49% with BMI >30 kg/m²	Randomized to 36 sessions of supervised aerobic exercise, then home-based exercise for 4 years vs standard of care	No significant weight loss	No significant difference in composite of morality and hospitalization Exercise associated with improved QoL, greatest benefit in obese
Pritchett et al 2012[120]	20, HFrEF with metabolic syndrome	Randomized to 3 months of a walking program + portion-controlled diet with 2 Slim Fast meal replacements daily vs standard of care	No difference in weight loss (−1.2 ± 4.1 vs −0.6 ± 3.7 kg; $P = .71$)	No difference in QoL, 6MWT, blood pressure, lipid profile, glucose, leptin
Ritzel et al 2015[121]	40, HFpEF with metabolic syndrome or pre-DM	All subjects underwent a 3-month lifestyle program (no control group)	58% achieved ≥2% weight loss	≥ 2% weight loss associated with improved peak VO$_2$, NYHA class and freedom from hospitalization
Kitzman et al 2016[122]	100, HFpEF >60 y, with BMI >30 kg/m²	Randomized 2 × 2 factorial trial of 20 weeks of exercise vs diet vs exercise + diet	Both exercise and diet associated with weight loss: exercise, −3 kg (95% CI −5 to −1; $P < .001$); diet, −7 kg (95% CI, −9 to −5; $P < .001$); best weight loss in exercise + diet group: 11 kg (10% loss)	Peak VO$_2$ was increased significantly by both interventions: exercise, 1.2 mL·kg^{-1}·min^{-1} (95% CI 0.7−1.7; $P < .001$); diet, 1.3 mL·kg^{-1}·min^{-1} (95% CI 0.8 to 1.8; $P < .001$); combination of exercise + diet was additive for peak VO$_2$ (joint effect, 2.5 mL·kg^{-1}·min^{-1}); With diet main effect analysis, LV mass −4 g (95% CI −7 to 0; $P = .03$); with diet + exercise, NYHA class improved (main effect): exercise, −0.4 class (95% CI −0.6 to −0.2; $P < .001$); diet, −0.4 class (95% CI −0.5 to −0.2; $P = .001$)
González-Islas et al 2017[123]	88, HF NYHA I−III, any LVEF (73 completed)	Randomized to 2 months of low-carbohydrate diet (40% carbohydrates, 20% protein, and 40% fats) vs standard diet (50% carbohydrates, 20% protein, and 30% fats), both normocaloric	No significant weight loss	No significant changes in blood pressure, body composition, or handgrip strength

BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; QoL, quality of life, VO$_2$, oxygen consumption.

associated with small increases in heart rate for drugs such as phentermine/extended-release topiramate (on average 1−2 beats/min) may be offset by improvements in blood pressure and glycemia.[77]

Lorcaserin is a centrally acting selective serotonin receptor agonist ($5HT_{2B}$ receptor) that promotes satiety; $5HT_{2B}$ may be overexpressed in HF, so caution is recommended in this population.[78] Despite theoretic concerns, the recent lorcaserin cardiovascular safety study reported no excess of cardiovascular or HF events compared with placebo in a population with obesity and cardiovascular disease or risk factors, although NYHA functional class III−IV HF and LVEF <20% were exclusion criteria.[56] The naltrexone/bupropion cardiovascular safety study only excluded NYHA functional class IV HF patients, but it was terminated prematurely and did not report HF as an outcome.[79] Liraglutide has not been studied for weight loss in patients with HF, but in a randomized trial of 1.8 mg/d liraglutide as a therapy for advanced systolic HF, there was a nonsignificant trend toward more HF hospitalizations and mortality with liraglutide compared with placebo.[80] HF clinicians should also review patient's full medication list when counseling about obesity, because many common drugs promote weight gain (Supplemental Table S5).

Two retrospective studies lend some support for the use of bariatric surgery. An analysis of patients with obesity and LV systolic dysfunction (n = 42) who underwent bariatric surgery, compared with a large cohort without known systolic dysfunction (n = 2588), demonstrated good weight loss efficacy as well as similar safety between groups.[81] A retrospective self-controlled administrative database study of patients with HF who underwent bariatric surgery showed reductions in HF-related emergency department visits and hospitalizations in the second year following the procedure, compared with before bariatric surgery.[82] In case reports, during an average 20-month follow-up among 137 HFrEF bariatric surgery recipients, LVEF increased from 32% to 42% (weighted means).[81] Successful bariatric surgery has been reported also for patients with left ventricular assist device (LVAD) support,[83,84] which is an important strategy given that many patients gain weight during long-term LVAD support, but the existing case report literature does not sufficiently delineate the risks versus benefits. Surgical weight loss for patients with HF, with or without LVAD support, should be concentrated in high-volume centers with expertise in both bariatric surgery and HF cardiology. Further prospective studies of surgical and nonsurgical obesity management will be essential in guiding future clinical practice.

Recommendations for Obesity in Heart Failure Management

- A target weight loss of at least 5%−10% is recommended for individuals with BMI ≥35 kg/m², with the use of a combination of approaches including physical activity if HF symptoms permit.

- No specific weight loss diet recommended, but counseling with an RDN is advised. It is usual to recommend a negative energy balance of 500−750 kcal/d or absolute intake of 1200−1500 kcal/d diet for women and 1500−1800 kcal/d for men, aiming for a loss of 1−2 lb/wk.

- For patients with HF and obesity meeting standard indications, weight loss pharmacotherapies have theoretic benefits, particularly for HFpEF patients, but there is an absence of efficacy and safety data for these drugs in HF, so they must be used with caution and close monitoring.

- In selected patients with BMI ≥35 kg/m² and NYHA functional class II−III HF with or without an LVAD, whose eligibility for cardiac transplantation depends on weight loss, bariatric surgery can be considered within an experienced multidisciplinary team; consensus opinion favors laparoscopic sleeve gastrectomy to avoid the multiple surgical anastomoses of Roux-en-Y gastric bypass.

- Well designed randomized controlled trials of weight loss safety and efficacy by means of intensive lifestyle interventions, pharmacotherapy, and bariatric surgery in patients with both HFrEF and HFpEF are urgently needed to define best practices.

Cachexia and Sarcopenia

Cardiac cachexia, sarcopenia, insulin resistance, low serum cholesterol, and low albumin are all predictors of adverse clinical outcomes in HF.[85−88] Cachexia is a complex metabolic wasting syndrome characterized by unintentional edema-free weight loss (muscle mass loss, with or without fat mass loss), anorexia, inflammation and abnormal biochemistry.[89,90] Sarcopenia is the age-related decline in skeletal muscle mass, function and quality, which can be accelerated by medical comorbidities (Supplemental Table S6).[91,92] Both syndromes have been associated with increased mortality, but loss of muscle mass appears to be associated with greater deficits in functional capacity (eg, as represented by handgrip strength, quadriceps strength, or 6-minute walk) and health-related QoL (represented by EQ-5D), as compared to weight loss alone.[93] Sarcopenia is a contributor toward the frailty syndrome, but frailty represents a broader age-related decline in reserve and function across multiple physiologic systems resulting in physical, cognitive and social impairments that increase vulnerability to stressors.

Cachexia and sarcopenia diagnostic criteria specific to HF are poorly defined, but it is estimated that at least 10% of patients with ambulatory systolic HF develop cachexia.[94] Sarcopenia prevalence was 20% among 200 patients, based on dual x-ray absorptiometric (DXA) body composition criteria,[85] and 47% among a younger systolic HF cohort.[95] Updated sarcopenia guidelines favor the SARC-F questionnaire or gait speed for screening[91,92]; diagnostic thresholds based on muscle mass and strength are presented in Supplemental Table S6. Lower BMI (eg, ≤18.5−20 kg/m²) has been associated with higher mortality after LVAD implantation or cardiac transplantation.[96]

Identification of Cardiac Cachexia and Wasting

The diagnosis of wasting in HF is currently limited by uncertain applicability of cachexia scores developed in cancer populations (eg, the CAchexia SCOre) and limited validation of body composition assessment methods, such as DXA, in patients with expanded extracellular water volume (Supplemental Table S6). Bioelectrical impedance has shown poor agreement with DXA and isotope techniques in HF validation studies and is contraindicated with implantable cardiac devices.[97] Computerized tomographic or magnetic resonance quantification of pectoralis, psoas, or quadriceps muscle mass have more recently been used to assess muscle mass in HF.[98,99] Cardiac cachexia is strongly associated with mortality in systolic HF.[100] Risk scores incorporating serum albumin and BMI have also shown some prognostic utility in HF,[101] although the search is ongoing for optimal biomarkers of cardiac cachexia that enable early diagnosis before substantial weight loss.

Improvements in Metabolism With Mechanical Circulatory Support

Patients with end-stage systolic HF exhibit the most marked systemic metabolic and inflammatory derangement and the highest risk for cachexia. Reversal of low albumin and total cholesterol levels, insulin resistance, skeletal muscle adiponectin resistance, and systemic inflammatory activation have all been observed in the months after LVAD implantation.[87,102–105] LVAD patients tend to gain weight after device implantation, especially if underweight or normal-weight before implantation.[106] The mechanisms of this metabolic recovery are uncertain, although normalized perfusion to the gut and skeletal muscle, relief of liver congestion, and improvements in dietary quality and physical activity levels could all be contributors. Metabolomic profiling has associated elevated long-chain acylcarnitines with poor prognosis in HF; this metabolic abnormality reverses after LVAD implantation.[107]

Interventions to Correct Cachexia, Sarcopenia, and Malnutrition in Heart Failure

There are no large randomized trials to investigate whether dietary or pharmacologic interventions can correct cachexia or sarcopenia in HF. It is possible that simply augmenting protein-calorie intake, eg, by adopting the PROT-AGE protein goals,[20] may be insufficient to overcome the wasting process without addressing the abnormal inflammatory and metabolic state driven by HF. However the PICNIC study did establish that focused nutrition consultation after an acute HF admission can improve outcomes for patients with malnutrition. That clinical trial randomized 120 Spanish patients identified as malnourished by the MNA score to a 6-month intervention consisting of dietary quality optimization, practical recommendations for overcoming poor food intake, and nutritional supplementation when required, versus standard care.[108] The intervention was delivered by a physician and an RDN and involved monthly nutrition outpatient visits. At 12 months, the primary composite end point of death or readmission for worsening HF occurred in 27% of the intervention group versus 61% of the control group (hazard ratio 0.45, 95% CI 0.19−0.62; $P = .0004$). Clinical trials that validate malnutrition interventions similar to the PICNIC study in other HF populations will be necessary to formulate future clinical recommendations.

Successful cardiac cachexia therapies will likely be multidimensional and include antiinflammatory and anabolic components in addition to caloric substrate (Fig. 2; Supplemental Table S7). Along these lines, a small clinical trial randomized 31 patients with HFrEF to 1-alanyl-1-glutamine (8 g/d) plus polyunsaturated fatty acid (6.5 g/d) versus placebo for 3 months.[109] Fat free mass (FFM) increased (from 54.4 ± 3.2 to 56.1 ± 2.5 kg; $P = .04$), but skeletal muscle function and potential mechanistic markers remained unchanged. There has been significant interest in the ghrelin agonists as candidates for the reversal of cachexia and sarcopenia. Ghrelin is a gut peptide hormone that, in addition to being the main human hunger signal, has antiinflammatory and anabolic effects. In patients with cachectic non−small cell lung cancer, the ghrelin agonist anamorelin was associated with small FFM increases over 12 weeks.[110] However, the European Medicines Agency declined an application as a cachexia therapy in 2017 owing to the clinically marginal effect on FFM and the absence of an impact on handgrip strength or QoL.

Selected appetite stimulants may have a role in addressing the anorexia component of cachexia (Table 5). Structured physical activity may also be a necessary component for sarcopenia reversal, with resistance training being particularly effective and feasible for patients with anaerobic limitations. Resistance exercise performed for 1 hour twice weekly for 12 weeks in 66 subjects—of which 41 had baseline cardiac cachexia—was associated with an 11 kg increase in handgrip strength, although there was no comparator group without exercise.[111] A meta-analysis of 240 patients with HF also demonstrated an improvement in lower body muscle strength.[112] High-intensity interval training is a more recent approach suggesting benefits.[113] The updated Physical Activity Guidelines for Americans from the Department of Health and Human Services emphasize personalized exercise recommendations that support patients with chronic conditions to maximize their activity levels within the boundaries of symptom limitations.[114]

Despite the absence of literature to support screening for and treatment of cardiac cachexia, the strong association between cachexia and mortality suggests that it is reasonable to try to address protein-calorie inadequacy in selected patients, and that functional status may be improved with protein intake that exceeds the 0.8 g/kg daily general population recommendation.[23] Patients with advanced HF and cachexia or malnutrition (or at high risk of malnutrition) may require particularly aggressive nutritional interventions if hospitalized with cardiogenic shock (as long as this is consistent with the patient's goals of care) or if cardiac surgery is indicated.[115,116] Although there is no evidence specific to the HF population, enteral and parenteral nutritional support guidelines for adult critical care and perioperative patients offer potentially useful guidance (Table 6). Of
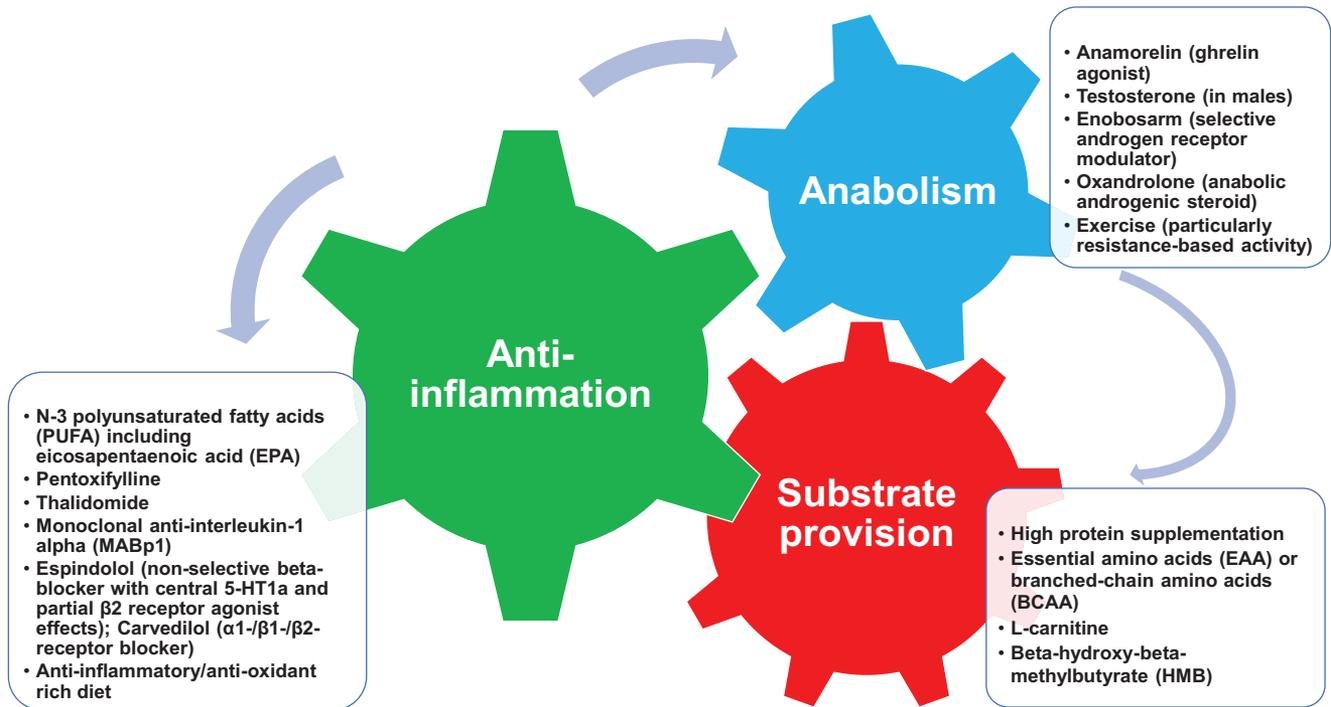
Fig. 2. Candidate interventions for patients with chronic heart failure and cachexia or sarcopenia (see Supplemental Table S7 for references list). Reversal of cardiac cachexia or sarcopenia is likely to require a multidimensional approach with components including antiinflammatory and proanabolic interventions in addition to substrate provision.

note, the 2017 European Society for Clinical Nutrition and Metabolism guidelines minimize fasting before most major surgeries, and instead endorse oral carbohydrate loading.

Recommendations for Managing Cardiac Cachexia and Sarcopenia

- It is reasonable for patients with HF to be screened for unintentional weight loss at least annually, because of the strong association between cachexia and adverse clinical outcomes.
- Until HF-specific diagnostic criteria are developed, it is reasonable to adopt the definition of cachexia as unintentional edema-free weight loss >7.5% in the preceding 6−12 months or BMI <20 kg/m^2, with evidence of sarcopenia, wasting, or abnormal biochemistry.
- Patients who meet cachexia criteria or have an elevated nutritional risk based on a validated malnutrition screening tool should receive RDN consultation (Fig. 1).
- Sarcopenia screening with the use of the 5-item SARC-F questionnaire (score ≥4), gait speed (≤0.8 m/s), or handgrip strength (<27 kg in men, <16 kg in women) could be adopted in the inpatient or outpatient HF settings (thresholds as per European Working Group on Sarcopenia in Older People 2 criteria, outlined in Supplemental Table S6).
- Further validation of body composition measurement techniques in HF populations is required.
- For patients identified with (or at high risk of) malnutrition or cachexia, a goal protein intake of ≥1.1 g/kg daily

is reasonable (per PROT-AGE and Academy of Nutrition and Dietetics recommendations).
- Patients with cachexia or malnutrition in the setting of critical illness or anticipated cardiac surgery should be specifically evaluated for enteral or parenteral nutritional support per guidelines (Table 6); in the absence of prospective data, consensus preoperative nutritional targets may include albumin ≥3.0 g/dL, prealbumin ≥16 g/dL, BMI ≥18.5−20 kg/m^2, and an iron-replete state (eg, transferrin saturation ≥20% and ferritin ≥300 ng/mL).
- Mirtazapine, megesterol acetate, dronabinol and n-3 polyunsaturated fatty acids can be considered for anorexic patients within the limitations of their adverse effect profiles (Table 5).
- Clinical trials are required to evaluate the candidate nutritional and pharmacologic interventions for reversal of cachexia and sarcopenia in HFrEF and HFpEF; study end points should include physical function and QoL in addition to muscle mass gains.

Conclusions and Future Research Priorities

Each of the 4 priority HF nutrition domains—dietary quality, micronutrient supplementation, management of obesity, and management of cardiac cachexia—are poorly informed by the currently available scientific literature. Significant gaps in our basic and translational understanding of the progression from obesity to HF and from HF to cachexia, have hampered the development of effective interventions to disrupt these

Table 5. Appetite Simulants and Their Suitability in Heart Failure (HF)

Suitability	Medication	Dose Range	Major Adverse Effects in General Populations*
May be appropriate in some patients with HF and anorexia	Mirtazapine[†] (off-label use)	Oral tablet, 15−30 mg at bedtime	Drowsiness (54%), dry mouth (25%), constipation (13%), asthenia (8%), dizziness (7%), flu syndrome, (5%) nausea (1.5%), edema (1%), rare QT prolongation (<1%)
	Megestrol acetate[‡] (off-label use, approved for AIDS cachexia)	Oral suspension, 160−800 mg daily	Hypertension (4%−8%), thromboembolic events (1%−3%), volume retention (1%−3%), palpitations (1%−3%)
	Dronabinol[§] (off-label use, approved for AIDS cachexia and nausea/vomiting in chemotherapy patients)	Oral capsule, 2.5−5 mg bid	Drowsiness (3%−10%), tachycardia (>1%), hypotension (<1%), orthostatic hypotension (<1%), confusion (>1%), lower seizure threshold (<1%)
	Fish oils[ǁ] (off-label use)	Oral capsule, 1−4 g daily	Diarrhea (7%−15%), nausea (4%−6%), belching (3%)
Consider in all patients with HF and anorexia	Where possible, discontinuation of anorexigenic medications, including digoxin, amiodarone, mexilitine, some oral diabetes medications and antihypertensives		

AIDS, acquired immunodeficiency syndrome.

*Adverse event percentages are from general populations and may be different in HF populations.

[†]Remeron [package insert]. Kenilworth, NJ: NV Organon; 2009.

[‡]Megace [package insert]. Spring Valley, NY: Par Pharmaceutical Companies; 2013.

[§]Marinol [package insert]. North Chicago, IL: Abbvie; 2017.

[ǁ]Lovaza [package insert]. Research Triangle Park, NC: Glaxo Smith Kline; 2015.

Table 6. Society Recommendations for Nutrition Support Therapy in Critically Ill and Perioperative Heart Failure Patients

Key Recommendations for Nutrition Support Therapy in the Adult Critically Ill Patient	Key Recommendations for Nutrition Support Therapy in Perioperative Patients
Routinely screen for nutritional risk on admission to the intensive care unit (ICU), for example with a NUTRIC-ICU score ≤5, and calculate both energy and protein requirements to determine goals (ideally with the use of indirect calorimetry if available)	ESPEN guidelines recommend against routine preoperative fasting in patients at standard risk of aspiration, instead advising solids until 6 hours before and clear fluids until 2 hours before anesthesia
Initiate enteral nutrition (EN) within 24−48 h of ICU admission and advance to goal over the first week to provide 25−30 kcal/kg daily	An 800-mL carbohydrate drink is recommended on the evening before anesthesia, and 400 mL 2 hours before anesthesia is recommended for patients undergoing major surgery
Use standard ICU bundles to reduce aspiration risks and do not use gastric residual volumes to routinely monitor EN delivery	Patients with severely elevated nutritional risk should receive nutritional support before major surgery for 7−14 d even if operations have to be delayed
Start parenteral nutrition (PN) early when EN is not feasible or sufficient in malnourished or high-risk patients	Initiate nutritional support if <50% of energy requirements are met for more than 7 d
Consider immune-modulating formulas containing both arginine and fish oil for postoperative patients requiring EN	Consider immune-modulating formulas (arginine, fish oil) for malnourished peri- or postoperative patients undergoing major cancer surgery
McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN). JPEN J Parenter Enteral Nutr 2016;40:159−211.[115]	Weimann A, Braga M, Carli F, Higashiguchi T, Hübner M, Klek S, et al. ESPEN guideline: clinical nutrition in surgery. Clin Nutr 2017;36:623−50.[116]

Table 7. Recommendations for Future Research Priorities Regarding Nutrition in Heart Failure

Area of Focus	Example Research Questions	Recommendations for Design	Anticipated Challenges
Dietary composition	Is a higher (1.1−1.5 g/kg daily) vs standard (0.8 g/kg daily) protein diet associated with better preservation of muscle mass and functional status? Is the DASH vs Mediterranean vs standard diet associated with freedom from HF hospitalizations and mortality?	Randomized clinical trials, with HFrEF and HFpEF subgroups represented; study duration would be limited by feasibility of research diet implementation, but a minimum of 3−4 mo intervention is likely required for impact on clinically relevant end points	Logistics and funding are challenging for prospective dietary studies; would likely require collaboration with nutrition companies to supply complete research diets
Micronutrient supplementation	Is thiamine supplementation associated with freedom from HF hospitalizations and mortality?	Randomized clinical trial, with HFrEF and HFpEF subgroups represented	Optimal methods for assessing circulating levels of thiamine
Malnutrition screening	Which history- or laboratory-based screening tool offers superior malnutrition screening performance and best prediction of HF hospitalizations and mortality?	Prospective cohort design, with HFrEF and HFpEF subgroups represented, both inpatients and outpatients	Selection of criterion-standard malnutrition diagnostic criteria
Dietary interventions for weight loss	Is a low-carbohydrate diet or a low-fat diet most effective and safe in achieving weight loss? Is intermittent fasting safe and effective as a weight loss strategy for patients with HF?	Randomized clinical trial, with HFrEF and HFpEF subgroups represented	Logistics and funding are challenging for prospective dietary studies; would likely require collaboration with nutrition companies to supply complete research diets
Pharmacologic interventions for weight loss	Is 3 mg liraglutide or phentermine/topiramate safer and more effective in achieving weight loss for patients with HFpEF?	Randomized clinical trial, potentially also cardiovascular events outcomes end point	Collaboration with pharmaceutical companies for funding
Bariatric surgery for weight loss	Is bariatric surgery effective and safe for patients with BMI $\geq$40 kg/m^2 vs intensive lifestyle intervention?	Randomized clinical trial, with HFrEF and HFpEF subgroups represented; additional myocardial structure and function end points	May not be ethical and/or feasible to randomize to surgery; collaboration with industry for funding
Calorie supplementation in patients with malnutrition or cardiac cachexia	Is oral protein-calorie supplementation alone effective in promoting skeletal muscle mass, with or without fish oil supplementation (as an antiinflammatory)? Are diets that are higher in fats or protein, compared with current diet guidance for patients with cardiac disease, safe and effective for weight regain? Are proanabolic therapies, eg, ghrelin agonism or oxandrolone, effective in promoting skeletal muscle mass? Are mirtazapine, megesterol acetate, dronabinol, or n-3 polyunsaturated fatty acids safe and effective as appetite stimulants for patients with cardiac cachexia and anorexia?	Randomized clinical trial, with HFrEF, HFpEF and LVAD patient subgroups represented	Collaboration with industry for funding; agreement on cardiac cachexia criteria to define eligibility for study participation

BMI, body mass index; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVAD, left ventricular assist device.

pathways. Given the public health burden of HF and the accumulated evidence that dietary intake can affect clinical outcomes, nutritional strategies should be a key component of future HF clinical investigation. The prevalence of obesity in HF continues to increase, and both dietary and surgical interventions for weight loss are yet to be studied in robustly designed prospective trials. A clinical trial of sleeve gastrectomy in stable HFrEF and HFpEF patients with severe obesity would be particularly informative for clinical practice (Table 7).

On the opposite end of the spectrum, the morbidity and mortality burden attributable to cachexia also is significant, and HF-specific prospective trials of candidate cachexia therapies could change the paradigm of care in this high-risk HF subgroup. Future micronutrient and nutraceutical trials in HF must be carefully conducted to provide more robust data than currently exist to confirm whether nutritional interventions improve QoL, functional capacity, or survival beyond optimal medical therapy. Nutritional clinical trials should be conducted with the same rigor and attention to bias as drug trials in HF populations to enable these interventions to gain acceptance and support within the cardiology community. In a field with few new pharmacologic therapies on the horizon, nutritional interventions hold the potential to significantly improve clinical outcomes for thousands of patients with HF within the coming decade.

Disclosures

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.03.007.

References

1. Bozkurt B, Aguilar D, Deswal A, Dunbar SB, Francis GS, Horwich T. American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular and Stroke Nursing; Council on Hypertension; Council on Quality and Outcomes Research. Contributory risk and management of comorbidities of hypertension, obesity, diabetes mellitus, hyperlipidemia, and metabolic syndrome in chronic heart failure: a scientific statement from the American Heart Association. Circulation 2016;134:e535–78.
2. Heart Failure Society of America. Executive summary: HFSA 2010 comprehensive heart failure practice guideline. J Card Fail 2010;16:475–539.
3. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62: e147–239.
4. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2016;37:2129–200.
5. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Card Fail 2017;23:628–51.
6. Heart failure evidence-based nutritional practice guideline. Am Acad Nutr Diet 2017: 1–34.
7. White JV, Guenter P, Jensen G, Malone A, Schofield M. Academy Malnutrition Work Group; ASPEN Malnutrition Task Force; ASPEN Board of Directors. Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition. JPEN J Parenter Enteral Nutr 2012;36:275–83.
8. Jefferson K, Ahmed M, Choleva M, Mak S, Allard JP, Newton GE, Arcand J. Effect of a sodium-restricted diet on intake of other nutrients in heart failure: implications for research and clinical practice. J Card Fail 2015;21:959–62.
9. Colin-Ramirez E, McAlister FA, Zheng Y, Sharma S, Ezekowitz JA. Changes in dietary intake and nutritional status associated with a significant reduction in sodium intake in patients with heart failure. A sub-analysis of the SODIUM-HF pilot study. Clin Nutr ESPEN 2016;11:e26–32.
10. American Diabetes Association. Lifestyle management: standards of medical care in diabetes. Diabetes Care 2018;41:S38–50.
11. Tyson CC, Nwankwo C, Lin P-H, Svetkey LP. The Dietary Approaches to Stop Hypertension (DASH) eating pattern in special populations. Curr Hypertens Rep 2012;14:388–96.
12. Hummel SL, Seymour EM, Brook RD, Kolias TJ, Sheth SS, Rosenblum HR, et al. Low-sodium dietary approaches to stop hypertension diet reduces blood pressure, arterial stiffness, and oxidative stress in hypertensive heart failure with preserved ejection fraction. Hypertension 2012;60:1200–6.
13. Hummel SL, Seymour EM, Brook RD, Sheth SS, Ghosh E, Zhu S, et al. Low-sodium DASH diet improves diastolic function and ventricular-arterial coupling in hypertensive heart failure with preserved ejection fraction. Circ Heart Fail 2013;6:1165–71.
14. Mathew AV, Seymour EM, Byun J, Pennathur S, Hummel SL. Altered metabolic profile with sodium-restricted dietary approaches to stop hypertension diet in hypertensive heart failure with preserved ejection fraction. J Card Fail 2015;21:963–7.
15. Levitan EB, Lewis CE, Tinker LF, Eaton CB, Ahmed A, Manson JE, et al. Mediterranean and DASH diet scores and mortality in women with heart failure: the Women's Health Initiative. Circ Heart Fail 2013;6:1116–23.
16. Hummel SL, Karmally W, Gillespie BW, Helmke S, Teruya S, Wells J, et al. Home-delivered meals post discharge from heart failure hospitalization. Circ Heart Fail 2018;11: e004886.
17. Miró Ò, Estruch R, Martín-Sánchez FJ, Gil V, Jacob J, Herrero-Puente P. ICA-SEMES Research Group. Adherence to Mediterranean diet and all-cause mortality after an episode of acute heart failure: results of the MEDIT-AHF study. JACC Heart Fail 2018;6:52–62.
18. Sze S, Pellicori P, Kazmi S, Rigby A, Cleland JGF, Wong K, Clark AL. Prevalence and prognostic significance of malnutrition using 3 scoring systems among outpatients with heart failure: a comparison with body mass index. JACC Heart Fail 2018;6:476–86.
19. Aquilani R, Opasich C, Verri M, Boschi F, Febo O, Pasini E, Pastoris O. Is nutritional intake adequate in chronic heart failure patients? J Am Coll Cardiol 2003;42:1218–23.

20. Bauer J, Biolo G, Cederholm T, Cesari M, Cruz-Jentoft AJ, Morley JE, et al. Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE Study Group. J Am Med Dir Assoc 2013;14:542–59.

21. Bernstein AM, Sun Q, Hu FB, Stampfer MJ, Manson JE, Willett WC. Major dietary protein sources and risk of coronary heart disease in women. Circulation 2010;122:876–83.

22. Virtanen HEK, Voutilainen S, Koskinen TT, Mursu J, Tuomainen T-P, Virtanen JK. Intake of different dietary proteins and risk of heart failure in men. Circ Heart Fail 2018;11:1–12.

23. Mustafa J, Ellison RC, Singer MR, Bradlee ML, Kalesan B, Holick MF, Moore LL. Dietary protein and preservation of physical functioning among middle-aged and older adults in the Framingham Offspring Study. Am J Epidemiol 2018;187:1411–9.

24. Shetty PM, Hauptman PJ, Landfried LK, Patel K, Weiss EP. Micronutrient deficiencies in patients with heart failure: relationships with body mass index and age. J Card Fail 2015;21:968–72.

25. Song EK, Kang S-M. Micronutrient deficiency independently predicts adverse health outcomes in patients with heart failure. J Cardiovasc Nurs 2017;32:47–53.

26. Yoshihisa A, Abe S, Kiko T, Kimishima Y, Sato Y, Watanabe S, et al. Association of serum zinc level with prognosis in patients with heart failure. J Card Fail 2018;24:375–83.

27. Lennie TA, Andreae C, Rayens MK, Song EK, Dunbar SB, Pressler SJ, et al. Micronutrient deficiency independently predicts time to event in patients with heart failure. J Am Heart Assoc 2018:e007251.

28. McKeag NA, McKinley MC, Harbinson MT, Noad RL, Dixon LH, McGinty A, et al. The effect of multiple micronutrient supplementation on left ventricular ejection fraction in patients with chronic stable heart failure: a randomized, placebo-controlled trial. JACC Heart Fail 2014;2:308–17.

29. Jain A, Mehta R, Al-Ani M, Hill JA, Winchester DE. Determining the role of thiamine deficiency in systolic heart failure: a meta-analysis and systematic review. J Card Fail 2015;21:1000–7.

30. Fotino AD, Thompson-Paul AM, Bazzano LA. Effect of coenzyme Q10 supplementation on heart failure: a meta-analysis. Am J Clin Nutr 2013;97:268–75.

31. Mortensen SA, Rosenfeldt F, Kumar A, Dolliner P, Filipiak KJ, Pella D. Q-SYMBIO Study Investigators. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. JACC Heart Fail 2014;2:641–9.

32. Aune D, Sen A, Norat T, Janszky I, Romundstad P, Tonstad S, Vatten LJ. Body mass index, abdominal fatness and heart failure incidence and mortality: a systematic review and dose-response meta-analysis of prospective studies. Circulation 2016;133:639–49.

33. Pandey A, LaMonte M, Klein L, Ayers C, Psaty BM, Eaton CB, et al. Relationship between physical activity, body mass index, and risk of heart failure. J Am Coll Cardiol 2017;69:1129–42.

34. del Gobbo LC, Kalantarian S, Imamura F, Lemaitre R, Siscovick DS, et al. Contribution of major lifestyle risk factors for incident heart failure in older adults: the Cardiovascular Health Study. JACC Heart Fail 2015;3:520–8.

35. Ebong IA, Goff Jr DC, Rodriguez CJ, Chen H, Bluemke D, Szklo M, Bertoni AG. The relationship between measures of obesity and incident heart failure: the Multi-Ethnic Study of Atherosclerosis. Obesity 2013;21:1915–22.

36. Pandey A, Cornwell WK, Willis B, Neeland IJ, Gao A, Leonard D, et al. Body mass index and cardiorespiratory fitness in mid-life and risk of heart failure hospitalization in older age: findings from the Cooper Center Longitudinal Study. JACC Heart Fail 2017;5:367–74.

37. Carbone S, Lavie CJ, Arena R. Obesity and heart failure: focus on the obesity paradox. Mayo Clin Proc 2017;92:266–79.

38. Kharod AM, Ramlogan SR, Kumar S, Raghuveer T, Drake W, Dai H, Raghuveer G. Childhood obesity increases left-ventricular mass irrespective of blood pressure status. Pediatr Cardiol 2013;35:353–60.

39. Gadde KM, Martin CK, Berthoud H-R, Heymsfield SB. Obesity. J Am Coll Cardiol 2018;71:69–84.

40. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA. American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Obesity Society. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society. Circulation 2014;129:S102–38.

41. Aggarwal M, Bozkurt B, Panjrath G, Aggarwal B, Ostfeld RJ, Barnard ND, et al. Lifestyle modifications for preventing and treating heart failure. J Am Coll Cardiol 2018;72:2391–405.

42. Fothergill E, Guo J, Howard L, Kerns JC, Knuth ND. Persistent metabolic adaptation 6 years after "The Biggest Loser" competition. Obes Biol Integr Physiol 2016;24:1612–9.

43. Levitan EB, Wolk A, Mittleman MA. Consistency with the DASH diet and incidence of heart failure. Arch Intern Med 2009;169:851–7.

44. Nettleton JA, Steffen LM, Loehr LR, Rosamond WD, Folsom AR. Incident heart failure is associated with lower whole-grain intake and greater high-fat dairy and egg intake in the Atherosclerosis Risk in Communities (ARIC) study. J Am Diet Assoc 2008;108:1881–7.

45. Rautiainen S, Levitan EB, Mittleman MA, Wolk A. Fruit and vegetable intake and rate of heart failure: a population−based prospective cohort of women. Eur J Heart Fail 2015;17:20–6.

46. Papadaki A, Martínez-González MÁ, Alonso-Gómez A, Rekondo J, Salas-Salvadó J, Corella D, et al. Mediterranean diet and risk of heart failure: results from the PREDIMED randomized controlled trial. Eur J Heart Fail 2017;19:1179–85.

47. Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145–54.

48. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009;360:859–73.

49. Tobias DK, Chen M, Manson JE, Ludwig DS, Willett W, Hu FB. Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2015;3:968–79.

50. Ebbeling CB, Feldman HA, Klein GL, Wong JMW, Bielak L, Steltz SK, et al. Effects of a low carbohydrate diet on energy expenditure during weight loss maintenance: randomized trial. Br Med J 2018;363:k4583.

51. Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I. For the Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med 2008;359:229–41.

52. Coleman CD, Kiel JR, Mitola AH, Langford JS, Davis KN, Arterburn LM. Effectiveness of a Medifast meal replacement program on weight, body composition and cardiometabolic risk factors in overweight and obese adults: a multicenter systematic retrospective chart review study. Nutr J 2015;14:77.

53. Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, et al. Pharmacological management of obesity: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2015;100:342–62.

54. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M. SCALE Obesity and Prediabetes NN8022-1839 Study Group. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med 2015;373:11–22.

55. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–22.

56. Bohula EA, Wiviott SD, McGuire DK, Inzucchi SE, Kuder J, Im K, et al. Cardiovascular safety of lorcaserin in overweight or obese patients. N Engl J Med 2018;379:1107–17.

57. Adams TD, Davidson LE, Litwin SE, Kim J, Kolotkin RL, Nanjee MN, et al. Weight and metabolic outcomes 12 years after gastric bypass. N Engl J Med 2017;377:1143–55.

58. Mechanick JI, Youdim A, Jones DB, Garvey WT, Hurley DL, McMahon MM. American Association of Clinical Endocrinologists; Obesity Society; American Society for Metabolic and Bariatric Surgery. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient—2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic and Bariatric Surgery. Obesity 2013;21(Suppl 1)):S1–27.

59. Netto BDM, Bettini SC, Clemente APG, de Carvalho Ferreira JP, Boritza K, de Fátima Souza S, et al. Roux-en-Y gastric bypass decreases pro-inflammatory and thrombotic biomarkers in individuals with extreme obesity. Obes Surg 2014;25:1010–8.

60. Vest AR, Heneghan HM, Agarwal S, Schauer PR, Young JB. Bariatric surgery and cardiovascular outcomes: a systematic review. Heart 2012;98:1763–77.

61. Aggarwal R, Harling L, Efthimiou E, Darzi A, Athanasiou T, Ashrafian H. The effects of bariatric surgery on cardiac structure and function: a systematic review of cardiac imaging outcomes. Obes Surg 2015;26:1030–40.

62. Sundström J, Bruze G, Ottosson J, Marcus C, Näslund I, Neovius M. Weight loss and heart failure: a nationwide study of gastric bypass surgery versus intensive lifestyle treatment. Circulation 2017;135:1577–85.

63. Benotti PN, Wood GC, Carey DJ, Mehra VC, Mirshahi T, Lent MR, et al. Gastric bypass surgery produces a durable reduction in cardiovascular disease risk factors and reduces the long-term risks of congestive heart failure. J Am Heart Assoc 2017;6:e005126.

64. Persson CE, Björck L, Lagergren J, Lappas G, Giang KW, Rosengren A. Risk of heart failure in obese patients with and without bariatric surgery in Sweden—a registry-based study. J Card Fail 2017;23:530–7.

65. Joyce E, Lala A, Stevens SR, Cooper LB, AbouEzzeddine OF, Groarke JD, et al. Heart Failure Apprentice Network. Prevalence, profile, and prognosis of severe obesity in contemporary hospitalized heart failure trial populations. JACC Heart Fail 2016;4:923–31.

66. Ndumele CE, Matsushita K, Sang Y, Lazo M, Agarwal SK, Nambi V, et al. N-Terminal pro−brain natriuretic peptide and heart failure risk among individuals with and without obesity: the Atherosclerosis Risk in Communities (ARIC) study. Circulation 2016;133:631–8.

67. Daniels LB, Clopton P, Bhalla V, Krishnaswamy P, Nowak RM, McCord J, et al. How obesity affects the cut-points for B-type natriuretic peptide in the diagnosis of acute heart failure. Results from the Breathing Not Properly multinational study. Am Heart J 2006;151:999–1005.

68. Frankenstein L, Remppis A, Nelles M, Schaelling B, Schellberg D, Katus H, Zugck C. Relation of N-terminal pro−brain natriuretic peptide levels and their prognostic power in chronic stable heart failure to obesity status. Eur Heart J 2008;29:2634–40.

69. Clark AL, Fonarow GC, Horwich TB. Obesity and the obesity paradox in heart failure. Prog Cardiovasc Dis 2014;56:409–14.

70. Padwal R, McAlister FA, McMurray JJV, Cowie MR, Rich M, Pocock S. Meta-Analysis Global Group In Chronic Heart Failure (MAGGIC). The obesity paradox in heart failure patients with preserved versus reduced ejection fraction: a meta-analysis of individual patient data. Int J Obes Relat Metab Disord 2014;38:1110–4.

71. Charnigo R, Guglin M. Obesity paradox in heart failure: statistical artifact, or impetus to rethink clinical practice? Heart Fail Rev 2016;22:13–23.

72. O'Brien EC, Thomas LE. Untangling the paradox: obesity as prognostic marker in prevalent cardiovascular disease. Am Heart J 2016;172:170–2.

73. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. J Heart Lung Transplant 2016;35:1–23.

74. Trepanowski JF, Kroeger CM, Barnosky A, Klempel MC, Bhutani S, Hoddy KK, et al. Effect of alternate-day fasting on weight loss, weight maintenance, and cardioprotection among metabolically healthy obese adults: a randomized clinical trial. JAMA Intern Med 2017;177:930–8.

75. Khera R, Murad MH, Chandar AK, Dulai PS, Wang Z, Prokop LJ, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. JAMA 2016;315:2424–34.

76. Beck-da-Silva L, Higginson L, Fraser M, Williams K, Haddad H. Effect of orlistat in obese patients with heart failure: a pilot study. Congest Heart Fail 2005;11:118–23.

77. Jordan J, Astrup A, Engeli S, Narkiewicz K, Day WW, Finer N. Cardiovascular effects of phentermine and topiramate. J Hypertens 2014;32:1178–88.

78. Weissman NJ, Sanchez M, Koch GG, Smith SR, Shanahan WR, Anderson CM. Echocardiographic assessment of cardiac valvular regurgitation with lorcaserin from analysis of 3 phase 3 clinical trials. Circ Cardiovasc Imaging 2013;6:560–7.

79. Nissen SE, Wolski KE, Prcela L, Wadden T, Buse JB, Bakris G, et al. Effect of naltrexone-bupropion on major adverse cardiovascular events in overweight and obese patients with cardiovascular risk factors. JAMA Intern Med 2016;315:990–1004.

80. Margulies KB, Hernandez AF, Redfield MM, Givertz MM, Oliveira GH, Cole R. National Heart, Lung, and Blood Institute Heart Failure Clinical Research Network. Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: a randomized clinical trial. JAMA 2016;316:500–8.

81. Vest AR, Patel P, Schauer PR, Satava ME, Cavalcante JL, Brethauer S, Young JB. Clinical and echocardiographic outcomes after bariatric surgery in obese patients with left ventricular systolic dysfunction. Circ Heart Fail 2016;9: e002260.

82. Shimada YJ, Tsugawa Y, Brown DFM, Hasegawa K. Bariatric surgery and emergency department visits and hospitalizations for heart failure exacerbation: population-based, self-controlled series. J Am Coll Cardiol 2015;67:895–903.

83. Shah SK, Gregoric ID, Nathan SS, Akkanti BH, Kar B, Bajwa KS. Simultaneous left ventricular assist device placement and laparoscopic sleeve gastrectomy as a bridge to transplant for morbidly obese patients with severe heart failure. J Heart Lung Transplant 2015;34:1489–91.

84. Lim C-P, Fisher OM, Falkenback D, Boyd D, Hayward CS, Keogh A, et al. Bariatric surgery provides a "bridge to

transplant" for morbidly obese patients with advanced heart failure and may obviate the need for transplantation. Obes Surg 2016;26:486–93.

85. Fülster S, Tacke M, Sandek A, Ebner N, Tschöpe C, Doehner W, et al. Muscle wasting in patients with chronic heart failure: results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). Eur Heart J 2013;34:512–9.

86. Greene SJ, Vaduganathan M, Lupi L, Ambrosy AP, Mentz RJ, Konstam MA. EVEREST Trial Investigators. Prognostic significance of serum total cholesterol and triglyceride levels in patients hospitalized for heart failure with reduced ejection fraction (from the EVEREST trial). Am J Cardiol 2013;111:574–81.

87. Kato TS, Kitada S, Yang J, Wu C, Takayama H, Naka Y, Farr M, et al. Relation of preoperative serum albumin levels to survival in patients undergoing left ventricular assist device implantation. Am J Cardiol 2013;112:1484–8.

88. Mebazaa A, Gayat E, Lassus J, Meas T, Mueller C, Maggioni A, et al. Association between elevated blood glucose and outcome in acute heart failure. J Am Coll Cardiol 2013;61:820–9.

89. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. Clin Nutr 2008;27:793–9.

90. 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;14:323–41.

91. Dent E, Morley JE, Cruz-Jentoft AJ, Arai H, Kritchevsky SB, Guralnik J, et al. International Clinical Practice Guidelines for Sarcopenia (ICFSR): screening, diagnosis and management. J Nutr Health Aging 2018;22:1148–61.

92. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T. Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2); Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48:16–31.

93. Emami A, Saitoh M, Valentova M, Sandek A, Evertz R, Ebner N, et al. Comparison of sarcopenia and cachexia in men with chronic heart failure: results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). Eur J Heart Fail 2018;1:4.

94. Christensen HM, Kistorp C, Schou M, Keller N, Zerahn B, Frystyk J, et al. Prevalence of cachexia in chronic heart failure and characteristics of body composition and metabolic status. Endocrine 2012;43:626–34.

95. Hajahmadi M, Shemshadi S, Khalilipur E, Amin A, Taghavi S, Maleki M, et al. Muscle wasting in young patients with dilated cardiomyopathy. J Cachexia Sarcopenia Muscle 2017;8:542–8.

96. Russo MJ, Hong KN, Davies RR, Chen JM, Mancini DM, Oz MC, et al. The effect of body mass index on survival following heart transplantation: do outcomes support consensus guidelines? Ann Surg 2010;251:144–52.

97. Alves FD, Souza GC, Biolo A, Clausell N. Comparison of two bioelectrical impedance devices and dual-energy x-ray absorptiometry to evaluate body composition in heart failure. J Hum Nutr Diet 2014;27:632–8.

98. Heberton GA, Nassif M, Bierhals A, Novak E, LaRue SJ, Lima B, et al. Usefulness of psoas muscle area determined by computed tomography to predict mortality or prolonged length of hospital stay in patients undergoing left ventricular assist device implantation. Am J Cardiol 2016;118:1363–7.

99. Teigen LM, John R, Kuchnia AJ, Nagel EM, Earthman CP, Kealhofer J, et al. Preoperative pectoralis muscle quantity and attenuation by computed tomography are novel and powerful predictors of mortality after left ventricular assist device implantation. Circ Heart Fail 2017;10:e004069.

100. Loncar G, Springer J, Anker M, Doehner W, Lainscak M. Cardiac cachexia: hic et nunc. J Cachexia Sarcopenia Muscle 2016;7:246–60.

101. Kaneko H, Suzuki S, Goto M, Yuzawa Y, Arita T, Yagi N, et al. Geriatric nutritional risk index in hospitalized heart failure patients. Int J Cardiol 2015;181:213–5.

102. Khan RS, Kato TS, Chokshi A, Chew M, Yu S, Wu C, et al. Adipose tissue inflammation and adiponectin resistance in patients with advanced heart failure: correction after ventricular assist device implantation. Circ Heart Fail 2012;5:340–8.

103. Vest AR, Mistak SM, Hachamovitch R, Mountis MM, Moazami N, Young JB. Outcomes for patients with diabetes after continuous-flow left ventricular assist device implantation. J Card Fail 2016;22:789–96.

104. Vest AR, Kennel PJ, Maldonado D, Young JB, Mountis MM, Naka Y, et al. Recovery of serum cholesterol predicts survival after left ventricular assist device implantation. Circ Heart Fail 2016;9:e002881.

105. Ahmad T, Wang T, O'Brien EC, Samsky MD, Pura JA, Lokhnygina Y, et al. Effects of left ventricular assist device support on biomarkers of cardiovascular stress, fibrosis, fluid homeostasis, inflammation, and renal injury. JACC Heart Fail 2015;3:30–9.

106. Emani S, Brewer RJ, John R, Slaughter MS, Lanfear DE, Ravi Y, Sundareswaran KS, et al. Patients with low compared with high body mass index gain more weight after implantation of a continuous-flow left ventricular assist device. J Heart Lung Transplant 2013;32:31–5.

107. Ahmad T, Kelly JP, McGarrah RW, Hellkamp AS, Fiuzat M, Testani JM, et al. Prognostic implications of long-chain acylcarnitines in heart failure and reversibility with mechanical circulatory support. J Am Coll Cardiol 2016;67:291–9.

108. Bonilla-Palomas JL, Gámez-López AL, Castillo-Domínguez JC, Moreno-Conde M, López-Ibáñez MC, Alhambra-Expósito R, et al. Nutritional intervention in malnourished hospitalized patients with heart failure. Arch Med Res 2016;47:535–40.

109. Wu C, Kato TS, Ji R, Zizola C, Brunjes DL, Deng Y, et al. Supplementation of l-alanyl-l-glutamine and fish oil improves body composition and quality of life in patients with chronic heart failure. Circ Heart Fail 2015;8:1077–87.

110. Temel JS, Abernethy AP, Currow DC, Friend J, Duus EM, Yan Y, Fearon KC. Anamorelin in patients with nonsmall-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. Lancet Oncol 2016;17:519–31.

111. Pineda-Juárez JA, Sánchez-Ortiz NA, Castillo-Martinez L, Orea-Tejeda A, Cervantes-Gaytán R, Keirns-Davis C, et al. Changes in body composition in heart failure patients after a resistance exercise program and branched chain amino acid supplementation. Clin Nutr 2016;35:41–7.

112. Giuliano C, Karahalios A, Neil C, Allen J, Levinger I. The effects of resistance training on muscle strength, quality of life and aerobic capacity in patients with chronic heart failure—a meta-analysis. Int J Cardiol 2017;227:413–23.

113. Tzanis G, Philippou A, Karatzanos E, Dimopoulos S, Kaldara E, Nana E, et al. Effects of high-intensity interval exercise training on skeletal myopathy of chronic heart failure. J Card Fail 2017;23:36–46.

114. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, et al. The Physical Activity Guidelines for Americans. JAMA 2018;320:2020–8.

115. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C. Society of Critical Care Medicine; American Society for Parenteral and Enteral Nutrition. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for

Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr 2016;40:159–211.

116. Weimann A, Braga M, Carli F, Higashiguchi T, Hübner M, Klek S, et al. ESPEN guideline: clinical nutrition in surgery. Clin Nutr 2017;36:623–50.

117. Evangelista LS, Heber D, Li Z, Bowerman S, Hamilton MA, Fonarow GC. Reduced body weight and adiposity with a high-protein diet improves functional status, lipid profiles, glycemic control, and quality of life in patients with heart failure: a feasibility study. J Cardiovasc Nurs 2009;24:207–15.

118. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, et al. for the HF-ACTION Investigators. (HF-ACTION=Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training). Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439–50.

119. Horwich TB, Broderick S, Chen L, McCullough PA, Strzelczyk T, Kitzman DW, et al. Relation among body mass index, exercise training, and outcomes in chronic systolic heart failure. Am J Cardiol 2011;108:1754–9.

120. Pritchett AM, Deswal A, Aguilar D, Foreyt JP, Chan W, Mann DL, et al. Lifestyle modification with diet and exercise in obese patients with heart failure—a pilot study. J Obes Weight Loss Ther 2012;2:1–8.

121. Ritzel A, Otto F, Bell M, Sabin G, Wieneke H. Impact of lifestyle modification on left ventricular function and cardiopulmonary exercise capacity in patients with heart failure with normal ejection fraction and cardiometabolic syndrome: a prospective interventional study. Acta Cardiol 2015;70: 43–50.

122. Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, Kraus WE, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 2016; 315:36–46.

123. González-Islas D, Orea-Tejeda A, Castillo-Martinez L, Olvera-Mayorga G, Rodríguez-García WD, Santillán-Díaz C, et al. The effects of a low-carbohydrate diet on oxygen saturation in heart failure patients: a randomized controlled clinical trial. Nutr Hosp 2017;34:792–8.