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Nutrition, Obesity and Cachexia in Patients with Heart Failure: A Consensus Statement from the HFSA Scientific Statements Committee

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Highlights:

- Patients with heart failure should be offered at least one session from a RDN, or other health professional with specialist nutrition knowledge, for nutritional evaluation and education
- DASH or Mediterranean dietary patterns both appear reasonable to recommend for normal-weight patients at risk of heart failure or with established heart failure
- At least 5-10% weight loss is recommended for patients with heart failure and BMI ≥ 35 kg/m²
- For patients identified with malnutrition or cachexia, a goal protein intake of at least 1.1 g/kg/day is reasonable

**Nutrition, Obesity and Cachexia in Patients with Heart Failure: A Consensus Statement
from the HFSA 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 dietary counselling 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, 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 due to an obesity survival paradox. Dietary interventions and pharmacologic weight loss therapies are under-studied 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 proposed.

Abbreviations and Acronyms

ACC, American College of Cardiology

AHA, American Heart Association

AND, Academy of Nutrition and Dietetics

ASPEN, American Society for Parenteral and Enteral Nutrition

BMI, body mass index

CASCO, CAchexia SCOr

CAD, coronary artery disease

CKD, chronic kidney disease

CI, confidence interval

CMS, Centers for Medicare and Medicaid Services

CONUT, controlling nutritional status

CoQ10, coenzyme Q10

DASH, dietary approaches to stop hypertension

DM, diabetes mellitus

DXA, dual-energy X-ray absorptiometry

ESC, European Society of Cardiology

ESPEN, European Society for Clinical Nutrition and Metabolism

FFM, fat-free mass

GLP-1, glucagon-like peptide-1

HF, heart failure

HFpEF, heart failure with preserved ejection fraction

HFrEF, heart failure with reduced ejection fraction

HFSA, Heart Failure Society of America

IV, intravenous

LV, left ventricle

LVEF, left ventricular ejection fraction

MNA, Mini-Nutritional Assessment

MUST, Malnutrition Universal Screening Tool

NT-proBNP, N-terminal pro-B-type natriuretic peptide

NUTRIC, Nutrition Risk in the Critically Ill

NYHA, New York Heart Association

PNI, prognostic nutritional index

QoL, quality of life

RDN, registered dietitian nutritionist

REE, resting energy expenditure

SGA, Subjective Global Assessment

SNAQ, Short Nutritional Assessment Questionnaire

VLCD, very low calorie diet

VO₂, oxygen consumption

Introduction

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 Amongst 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 is little 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, this 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 gram/day sodium intake for most patients with HF and < 2 L/day 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 (IV) iron replacement in patients with New York Heart Association (NYHA) 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 due to the lack of efficacy data, concerns about supplement purity and regulation, and the potential for pharmacological interactions, though n-3 polyunsaturated fatty acids (PUFAs) 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) only cover RDN services for patients with type 1 or 2 DM, CKD or a renal transplant within the prior 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 healthcare professionals develop expertise in clinical nutrition to improve patient access to dietary

counselling (Figure 1). Using appropriate billing codes to document malnutrition may help 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/day sodium intake for a week resulted in a significant reduction in caloric ($2,467 \pm 748$ to $1,931 \pm 388$ kcal/day, $p=0.016$), 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 chronic kidney disease (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 (e.g. glomerular filtration rate <25 mL/min per 1.73 m²).¹¹ The DASH diet has the advantages of limiting sodium intake, being rich in plant-based foods and anti-oxidants, and decreasing dietary confusion because it is compatible with comorbid DM or CKD. Small clinical trials in patients with 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 post-menopausal 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 towards 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 upon the diagnostic tool used, ranging from 8% using the prognostic nutritional index (PNI) to 54% using 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 (MUST), Mini-Nutritional Assessment (MNA), Nutrition Risk in the Critically Ill (NUTRIC) score, and Subjective Global Assessment (SGA). None are 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, and also 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/day. Results from a 57-patient nitrogen balance study in non-obese patients with HF,

as compared to 49 controls, suggested a higher protein goal of 1.1 g/kg or greater may be necessary,¹⁹ consistent with recommendations from the Academy of Nutrition and Dietetics (AND)⁶ for patients with any stage of HF, and also 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, specifically 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 greater in middle and older-aged 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, K, and folate (Supplemental Table S2)²⁴, although evidence that these cause clinically-relevant deficiencies is currently sparse.²⁵⁻²⁷ Amongst 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=0.0065).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 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 upon initiation or dose changes of renin-angiotensin-aldosterone

system antagonists due to the potential for hyperkalemia, and of loop/thiazide diuretics due to the potential for hypokalemia and hypomagnesemia. Patients with elevated serum potassium should observe a low-potassium diet as part of a multi-component 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 avocado, spinach, potatoes, tomatoes, beans and fruits (e.g. bananas) for potassium, and many vegetables and nuts – specifically pumpkin seeds – for magnesium.

Micronutrient Supplementation in Heart Failure

Micronutrient supplementation may either be provided 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 due to broader anti-oxidant and anti-inflammatory 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. Intravenous, but not oral, iron supplementation is now an established intervention for correcting iron deficiency (ferritin <100 ng/mL or 100 to 300 ng/mL if transferrin saturation <20%) and improving HF functional status and QoL. Although the clinical trials were conducted in HFrEF, the ACC/AHA/HFSA recommendation for IV iron repletion does not specify an ejection fraction criterion.⁵ There has been a long-standing concern that high-dose diuretics may encourage thiamine (vitamin B1) deficiency, because of its water solubility and poor reabsorption during renal depletion of hydrogen ions with diuresis, although definitive evidence is lacking.²⁹ In a 9-study meta-

analysis, low thiamine levels were more common in patients with HF than controls; some small (less than 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 (CoQ10) doses ranging 60-300 mg/day have been studied in HF, with some small trials suggesting improvements in NYHA class, LVEF, exercise capacity, QoL and even mortality, although others have been neutral.³⁰ Q-SYMBIO was a randomized controlled trial of CoQ10 300 mg/day in NYHA III-IV HFrEF/HFpEF (n=420), powered to address major clinical endpoints.³¹ There were no changes in NYHA class, 6-minute walk test or NT-proBNP at 16 weeks. However, the incidence of the primary composite endpoint of major adverse cardiovascular events at 2 years was significantly reduced by CoQ10 supplementation (hazard ratio 0.50, 95% CI 0.32-0.80, p=0.003). Despite these findings, concerns about slow recruitment in this trial that 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 one evaluation and counseling session as an outpatient or inpatient from a registered dietitian nutritionist (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 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 is lacking, the DASH diet or the Mediterranean diet 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 protein intake per kg actual body weight per day to prevent cachexia, and at least 1.1 g/kg/day is reasonable if malnutrition or cachexia is present (as per the PROT-AGE and Academy of Nutrition and Dietetics recommendations)
- Other than 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, adequately powered, distinguish between HFrEF and HFpEF, of sufficient duration and use clinically relevant HF endpoints

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/m².³² The dose-response relationship between BMI and incident HF appears stronger for heart failure with preserved ejection fraction (HFpEF) than heart failure with reduced ejection fraction (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 co-morbidities 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 left ventricular (LV) mass independent of 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 impact 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 stand to benefit the most.⁴² Food intake rich in whole grains, 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 Furthermore 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/m² showed a non-significant trend towards 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} however a 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, for example with high-protein shakes, may help support short- and medium-term weight loss.⁵² Cardiovascular obesity management guidelines recommend a 1200-1500 kcal/day diet for women or 1500-1800 kcal/day for men without endorsing any specific dietary strategies, but do recommend a personalized approach and professional nutrition counselling.⁴⁰

Weight loss pharmacotherapy is indicated when lifestyle modifications alone are unsuccessful, with BMI ≥ 30 kg/m² or ≥ 27 kg/m² and one or more obesity-associated comorbidities; if $< 5\%$ weight loss at 3 months, an alternate therapy should be sought.⁵³ Orlistat and lorcaserin are associated with modest reductions in blood pressures, but also only modest weight reductions, whereas greater weight loss efficacy is seen with the combination medications (Table 3). Liraglutide is specifically approved for weight loss at the 3mg dose,⁵⁴ with good efficacy. A reduction in major adverse cardiovascular events was observed in the DM population using 1.8 mg liraglutide, although the HF endpoint 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, as opposed to 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
- A target weight loss of at least 5-10% is recommended for individuals with BMI ≥ 25 kg/m²
- Weight loss diets: No specific diet recommended, but counselling with a RDN is advised; it is usual to recommend a negative energy balance of 500-750 kcal/day or absolute intake of 1200-1500 kcal/day diet for women and 1500-1800 kcal/day for men, targeting 1-2 lbs loss per week
- Weight loss pharmacotherapy: There is currently no data demonstrating HF prevention with weight loss pharmacotherapy for patients with BMI ≥ 30 kg/m² or ≥ 27 kg/m² with 1+ obesity-associated comorbidities, but liraglutide 3 mg daily is an attractive option given the weight loss efficacy and prevention of other cardiovascular events
- Weight loss surgery: For patients with BMI ≥ 40 kg/m², BMI ≥ 35 kg/m² and 1+ obesity-related comorbidities, or BMI ≥ 30 kg/m² 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 at least 50% of patients who are classified as obese by BMI criteria (≥ 30 kg/m²).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 distinguish central versus peripheral obesity.

Patients with obesity have lower levels of circulating natriuretic peptides than normal-weight patients with comparable 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/m², versus 110 pg/mL for BMI 25-34.9 kg/m², and 170 pg/mL for BMI < 25 kg/m², to achieve 90% sensitivity for the diagnosis of HF.⁶⁷ The prognostic power of NT-proBNP in chronic HF appears consistent between 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 HF observational studies concluded that an obesity survival paradox was present in both those with HFrEF and HFpEF.⁷⁰ It has been suggested that the obesity paradox is a statistical aberration due to residual confounding or presentation of patients 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 theoretical 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 $>35 \text{ kg/m}^2$ as a contraindication to transplantation.⁷³

Weight Loss for Heart Failure Management

Small clinical trials of diet and/or 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). Since 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 (e.g. BMI $\geq 35 \text{ kg/m}^2$). However weight loss may be especially challenging for patients and caregivers already managing chronic HF. The ability to exercise may be limited due to 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 counselling with a RDN is advised to target 1200-1500 kcal/day for women and 1500-1800 kcal/day for men, aiming at 1-2 lbs loss per week.⁴⁰ Ketogenic and very-low calorie diets (VLCD) 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 gastrointestinal adverse effects and could provoke a ketoacidosis crisis with comorbid DM; VLCDs provide ≤ 800 kcal/day, but 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 pharmacological 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 is relatively low compared to other approved medications and gastrointestinal intolerance is common. Many anorectic drugs have theoretical concerns in HF (Supplemental Table S4), although the risks associated with small increases in heart rate for drugs such as phentermine/extended release topiramate (on average 1-2 bpm) 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 and therefore caution is recommended in this population.⁷⁸ Despite theoretical concerns, the recent lorcaserin cardiovascular safety study reported no excess of cardiovascular or HF events, compared to placebo, in a population with obesity and cardiovascular disease or risk factors, although NYHA class III-IV HF or LVEF $< 20\%$ were exclusion criteria.⁵⁶ The naltrexone/bupropion cardiovascular safety study only excluded NYHA class IV HF patients, but 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 liraglutide 1.8 mg/day as a therapy for advanced systolic HF, there was a

non-significant trend towards more HF hospitalizations and mortality with liraglutide, compared to placebo.⁸⁰ HF clinicians should also review the full medication list when counseling patients with 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 to a large cohort without known systolic dysfunction (n=2588), demonstrated good weight loss efficacy and comparable 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, as compared to pre-bariatric surgery.⁸² In case reports, during an average 20-month follow-up amongst 137 HFrEF bariatric surgery recipients, LV ejection fraction increased from 32% to 42% (weighted means).⁸¹ Successful bariatric surgery has also been reported 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 non-surgical obesity management will be essential in guiding future clinical practice.

Recommendations for Obesity in HF Management:

- A target weight loss of at least 5-10% is recommended for individuals with BMI ≥ 35 kg/m² using a combination of approaches including physical activity if HF symptoms permit
- Weight loss diets: No specific diet recommended, but counselling with a RDN is advised; it is usual to recommend a negative energy balance of 500-750 kcal/day or absolute intake of

1200-1500 kcal/day diet for women and 1500-1800 kcal/day for men, targeting 1-2 lbs loss per week

- Weight loss pharmacotherapy: For patients with HF and obesity meeting standard indications, weight loss pharmacotherapies have theoretical benefits, particularly for HFpEF patients, but there is an absence of efficacy and safety data for these drugs in HF and hence they must be used with caution and close monitoring
- Weight loss surgery: In select patients with BMI ≥ 35 kg/m² and NYHA class II-III HF with or without an LVAD, whose eligibility for cardiac transplantation is dependent upon weight loss, bariatric surgery can be considered within an experienced multi-disciplinary 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 intensive lifestyle interventions, pharmacotherapy and bariatric surgery in patients with both HFrEF and HFpEF are urgently needed to define best practice

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 (e.g. 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 towards 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% amongst 200 patients, based on dual X-ray absorptiometry (DXA) body composition criteria,⁸⁵ and 47% amongst 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 displayed in Supplemental Table S6. Lower BMI (e.g. ≤ 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 (e.g. the CACHexia SCORe, CASCO) and limited validation of

body composition assessment methods such as DXA in patients with expanded extracellular water (ECW) 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 Computed tomography or magnetic resonance imaging 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 preoperatively.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 pharmacological interventions can correct cachexia or sarcopenia in HF. It is possible that simply augmenting protein-calorie intake, for example 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. This 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 of care.¹⁰⁸ The intervention was delivered by a physician and a RDN and involved monthly nutrition outpatient visits. At 12 months, the primary composite endpoint of death or readmission for worsening HF occurred in 27% of the intervention group versus 61% of controls (hazard ratio 0.45, 95% CI 0.19-0.62, $p=0.0004$). Clinical trials that validate similar malnutrition interventions as the PICNIC study in other HF populations will be necessary to formulate future clinical recommendations.

Successful cardiac cachexia therapies will likely be multi-dimensional and include anti-inflammatory and anabolic components, in addition to caloric substrate (Figure 2, Supplemental Table S7). Along these lines, a small clinical trial randomized 31 patients with HFrEF to 1-alanyl-1-glutamine (8 g/day) plus polyunsaturated fatty acid (6.5 g/day) versus placebo for 3 months.¹⁰⁹ Fat free mass (FFM) increased (54.4 ± 3.2 to 56.1 ± 2.5 kg, $p=0.04$), 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, which in addition to being the main human hunger signal also has anti-inflammatory 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 due to the clinically marginal effect on FFM and the absence of an impact on handgrip strength or QoL.

Select 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' 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/day 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 (so long as this is consistent with the patient's goals of care), or if a 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 peri-operative patients offer potentially useful guidance (Table 6). Of note, the 2017 European Society for Clinical Nutrition and Metabolism (ESPEN) 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, due to 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 prior 6-12 months or BMI $<20 \text{ kg/m}^2$, with evidence of sarcopenia, wasting or abnormal biochemistry
- Patients who meet cachexia criteria, or who screen in with elevated nutritional risk based on a validated malnutrition screening tool, should receive RDN consultation (Figure 1)
- Sarcopenia screening using the 5-item SARC-F questionnaire (score ≥ 4), gait speed ($\leq 0.8 \text{ m/s}$) or handgrip strength ($<27 \text{ kg}$ in men, $<16 \text{ kg}$ 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 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 at least 1.1 g/kg/day is reasonable (as per the 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 as per guidelines in Table 6; in the absence of prospective data, consensus pre-operative nutritional targets may include albumin $\geq 3.0 \text{ g/dL}$, pre-albumin $\geq 16 \text{ g/dL}$, BMI $\geq 18.5\text{-}20 \text{ kg/m}^2$, and an iron replete state (e.g. iron saturation $\geq 20\%$ and ferritin $\geq 300 \text{ ng/ml}$)

- Mirtazapine, megestrol acetate, dronabinol and n-3 polyunsaturated fatty acids can be considered for anorectic patients within the limitations of their adverse effect profiles (Table 5)
- Clinical trials are required to evaluate the candidate nutritional and pharmacological interventions for reversal of cachexia and sarcopenia in HFrEF and HFpEF; study endpoints should include physical function and QoL in addition to muscle mass gains

Conclusions and Future Research Priorities

Each of the four 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 HF to cachexia, have hampered the development of effective interventions to disrupt these 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 HF clinical investigation moving forwards. 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 is also 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 exists 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 pharmacological therapies on the horizon, nutritional interventions hold the potential to significantly improve clinical outcomes for thousands of patients with HF within the coming decade.

Tables:**Table 1: Summary of Heart Failure Nutritional Recommendations from Society Guidelines**

	HFSA 2010²	ACC/AHA 2013³, ACC/AHA/HFSA 2017⁵	ESC 2016⁴	AND 2017⁶
Sodium	2-3 g/day (or < 2 g if refractory hypervolemia) <i>strength of evidence=C</i>	<3 g/day (class IIa) <i>strength of evidence=C</i>	Avoid excessive salt intake (>6 g/day), without a specific recommendation	2-3 g/day <i>strength of evidence=Fair</i>
Fluid	<2 L/day for serum sodium < 130 mEq/L or diuretic resistance <i>strength of evidence=C</i>	1.5-2 L/day in stage D HF, especially with hyponatremia (class IIa) <i>strength of evidence=C</i>	1.5-2 L/day may be considered in patients with severe HF, without a specific recommendation	1-2 L day <i>strength of evidence=Fair</i>
Energy	No specific recommendation	No specific recommendation	No specific recommendation	Recommend 22 kcal/kg actual bodyweight nourished, or 24 kcal/kg malnourished, or base upon REE <i>strength of evidence=Fair</i>
Protein	No specific recommendation	No specific recommendation	No specific recommendation	Individualized, but at least 1.1 g/kg <i>strength of evidence=Fair</i>
Folate Vitamin B6 Vitamin B12 supplements	Consider daily multivitamin-mineral supplementation for those of diuretic therapy and restricted diets <i>strength of evidence=C</i>	Not recommended	NA	Not recommended for routine care <i>strength of evidence=Weak</i>
Thiamine supplements		Not recommended	NA	Not recommended for routine care <i>strength of evidence=Weak</i>
Vitamin D supplements		Not recommended	NA	Not recommended for routine care <i>strength of evidence=Weak</i>
Nutritional supplements		Not recommended (class III) <i>strength of evidence=B</i>	NA	Not recommended for routine care <i>strength of evidence=Weak</i>

Iron	Intravenous iron can be considered for documented deficiency	2017 update: Intravenous iron reasonable in NYHA class 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 to 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 class II-IV strength of evidence=B	Reasonable as adjuvant therapy for HFrEF or HFpEF NYHA class 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 are not recommended strength of evidence=C	No recommendations; importance as a component of advanced HF emphasized	No specific recommendations	Provide at least 1.1 g/day 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/m ² , 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; BMI, body mass index; HFSA, Heart Failure Society of America; AND, Academy of Nutrition and Dietetics; NA, not addressed; REE, resting energy expenditure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction

Table 2: Suggestions for heart failure clinicians when screening for nutritional inadequacies and deficiencies

	Metrics	Tools and resources	Macro-nutrients	Micro-nutrients
History	medical history and disease chronicity can indicate the likelihood of malnutrition and inflammation	<p>identify malabsorption history: prior 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</p> <p>dental health</p> <p>history of aspiration events</p> <p>history of diabetes and gastroparesis</p> <p>medication history including allergies, herbals and other supplements</p> <p>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</p>	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	<p>wasting of subcutaneous fat and/or skeletal muscle</p> <p>physical signs specific to micronutrient deficiencies</p>	<p>Table 3 in Esper DH. Utilization of nutrition-focused physical assessment in identifying micronutrient deficiencies. <i>Nutr Clin Pract.</i> 2015;30:194–202</p> <p><i>nutrition examination training workshops:</i> https://www.eatrightpro.org/practice/professional-development/face-to-face-learning/nfpe-workshop</p>	<p>cachexia: loss of subcutaneous fat in orbital, triceps regions and overlying the ribs</p> <p>cachexia/sarcopenia: loss of temporalis, pectoralis, deltoids, interosseous muscles, latissimus dorsi, trapezius, quadriceps, gastrocnemius muscle mass</p> <p>Muehrcke lines in nails suggest</p>	nail, hair and skin changes characteristic of: vitamins A, B (any), C, K, zinc, or iron deficiencies

			hypoalbuminemia, alopecia associated with protein deficiency and scaling of scalp with essential fatty acid deficiency	
Anthropometric data	body mass index: weight, kg / (height, 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	
	percent weight change: ((usual weight – current weight) / usual weight) x 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, GNRI – using albumin, weight, height: http://touchcalc.com/calculators/gnri a simple tool with some data for prognostic utility in HF cohorts (Kaneke 2015) <i>controlling nutritional status, CONUT nutrition risk in the critically ill, NUTRIC prognostic nutritional index, PNI less established in HF cohorts</i> 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. <i>JACC Heart Fail.</i> 2018;6:476–486.	albumin and pre-albumin: these biomarkers have prognostic utility in HF, but although related to nutritional status, but there is insufficient evidence they change in response nutritional interventions C-reactive protein (CRP) or neutrophil-lymphocyte ratio (NLR) for inflammatory	hemoglobin, % iron saturation and ferritin to screen for IV iron eligibility United States Preventive Services Task force recommends against screening for vitamin D deficiency

			state assessment	y in asymptomatic adults
Dietary assessment	nutritional risk assessment tools	<p>short nutritional assessment questionnaire, SNAQ: http://www.fightmalnutrition.eu/wp-content/uploads/2017/04/SNAQ_Engels.jpg</p> <p>quick screening tool incorporating weight change, appetite and supplementation, unlike MUST and MNA does not incorporate medical diagnoses or inpatient status</p> <p><i>malnutrition universal screening tool, MUST:</i> https://www.bapen.org.uk/screening-and-must/must-calculator</p> <p><i>mini nutritional assessment, MNA:</i> https://www.mna-elderly.com/mna_forms.html</p>		
	assessment of dietary intake	<p>patient dietary intake self-collection and analysis can be performed on a mobile-health application such as MyFitnessPal for food record</p> <p><i>predominantly research tools:</i> <i>inpatient nutrient intake analysis</i> <i>daily food record or diary (typically at least 3-4 days)</i> <i>food frequency questionnaire</i> https://sharedresources.fredhutch.org/content/ffq-sample-booklets <i>24-hour recall</i> https://epi.grants.cancer.gov/asa24/</p>	consult Institute of Medicine macronutrient (total calories, protein, carbohydrates and fat) and micronutrient reference intakes for adequacy: http://www.fightmalnutrition.eu/wp-content/uploads/2017/04/SNAQ_Engels.jpg	
Functional assessment	handgrip strength	<p>handgrip thresholds <27 kg males, <16 kg females (European Working Group on Sarcopenia in Older People 2, see Supplemental Table S6)</p> <p><i>subjective global assessment, SGA – weight change, intake change, gastrointestinal symptoms, functional status, metabolic demand, physical examination</i></p>	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	
<p>This list is not exhaustive, but summarizes the most clinically useful tools for clinicians Recommended resources are in standard type, <i>additional resources in italics</i></p>				

Table 3: Weight loss medications and considerations for use in heart failure

Medication (FDA Approval) Mechanism	1-yr placebo- adjusted weight loss	Potential benefits in heart failure prevention or management	Potential risks in heart failure
Orlistat (1999) Gastrointestinal lipase inhibitor, decreased fat absorption	-2.5kg with 60 mg -3.4kg 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	-3.2kg	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	-3.6kg		Potential for heart rate and blood pressure elevations Considered to be contraindicated in patients with heart disease, including HF, as well as with arrhythmias, CAD and uncontrolled hypertension Associated with primary pulmonary hypertension, regurgitant cardiac valvular disease, palpitations/tachyarrhythmias

Phentermine/ topiramate extended release (2012) Amine anorectic + possible increased GABA activity	-6.7kg with 7.5/46 mg -8.9kg 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	-6.2kg	Minor improvements in blood glucose for patients with diabetes	Minor increases in blood pressure and heart rate Potential association with palpitations/ tachyarrhythmias
Liraglutide 3mg (2014) GLP-1 agonist	-6.2kg -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 drug adverse effects and study references			

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 class II-III and BMI >27 kg/m ² with non-insulin treated type 2 DM	12 weeks 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<0.001)	All 3 groups had significant improvements in hemoglobin A _{1c} and QoL. Between-group differences in percent body fat, 6MWT, peak VO ₂ , 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/m ²	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 mortality 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=0.71)	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	58% achieved ≥2% weight loss	≥2% weight loss associated with improved peak VO ₂ , NYHA class and

		control group)		freedom from hospitalization
Kitzman et al. 2016 ¹²²	100, HFpEF >60 years, with BMI >30 kg/m ²	Randomized 2x2 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<0.001; diet, -7 kg, 95% CI, -9 to -5), p<0.001 Best weight loss in exercise + diet group of 11kg (10% loss)	Peak VO ₂ was increased significantly by both interventions: exercise, 1.2 mL/kg/min, 95% CI 0.7 to 1.7, p<0.001; diet, 1.3 mL/kg/min, 95% CI 0.8 to 1.8, p<0.001 Combination of exercise + diet was additive for peak VO ₂ (joint effect, 2.5 mL/kg/min). With diet main effect analysis, left ventricular mass -4g, 95% CI -7 to 0, p=0.03 With diet + exercise, NYHA class improved (main effect: exercise, -0.4 class, 95% CI -0.6 to -0.2, p<0.001; diet, -0.4 class, 95% CI -0.5 to -0.2, p=0.001)
González-Islas et al. 2017 ¹²³	88, HF NYHA class 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

Abbreviations: BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; QoL, quality of life, VO₂, oxygen consumption

Table 5: Appetite simulants and their suitability in heart failure

	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 – 30mg 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 mg – 800mg 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 2.5mg bid – 5mg bid	Drowsiness (3-10%), tachycardia (>1%), hypotension (<1%), orthostatic hypotension (<1%), confusion (>1%), lowers seizure threshold (<1%)
	Fish oils (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		

Abbreviations: AIDS, acquired immunodeficiency syndrome; HF, heart failure

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

Remeron [package insert]. Kenilworth, NJ: N.V. Organon; 2009.

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

Marinol [package insert]. North Chicago, IL: AbbVie Inc; 2017.

Lovaza [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2015.

Table 6: Society recommendations for nutrition support therapy in critically ill and peri-operative heart failure patients

Key recommendations for nutrition support therapy in the adult critically ill patient	Key recommendations for nutrition support therapy in peri-operative 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 indirect calorimetry if available)	ESPEN guidelines recommend against routine pre-operative fasting in patients at standard risk of aspiration, instead advising solids until 6 hours pre- and clear fluids until 2 hours pre-anesthesia
Initiate enteral nutrition (EN) within 24-48 hours of ICU admission and advance to goal over the first week to provide 25-30 kcal/kg/day	An 800ml carbohydrate drink is recommended on the evening pre-anesthesia and 400mls 2 hours pre-anesthesia are 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 prior to major surgery for 7-14 days 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 less than 50% of energy requirements are met for more than 7 days
Consider immune-modulating formulae containing both arginine and fish oil for post-operative patients requiring EN	Consider immune-modulating formulae (arginine, fish oil) for malnourished peri- or post-operative patients undergoing major cancer surgery
Source: 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). Journal of Parenteral and Enteral Nutrition 2016;40:159–211 ¹¹⁵	Source: Weimann A, Braga M, Carli F, Higashiguchi T, Hübner M, Klek S, et al. ESPEN guideline: Clinical nutrition in surgery. Clinical Nutrition 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/day) versus standard (0.8 g/kg/day) protein diet associated with better preservation of muscle mass and functional status? Is the DASH versus Mediterranean versus standard diet associated with freedom from HF hospitalizations and mortality?	Randomized clinical trials, with HFrEF and HFpEF subgroups represented Study duration will be limited by feasibility of research diet implantation, but a minimum of 3-4 months intervention is likely required for impact on clinically-relevant endpoints	Logistics and funding are challenging for prospective dietary studies; will 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 gold standard malnutrition diagnostic criteria
Dietary interventions for weight loss	Is a low carbohydrate diet or 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; will likely require collaboration with nutrition companies to supply complete research diets
Pharmacological interventions for weight loss	Is liraglutide 3 mg or phentermine/topiramate most safe and effective in achieving weight loss for patients with HFpEF?	Randomized clinical trial, potentially also cardiovascular events outcomes endpoint also	Collaboration with pharmaceutical companies for funding

Bariatric surgery for weight loss	Is bariatric surgery effective and safe for patients with BMI ≥ 40 kg/m ² versus intensive lifestyle intervention	Randomized clinical trial, with HFrEF and HFpEF subgroups represented Additional myocardial structure and function endpoints	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 anti-inflammatory)? Are diets that are higher in fats or protein, compared to current diet guidance for patients with cardiac disease, safe and effective for weight regain? Are pro-anabolic therapies, e.g. ghrelin agonism or oxandrolone, effective in effective in promoting skeletal muscle mass? Are mirtazapine, megestrol 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

Figures:**Figure 1: A proposed pathway for nutritional evaluation and counseling for patients with heart failure**

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 an RDN or another health professional with specialist nutrition knowledge, such as a nurse, advanced practice provider or physician.

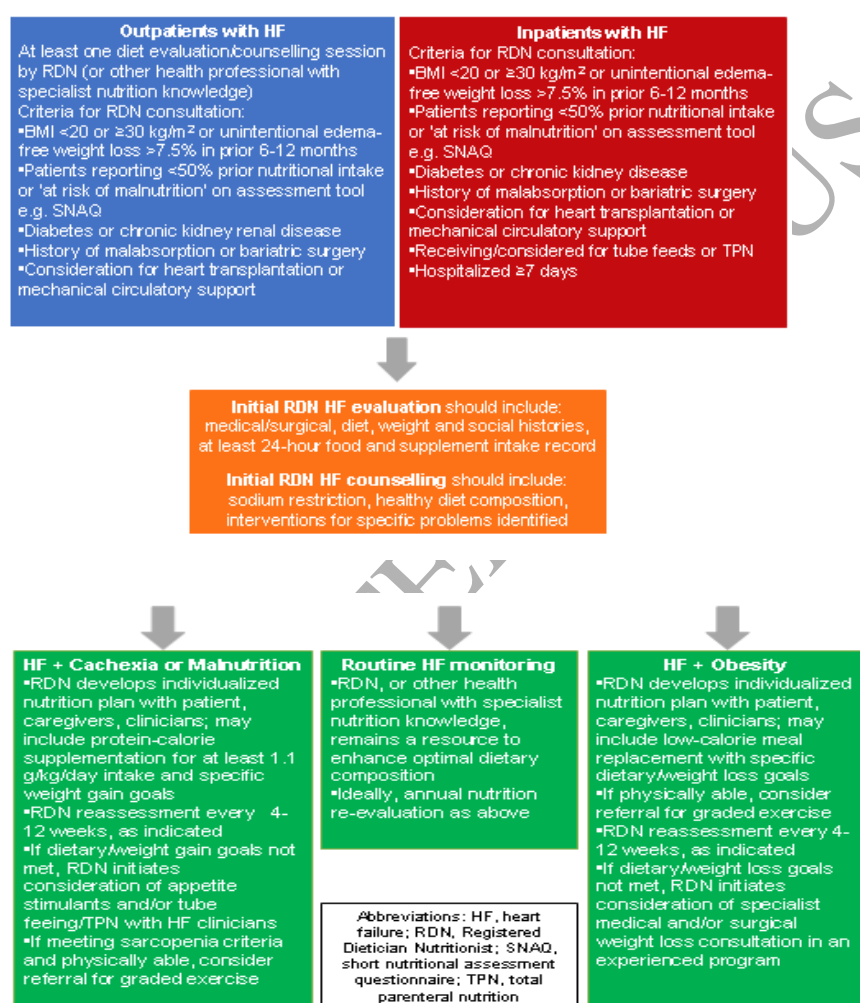
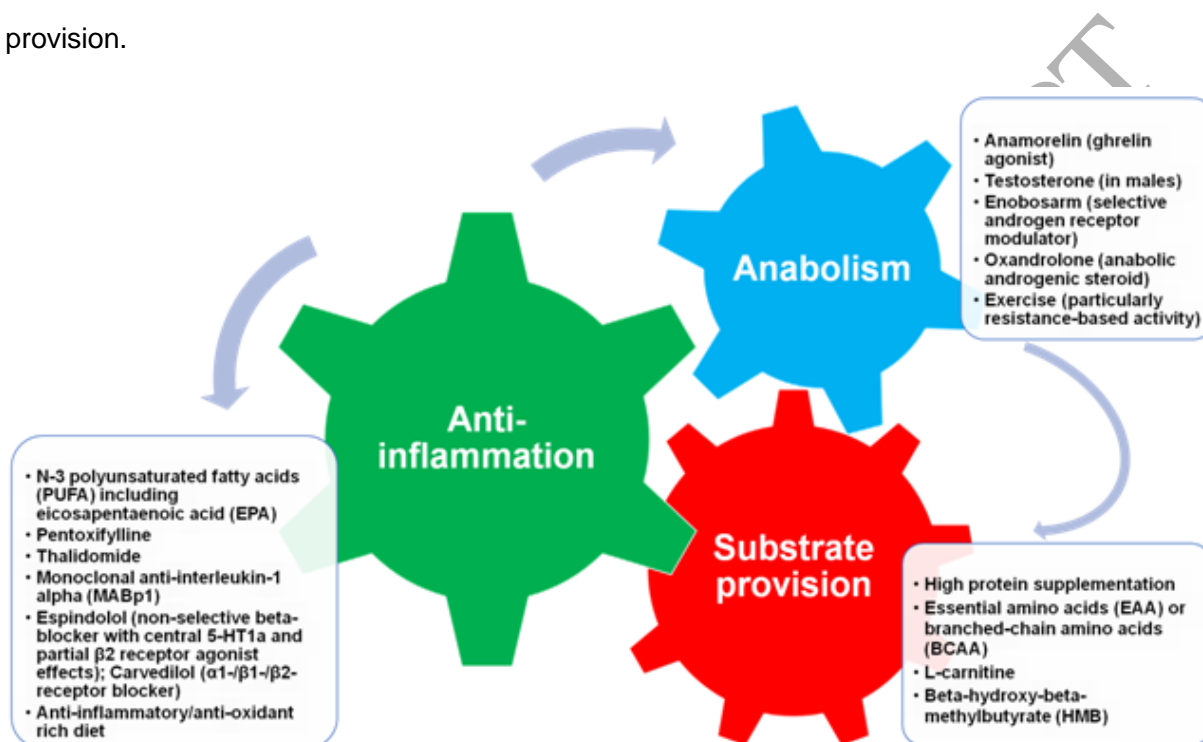


Figure 2: Candidate interventions for patients with chronic heart failure and cachexia or sarcopenia (see Supplemental Table S7 for reference list)

Reversal of cardiac cachexia or sarcopenia is likely to require a multi-dimensional approach with components including anti-inflammatory and pro-anabolic interventions in addition to substrate provision.



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