

Nutrition and Heart Failure: Impact of Drug Therapies and Management Strategies

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Nutrition impairment commonly occurs in patients with heart failure and affects disease progression. Vitamin and mineral deficiencies are associated with early mortality, particularly in patients classified as cachectic. Guideline-based therapies approved for heart failure, such as loop diuretics, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, aldosterone antagonists, and β -adrenergic blockers, can lead to electrolyte abnormalities and predispose to some vitamin and micronutrient deficits. Clinical trial evidence in support of supplementary vitamin and mineral therapies for heart failure patients is limited with

the exception of documented calcium and possibly vitamin D, thiamine, and coenzyme Q₁₀ deficiencies. This area is gaining significant attention, and research is ongoing. The clinician can help minimize morbidity from nutrition impairment through appropriate monitoring and correction of baseline and medication-induced electrolyte imbalances, in addition to vitamin and mineral supplementation when appropriate. (*Nutr Clin Pract.* 2009;24:60-75)

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General Issues

Heart failure (HF) has emerged as a disease with significant public health implications. There are more than 5 million individuals with HF in the United States, and more than 600,000 new cases are diagnosed annually.¹ These patients generate 12–15 million office visits for HF each year; more than 280,000 patients die of HF each year.² Despite improved availability of sophisticated diagnostic techniques and use of modern therapies, the risk of death within 5 years of diagnosis is > 50%.² Among the risk factors for mortality in

chronic HF is nutrition impairment, which predicts early death in patients of all ages with HF.³

Independently living patients with HF require similar total daily calories to those of age-matched healthy control individuals, despite decreases in both total body and lean body mass in the HF group.⁴ However, some investigators report an increase in resting energy expenditure among those with severe HF due to elevated resting peripheral oxygen consumption and increased cardiac and ventilatory work.⁴⁻⁷ Drug therapy in patients with HF creates multiple nutrition issues that are problematic. As numerous medications are associated with a variety of adverse effects, it is typically reasonable to treat the underlying cause in a symptomatic patient and discontinue the offending agent. However, many of the medications used for HF either alleviate symptoms or strongly affect disease progression and HF-related mortality, and it would therefore not be desirable to discontinue the causative medication.

Remarkably, apart from the fact that a high-sodium diet is detrimental, little is known about specific consequences of nutrient deficiencies or long-term outcomes of dietary supplementation. This review summarizes drug- and disease-specific nutrition issues, evidence for available treatment modalities, and strategies for the clinician treating HF patients with nutrition impairments.

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Malnutrition and HF

Excessive salt and fluid intakes are important factors that worsen HF symptoms, leading to acute HF and hospitalizations. Deficiencies of vitamins and micronutrients also play an important role in the pathophysiology of this syndrome.⁸ The frequency of malnutrition varies according to HF severity, ranging from 22% in New York Heart Association (NYHA) functional class II to 63% in class III.⁹ The impact of malnutrition was examined in a follow-up study of approximately 230 older adults admitted to an emergency department for various medical problems including HF. Mortality rates for the 41 malnourished patients was 44%, compared with 18% in 164 nonmalnourished patients ($P < .001$). Of note, the majority of malnourished patients concomitantly had HF.¹⁰ Other investigators studied the impact of cachexia on mortality in 171 HF patients. Cachectic participants exhibited 29% mortality at 6 months, 39% at 12 months, and 50% at 18 months. The cachectic state predicted 18-month mortality independent of age, NYHA class, left ventricular ejection fraction (EF), and peak oxygen consumption.³

The pathophysiology of HF exerts direct effects on metabolism and intestinal function. These include intestinal ischemia and inflammation, hypercatabolism, nutrition malabsorption, and anorexia.¹¹ Increased sympathetic nervous system (SNS) activity in HF patients causes vasoconstriction of splanchnic circulation^{12,13} and creates hypoxia and ischemia of the gut mucosa, which leads to impaired epithelial function and increased mucosal permeability.¹⁴ Intestinal ischemia is quantified by elevated intestinal pCO_2 and reduced intestinal pH, and may contribute to the inflammatory nature of HF pathophysiology.¹⁵ Reduced mucosal perfusion diminishes the mucus barrier that isolates epithelial cells from intestinal flora.¹⁶ Compromised by diminished protective mucus, reduced host immune function, and increased permeability, the ischemic mucosa is a prime target for bacterial translocation into the splanchnic lymphatic system.¹³ Bacterial translocation increases exposure to lipopolysaccharide endotoxin, which in turn stimulates macrophage release of inflammatory cytokines (eg, tumor necrosis factor [TNF]- α) and further SNS activation.^{13,16,17} Intestinal mucosal ischemia and inflammation may further contribute to the development of anorexia, malabsorption, and cardiac cachexia in HF patients.^{18,19}

Hypercatabolism stems from activation of catabolic factors such as norepinephrine, epinephrine, and inflammatory cytokines, which also worsen overall disease progression in HF.¹¹ Moreover, reduced concentrations of the anabolic hormone dehydroepiandrosterone sulfate in HF lend support to the link between malnutrition in cardiovascular disease and alterations in anabolic-catabolic balance.²⁰ The failing heart releases cytokines such as TNF- α , which exert exocrine and endocrine effects and cause significantly altered body composition including reduced lean body mass, bone mass, and fat content.²¹

Altered gut absorption can also affect nutrition deficiencies in patients with HF. Reduced gut circulation and disturbed microcirculation in HF contribute to local edema of the gastrointestinal (GI) tract. Gut edema causes GI malabsorption and impairs adequate nutrition. Fat absorption is particularly affected, leading to potential deficiencies in fat-soluble vitamins.^{22,23} Protein loss also occurs, contributing to development of cardiac cachexia.²⁴

Anorexia may develop in HF patients secondary to nausea from gut edema or as an adverse effect from medications, early satiety from hepatic edema, or depressive symptoms that cause a loss of appetite.

Cardiac Cachexia

Although there is no agreement as to how cachexia is defined, the hallmark clinical characteristic of cachexia is the process of losing weight, which can be defined as nonedematous weight loss of >6% of the previous normal weight over a period of >6 months.²⁵ The frequent presence of edema in HF patients complicates assessment of weight loss. Lean body assessments should ideally be performed by methods that account for total body water (bioimpedance) or non-weight-based assessments (anthropometric measurements).²⁶

The prognosis of HF worsens considerably once cardiac cachexia has been diagnosed, regardless of HF severity. Mortality rates are estimated at 50% for HF patients and cachexia compared to 17% for noncachectic patients of the same population.³ It is important to distinguish cachexia from malnutrition and anorexia, as the latter are reversible once nutrition is supplied. In addition, muscle mass is mostly spared in malnutrition and anorexia at the expense of fat mass. Patients exhibiting cachexia lose muscle mass in addition to total fat and bone mineral density.^{25,27} Some of the underlying pathophysiology concerning malnutrition and cachexia are similar, including neurohormonal activation and involvement of inflammatory cytokines as mentioned earlier. Acute illness in HF patients portends hypermetabolic changes and, combined with chronic cardiac cachexia, makes nutrition requirements difficult to assess (Table 1).

Obesity Paradox

The health hazards of obesity and elevated body mass index (BMI) are well accepted in the general population.²⁸⁻³² Recommendations for weight loss and target BMI are incorporated into contemporary guidelines for the management of hypertension, hyperlipidemia, and acute coronary syndromes.³³⁻³⁶ Among patients with HF, however, increasing BMI is paradoxically associated with improved cardiovascular outcomes and survival.³⁷⁻³⁹

Table 1. Physiologic Contributors to Malnutrition and Cachexia in Heart Failure

Intestinal ischemia	Decreased splanchnic circulation from increased SNS activity: (1) impaired epithelial function and increased mucosal permeability; (2) exposure to endotoxin and inflammatory cytokine release
Hypercatabolism	Increased levels of stress hormones and neurohormones: (1) epinephrine; (2) norepinephrine; (3) cortisol Decreased levels of anabolic hormones: (1) dehydroepiandrosterone sulfate; (2) insulin-like growth factor-1 Increased circulating levels of cytokines
Malabsorption	Reduced gut circulation Gut edema: (1) decreased fat absorption; (2) protein loss
Anorexia	Nausea and early satiety from gut/hepatic edema Multiple medication use Clinical depression

SNS, sympathetic nervous system.

The most compelling evidence for this association comes from an investigation of the impact of BMI on outcomes in 7767 HF patients enrolled in the Digitalis Investigation Group trial.⁴⁰ Over a mean follow-up of 37 months, patients with BMIs in the obese (>30 kg/m²) or overweight (25–29.9 kg/m²) ranges experienced mortality rates of 28.4% and 32.4%, respectively, whereas patients with BMIs in the underweight (<18.5 kg/m²) or normal (18.5–24.9 kg/m²) range experienced mortality rates of 37.8% and 45.0%, respectively. After multivariate analysis that included left ventricular EF, HF etiology, gender, and duration of HF symptoms, the mortality hazard ratios (HRs) for obese BMI (0.80; 95% confidence interval [CI], 0.72–0.92) and overweight BMI (0.88; 95% CI, 0.80–0.96) were statistically lower than was the reference normal BMI (predefined as 1.00) or underweight BMI (1.21; 95% CI, 0.95–1.53). Of note, these mortality effects were not associated with a measurable difference in hospitalization rates.

The physiologic mechanism underlying the obesity paradox is not well understood. Proposed mechanisms include increased health concerns for those with elevated BMI, resulting in earlier detection and treatment of HF in these patients, thus accounting for reduced mortality.^{41,42} Others hypothesized that malnourishment and cardiac cachexia are more prevalent in low BMI groups, driving the mortality findings.^{18,40} However,

the obesity paradox retains significance after exclusion of patients with cardiac cachexia.³⁸

Pharmacotherapy for the Prevention and Treatment of Cardiac Cachexia

Evidence supports pharmacotherapeutic interventions for preventing and treating cardiac cachexia. In the SOLVD trial, participants treated with enalapril had less weight loss of ≥6% (HR, 0.81; 95% CI, 0.70–0.94; $P = .0054$).¹⁸ Similar results in anthropometric indices were observed in 8 patients receiving a combination of enalapril, digoxin, and furosemide therapy.⁴³ Investigators found significant increases in midupper arm circumference and plasma albumin in individuals receiving the combination compared to healthy volunteers. Beta-blockers have also shown beneficial effects on nutrition status. Anker et al demonstrated that both carvedilol and bisoprolol increased the percentage of patients without significant weight loss in the COPERNICUS and CIBIS-II trials, respectively.^{44,45} Similarly, Hryniewicz et al prospectively measured changes in nutrition status in 27 cachectic and noncachectic HF patients after 6 months of treatment with extended release metoprolol or carvedilol.⁴⁶ Cachectic patients demonstrated significant nonedematous weight gain (5.2 ± 9.6 vs 0.8 ± 5.0 kg, $P = .027$) and plasma leptin levels (3.7 ± 3.9 vs 1.2 ± 4.3 ng/mL, $P = .030$) when compared with noncachectic patients. Although precise mechanisms that these medications have on preventing or improving cachexia have not been fully identified, the actions of angiotensin-converting enzyme inhibitors (ACEIs) and beta-blockers on attenuating overregulated neurohormonal systems by decreasing circulating catecholamines and harmful inflammatory cytokines such as TNF- α and interleukin-6 appear to play a prominent role. Multiple effects of the SNS on resting metabolic state in HF have been documented.⁴⁷ As both β -blockers and renin-angiotensin-aldosterone system (RAAS) inhibition with ACEI or angiotensin receptor blockers (ARBs) improve mortality and morbidity in this disease state, maximizing the use of these agents is the first step in preventing cardiac cachexia.

Many pharmacotherapeutic options are available to treat cachexia, although few have been optimally evaluated in clinical trials with HF patients. Malkin et al conducted a double-blind, randomized controlled trial of testosterone replacement in 76 men with HF over 12 months.⁴⁸ At the end of the study, participants receiving testosterone demonstrated increases in incremental shuttle walk test (25 ± 15 m in the treatment group, $P = .006$, ANOVA vs placebo). In addition, Pugh et al observed acute changes in cardiac output with the use of testosterone at

180 minutes ($10.3\% \pm 4.6\%$, $P = .035$; 95% CI, 0.8–19.8) in a randomized, placebo-controlled, crossover trial in 12 men with HF.⁴⁹ The use of growth hormone was examined by Tritos and Danias in a meta-analysis of 14 trials totaling 212 patients with left ventricular systolic dysfunction. Findings indicated that growth hormone improved exercise duration (1.9 minutes; 95% CI, 1.1–2.7), maximum oxygen consumption (2.1 mL/kg/min; 95% CI, 1.2–3.0), NYHA functional class (–0.9; 95% CI, –1.5 to –0.3), and EF (4.3%; 95% CI, 2.2–6.4) relative to placebo.⁵⁰

Megestrol and medroxyprogesterone are oral derivatives of progesterone used to stimulate appetite in various conditions.⁵¹ Both successfully increase weight in patients with cancer.^{52,53} The appetite-enhancing mechanism of megestrol, the more commonly prescribed of the 2 agents, is still unknown but thought to be owing to the production of neuropeptide Y, a central appetite stimulant.⁵⁴ Medroxyprogesterone reduces humoral factors involved in the cachectic response, such as serotonin, interleukin-6, and TNF- α .⁵⁵ Data are lacking for use of megestrol or medroxyprogesterone for cachexia in HF patients. The dose of megestrol is 800 mg/d for appetite stimulation, not to be confused with dosing for other disease states. Side effects of megestrol include diarrhea, thrombotic events, confusion/hallucinations, hyperglycemia, headache, Cushing syndrome, and antitestosterone effects in men.⁵⁶ Because of its side effect profile, the use of megestrol should be reserved for extreme cases of cachexia in HF patients.

Growth hormone has been another target for improving appetite in cachexia. Ghrelin, a stimulator of growth hormone release from the pituitary, is secreted from the stomach and transmits the hunger signal to the peripheral and central nervous system. In HF, ghrelin has been shown to increase muscle strength and lean body mass as well as improve left ventricular EF.⁵⁷ Although initial studies showed promise, controlled studies of ghrelin in HF have been negative to date, and presently it is not available in the United States.^{58,59}

Cannabinoids, the active chemical in marijuana, are a group of molecules that positively affect appetite and weight in cancer patients.⁵¹ The mechanism of these agents remains unknown but is thought to be mediated by endorphin receptors or by inhibiting prostaglandin synthesis. These agents are controlled substances due to their abuse potential and should be used with caution for cachexia in HF.

Other agents that have been thought to improve cachexia include cyproheptadine, anabolic steroids, and corticosteroids.⁵⁶ None of the drugs discussed have been shown to effectively improve the disease process in HF cachexia. Therefore, the main therapeutic strategy for cachexia in HF is to treat the underlying condition through optimization of currently approved therapies.

Nutrition Effects of Drugs Commonly Used in HF

Loop Diuretics

Potassium and magnesium deficiency. Diuretic use is associated with electrolyte depletion, the most concerning of which is potassium, an essential cation for maintaining normal heart rhythm and function. Loop diuretics reduce potassium reabsorption at the site of action and enhance potassium secretion in the distal tubules of the nephron.⁶⁰ Secondary increases in aldosterone can also contribute to hypokalemia after administration of loop diuretics.⁶⁰ A pharmacodynamic evaluation of the loop diuretic bumetanide showed a 3-fold increase in urinary total potassium excretion compared with excretion associated with a placebo.⁶¹ This was similar to that observed with equipotent doses of furosemide and greater than the potassium excretion with the thiazide-type diuretic hydrochlorothiazide.⁶¹ Another study also demonstrated significant increases in urinary magnesium, calcium, and phosphate excretion with loop diuretics.⁶² The clinical implications of electrolyte depletion include ventricular proarrhythmia and sudden cardiac death, which have been independently associated with increases in all-cause mortality in an HF population.^{63–65}

Loop diuretics also contribute to the development of hypomagnesemia and hypocalcemia as magnesium and calcium reabsorption in the thick ascending limb is dependent on sodium and chloride concentrations. In a study of 68 patients admitted for HF, hypomagnesemia existed in 38% of the cohort on admission, and excessive magnesium loss was observed in 72% of patients.⁶⁶ Like hypokalemia, hypomagnesemia has also been associated with adverse cardiac events. In a trial of 45 HF patients who received 4 weeks of diuretic therapy, magnesium concentrations were not significantly different overall but were lower in the patients who experienced frequent premature ventricular contractions.⁶⁷

Management of hypokalemia and hypomagnesemia as a result of diuretic therapy is challenging in an aggressively managed HF patient. This challenge is further compounded by the fact that diuretic use is dynamic and frequently titrated according to patient symptoms. Furthermore, overly aggressive diuretic use can induce a prerenal acute renal failure as a result of intravascular volume depletion, potentially placing the patient at risk for hyperkalemia from potassium supplementation or other medications that can elevate serum potassium levels. Prevention of adverse effects from potassium and magnesium is therefore dependent on proper attention to diuretic requirement. An additional consideration is that homeostasis of magnesium and potassium is closely

related, possibly due to the influence of magnesium on the Na/K/ATPase pump.⁶⁸ Therefore, hypomagnesemia must be corrected before potassium replacement.

Although many clinicians elect to supplement potassium as hypokalemia is identified, proper focus should also be placed on prevention. Clinicians should consider proactive potassium supplementation when initiating or increasing doses of loop diuretics. Likewise, dietary supplementation may be reasonable with foods high in potassium, such as bananas, tomato juice, and potatoes, among other foods. Dietary approaches to prevent hypokalemia were validated in cardiac surgery patients receiving < 160 mg/d of furosemide and may be reasonable in a patient with mild HF.⁶⁹ However, many patients with severe HF receiving high-dose or combination diuretic therapy may have deficiencies that exceed even conscious efforts to increase dietary potassium. Concomitant use of medications that will both modify the disease progress of HF and increase serum potassium, such as ACEIs and ARBs, may offset the hypokalemic effect of loop diuretics,⁷⁰⁻⁷³ in a dose-dependent fashion.⁷⁴ Likewise, an aldosterone antagonist such as spironolactone or eplerenone may also increase serum potassium levels in an additive or even synergistic manner with other RAAS inhibitors.⁷⁵ The ACEIs or ARBs titrated to target doses are recommended for all patients with systolic HF due to their beneficial effects on ventricular remodeling and mortality.² Aldosterone antagonists are approved for patients with left ventricular systolic dysfunction after myocardial infarction or those with NYHA functional classes III to IV.² Some clinicians use spironolactone or eplerenone in patients with mild HF with persistent hypokalemia or for a patient intolerant of oral potassium supplementation. Because spironolactone has been associated with increased death from hyperkalemia in HF,⁷⁶ it is prudent to initiate therapy with lower doses such as 12.5 mg daily and monitor serum potassium during the initial phase of therapy.

Acutely ill HF patients undergoing aggressive diuresis at a rate of several liters per day will require daily monitoring of serum potassium and magnesium to prevent severe deficiency. Likewise, when diuretic therapy is changed in the outpatient setting, patients will have variable potassium and magnesium requirements. Clinicians should be cognizant of these medication changes and learn to anticipate supplement requirements. For example, discontinuation or modification of diuretic therapy should prompt discontinuation or reduction in potassium and magnesium supplementation. It is also worth noting that use of a thiazide diuretic in combination with a loop diuretic (a combination used in patients not responsive to loop diuretics alone) will result in synergistic diuresis as well as increased potassium and magnesium depletion.⁷⁷ Closer attention to potassium and magnesium supplementation is required with combination diuretic agents.

Thiamine deficiency. Thiamine is a water-soluble B vitamin (vitamin B1) that is an important coenzyme in carbohydrate energy metabolism. Thiamine is not synthesized by humans and requires routine ingestion to maintain adequate stores. Thiamine comes from a variety of food sources, such as whole grain cereals, lentils, nuts, and yeast.⁷⁸ Once ingested, a portion is retained in the skeletal muscle, the heart, and other highly metabolic tissues while excess is excreted in the urine. Thiamine deficiency can occur rapidly, within 2–3 weeks of diminished intake or increased excretion.⁷⁹ Wet beriberi is a syndrome of thiamine deficiency characterized by sodium retention, peripheral vasodilatation, and biventricular HF. Numerous studies have evaluated thiamine deficiency in patients with HF, and with the exception of alcoholic cardiomyopathy or with chronic diuretic use, most found a fairly low occurrence that increases with advanced age.⁸⁰

There are several potential factors associated with thiamine deficiency in HF patients, including alcohol ingestion, loop diuretic use, malnutrition, advanced age, and HF severity. Alcohol interferes with thiamine absorption, and the chronic alcoholic may present with severe nutrition deficiency and profound but reversible HF. The prognosis in these cases depends on the duration of chronic alcohol intake, underlying myocardial structural abnormalities, and other contributing HF etiologies.

Chronic diuretic therapy may precipitate thiamine deficiency. By increasing urinary flow, diuretics may prevent reabsorption of thiamine and increase its urinary excretion.⁸¹ One study in 25 patients with HF found a 98% prevalence of thiamine deficiency associated with furosemide use at doses of 80 mg/d or greater.⁸² The same study showed that 57% of patients taking lower diuretic doses developed thiamine deficiency as well. Suter observed a similar association with diuretic use and thiamine status in 149 older adult patients hospitalized with a cardiac condition.⁸³ Multiple regression modeling revealed that the only independent predictor of change in thiamine concentration was diuretic use.⁸³ Although thiamine deficiency occurs quickly and profoundly with high diuretic doses, the practitioner must also consider this potential adverse drug event in patients given smaller doses of diuretics on a chronic basis.⁸⁴

Given the potential adverse effects of diuretic-induced thiamine deficiency, several investigations have explored thiamine replacement in patients with HF. Seligmann et al reported pilot findings with 6 patients identified with loop diuretic-induced thiamine deficiency who received 100 mg of thiamine intravenously for 7 days.⁸⁵ Thiamine deficiency, as measured by thiamine pyrophosphate effect, improved in all 6 patients, and increases in EF were identified in 4 of the 5 patients who underwent echocardiography. A follow-up double-blind study was conducted by Shimon et al, in which 30 hospitalized patients with diuretic-induced thiamine deficiency

were randomized to either intravenous (IV) thiamine at 200 mg/d or placebo for 1 week.⁸⁶ After discharge, all 30 participants received oral thiamine at 200 mg/d for 6 weeks. After 1 week, EF was mildly improved in the participants randomized to receive thiamine (0.28 ± 0.11 to 0.32 ± 0.09 ; $P < .05$) and further improved in all 27 participants who completed the remaining 6-week study medication course (0.27 ± 0.10 to 0.33 ± 0.11 ; $P < .01$). No significant changes in EF were observed in participants receiving placebo. Mild, although statistically significant, changes in diuresis rates and sodium excretion were also observed in patients randomized to thiamine replacement (1731 ± 800 mL/d to 2389 ± 752 mL/d [$P < .02$] and 84 ± 52 mEq/d to 116 ± 83 mEq/d, respectively). Finally, Smithline reported the results of a trial in which 50 patients with acute decompensated HF on chronic diuretic therapy were randomized to receive 100 mg of IV thiamine within 30 minutes of arrival to the emergency department.⁸⁷ No changes were observed in the percentage of patients hospitalized, length of stay, or 4-hour dyspnea score.

Given the lack of robust randomized controlled data, it is difficult to make definitive recommendations on the use of thiamine supplementation in HF patients. Diuretic therapy has been widely associated with thiamine deficiency, although the clinical utility of normalizing thiamine in HF has not been optimally evaluated. It would be reasonable, however, given the apparent lack of harm with replacement, to periodically test for thiamine deficiency in patients on high-dose, chronic loop diuretic therapy and administer replacement (100-200 mg/d) if deficiency is identified. Further clinical studies evaluating the effects of thiamine deficiency on disease progression in HF and trials of thiamine replacement are warranted to solidify replacement recommendations.

Drugs Modifying the RAAS

Inhibitors of the RAAS have the potential to cause hyperkalemia by interfering with the production and secretion of aldosterone (Table 2). Hyperkalemia was observed at statistically higher rates with RAAS inhibitors than with placebo during clinical trials in patients with HF.⁸⁸⁻⁹² The RAAS inhibitor-induced hyperkalemia may also be dose related. In the ATLAS trial, a nonsignificant increase in incidence of hyperkalemia was observed with high-dose lisinopril compared with low-dose lisinopril, but there was no resulting difference in discontinuation rates of study medication.⁷⁴ Target ACEI doses used in clinical trials have demonstrated a decrease for morbidity; therefore, dose titration is recommended in all patients if tolerated.⁷⁴ In addition to effects on potassium, ACEI and/or ARB therapy has been shown to increase urinary excretion of zinc,^{93,94} which is also the suggestive mechanism for ACEI/ARB-induced dysgeusia.⁹⁵

The ARBs are among the newest RAAS inhibitors in the armamentarium for the treatment of HF. It was originally theorized that ARBs caused potassium retention to a lesser extent than did ACEIs; however, this was not observed in patients with normal glomerular filtration rates in the double-blind, randomized, crossover VAL-K study.⁹⁶ The rates of ARB-induced severe hyperkalemia incidence was 2%–5.5% in clinical trials, compared to 1.7%–6.4% for ACEIs.^{92,97,98}

Aldosterone antagonists, such as spironolactone and eplerenone, also demonstrate hyperkalemia, which occurs more commonly at doses of 50 mg daily and higher.^{90,91} Patients with elevated baseline serum creatinine or potassium should begin therapy with low doses of 12.5 mg daily for spironolactone and 25 mg daily for eplerenone and receive frequent laboratory monitoring.

Combinations of RAAS inhibitors are often used for improved outcomes in the treatment of HF. A post hoc evaluation of hyperkalemia reported in the CHARM trials showed that age ≥ 75 years, male gender, baseline serum creatinine ≥ 2.0 mg/dL or potassium ≥ 5.0 mEq/L, diabetes, and combined RAAS blockade (with an ACEI or spironolactone) increased the incidence of hyperkalemia with candesartan.⁹⁹ A meta-analysis that included 4 trials of patients receiving combination therapy with an ACEI and ARB found the incidence of severe hyperkalemia (≥ 5.5 mEq/L) to be 3.5% compared with 0.7% in the placebo group (95% CI, 2.39-9.94).¹⁰⁰ The American Heart Association and the American College of Cardiology (AHA/ACC) consensus guidelines for the treatment of HF recommend that the combination of ACEI plus ARB be considered only if the patient remains symptomatic on optimal medical therapy.² These guidelines also caution against use of triple RAAS inhibition due to risk of hyperkalemia.

The risks of hyperkalemia should be carefully considered in comparison to the known benefits of ACEIs, ARBs, and aldosterone antagonists on cardiac mortality before these agents are discontinued. The American Heart Association/American College of Cardiology (AHA/ACC) recommend against withdrawal of ACEIs unless serum creatinine increases by $> 30\%$ of baseline or unless serum potassium rises above 5.5 mEq/L. The AHA scientific statement specifically addressing renal considerations with ACEI therapy recommends reducing potassium supplements, decreasing aldosterone antagonist doses, and increasing diuretic doses as strategies to help with potassium homeostasis during ACEI initiation.¹⁰¹

Beta-Blockers

Beta-adrenergic blockers may precipitate hyperkalemia by causing redistribution of potassium through the β_2 adrenergic receptor, rather than impairing renal excretion.⁹⁶ Stimulated by the α -adrenergic action of epinephrine, potassium is released from the intracellular space into the

Table 2. Recommendations for the Treatment and Prevention of Detrimental Drug-Induced Nutrition Effects in Patients with Heart Failure

Effect	Drug-Induced Cause	Recommendation
Hypokalemia	Loop diuretics	Monitor serum potassium level every 3–6 months if stable; monitor every 2–4 weeks until stable if initiation or change in dosage of any of the following: (1) ACEI/ARB; (2) loop or thiazide diuretic; (3) potassium supplement; (4) aldosterone antagonist Maximize ACEI/ARB therapy Consider the addition of an aldosterone inhibitor Consider dietary or pharmacologic potassium supplementation Anticipate use of diuretic therapy
Hyperkalemia	Potassium supplements; ACEIs; aldosterone antagonists; beta-blockers; aggressive diuretic use	Monitor serum potassium level every 3–6 months if stable; monitor every 2–4 weeks until stable if initiation or change in dosage of any of the following: (1) ACEI/ARB; (2) loop or thiazide diuretic; (3) potassium supplement Monitor serum potassium within a week of initiation of aldosterone antagonist, then every 2–4 weeks until stable or following dose adjustment; monitor every 3–6 months if stable Monitor serum potassium closely when combination inhibitors of RAAS are used; guidelines recommend clinical trial protocols of 48 hours after initiation, then at 1, 4, and 5 weeks Adjust use of potassium supplementation with diuretic use or when combination inhibitors of RAAS are used
Hypomagnesemia	Loop diuretics	Monitor serum magnesium level weekly after initiation or change in diuretic dose and every 3–6 months afterwards if stable Consider dietary and pharmacologic magnesium supplementation Anticipate use of diuretic therapy
Thiamine deficiency	Loop diuretics	Consider supplementation with 100–200 mg/d if receiving chronic, high-dose, loop diuretic therapy and deficient in TPPE
Calcium deficiency	Loop diuretics	Aggressively supplement if hypocalcemia is the suspected cause of heart failure Monitor serum calcium levels and supplement if receiving chronic loop diuretic therapy
Zinc deficiency	ACEIs or ARBs; thiazide diuretics	Routine monitoring and supplementation not recommended Consider supplementation if dysgeusia symptoms present in patient receiving ACEI or ARB therapy

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; RAAS, renin-angiotensin-aldosterone system; TPPE, thiamine pyrophosphate effect.

serum.¹⁰² Subsequently, the beta-adrenergic effects of epinephrine are thought to restore balance. Therefore, serum potassium is expected to rise with increasing β 2 adrenergic blockade.¹⁰² Although the clinical importance of this is yet to be determined, increased percentage of beta-blocker use might have contributed to the high rates of hyperkalemia (5.5%) observed in the eplerenone post-acute myocardial infarction HF efficacy and survival study as compared to earlier spironolactone studies involving a lower percentage of patients on beta-blockers.^{91,103} As previously discussed, hyperkalemia with aldosterone antagonists appears to be dose related. However, a retrospective evaluation of 59 patients with HF receiving carvedilol, spironolactone, furosemide, and enalapril or candesartan observed hyperkalemia (≥ 5.5 mEq/L) in 11.9% of patients regardless of spironolactone dose.¹⁰⁴

Vitamins and Over-the-Counter Medications in HF

Vitamin Deficiencies and Supplementation

HF patients are often deficient in many vitamins and micronutrients crucial to the maintenance of calcium homeostasis, control of oxidative stress, and adequate protein metabolism.¹⁰⁵ Excess reactive oxygen species and markers of increased oxidative stress have been correlated with the failing myocardium and may contribute to beta-receptor hyporesponsiveness.²² Moreover, patients with HF may possess different nutrition needs compared to individuals with a normal myocardium, leading to higher requirements for certain vitamins and micronutrients (Table 3). As such, the following section includes vitamins

Table 3. Recommendations for Supplementary Vitamins, Over-the-Counter Medications, and Complementary and Alternative Medications (CAMs) in Patients with Heart Failure (HF)

Vitamin/Medication	Biological Action Relevant to HF	Clinical Effect	Recommendation
Calcium	Increased myocardial contractility; reduced incidence of osteoporosis	Improvement of systolic dysfunction where hypocalcemia is suspected cause	Rule out hypocalcemia as reversible cause of cardiomyopathy; monitor and supplement if on chronic loop diuretic therapy
Vitamin D	Regulation of bone metabolism and myocardial contractility	Reduction in neurohormones, blood pressure; decreased inflammation	Consider increased environmental exposure or supplementation with 50 µg/d of vitamin D or calcitriol if severe cardiorenal syndrome present
B vitamins	Red blood cell production; regulation of homocysteine	Decreased homocysteine; no proven effect on cardiovascular events	Routine supplementation or monitoring not recommended, except in cases of alcoholic cardiomyopathy or macrocytic anemia
Thiamine	Co-enzyme in carbohydrate metabolism	Hemodynamic improvements in patients receiving loop diuretics	Consider monitoring and supplementation if on chronic, high-dose diuretic therapy; routine supplementation or monitoring not recommended at this time except in cases of suspected alcoholic cardiomyopathy
Vitamin C	Reduction in oxidative stress	Increased myocardial contractility with inotropes	Routine supplementation or monitoring not recommended at this time
Vitamin E	Reduction in oxidative stress	Increased incidence of HF in a cardiovascular population	Administration not recommended and may be harmful
Coenzyme Q ₁₀	Mitochondrial synthesis, reduction in oxidative stress	Improved hemodynamic parameters, improvement in ejection fraction, reduction in hospitalizations, improvement in exercise tolerance	Administration may be reasonable but data is conflicting efficacy; lack of clear dose range (studied at 60-200 mg/d); not recommended by major guidelines
Selenium	Reduction in oxidative stress	Reversal of cardiomyopathy in Keshan disease	Identify whether deficiency is present in new diagnosis of HF; routine supplementation or monitoring not recommended at this time
Zinc	Reduction in oxidative stress	Unknown	Routine supplementation or monitoring not recommended at this time
Copper	Reduction in oxidative stress	Unknown	Routine supplementation or monitoring not recommended at this time
Fish Oil	Unknown; may be related to decrease in serum triglyceride concentration, reduction in sudden cardiac death, or antiplatelet effects	Decreased mortality, cardiovascular admissions	Consider use (1 g/d) in all symptomatic HF patients
Hawthorn	Increased myocardial contractility, improved endothelial function, reduction in oxidative stress	Improvements in exercise capacity; reduced symptoms of HF	Supplementation not recommended at this time

and micronutrients that either are deficient in HF and/or are deemed especially important in this setting.

Calcium and vitamin D. Calcium and vitamin D deficiencies have been identified in HF patients. Vitamin D is a

major factor in calcium homeostasis, and long-term hypocalcemia or vitamin D deficiency can lead to clinical features such as osteoporosis and secondary hyperparathyroidism. There is also increasing evidence that vitamin D deficiency may play a role in the pathogenesis

of HF and has been implicated in a number of studies and case reports as a probable cause for cardiomyopathy.¹⁰⁶⁻¹⁰⁸ Excess parathyroid hormone levels have also been associated with increased blood pressure and contractility,¹⁰⁹ which are potentially deleterious in a failing myocardium. Loop diuretic therapy is also a well-known calciuric.¹¹⁰

Calcitriol (or 1,25-dihydroxyvitamin D₃) administration has been associated with beneficial endocrine response on the RAAS, reducing plasma renin activity,¹¹¹ angiotensin II, and, subsequently, blood pressure.^{111,112} This may have important implications for a patient with hypertension as an underlying etiology for HF. Schleithoff et al reported the effects of vitamin D in addition to calcium supplementation in a randomized, controlled trial of 93 HF patients, demonstrating that those assigned to the addition of 50 µg of vitamin D₃ to 500 mg of calcium had significantly decreased inflammatory markers after 9 months.¹¹³

Low calcium levels are also associated with proarrhythmia,¹¹⁴ although typically only in cases of severe deficit. If hypocalcemia is identified in a patient presenting with new onset HF as a possible etiology, it should be treated aggressively with oral or IV calcium plus vitamin D analogs to gradually normalize serum calcium levels. Typically, calcium deficit in these cases is severe, with total serum concentrations measuring as low as 3–7 mg/dL or ionized calcium levels of <2 mg/dL. Case reports note reversal of cardiomyopathy in several cases after prolonged supplementation.^{115,116} Given the potential adverse effects of hypocalcemia and the high incidence of osteoporosis in the HF population,¹¹⁷ routine monitoring of serum calcium is desirable in a patient on chronic loop diuretic therapy and supplementation administered if deficiency is identified. Further clinical trials should explore the role of vitamin D as an anti-inflammatory agent on disease progression in HF, but supplementation should be considered if outdoor activity is limited by disability or climate, or if renal calcitriol synthesis is impaired by poor renal perfusion (ie, cardiorenal syndrome) or other comorbid conditions.

B vitamins. Riboflavin (vitamin B₂) and pyridoxine (vitamin B₆) influence the production of red blood cells and play a role in carbohydrate-mediated energy production. Similar to thiamine, these vitamins are water soluble and have limited tissue storage.¹⁰⁵ Furthermore, a combination of B vitamins (as part of a regimen of various micronutrients) has also been shown to reduce blood pressure and improve vasodilatory response in an older adult population with HF.¹¹⁸ However, large-scale clinical evaluations are lacking in an HF population. Supplementation of B vitamins, along with folate, reduced serum homocysteine levels effectively¹¹⁹ but failed to demonstrate reductions in cardiovascular morbidity and mortality in large-scale clinical trials.^{120,121} B vitamin deficiency may also be identified if macrocytic anemia is present, which may contribute to or worsen symptoms in

patients with HF. Current evidence does not support the monitoring or supplementation of B vitamins routinely, except in cases in which macrocytic anemia is present or in alcoholic cardiomyopathies.

Vitamin C. Vitamin C has been the subject of several investigations in both animals and humans with HF due to its potent antioxidant effects. Mak and Newton demonstrated that administration of vitamin C (2 g IV bolus followed by 50 mg/min infusion) augmented the inotropic response of dobutamine in patients with normal left ventricular dysfunction, although not in those with decreased left ventricular dysfunction.¹²² In addition, Shinke et al conducted a trial in which 19 patients with ischemic HF after anterior infarction were randomized to receive either vitamin C (2 g IV bolus followed by 50 mg/min infusion) or placebo.¹²³ Patients randomized to receive vitamin C exhibited an increased inotropic response to 4 µg/kg/min of dobutamine. Although these results are promising, future clinical trials examining meaningful clinical end points should be conducted before acute or chronic supplementation of vitamin C is recommended.

Vitamin E. Vitamin E was once a promising supplement for patients with coronary disease or those with high risk of developing coronary artery disease. Dietary intake of vitamin E appeared to negatively correlate with the risk of coronary artery disease. Like vitamin C, vitamin E was thought to improve endothelial function, and initial studies were promising in animal models. However, large-scale clinical trials consistently failed to demonstrate a benefit and even associated increased mortality from routine vitamin E supplementation for prevention of cardiovascular morbidity or mortality.¹²⁴⁻¹²⁶ In addition, vitamin E supplementation in both the GISSI-Prevenzione trial and the HOPE trial significantly increased the risk of developing HF.^{126,127} This may be owing to paradoxical pro-oxidative and myocardial depressive effects of vitamin E.¹²⁸ Vitamin E supplementation is not recommended in patients with HF and may be harmful.

Coenzyme Q₁₀. Coenzyme Q₁₀ (CoQ₁₀) is a vitamin-like element that plays a large role in mitochondrial synthesis and is a strong regulator of oxidative stress. Low plasma levels of CoQ₁₀ have been identified in patients with HF.¹²⁹ Multiple CoQ₁₀ supplementation trials in HF patients have been performed, with doses ranging from 60 mg/d to more than 200 mg/d.¹³⁰⁻¹³⁷ Unfortunately, the results of these trials are largely conflicting. Many data, although not all,^{131,133,134} show that CoQ₁₀ improves hemodynamic parameters in HF. Indeed, Sander et al recently conducted a meta-analysis of 10 CoQ₁₀ trials in HF and found that the addition of CoQ₁₀ vs placebo modestly benefited several parameters of systolic function, improving EF by a net of 3.7% (95% CI, 1.59-5.77; $P < .00001$ for statistical heterogeneity).¹³⁸ The effect was

stronger in subgroups of patients not receiving an ACEI. In addition, Morisco et al studied the addition of 2 mg/kg/d of CoQ₁₀ to standard therapy, which was found to reduce hospitalizations for HF compared with placebo over 1-year follow-up (22.9% vs 36.6%, $P < .001$).¹³² CoQ₁₀ deficiency is also a suspected cause of statin-induced myopathy, statin drugs are widely prescribed medications in the HF population.^{139,140} Investigations are ongoing as to whether supplementation improves myopathy and tolerability. Given the conflicting data and the inconsistent dosing surrounding the use of CoQ₁₀ in HF, it is difficult to make definitive recommendations regarding its use. In addition, available HF guidelines do not endorse the use of CoQ₁₀ in HF. Nevertheless, its use may be reasonable, particularly in a symptomatic patient unable to tolerate standard of care medications. Large and well-designed studies powered to assess optimal dosing, efficacy, and safety of CoQ₁₀ are required before widespread use is recommended.

Other minerals. Selenium and zinc are 2 minerals that, like many micronutrients, play a role in the regulation of oxidative stress. Deficiencies of these minerals have been identified in patients with HF.^{141,142} Keshan disease, a cardiomyopathy endemic to China, is primarily thought to be caused by selenium deficiency.¹⁴³ Case reports describe reversible cardiomyopathies in patients receiving parenteral nutrition as a result of selenium deficiency.^{144,145} The ACEIs and ARBs are associated with zinc deficiency as previously discussed,^{93,94} as are thiazide diuretics, which significantly increase urinary zinc excretion.⁹³ Loop diuretic use does not appear to alter zinc concentration in humans.¹⁴⁶

Other minerals have been identified as potential supplementary therapy for HF patients. Similar to several previously discussed supplements, copper and manganese could affect the regulation of oxidative stress. Manganese deficiency may play a role in the pathogenesis of doxorubicin-induced cardiac toxicity.¹⁴⁷ Copper deficiency is a long-suspected cause of cardiomyopathy and other detrimental cardiovascular conditions.¹⁴⁸ However, paradoxically elevated serum copper levels were shown in HF patients when compared with copper levels of controls.¹⁴⁹⁻¹⁵¹ Definitive evidence regarding the etiology of increased serum copper concentrations in the setting of other mineral deficiencies is lacking, although it is logical that copper is a marker of oxidative stress. Elevation in serum copper level also appears to be prognostic for morbidity and mortality in HF patients.¹⁵²

Although this evidence clearly advocates identifying mineral deficiency in HF patients without a clear etiology, fewer data examine the clinical effects of supplementation in which the deficiency is not the identified cause of the cardiomyopathy. Witte et al randomized 30 elderly HF patients to a combination micronutrient regimen (containing calcium, magnesium, zinc, copper, selenium, vitamin A, thiamine, riboflavin, vitamin B₆, folate, vitamin B₁₂,

vitamin C, vitamin E, vitamin D, and CoQ₁₀) or placebo for 9 months in a double-blind, randomized controlled trial.¹¹⁸ At the end of the follow-up period, the micronutrient supplementation group demonstrated modest although statistically significant gains in EF vs placebo and improved quality of life. Although definitive clinical data are lacking regarding mineral supplementation, it would be reasonable to periodically monitor zinc levels in patients receiving ACEI/ARB therapy or thiazide diuretics and supplement if deficiency is identified. Selenium deficiency may be ruled out as a reversible cause of cardiomyopathy, particularly those endemic to areas with Keshan disease, but widespread monitoring or supplementation has not been optimally evaluated at this time. Patients receiving administered feedings, particularly parenteral nutrition, may require more intensive monitoring. Supplemental administration of copper or manganese has not been optimally evaluated at this time and is not recommended.

Complementary and Alternative Medications

Complementary and alternative medications (CAMs) are defined as therapies not commonly used in Western medicine and are treated as nutrition supplements by the Food and Drug Administration (FDA) in the United States. It is estimated that one-third of patients with HF are taking CAMs.¹⁵³ Researchers in the HERB-HF study found that patients with HF took CAMs for treatment of heart problems, anxiety, weight loss, and arthritis.¹⁵³ Several of the CAMs taken by patients were noted to interact with concomitant medications used in HF.

Fish oils, ω -3 polyunsaturated fatty acids, or ω -3 fatty acids are commonly used in the treatment of elevated serum triglyceride levels. Although the mechanism of action is not completely understood, ω -3 fatty acids appear to interfere with hepatic triglyceride synthesis, producing favorable effects on serum levels of triglycerides (−20% to −50%), very low density lipoprotein (−20% to −40%), and high-density lipoproteins (5%-10%), at the expense of unfavorable increases in low-density lipoproteins (15%-30%).^{154,155} Beyond direct lipid effects, other postulated actions of ω -3 fatty acids include favorable changes in arrhythmogenesis (decreased membrane excitability), inflammation, platelet aggregation, blood pressure, heart rate, ventricular function, and autonomic tone. However, none of these actions has been systematically evaluated in HF patients.

A recent study examined the clinical efficacy of ω -3 fatty acids in HF patients without baseline lipid abnormalities.¹⁵⁶ Patients with NYHA class II to IV symptoms were randomized to treatment with ω -3 fatty acids (Lovaza, 1 g daily [n = 3494], GlaxoSmithKline, Research Triangle Park, NC) or placebo (n = 3481). All study medications were in addition to standard care regimens that consisted of ACEIs/ARBs (77%/19%), beta-blockers (65%), and diuretics

(90%). After a mean follow-up of 3.9 years, investigators reported a small but statistically significant reduction in all-cause mortality in patients receiving ω -3 fatty acids (27%) vs placebo (29%; hazard ratio [HR], 0.91; 95% CI, 0.833–0.998; $P = .041$). Among secondary outcomes, ω -3 fatty acids reduced cardiovascular mortality (HR, 0.90; $P = .045$) and cardiovascular admissions (HR, 0.93; $P = .049$) but did not affect HF admissions, sudden cardiac death, patients with myocardial infarction, or patients with stroke. There were no significant increases in adverse events among patients taking ω -3 fatty acids. Of note, this study used an FDA-approved formulation of prescription ω -3 fatty acids indicated for the treatment of very-high serum triglyceride levels (>500 mg/dL).

Ma huang is a nutrition supplement that many patients use for weight loss, either alone or in combination with other CAMs. Ma huang is also commonly used in the treatment of asthma, obesity, colds, fever, and chills.¹⁵⁷ It has been suggested that ma huang contains 1% ephedrine and therefore contributes to weight loss through SNS stimulation. Stimulation of the SNS has led to serious complications with ma huang use. Two recent reviews reported that ma huang was temporally related to cases of stroke, HF, myocardial infarction, and sudden death.^{158,159} Furthermore, cardiovascular toxic effects were not necessarily related to excessive doses of ma huang.¹⁶⁰ Based on these reported risks, patients with HF should not use ma huang. In April 2004, the FDA announced a ban on ephedrine-containing dietary products because of the risk of harm to the public.¹⁶¹

Hawthorn is the most well-studied CAM for the treatment of HF. The pharmacological effects of hawthorn come from the flavonoids found in the leaf, fruit, or flower of these plants.¹⁶² The beneficial effects of flavonoids in HF include increases in the force of contraction, improved coronary blood flow, and higher cardiac output. After 16 weeks of hawthorn therapy combined with diuretics, improvements in exercise capacity and reduced symptoms of HF were observed.¹⁶³ The difficulty in recommending hawthorn as a standard therapy in patients with HF is that such use has not been rigorously studied in large randomized clinical trials in patients on standard medical therapy. To date, neither the ACC/AHA nor the Heart Failure Society of America guidelines advocate the use of hawthorn in patients with HF.

In a recent survey, 82% of patients with HF reported use of an over-the-counter medication at least once per week, which included nonsteroidal anti-inflammatory drugs (NSAIDs).¹⁶⁴ These NSAIDs, such as ibuprofen, ketoprofen, and naproxen, inhibit the breakdown of arachidonic acid via the cyclooxygenase enzyme and are used for the treatment of pain and inflammation. Cyclooxygenase enzyme inhibition also interrupts renal blood flow, causing fluid retention. This effect is particularly detrimental in patients with HF because fluid retention produced by NSAIDs may counteract the fluid

restriction and medications used to control intravascular and extravascular volume. One study reported a 2-fold increase in HF admission among patients with HF taking NSAIDs compared with admission rate of those not taking NSAIDs.¹⁶⁵ Patients with HF should be encouraged to use acetaminophen in place of NSAIDs for pain and headache.

Conclusion

Research regarding nutrition aspects of HF is limited. In fact, the National Institutes of Health recently announced a funding program specifically targeting nutrition and HF (PA-06-136, Nutrition and Diet in the Causation, Prevention, and Management of Heart Failure, R21). Despite this encouraging news, we as practitioners have very little guidance or evidence-based approaches addressing dietary issues, including supplements, for our HF patients. Fortunately, concepts can be put forth that are reasonable, embroil little controversy, and will likely be of benefit for the patient. An initial step to consider for patients is to evaluate current nutrition status and dietary pattern and, if needed, consult the patient regarding healthy dietary choices (which may include sodium restriction). For many patients, an appointment with a nutrition expert may be beneficial, especially if a patient appears to be malnourished. Working with a registered dietitian may lead to healthier dietary choices, which may reduce overall cardiac risk. In addition, counseling patients about foods that may have high amounts of potassium may be appropriate for individual patients taking certain drugs or combination of drugs. Obviously, patients at risk for electrolyte disturbances due to drug therapy (ie, hyperkalemia, hypokalemia, or hypomagnesemia) must be routinely monitored and supplemented as necessary. For patients who appear to be cachectic, the best approach to reversing cachexia is not known but must include at least optimization of standard of care medications for HF. Addition of secondary drugs such as aldosterone antagonists or angiotensin II blockers should be considered if a patient has continued symptoms of HF. Another consideration for patients with documented calcium deficiency is to recommend calcium supplementation. Beyond these general recommendations, how we should nutritionally treat HF patients is not known and is left to clinical judgment. For example, although it appears reasonable that patients taking diuretics or patients who live in northern climates should be routinely given a vitamin supplement that includes thiamine, vitamin D, CoQ₁₀, and perhaps vitamin C, we have no outcome data. Without outcome data, it is not advisable to make this a general recommendation (see vitamin E). However, when evaluating an individual patient, clinical circumstances and judgment may suggest that vitamin supplementation is reasonable. Overall, this example highlights the fact that the role of nutrition in

the development and progression of HF has been an area that until recently has been largely ignored. Fortunately, this is changing, and it is hoped that in addition to drug therapy, nutrition aspects to the management of HF will be at the forefront of care.

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