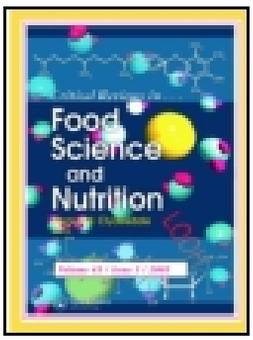

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: http://www.tandfonline.com/loi/bfsn20

Benefits of multiple micronutrient supplementation in heart failure: A comprehensive review

Simona Dragan, Florina Buleu, Ruxandra Christodorescu, Florin Cobzariu, Stela Iurciuc, Dana Velimirovici, Jianbo Xiao & Constantin Tudor Luca

To cite this article: Simona Dragan, Florina Buleu, Ruxandra Christodorescu, Florin Cobzariu, Stela Iurciuc, Dana Velimirovici, Jianbo Xiao & Constantin Tudor Luca (2018): Benefits of multiple micronutrient supplementation in heart failure: A comprehensive review, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2018.1540398

To link to this article: https://doi.org/10.1080/10408398.2018.1540398

Published online: 03 Dec 2018.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2018.1540398

Taylor & Francis
Taylor & Francis Group

REVIEW

Benefits of multiple micronutrient supplementation in heart failure: A comprehensive review

Simona Dragan[a], Florina Buleu[a], Ruxandra Christodorescu[b], Florin Cobzariu[a], Stela Iurciuc[a], Dana Velimirovici[a], Jianbo Xiao[c], and Constantin Tudor Luca[d]

[a]Department of Cardiology, Discipline of Preventive Cardiology, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania; [b]Department of Internal Medicine, Discipline of Medical Semiology II, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania; [c]Institute of Chinese Medical Sciences, University of Macau, Taipa, China; [d]Department of Cardiology, Discipline of Cardiology II, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania

ABSTRACT

Background: Multiple micronutrient supplementation has been suggested to have a role on health outcomes in patients with heart failure (HF), but the evidence is inconclusive. **Objective:** To elucidate the role of multiple micronutrient supplementation in heart failure we performed a comprehensive review of the literature. **Methods and results:** The search in databases included PUBMED (until June 2018) to detect randomized controlled trials (RCTs) and meta-analyzes that investigated the impact of micronutrient supplementation in HF. **Results:** With more than 2357 titles and abstracts reviewed, we included only the studies suitable for the final review. Whether alone or in combination, micronutrients have been found to improve the health outcomes of patients with HF by improving symptoms, work capacity and left ventricular ejection fraction (LVEF), thus increasing the quality of life in these patients. **Conclusion:** Future studies are needed to document the effects of multiple micronutrient associations in order to include them in nutritional guidelines to increase survival and to improve quality of life in patients with heart failure.

KEYWORDS

Heart failure; energetic metabolism; coenzyme Q10; vitamin D; micronutrient supplementation; comprehensive review

Introduction

Extensive research data, resulting from epidemiologic, clinical and experimental studies supports the evidence that multiple dietary traits are associated with increased cardiovascular disease (CVD) risk. High intakes of carbohydrates, saturated and trans-fatty acids, dietary cholesterol and animal protein have been incriminated versus inadequate intakes of vitamins, minerals, fibers, protein and fats of vegetal origin in the pathogenesis of CVD. Some of these diseases are coronary heart disease (CHD), hypertension, heart failure, stroke, renal disease, type 2 diabetes mellitus (T2DM), metabolic syndrome (MS) and obesity (Shay et al. 2012).

There is a growing interest in the role of the micronutrients (essential trace elements and vitamins) in optimizing health, and in prevention or treatment of CVD. This is partly due to the increasing knowledge and understanding of the biochemical functions of these nutrients (Mozaffarian, Appel, and Van Horn 2011). In maintaining the function of tissues, micronutrients play a central role, acting as co-factors in metabolism, coenzymes or antioxidants. They also display genetic control functions.

Trace elements are frequently involved in modulation enzymatic activity or are integral parts of prosthetic enzyme groups (e.g. zinc is a cofactor for more than 100 enzymes, whereas selenium is required within the enzyme glutathione peroxidase). In complex biochemical reactions, many vitamins or vitamin metabolites play an active role, for example, niacin and riboflavin in the electron transport chain or folic acid as part of the methyl group transfer. Essential to the intermediate metabolism, these reactions ensure the use of key nutrients to provide energy, proteins and nucleic acids (Houston 2014).

Many of the micronutrients have antioxidant properties. Free radicals cause oxidative reactions, especially to the parts of the cell in a relatively reduced state, such as cell membranes or nucleic acids. Potential for causing damage is limited by mechanisms that include the direct cessation of oxidative activity of tocopherols (vitamin E) or carotenoids (vitamin A), or by enzymatic systems that help eliminate oxidation products, like superoxide dismutase (either zinc/copper or manganese dependent) and glutathione peroxidase (selenium dependent) (Dandona et al. 2010).

Macronutrients and micronutrients contribute through nutrient-gene interactions and epigenetic variations to regulate oxidative stress, inflammatory mediators and signaling cascades. The high incidence of CVD and HF can be explained through these complex interactions (Lundberg and Yan 2011).

CONTACT Florina Buleu buleu.florina@gmail.com Department of Cardiology, Faculty of Medicine, "Victor Babes" University of Medicine and Pharmacy, Blvd C.D.Loga 49, 300030, Timisoara, Romania.

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/bfsn.

Eaton et al. consider that the human genetic make-up 99.9% resembles that of our ancestors from the Paleolithic, but our nutritional intakes are very different. The evolution towards intensive agriculture and refrigerated products has led to an unnatural nutritional process. Diet has changed more than it is possible to our genetics to adapt. Nutrient deficiencies are very common in the general population and may impact the present and future of cardiovascular health. The authors conclude that diagnosis and treatment of these conditions will reduce cardiovascular events and improve vascular biology (Eaton, Eaton, and Konner 1997).

Heart failure is an end-stage disease resulting in loss of function of cardiomyocytes and consequently in impairment of the pumping function of the heart. Hypoxia aggravates the symptoms of fatigue and shortness of breath, making daily life activities difficult.

HF has become a major burden with estimated cases of over 23 million worldwide. The survival rate has constantly increased, but despite of the introduction of ACE inhibitors, beta-blockers and devices that improve the quality of life and the functional capacity, fifty percent of HF patients die within five years from the initial diagnosis (Roger 2013).

Nutritional status is deeply affected by most disease, usually by a combination of demand growth at times when there is a reduction in intake. This may particularly affect the state of the micronutrient. During build-up and development of chronic diseases, patients experience progressively more severe depletion of one or more micronutrients, while they pass through consecutive stages of disease, each with biochemical and/or physiological consequences. At the onset of chronic diseases, these situations are defined as "subclinical deficiency". The time to develop a subclinical deficiency is different for each micronutrient and depends on the nature and amount of body stores (Shenkin 2006).

Micronutrients play an important role in the etiology and prognosis of HF, where increased risk of poor dietary intake is associated with lower quality of life. Evidence suggests that the failing heart is deficient in several micronutrients (Soukoulis et al. 2009). Despite growing evidence regarding the role of micronutrient deficiencies, HF guidelines do not recommend specific nutritional strategies in chronic HF (Ponikowski et al. 2016). Clinical research investigating the effects of micronutrient supplementation in HF is considered insufficient to allow conclusions.

The purpose of this review is to comprehensively summarize the present evidence about the impact of micronutrients on severity and evolution of heart failure.

Search strategy

All available data provided by a www.PubMed.com search until June 2018 was used in the survey, in English language. The following words were selected for our research: taurine, L-carnitine, coenzyme Q10, thiamin (or vitamin B1), riboflavin (or vitamin B2), pyridoxine (or vitamin B6), vitamin C, vitamin D, omega-3 and 6 fatty acids, magnesium, potassium and selenium, folate and homocysteine.

All the micronutrients were searched in combination with keywords "heart failure" and "energetic metabolism".

Mechanisms of progression in heart failure

HF is a state where the heart muscle progressively fails to pump blood in order to meet the requirements of tissues during ordinary activity. Based on the hemodynamic concept, HF is expressed by decreased left ventricular ejection fraction and cardiac output due to alterations in cardiac contractility and blood flow. Decreased cardiac output determines neuro-hormonal activation of the sympathetic nervous system and increased retention of sodium and water. Vasodilation through natriuretic peptides, nitric oxide and prostaglandins is enhanced to improve blood flow (Hartupee and Mann 2017). These mechanisms are adaptive and compensatory at the beginning of disease, but as it progresses they become deleterious and determine symptoms.

Disease progression in HF is determined by norepinephrine, aldosterone, angiotensin II and endothelin. Their detrimental effects are expressed in time by hyperplasia of cardiomyocytes and fibroblasts, myopathy and apoptosis of myocytes, which determine proarrhythmogenic effects and increased energy expenditure (Roig 2006). In this stage, patients become symptomatic and require constant follow-up and frequent hospitalizations.

Progression over time towards HF and end-stage disease has been explained by the cardiovascular disease continuum (CVDC), a succession of events that begins from increased cardiovascular risk determined by association to various degrees of hypertension, dyslipidemia, type 2 diabetes mellitus (T2DM), smoking and visceral obesity, which all lead to atherosclerosis. In the heart atherosclerosis is the main cause of coronary artery disease and myocardial infarction, followed by left ventricular hypertrophy and dilatation, diastolic and systolic dysfunction and HF.

The concept of CVDC is the result of several epidemiological studies, which have shed light on underlying mechanisms of progression in heart failure and consequently on various interventions that could stop or reverse this condition. It has been presented for the first time in 2006 by Dzau and colleagues (Dzau et al. 2006), explaining the progression to HF in coronary artery disease. Michael F. O'Rourke (O'Rourke, Safar, and Dzau 2010) published the aging CVDC approach four years later, introducing the role of vascular aging and giving a more comprehensive explanation for development of end-stage HF. The pulse wave in the cardiac cycle causes repetitive mechanical stretching of the aorta which causes damage of the small elastin fibers with age and consecutive stiffening, leading to systolic hypertension. Left ventricular hypertrophy and myocardial ischemia develop, explaining the CVDC events in patients with end-stage HF and the presence of microvascular diseases in the brain and kidneys. It is important to integrate vascular aging in the CVDC.

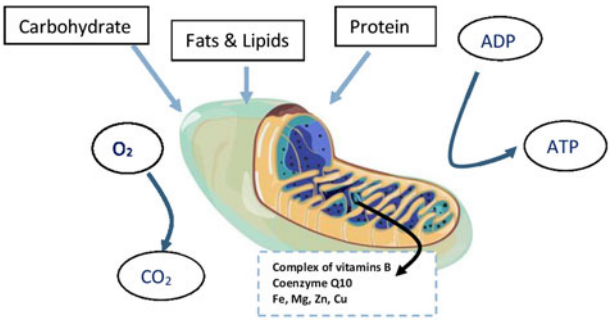

Figure 1. The role of mithocondria in connecting energy substrate, micronutrients and ATP synthesis.

Energetic metabolism of the myocardium

The heart has a higher resting energy expenditure than any other organ because of the high energy needed to sustain its workload. Biochemical energy is required to support contraction, relaxation and molecular synthesis of adenosine triphosphate (ATP). The heart maintains a stable ATP concentration even if large fluctuations in energy demand are present. ATP synthesis by ADP re-phosphorylation occurs with matching ATP utilization, energy being generated by two main substrates: fatty acids and glucose (Wong, Niedzwiecki, and Rath 2016).

The main intracellular site for ATP re-phosphorylation is the mitochondria. Due to high energy demands, cardiomyocytes contain almost 5000 mitochondria per cell. Although beta-oxidation of fatty acids is more efficient in producing ATP per molecule oxidized than glucose oxidation, it requires more oxygen. The heart relies mainly on fatty acids in normal physiological conditions, 60% to 70% of total ATP production being provided by beta-oxidation, and the remaining 30% to 40% by glucose and lactate oxidation (Wong, Niedzwiecki, and Rath 2016).

In HF substrate utilization is switched from fatty acids to glucose to conserve energy. Consecutively, in the failing heart, the total capacity for ATP synthesis decreases, while the demand for ATP continually increases. The result of this energy imbalance is a decrease in the concentration of ATP that lowers the energy reserve in the heart.

The conversion of ATP to biological energy also requires the presence of micronutrients for energy production and transfer and cofactor function (e.g. aminoacids L-carnitine and taurine, coenzyme Q10, thiamin, riboflavin) (Krim et al. 2013) (Fig. 1).

Role of oxidative stress

Reactive oxygen species (ROS) have an important role in inflammation and tissue damage. Oxidative stress and inflammation work together affecting arteries and cardiac function. There are several antioxidant nutrients that minimize the inflammatory process. The most potent intracellular antioxidant, glutathione, contributes to regenerate other antioxidants in the body. Glutathione and micronutrients like cysteine, selenium and vitamins (B2, E and C) reduce oxidative stress of the entire cardiovascular system (Panth, Paudel, and Parajuli 2016).

The concept that oxidative stress may contribute to cardiovascular disease progression was the rationale for many clinical trials of interventions, especially with antioxidant vitamins. These studies were conducted in order to demonstrate the cytoprotective or therapeutic benefit of antioxidants and to promote phytochemicals, functional foods, and antioxidant (vitamin) supplements. However, antioxidants have failed to show any therapeutic benefit in most large clinical trials, such as HOPE (Heart Outcome Prevention Evaluation) and HOPE-TOO (Heart Outcome Prevention Evaluation—The Ongoing Outcomes), which demonstrated that vitamin E causes more heart failure and left heart decompensation (Lonn et al. 2005).

These large-scale clinical trials on chronic oral antioxidant supplementation are contrasted by multiple small cohort studies with acute (parenteral) administration of antioxidants with highly beneficial effects on the surrogate parameters of disease (e.g., endothelial dysfunction) in patients with diabetes or coronary artery disease. The advantage of parenteral administration of water-soluble antioxidants is that high plasma concentrations are achieved, thereby omitting the complications of oral absorption and insufficient compliance. High-dose intravenous infusion of vitamin C also improved endothelial function in patients with kidney dysfunction and hypertension (Schmidt et al. 2015).

While oxidative stress has been looked at as detrimental, the wider role of redox balance and regulation as protective or adaptive pathway was neglected. In the failing heart phenotype, redox signaling characterized by specific, usually reversible, oxidation/reduction by ROS, is implicated in cardiomyocyte hypertrophy and cell death, fibrosis and chamber dilation, contractile dysfunction, Ca dysregulation and arrhythmia (Burgoyne et al. 2012).

In the failing heart abnormalities of Ca homeostasis are a fundamental feature. Redox signaling has a significant impact on Ca homeostasis in the cardiomyocyte. Ca^{2+} sensitivity and elasticity of contractile myofilaments depend on redox modifications which determine contractile dysfunction, arrhythmias and transcriptional changes (Zima and Blatter 2006).

Different cellular and enzymatic sources of ROS production have been suggested in HF patients with reduced ejection fraction (HF-rEF) compared to patients with preserved ejection fraction (HF-pEF). As suggested by Paulus *et al*, comorbidities also contribute to induce a pro-inflammatory state in patients with HF-pEF, where elevated plasma levels of TNF-α, interleukin-6 and pentraxin 3 may induce ROS production (Paulus and Tschope 2013).

In HF-pEF non-cardiac comorbidities like obesity, hypertension, anemia, chronic kidney disease, T2DM, and chronic obstructive pulmonary disease increase hospitalizations, with more non-HF admissions compared to HF-rEF (van Heerebeek and Paulus 2016). This fact is accompanied by an increased micronutrient deficit (e.g. iron, folate, vitamin B6

Table 1. The most important micronutrients with impact in heart failure.

Amino Acids	Enzymes	Vitamins	Fatty Acids	Microelements
Taurine L-carnitine	Coenzyme Q10	Thiamine (vitamin B1) Riboflavin (vitamin B2) Pyridoxine (vitamin B6) Vitamin C Vitamin D	Omega-3	Magnesium Potassium Selenium

and vitamin B12), which further contributes to decreased efficiency of antioxidant enzymes and of tissue oxygenation.

Aging per se is associated with arterial stiffening, atherosclerosis and endothelial dysfunction (Barodka et al. 2011), but in the presence of a sedentary lifestyle (Sîrbu et al. 2015) and HF, it becomes an important risk factor for future cardiovascular events. Endothelial dysfunction in heart failure can be corrected with oral or intra-arterial administration of vitamin C, suggesting a role for oxidative stress in this phenomenon (Hornig et al. 1998).

Implications for therapy

An accurate assessment of prognosis in patients with heart failure should take into account in addition to the echocardiographic parameters already consecrated (Mornos et al. 2014), also the deficiency of micronutrients.

Present treatment strategies in HF include increase of inotropic function and hemodynamic and/or neuro-hormonal cardio-active medications (Bistola and Chioncel 2017). They are not designed for regeneration of normal cardiac myocytes and are not oriented towards increasing the energy needs of the failing heart.

The concept of energy depletion in the failing heart is not adequately investigated. Instead of focusing on increases in energy supply, most treatments have energy-sparing effects like ACE inhibitors, angiotensin II blockers and beta-receptor blockers. They may determine improvements of symptoms, but they ignore the most important underlying cause of HF, which is insufficient energy production. This might explain the poor prognosis in HF patients. The new treatment paradigm is, therefore, a shift to a more promising therapeutic strategy for functional recovery of cardiomyocytes, and consecutive enhancement of energetic metabolism in the heart (Stanley and Chandler 2002; Sinatra 2009).

From this perspective, the effects of cardio-active medications might be misleading. It has been established that vasodilation therapy decreases oxygen demand in the myocardium, while inotropic medication increases myocardial oxygen demand. By consuming energy in chronic ischemic conditions with compromised oxygen supply, inotropes may contribute to increased heart failure mortality. Beta-blockers may also hasten energy depletion in HF patients performing high intensity exercise (Wong, Niedzwiecki, and Rath 2016). Heart failure patients on long term furosemide therapy may present water-soluble vitamin deficits, especially of B vitamins (Zenuk et al. 2003).

The energy depletion hypothesis in HF seems promising, by rendering a role to micronutrients for correcting symptoms of HF. The specific metabolic deficiencies found in the failing myocardium are represented by a reduction in myocardial energy production by decrease of coenzyme Q10, L-carnitine, and thiamin; a relative deficiency of taurine responsible for intracellular calcium homeostasis and increased oxidative stress due to impairment of antioxidant defenses. Each deficiency can be corrected by dietary supplementation. Nutritional supplementation in HF designed for correcting these complex metabolic abnormalities needs further research. Numerous nutrients have been investigated as single therapeutic agents in pharmacologic fashion, without any broad-based approach. Micronutrients include coenzyme Q10 (Co Q10), fatty acids, amino acids (AAs) and vitamins (Lee et al. 2011).

The most important micronutrients with impact in heart failure are represented in Table 1.

Aminoacids

Amino acids are compounds of proteins which are highly metabolized in skeletal muscles of patients with HF even at rest (Sciatti et al. 2016). During the hyper-catabolic state characteristic of HF, AAs are released consecutive to degradation of muscle proteins, determining a progressive loss of muscle volume. Myocardial performance may be improved by AAs (Drake et al. 2012).

Taurine

Taurine is a sulfur containing conditionally essential AA, being the most abundant intracellular amino acid in humans with physiological functions as AA and as micronutrient. Diet is the main source of taurine in healthy individuals. Taurine has important antiarrhythmic, inotropic and chronotropic effects, as well as endocrine, metabolic and anti-inflammatory properties (Lourenco and Camilo 2002) which impact heart failure.

Taurine contributes to the function of mitochondrial enzymes and has antioxidant properties. Taurine deficiency in the failing heart is associated with reduced oxygen consumption, increased glycolysis and lactate concentration and decreased ATP activity (Sciatti et al. 2016).

A recent randomized controlled trial in HF patientson taurine supplementation demonstrated better exercise capacity and lower left ventricular (LV) end-diastolic pressures in the supplement group vs. placebo (Beyranvand et al. 2011).

Jeejeebhoy et al. tested multiple nutritional supplementation with an association of carnitine, CoQ10, and taurine vs. placebo in a study made on 49 HF patients after aorto-coronary artery bypass graft, with an ejection fraction <or =40%. They looked at the levels of micronutrients and

at the left ventricular function. Radionuclide ventriculography was performed at randomization and before surgery. Intraoperative myocardial biopsies were analyzed for carnitine, CoQ10, and taurine levels. The study demonstrated for the first time that supplementation determines higher myocardial levels of CoQ10, taurine, and carnitine associated with a decrease of left ventricular end-diastolic volume in patients with LV dysfunction. The authors concluded that supplementation made before intervention could improve the outcomes of revascularization due to the direct link between the risk of death and preoperative left ventricular end-diastolic volume (Jeejeebhoy et al. 2002).

However, a clear association between taurine supplementation and survival rates in HF has not yet been demonstrated. Further studies are necessary to determine the benefits of supplementation with taurine in HF.

Carnitine

Levocarnitine (L-carnitine) is a non-essential AA with cofactor role in fatty acid transport and glucose metabolism. L-carnitine supplementation has protection on the ischemic myocardium. L-carnitine serum levels are reduced to 50%in HF (Wende et al. 2017).

The cardio-protective effect of propionyl-L-carnitine (PLC) has been studied in different models of cardiac and endothelial dysfunction. Most of the clinical trials conducted in humans have concluded that PLC represents a potential treatment option in HF, peripheral arterial disease, stable angina and T2DM (Mingorance et al. 2011). Krim et al. have reviewed the genetic deficiencies of thiamin, L-carnitine, and taurine that are associated with specific cardiomyopathies. These deficiencies might worsen the prognosis in HF of other causes (Krim et al. 2013).

Supplementation with L-carnitine has been demonstrated to have anti-ischemic properties. In a trial on 472 coronary patients, randomized multicenter, L-carnitine was administered by intravenous infusion in the first 5 days to the total dose of 9 g/day. Chronic supplementation in a dose of 6 g/day orally followed for the next 1 year. The results demonstrated that L-carnitine prevented left ventricular dilatation and ventricular remodeling, helping to reduce the combined incidence of death and HF in the treated group (Iliceto et al. 1995).

During hypoxia, L-carnitine has been shown to improve the efficiency of the Krebs cycle. Results of phase-2 studies in HF patients demonstrated that long-term oral supplementation with propionyl-L-carnitine increases maximum oxygen consumption and exercise duration vs. placebo. In an multicenter trial on 537 patients, Ferrari et al. demonstrated that PLC significantly improves exercise capacity in HF-pEF (Ferrari and De Giuli 1997).

Zhi-Cheng et al. conducted a multicenter, randomized, placebo-controlled, double-blind study on 265 Chinese patients with HF. Patients were randomized to L-carnitine or placebo twice daily. After 7 days of treatment the reduction of the New York Heart Association (NYHA) functional class, changes in the 6-min walked distance test (6MWT), left ventricular ejection fraction and NT-proBNP levels were measured. 6MWT, alone or in combination with NYHA class, improved significantly in the treated group compared to placebo ($p = 0.0497$ and respectively $p = 0.003$). The lowest baseline values of free-plasma carnitine were noted in patients with higher NYHA who presented the most benefits of L-carnitine supplementation ($p = 0.002$). L-Carnitine was well tolerated in all patients (Jing et al. 2016).

CoenzymeQ10

CoQ10 or ubiquinol is a fat-soluble, vitamin-like substance widely distributed in the human body but especially in the heart, liver, kidney, and brain. CoQ10 acts as a lipophilic inner mitochondrial membrane cofactor that is used to shuttle electrons in the formation of ATP. The compound is synthesized in a number of reactions from mevalonic acid, whose production itself is inhibited by hydroxyl-methyl-glutaryl coenzyme A (HMG CoA) reductase inhibitors (Saini 2011).

CoQ10 acts as both antioxidant and electron acceptor at the level of the mitochondria. It is a key component in mitochondrial bioenergy transfer. Its enzymatic processes facilitate electron transfer in the generation of ATP (Maladkar 2016).

In mitochondria sequential redox reactions take place in the respiratory chain and a proton gradient which determines ATP production is formed. Mitochondrial complexes I through V are specialized protein complexes found in the inner mitochondrial membrane that facilitate the transfer of electrons. The ATP pool in cardiomyocytes is rapidly consumed, but cardiac output can be increased several fold in situations of stress. The ATP supply/demand balance is critical for normal function of cardiomyocytes. The mechanism for ATP supply in situations of increased demand (e.g. beta-adrenergic stimulation in exertion or in HF) is to accelerate regeneration of oxidized NAD + to reduced NADH. NADH is produced in the Krebs cycle, resulting electrons that will be donated to the electron transport chain. Proton translocation takes place across the inner mitochondrial membrane.The crucial cofactor, coenzyme Q10, lies at the intersection of electron transfers from both the Krebs cycle and in the reaction to reduced NADH (Maladkar 2016; Deichmann, Lavie, and Andrews 2010).

In addition to showing potential as an antioxidant and functioning as a cofactor in the mitochondrial respiratory chain, CoQ10 may have gene regulatory properties that might account for its effects on overall tissue metabolism (Linnane et al. 2002).

The biosynthesis of CoQ10 peaks in the early 20 s and declines with increasing age. Supplementation is needed to provide adequate intakes for energy production and antioxidant defense.

Supplementation with CoQ10 has been clinically tested in many diseases in more than 200 randomized controlled trials archived on PubMed. None of the trials reported serious adverse effects, except mild gastrointestinal discomfort, most probably due to the solvents used in the capsule, not to

CoQ10 per se (Ayer, Macdonald, and Stocker 2015).The therapeutic benefit of CoQ10 supplements was evident in rare cases of primary CoQ10 deficiencies. Furthermore, in cardiac patients, plasma CoQ10 has been found as independent predictor of mortality. Based on the fundamental role of CoQ10 in mitochondrial bioenergetics and its well-acknowledged antioxidant properties, several clinical trials evaluating CoQ10 have been undertaken in cardiovascular disorders of ageing including chronic HF, hypertension, and endothelial dysfunction (Rosenfeldt et al. 2003).

In the 2005 American College of Cardiology/American Heart Association HF guidelines, CoQ10 was acknowledged for the first time to bring possible benefits in HF patients, based on some studies, but supplementation has not been recommended until more data is available (Hunt et al. 2005).

In 1993 Morisco *et al.,* in a study on 641 patients with chronic congestive HF NYHA class III and IV, have provided persuasive evidence that supplementation with CoQ10 in addition to standard medication improved patient's symptoms, survival and incidence of events compared to placebo. Patients were randomly assigned to receive either placebo ($n = 322$) or CoQ102mg/kg per day ($n = 319$). After 1 year of supplementation, there were less hospitalizations for worsening HF in the CoQ10group ($n = 73$) vs. control ($n = 118$, $p < 0.001$). Episodes of pulmonary edema were reduced in the CoQ10 group (20 vs. 51 $p < 0.001$)compared to placebo (Morisco, Trimarco, and Condorelli 1993).

Judy *et al.* studied the myocardial protective effects of CoQ10 in high-risk patients ($n = 10$) during heart surgery compared to placebo ($n = 10$). Prior to surgery CoQ10 deficiency <0.6 microgram/ml was present in both groups, associated to low cardiac index (CI) (<2.4 l/m^2 per minute) and low LVEF (<35%). CoQ10 100 mg per day was given orally for 14 days before and 30 days after surgery. Pre-surgical CoQ10 treatment significantly improved blood and myocardial CoQ10 and myocardial ATP compared to placebo ($p < 0.01$). CI and LVEF were improved, but not significantly. The recovery course was short (3–5 days) and uncomplicated in the treated group. In the placebo group the recovery course was long (15–30 days) and complicated. Positive relationships between blood and myocardial CoQ10, myocardial ATP, cardiac function, and the postoperative recovery time course found in both study groups showed the therapeutic benefits of CoQ10 in preserving the myocardium during heart surgery (Judy, Stogsdill, and Folkers 1993).

In the last 20 years three meta-analyses on the effect of CoQ10 supplementation in chronic HF were published. These three meta-analyses selected for analysis only the studies double-blind, randomized and placebo-controlled. In at least eight other smaller randomized controlled trials of CoQ10 supplementation in HF patients, the investigators reported significant improvement of LVEF compared with placebo supplementation. LVEF is the measure of the volume of blood that the heart pumps with each contraction. It is exactly what needs to be improve in HF.

The Soja et al. meta-analysis examined the results of 14 clinical trials involving CoQ10 supplement added to the conventional medications of chronic HF. Only 8 of the 14 studies have fulfilled the inclusion criteria. The meta-analysis focused on the effect of CoQ10 supplementation on the most important parameters of heart function: total work capacity, stroke volume, cardiac output, ejection fraction, cardiac index, end-diastolic volume and systolic time intervals. In seven studies, CoQ10 supplementation has showed statistically significant improvement in all of the parameters except total work capacity and systolic time intervals. They concluded that these data were sufficient to consider CoQ10 supplements as adjunctive treatment of chronic HF (Soja and Mortensen 1997).

In 2006 Sander *et al.* published a second meta-analysis of 11 small randomized placebo controlled studies on the efficacy of CoQ10 supplementation in HF patients. The CoQ10 doses used in these trials ranged between 60 mg/day and 200 mg/day being administered for one or six months. This meta-analysis showed significant improvement in cardiac output and in ejection fraction. The authors concluded that systolic function in chronic HF is improved with the use of CoQ10 supplementation, which proved to be more effective in patients not being treated with angiotensin-converting enzyme inhibitors (Sander et al. 2006).

The third meta-analysis was published by Fotino et al. in 2013, and evaluated the effect of CoQ10 supplementation in HF in 13 studies, 11 of which had LVEF as an end-point and 3 of which had NYHA class as an end-point. All these studies ran from 4 to 28 weeks. The dosage of CoQ10 supplementation ranged from 60 mg/day to 300 mg/day. The results of the meta-analysis revealed a positive change in LVEF. NYHA classification was also positively change, but not statistically significant. Sub-group analysis revealed that positive effects of CoQ10 small doses (100 mg/day or less) appeared relatively quickly, in less than 12 weeks. Although sample sizes were small and had to be analyzed with caution, the authors considered the results encouraging. They concluded that were needed some well-designed studies enrolling diverse populations (Fotino, Thompson-Paul, and Bazzano 2013).

A new preparation of Coenzyme Q10 dissolved in vegetable oil has shown long-standing health benefits in the following randomized controlled trials: Q-Symbio study and KiSel-10 study.

Results of the Q-SYMBIO trial (Coenzyme Q10 as adjunctive treatment of chronic heart failure: a randomized, double-blind, multicentre trial with focus on SYMptoms, BIomarker status [Brain-Natriuretic Peptide (BNP)], and long-term Outcome [hospitalizations/mortality]) demonstrated that long-term use of CoQ10 in HF patients was safe and improved symptoms. The prospective study included 420 patients with moderate to severe HF randomized to receive 100 mg of CoQ10 3 times daily vs. placebo for two years, in addition to standard treatment. NYHA class presented a significant improvement in the CoQ10 supplementation group after 2 years vs. placebo ($p = 0.028$). Cardiovascular mortality, all-cause mortality and incidence

of hospitalizations for HF were significantly lower in the supplementation group compared to the placebo group ($p = 0.033$) (Mortensen et al. 2014).

The positive survival data from the meta-analyses of RCTs and the Q-SYMBIO study regarding NYHA classification and/or ejection fraction offer a very good evidence for CoQ10 supplementation in HF. Treatment with CoQ10 restores a deficiency state that reduces survival and quality of life in patients with HF. Previous RCTs with similar numbers of patients were considered enough to change treatment guidelines in HF. The CONSENSUS study (Cooperative North Scandinavian Enalapril Survival Study) from 1987 with enalapril, made on 253 patients, had an important impact on clinical practice in HF (1987). Also, the initial beta-blocker trial PRECISE (Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise) had fewer participants compared with the Q-SYMBIO study (PRECISE, $n = 278$ patients) (Packer et al. 1996).

A recent review published by Iyngkaran et al. on the validity of clinical trials in HF regarding beta-blocker treatment considers that the extent to which evidence from RCTs is generalizable to be included in guidelines of treatment in HF patients has not been well described (Iyngkaran et al. 2016).

Ezekowitz *et al.* questioned if the results of the Q-SYMBIO study could be replicable. A larger study with CoQ10 supplements for confirmation was considered useful (Ezekowitz 2014).

Kisel-10 was a study conducted in Sweden analyzing the effects of selenium and CoQ10 supplementation. KiSel-10 is short for Kinda + Selenium + CoQ10. The combination of selenium and CoQ10 proved to be particularly beneficial for elderly people in a small village called Kinda. KiSel-10 was a prospective randomized, placebo-controlled, double-blind clinical trial of supplementation with organic selenium and CoQ10 capsules in 443 healthy elderly Swedish volunteers for 48 months.The first results of the KiSel-10 study reported statistically significant reduction in cardiovascular deaths and in the levels of bio-markers for heart disease and improved of cardiac function on echocardiograms (Alehagen et al. 2013). Data sharing results in quintiles showed that long-term supplementation combination was most effective in elderly study participants who were in early to middle stages of developing cardiac dysfunction (quintiles 2 – 4). Analysis of two biomarkers in the KiSel-10 study (sP-selectin for atherosclerosis and hs-CRP for inflammation) showed significantly better outcomes in the group that received the combination supplements than in the placebo group (Alehagen et al. 2015).

After four years, subjects from the group that received the combination supplements had a slower deterioration of quality of life and less hospitalization. Follow-up analysis data from the four-year combined supplementation with selenium and CoQ10 extending to ten years showed statistically significantly lower mortality rates from CVD in the treatment group. The combined selenium and CoQ10 treatment showed positive risk reductions in participants who developed ischemic heart disease, in both genders, and in different NYHA functional classes, extending beyond the intervention period. The protection against CVD was not limited only to the four years, but persisted throughout the follow-up period (Alehagen, Aaseth, and Johansson 2015).

Onur et al. investigated the link between NT-proBNP and CoQ10 serum levels in an elderly population of healthy volunteers ($n = 871$). They noticed a negative association between them ($p < 0.001$). Compared to coronary patients with prior myocardial infarction ($n = 21$), volunteers had lower NT-proBNP levels and higher CoQ10 serum levels. Furthermore, CoQ10 supplementation in a dose of 150 mg/day for two weeks in a sub-group ($n = 53$) reduced the expression of CLCN6, a gene correlated to NT-proBNPserum level(Onur et al. 2015).

The results of another study made by Bellardinelli et al. demonstrated that in coronary patients with ischemic HF NYHA class II-III, oral CoQ10 supplementation significantly improved LV contractility, peak VO2 and endothelium-dependent relaxation in the brachial artery. CoQ10 supplementation combined with exercise training was more beneficial than CoQ10 or exercise alone(Belardinelli et al. 2006).

Vitamins

Vitamins B

Vitamins B are a group of water-soluble vitamins that function as coenzymes in the Krebs cycle and are required for ATP production. Their depletion in patients with HF also contributes to lower energy reserves in an already impaired metabolic environment.

One of the eight vitamins B, thiamin (vitamin B1), plays a direct role in providing myocardial energy by acting as a coenzyme in carbohydrate metabolism. Thiamine pyrophosphate serves as a cofactor of pyruvate dehydrogenase and trans-ketolase, mediators in the metabolism of energy substrate. It is an essential vitamin that cannot be endogenously synthesized and can only be stored in small quantities (Lonsdale 2006).

A recent cross-sectional study has shown that approximately one-third of patients hospitalized with HF have serum levels suggestive of thiamin deficiency. Shimon *et al.* determined the effect of thiamin supplementation on functional capacity and LVEF in patients with moderate or severe HF on furosemide at doses $\geq$80mg/day for at least 3 months. 30 patients were randomized a week for intravenous treatment with 200 mg thiamin/day or placebo, followed by oral administration of 200 mg thiamin/day for another 6 weeks. After intravenous administration, diuresis and sodium excretion significantly increased, as well as the LVEF ($p < 0.05$). After 7 weeks, LVEF increased by 22% ($p < 0.001$) (Shimon et al. 1995).

Another recent clinical trial where the patient's treatment was supplemented with 300 mg thiamin per day also showed improved ejection fraction. Considering that diuretic treatment in HF can cause increased thiamin excretion with a subsequent deficiency that further compromises cardiac function, Schoenenberger et al. evaluated the effect of high thiamin supplementation in these patients. 9 patients with

symptomatic HF under diuretic therapy with LVEF <40% were randomized to 300 mg thiamin/day or placebo for 28 days. After a 6 week wash-out period, the groups were crossed for the second treatment period. The results of the study demonstrated a significant increase in the ejection fraction by 32.8% ($p = 0.0024$) in the intervention group, and suggest that supplementation with thiamin in patients with symptomatic HF on high doses of diuretics has beneficial effects on cardiac function. The authors consider that the subclinical deficiency of thiamin is underestimated in these patients (Schoenenberger et al. 2012).

Riboflavin (vitamin B2) and pyridoxine (vitamin B6) are similar to thiamin in the sense that they are water-soluble, have renal elimination, their deposits in the body are limited, and their serum and tissue levels depend on ingestion (Said 2011). This is why it has been hypothesized that the levels of these B vitamins could be affected in HF (Keith et al. 2009). The two vitamins also have a role in the metabolism of carbohydrates. Although their role in energy metabolism is important, there are few evidences that document the effect of their deficiency in HF patients.

Keith et al. have studied the prevalence of vitamins B2 and B6 deficiencies in 100 hospitalized HF patients versus a group of healthy volunteers. 27% of HF patients had vitamin B2 deficiency and 38% vitamin B6 deficiency. These percentages were significantly higher than in the volunteer group ($p < 0.02$). The use of regular vitamin B supplements in HF patients did not significantly improve the deficit compared to those who did not use supplements. The deficiency of the two vitamins was not correlated with either the dose or the duration of diuretic treatment, although 80% of patients under study had furosemide treatment. The authors concluded that vitamin deficiency was not due to renal losses, and that supplementation should be done with higher doses than usual due to increased consumption in the hyper-catabolic state that characterizes HF (Keith et al. 2009).

Because of the physiological effect of these vitamins in HF, additional studies are needed to document the safety and efficacy of their administration in these patients.

Vitamin C

The source of vitamin C is exclusively represented by intake from natural sources, mainly fruits and vegetables. Vitamin C deficiency is very common in HF patients and is associated with increased mortality. The EPIC study "European Prospective Investigation into Cancer and Nutrition" correlated the plasma concentration of vitamin C with HF incidence and fatal and non-fatal events in 9,187 males and 11,122 females, with ages from 39 to 79 years. The study demonstrated an inverse association with cardiovascular risk in this population. Each increase in vitamin C plasma concentration by 20 mmol/L was associated with a 9% decrease in relative risk of HF after adjustment of age, gender, smoking, systolic blood pressure, diabetes, cholesterol and the body mass index (Pfister et al. 2011).

A study conducted on 20,536 patients with high cardiovascular risk from Great Britain, performed by the British Heart Foundation, has shown no benefit of supplementation with 250 mg/day of vitamin C, 600 mg/day of vitamin E and 20 mg/day of beta-carotene for 5 years, on the incidence or progression of coronary artery disease (2002).

In a double-blind trial vs. placebo Rossig et al. assessed endothelial cell (EC) protection by vitamin C in HF patients. Vitamin C administration to HF patients proved to significantly reduce plasma levels of circulating apoptotic microparticles of EC from baseline levels compared to placebo ($p < 0.005$). Vitamin C also significantly suppressed the pro-apoptotic activity on EC in the serum of HF patients ($p < 0.001$). The authors concluded that administration of vitamin C in HF patients suppresses EC apoptosis in vivo, determining important benefits on endothelial function and evolution of the disease (Rössig et al. 2001).

Vitamin D

The classic role of vitamin D is to increase intestinal calcium absorption to ensure adequate bone mineralization. The active form of vitamin D, 1,25-dihydroxy vitamin D3 ($1.25(OH)_2D3$), acts as a steroid hormone by binding to the vitamin D receptor (VDR) present in many cells in the body, including cardiomyocytes, smooth muscle cells and vascular endothelium. VDR is an intracellular hormonal receptor that binds specifically to $1.25(OH)_2D3$ and interacts with the target cell nucleus to produce biological effects. In vitro studies suggest that $1.25(OH)_2D3$ determines effects on muscle development, contractility and relaxation (Green et al. 2006).

VDR is found in endothelial cells, vascular smooth muscle cells, cardiomyocytes and inflammatory cells (Fig. 2). In endothelial cells, vitamin D has a key role in flux-mediated vasodilation with endothelial function and vascular tone optimization (Caraba et al. 2017, Norman and Powell 2014). In vascular smooth muscle cells, $1.25(OH)_2D3$ determines tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1) decrease, contributing to maintaining the physiological balance between fibrinolysis and thrombogenesis. Also at this level it ensures modulation of osteoblastic gene expression. In cardiomyocytes, $1.25(OH)_2D3$ modulates the proliferation, migration and differentiation of matrix proteins and normalizes sarcomeric function by regulating the calcium influx. All of these mechanisms provide adaptive physiological arterial and cardiac remodeling as well as the optimization of myocardial contractility(Norman and Powell 2014).

In *vitro* studies suggest that $1.25(OH)_2D_3$ decreases the production of pro-inflammatory cytokines and increases anti-inflammatory immune response in dendritic cells and macrophages, maintaining normal T-cell function, thus inhibiting vicious circles of inflammatory pathways worsening HF. There are epidemiological findings that link the low serum vitamin D levels to autoimmune diseases (multiple sclerosis and rheumatoid arthritis) (Caraba et al. 2017), as well as obstructive pulmonary diseases (asthma and chronic obstructive pulmonary disease) (Kell et al. 2002).

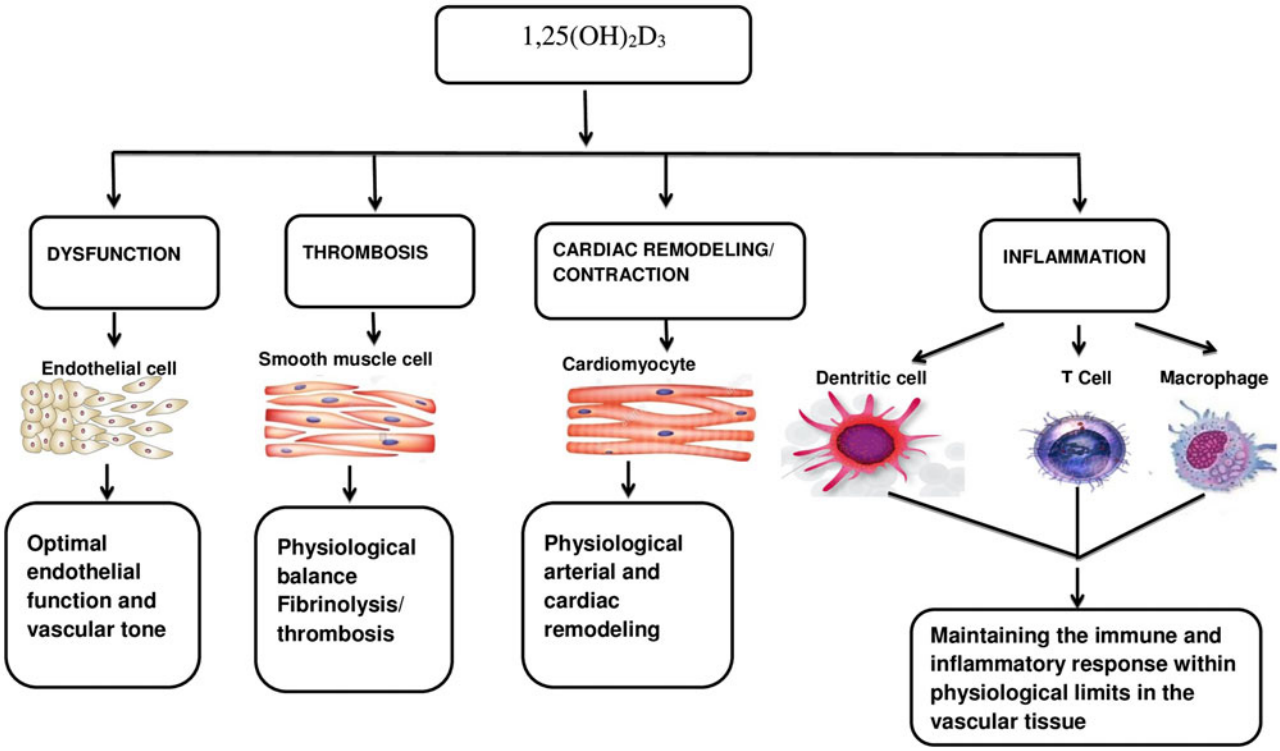

Figure 2. Multitarget effects of $1,25(OH)_2D_3$ (modified after Norman et al.) (Norman and Powell 2014).

Recent evidence shows that vitamin D deficiency contributes to increased incidence of cardiovascular disease, although not all the protective mechanisms have been fully elucidated. In addition to the mechanisms discussed above (Fig. 2), vitamin D achieves cardio-protection by regulating renin levels to lower blood pressure (BP), improving glycemic control and decreasing parathyroid hormone (PTH) levels. It is noted that excessive PTH increases BP and contractility, inducing cardiomyocyte hypertrophy and interstitial fibrosis of the heart as it is encountered in HF (Gardner, Chen, and Glenn 2013).

Currently, decreased vitamin D levels are endemic in the human population, especially in the elderly, which may explain its beneficial effect especially in this patient population (Bruyère et al. 2014). Vitamin D deficiency is accompanied by an increase in the incidence of HF precursor comorbidities such as hypertension, atherosclerosis and diabetes mellitus. The skin synthesis of vitamin D after exposure to ultraviolet radiation is the most important source of vitamin D in humans. In HF patients this exposure is insufficient due to the sedentary lifestyle with little outdoor activity(Zittermann, Schleithoff, and Koerfer 2006). Therefore, vitamin D deficiency is important, and hyperparathyroidism and impaired renal function common in these patients contribute to worsening of the disease.

From experimental studies it is known that vitamin D binds to VDRs and inhibits renin transcription by reducing plasma renin activity. Small studies have shown that $1.25(OH)_2D_3$ may also reduce angiotensin II levels by lowering blood pressure and myocardial hypertrophy (Schroten et al. 2013).

There are evidences from interventional trials demonstrating the beneficial effect of supplementation with vitamin D on blood pressure, endothelial function and cardiac hypertrophy in humans(Steven, Münzel, and Daiber 2015, Harris et al. 2011, Pfeifer et al. 2001). Although renin–angiotensin–aldosterone system (RAAS) blockers are the cornerstone for HF treatment by effectively reducing mortality and morbidity, continued elevation of plasma renin occurs. The only class of drugs that lowers renin levels in HF is β-blockers, by lowering the concentration and activity of plasma renin levels. New RAAS blockers are currently under investigation, but vitamin D could be an effective alternative and an already available RAAS blocker(Schroten et al. 2013).

However, large randomized placebo-controlled studies are needed to document the cardio-protective effects of vitamin D.

Most studies have so far focused on the benefits of supplementation with vitamin D on cardiovascular risk factors, not on HF parameters or biomarkers. A recent meta-analysis of observational studies suggests a positive effect of vitamin D supplementation on cardiovascular risk, although not all studies have shown positive results (Papandreou and Hamid 2015).

Future trials exploring the potential benefit of vitamin D in HF will have to accept surrogate end-points such as maximum oxygen consumption, left ventricular geometry measurements, and biomarkers like NT-proBNP, renin and aldosterone. The role of B-type natriuretic peptide (BNP) is largely represented by the counter-regulation of RAAS and is a marker widely used in this disease. Its production is stimulated by myocardial cell distension and it has been shown that $1.25(OH)_2D_3$ decreases the level of

immune-reactive native natriuretic peptide and its gene expression (Mandarino et al. 2015).

In an open-label study on 101 stable HF patients with reduced ejection fraction, Shroten et al. showed that after 6 weeks of administration of 2000 IU vitamin D3/day, plasma renin levels decreased compared to placebo ($p = 0.020$). There was no significant decrease in NT-proBNP and markers of fibrosis (Schroten et al. 2013). Although there is no consensus on the optimum vitamin D3 level, a normal value of 25 (OH) D_3 is considered more than 80 nmol/L, between 50 and 80 nmol/L hipovitaminosis and under 50 nmol/L deficiency. In the study conducted by Shroten et al., more than half of the patients had vitamin D deficiency at inclusion and only 10% had normal values (Schroten et al. 2013). A similar study effectuated by Witham *et al.*, demonstrated the decrease in NT-proBNP levels without effects on renin (Witham et al. 2010).

So far, it is unclear whether vitamin D supplementation is only beneficial in HF prevention or whether it can be included as an adjuvant treatment. An ongoing randomized trial investigates the impact of sustained daily supplementation with vitamin D on the 6 minute walk test, left ventricular function measured by magnetic resonance imaging, cardiopulmonary test parameters and biochemical changes in HF patients (VINDICATE, Vitamin D treatment in patients with Chronic heArTfailurE) (Witte et al. 2016). Another placebo-controlled, double-blind randomized study recruited HF patients with low vitamin D3 levels to demonstrate the effect of supplementation added to standard therapy on long-term prognosis (EVITA, Vitamin D and Mortality in Heart Failure) (Zittermann et al. 2017).

The levels of $1.25(OH)_2D_3$ decrease with age. Therefore, in elderly patients with HF, vitamin D deficiency is multifactorial, due in one part to limited mobility and, on the other to physiological decrease. In addition, by SNPs affecting the CYP27B1 gene, which is responsible for decoding the enzyme for activation of $1.25(OH)_2D_3$, increases in incidence and development of heart failure were noted in hypertensive patients(Wilke et al. 2009).

Microelements

Selenium

Selenium is an essential microelement for all living cells. The human body does not produce selenium, it comes exclusively from diet and the amount ingested depends on the content in the food or in the cultivated soil. There are regions in China, Northern Europe and New Zealand characterized by soils with low selenium content (Lopes, Ávila, and Guilherme 2017).

In the human body, selenium is incorporated into seleno-proteins such as glutathione peroxidase (GPx), thioredoxin reductase (TrxRs) and seleno-protein Sepp1, which protect against oxidative stress. Seleno-proteins exhibit a wide range of pleiotropic effects, from antioxidant and anti-inflammatory effects to active thyroid hormone production.

In the last 10 years, the discovery of diseases associated with polymorphisms of seleno-protein genes has highlighted their role in maintaining health. Low level of selenium has been associated with increased mortality, decreased immune response and cognitive deficits. The recommended daily dose of selenium in Europe is estimated at 40 µg/day, while in the United States it is 134 µg/day for men and 93 µg/day for women. These differences explain the inconsistency of selenium supplementation results in the Cochrane review published by Rees et al. (Rees et al. 2013).

The bioavailability of selenium is a limiting factor in the synthesis of many antioxidant seleno-proteins. Insufficient GPx-1 activity due to selenium deficiency was correlated with the occurrence of atherosclerosis in experimental studies and a reserved prognosis in patients with coronary artery disease (Blankenberg et al. 2003).

The correlation between ischemic heart diseases and selenium deficiency is controversial, as the results of selective intervention studies in coronary artery disease are conflicting.

Lubos et al. investigated the significance of selenium levels in patients with stable angina versus acute coronary syndromes on long-term prognosis in 1731 patients (852 with stable angina and 879 with acute coronary syndromes). During the follow-up of 6.1 years, 190 patients died of cardiovascular disease. The patients with acute coronary syndromes who died presented lower serum levels of selenium compared to survivors. In patients with stable angina were found no associations between selenium levels (Lubos et al. 2010).

Prospective studies that assessed the impact of tissue or serum selenium concentration on the incidence of coronary heart disease had discordant results. Progression of atherosclerosis does not appear to be altered by selenium supplementation, but supplementation may increase the risk of T2DM(Flores-Mateo et al. 2006).

Selenium deficiency can increase cardiovascular risk through various other mechanisms. By switching prostaglandin synthesis from prostacyclin to thromboxane, selenium deficiency can cause vasoconstriction and increased platelet aggregation. Randomized trials that followed-up the effect of selenium supplementation on platelet function, blood pressure, and lipid profile were contradictory. It appears that selenium supplementation only contributes to the decrease in the incidence of Keshan disease, a dilatative cardiomyopathy affecting young people in areas from China with poor concentration of selenium in the soil (Rees et al. 2012). For all these reasons, there is currently no recommendation for the use of selenium in cardiovascular prevention.

It was demonstrated that in heart failure there are low serum selenium concentrations compared to the healthy population. Witte et al. reported in 2005 the results of a randomized controlled trial in which supplementation with CoQ10, selenium and other micronutrients produced decreased LV volume, increased LVEF, and improved quality of life in elderly HF patients (Witte et al. 2005).

Leong *et al.* showed significant effects of supplementation for two months with selenium, CoQ10 and other micronutrients in preoperative preparation before coronary artery bypass grafting, followed by continued treatment for another

month post-surgery. Compared to placebo, patients in the intervention group experienced improved cardiac function parameters and required shorter postoperative hospitalization (Leong et al. 2010).

The results of the KiSel-10 study carried out by Alehagen et al. (Alehagen et al. 2013) on supplementation with CoQ10 and selenium in healthy elderly volunteers are presented in the section dealing with CoQ10.

Selenium can protect the cardiovascular system from the effect of heavy metals involved in atherogenesis such as mercury, cadmium, arsenic, by forming inactive complexes and consequently reducing oxidative stress.

Magnesium

Magnesium is a biologically active mineral that is essential for life. All cells require its presence. It acts as a cofactor in hundreds of enzymes involved in glucose metabolism, protein production and nucleic acid synthesis. Due to daily losses through urine, feces and sweating, the recommended daily dose is 350 mg/day for men and 300 mg/day for women. This is ensured by diets rich in whole grains, walnuts and green leafy vegetables. Magnesium deficiency is currently an important public health issue. European and American nutrition studies have shown that its daily intake is generally below the recommended level. Hypomagnesaemia is relatively common, it occurs at a serum concentration <0.74 mmol/L, with a prevalence of 2.5–15% in the general population. Low serum levels of magnesium were independently correlated with development or increased risk of worsening HF, but data about serum concentrations and evolution of patients are conflicting (Schuchardt and Hahn 2017).

In the study conducted by Song et al. there were measured the levels of 15 micronutrients after intake in 113 HF patients who have completed also a nutritional questionnaire and the Minnesota Living with Heart Failure Questionnaire for determining the quality of life. Patients were followed-up for 1 year for the number of hospitalizations and cardiac deaths. 58 patients (51%) had more than three micronutrient deficits. The most common micronutrient deficiencies were calcium, magnesium and vitamin D. They were independently associated with decreased quality of life. 39 patients were hospitalized or died by complications of HF (Song and Kang 2017).

Another study conducted by the same authors demonstrated an increase in the number of cardiac events due to the association of depressive symptoms that accompanied the deficiency of a large number of micronutrients in HF patients. In patients with a deficiency of more than 5 micronutrients, the depression scores were higher and the risk of cardiac events was 2.4 times higher compared to those with a deficit of less than 5 micronutrients. Survival without notable cardiac events in these patients was associated with the absence of depressive symptoms and was different depending on the micronutrient deficiency (Song et al. 2015).

A recent meta-analysis carried out by Angkananard et al. included 7 prospective studies on 5,172 patients with HF, mostly elderly men with LVEF $\leq$40%. Unlike all other studies, it showed that hypermagnesemia causes a significant increase in cardiovascular mortality, and hypomagnesaemia is not associated with such a risk. Hypermagnesemia was defined as serum magnesium $\geq$1.05 mmol/L. This result was limited to elderly patients with heart failure and altered systolic function (Angkananard et al. 2016).

The most recent meta-analysis of prospective cohort studies that have examined the dose-response effect of magnesium supplementation on cardiovascular risk, T2DM and all-cause mortality was made by Fang et al. The meta-analysis included 40 studies. The follow-up period ranged from 4 to 30 years, recording 701 cases of HF, 6,845 patients with coronary heart disease and 26,299 patients with T2DM. Notably, this is the first meta-analysis to investigate the effect of magnesium supplementation on the risk to develop HF. The dose-response analysis revealed that supplementation with 100 mg/day of magnesium is significantly associated with a 22% decrease in HF risk, 10% of all-cause deaths and 19% of T2DM. This study documented unequivocally the great advantage of administration of magnesium for maintaining health (Fang et al. 2016).

Kunutsor et al. have investigated the association of serum magnesium concentration with HF risk. 2,181 elderly men without HF enrolled in the Finnish Kuopio Ischemic Heart Disease Study were studied. The basal serum level of magnesium was inversely associated with markers of severity and directly associated with the risk of heart failure. During the follow-up period of 24.8 years, 278 cases of HF were recorded. The results were comparable in subgroups relevant for coronary artery disease and atrial fibrillation. The serum magnesium level was inversely and independently associated with the risk of HF. The authors conclude that further studies are needed to document the relevance of magnesium supplementation in the prevention of heart failure (Kunutsor, Khan, and Laukkanen 2016).

Potasium

Hypokalaemia is a strong independent predictor of mortality and is common in HF. The definition of normal serum potassium concentrationin the literature, depending on the incidence of malignant arrhythmias, especially associated ventricular fibrillation, varies between 3.5-5 mmol/l (Macdonald and Struthers 2004).

Hypokalaemia (serum levels less than 3.5 mmol/l) is more evident in advanced HF patients under high dose diuretic therapy with the most expressed activation of RAAS. In addition to this mechanism, catecholamines cause hypokalemia and increase arrhythmogenic risk. It appears that the benefit of decreasing mortality by β-blockers in HF is largely due to prevention of arrhythmias installed by hypokalemia (Cooper et al. 1999).

Also, hypokalemia may potentiate the arrhythmias associated with digital therapy in HF and may reduce the effectiveness of antiarrhythmic drugs by altering the electrophysiological properties of the myocardium. Hypokalaemia predisposes to digital toxicity by decreasing

renal clearance and facilitating myocardial use of digoxin with increased automatism and risk of ventricular arrhythmias. Frequency of ventricular extrasystoles and sudden death correlates with serum potassium levels. In patients with sudden cardiac death the myocardial potassium level is often lower versus control, and survivors may experience hypokalemia due to the migration of potassium from the intravascular compartment (Nolan et al. 1998).

Based on previous studies demonstrating that increased calcium, magnesium and potassium intake has beneficial effects in cardiovascular disease, Levitan et al. have conducted a study on 3,340 women with HF, participants in the Women's Health Initiative. They completed nutrition questionnaires, took the triple supplement and were followed-up for 4-6 years for all-cause mortality. The result showed that supplementation of these microelements was not significantly associated with mortality (Levitan et al. 2013).

Omega-3 and 6 fatty acids

The most important sources of omega-3 polyunsaturated fatty acids (N-3 PUFAs) include marine fish and seafood. N-3 PUFAs have been shown to decrease plasma triglyceride levels, heart rate and blood pressure, improve myocardial and vascular function, and decrease inflammation.

Long-chain nutritional intake of n-3 PUFA is now widely recommended for public health and medical practice. However, N-3 PUFAs are highly prone to oxidation, producing various degradation products, including mainly 4-hydroxy-2,3-trans-nonenal (HNE). Due to its high reactivity, HNE interacts with different cell macromolecules and the generated toxicity contributes clearly to a wide variety of pathological conditions. In addition, recent evidence suggests the more specific interaction of HNE in electrophilic signaling, acting as a second messenger of oxidative electrophilic stress. By modulation of major cellular processes such as autophagy, proliferation and apoptosis, HNE mediated signaling can greatly influence cell fate (Csala et al. 2015).

Moreover, increased HNE formation and myocardial dysfunction have been associated with various pathological conditions, such as myocardial ischemic reperfusion, HF and T2DM (Mali and Palaniyandi 2013).

Oxidative stress has been shown to be increased in the myocardium of patients with HF. The expression of HNE-modifying protein was 5-fold higher in patients with dilatated cardiomyopathy compared to controls (Csala et al. 2015).

In a study on 61 HF and 71 control patients, HNE products(HNE-P) were tested. All classes of circulating fatty acids and n-6 PUFAs were quantified. Significantly lower circulating levels of HDL- and LDL-cholesterol and linoleic acid were found in HF patients, even though circulating levels of HNE-P were similar in both groups. It has been suggested that the relative increase in HNE-P is associated with the decrease in HDL cholesterol in patients with HF. HNE-P levels in HF patients were also positively correlated with the classic symptoms of New York Heart Association (NYHA) (Asselin et al. 2014).

Experimental studies have shown that N-3 PUFAs also have a direct antiarrhythmic effect (Nair et al. 1997). In prospective observational studies and in randomized clinical trials, the clear effect of supplementation on coronary mortality and sudden death was demonstrated (Abdukeyum, Owen, and McLennan 2008). The effect is less documented on prognosis of nonfatal myocardial infarction, ischemic stroke, atrial fibrillation, ventricular arrhythmias and HF (Ander et al. 2003).

This is due to insufficient knowledge of physiological and molecular mechanisms, although N-3 PUFAs have been shown to modify the physical and chemical properties of cell membranes, interact directly with transmembrane channels or proteins, and regulate gene expression by nuclear receptors or transcription factors and they may alter the eicosanoid profile. However, the dose-response effect is not known, neither if fish oil has the benefits of full fish consumption, even if there are studies who concluded that eating fresh fish improveslipid profiles better than N-3 PUFAs supplementation (Zibaeenezhad et al. 2017). Clinical effects are also found in N-3 PUFAs of plant origin (Ramadeen and Dorian 2012).

Due to the clear effect on reducing cardiac death, international guidelines for healthy nutrition recommend consumption of at least 250 mg/day of N-3PUFAs or at least 2 servings of oily fish per week (Mozaffarian and Wu 2011).

Folate and homocysteine

Homocysteine is an independent risk factor for coronary heart disease. Its metabolism requires the presence of vitamins B12 and B6, and its conversion to methionine requires the presence of folate in the form of methylenetetrahydrofolate. Decreased plasma homocysteine levels have been investigated in many clinical trials. It is considered that decreases in serum concentration of homocysteine up to 3 µmol/L can be achieved by increasing the intake of folic acid by 0.8 mg/day, thus reducing the risk of stroke with 24%, ischemic heart disease by 16% and deep vein thrombosis by 25% (Jardine et al. 2012).

A study conducted on 205 patients after coronary angioplasty demonstrated that daily supplementation with 1 mg/day of folic acid, 400 µg/day of vitamin B12 and 10 mg/day of vitamin B6, resulted in a decrease in the mean plasma concentration of homocysteine from 11.1 to 7.2 µmol/L compared to placebo. There was also a significant decrease in the rate of restenosis and the need for myocardial revascularization in the intervention group (Schnyder and Rouvinez 2003).

A meta-analysis of 72 studies involving 16,849 cases analyzed the prevalence of tetrahydrofolate reductase gene mutations that increases the plasma homocysteine level in patients with cardiovascular diseases. As the increase in homocysteine is relatively low and the impact of the gene mutations depend on folate consumption, it is considered that these mutations are not relevant for determining cardiovascular risk (Wald, Law, and Morris 2002).

Effects of supplementation with multiple micronutrient associations

Considering that low-dose micronutrients are only useful in maintaining basal metabolic needs, while HF requires higher doses of micronutrients to achieve the therapeutic effect, 4 clinical trials have assessed HF from a multiple association perspective. Three of these were randomized controlled, and one was prospective. The micronutrients used were CoQ10, L-carnitine, taurine, thiamin and riboflavin because they are involved in the metabolic pathways of oxidative defense, energy production and balance of myocardial calcium.

All studies were performed in patients with HF with low LVEF $\leq$ 40%. In the three higher dose studies the results were positive, and in the low dose they did not show any benefit on LVEF, NYHA class, the distance ambulated by the 6MWT and LV diameters.

In the trials with high doses, a combination of 150 mg of CoQ10, 3 mg of L-carnitine, 3 mg of taurine, 25 mg of thiamin, 3 mg of riboflavin, and 250 mg of ascorbate was administered for 30–45 days (Jeejeebhoy et al. 2002), or 150 mg of CoQ10, 200 mg of thiamin, 2 mg of riboflavin and 500 mg of ascorbate for 9 months or 27 mg of CoQ10, 195 mg of L-carnitine, 200 mg of taurine, 22 mg of thiamin, 22 mg of riboflavin, 2450 mg of ascorbate, 1110 mg of lysine, 110 mg of proline and 790 mg of arginine for 4–8 months (Wong, Mohamed, and Niedzwiecki 2015).

Unlike all these, although it went on for the longest period (1 year), the study conducted by McKeag et al. was performed with very low doses, respectively 1.5 mg of thiamin, 1.6 mg of riboflavin and 60 mg of ascorbate and showed no benefit (McKeag et al. 2014).

In none of the previous studies, the micronutrient dose required to achieve therapeutic targets in HF is not commented on, neither is the need to stop supplementation and, as far as possible, reverse the hypercatabolic state. Under conditions of ischemia and hypercatabolism, the increase in energy demand determines the mobilization of all energy resources, therefore, to improve the nutrition of the heart, it is not enough to cover the energy substrate, but the supplementation must include high-dose amino acids and micronutrients (Wong, Niedzwiecki, and Rath 2016).

Kkeveetil *et al.* have published recently a systematic review about the role of micronutrients in HF, that looked at 3288 titles and abstracts. They considered only 11 trials encompassing 529 individuals appropriate to be included in their analysis. They concluded that micronutrients, either single or combined, improve health outcomes in HF patients by increasing LVEF, exercise tolerance and functional capacity, and that certain micronutrients may normalize endothelial function.This systematic review has found enough evidence to support the need for a large-scale trial on micronutrient supplementation in HF patients (Kkeveetil et al. 2016).

Conclusions

Heart failure is a multifactorial disease in which mechanisms have been analyzed from several perspectives: the hemodynamic concept, neurohormonal stimulation and energy metabolism. The main sources of energy, ATP, is synthetized in the heart muscle from fatty acids and glucose. The conversion of these macronutrients into biological energy requires the presence of micronutrients: CoQ10, L-carnitine, taurine,thiamin, riboflavin. Micronutrients act as cofactors in the production and transfer of energy and in maintaining the contractile function of the heart.

Micronutrient deficiencies are associated with survival and quality of life in patients with HF. Numerous studies on micronutrients conducted with single or combination preparations have shown beneficial effects on contractile parameters, incidence of cardiac events, and mortality in heart failure. However, it order to equally address all the pathways of energy production, antioxidant defense and myocardial calcium balance, multiple associations of micronutrients are necessary.

Heart failure is characterized by a hypercatabolic state in which ATP and micronutrients are consumed very quickly, and therefore increased micronutrient doses are required to achieve therapeutic effects.

Future studies are needed to document the effects of multiple micronutrient associations in order to include them in nutritional guidelines to increase survival and to improve quality of life in patients with heart failure.

Conflict of interest

None

References

CONSENSUS Trial Study Group. 1987. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Sztudy (CONSENSUS). *The New England Journal of Medicine* **316** (23):1429–35. doi:10.1056/nejm198706043162301.

Heart Protection Study Collaborative Group. 2002. MRC/BHF heart protection study of antioxidant vitamin supplementation in 20,536 high-risk individuals: A randomised placebo-controlled trial. *Lancet* **360** (9326):23–33. doi:10.1016/s0140-6736(02)09328-5.

Abdukeyum, G. G., A. J. Owen, and P. L. McLennan. 2008. Dietary (n-3) long-chain polyunsaturated fatty acids inhibit ischemia and reperfusion arrhythmias and infarction in rat heart not enhanced by ischemic preconditioning. *The Journal of Nutrition* **138** (10):1902–9. doi:10.1093/jn/138.10.1902.

Alehagen, U., J. Aaseth, and P. Johansson. 2015. Reduced cardiovascular mortality 10 years after supplementation with selenium and coenzyme Q10 for four years: Follow-Up results of a prospective randomized Double-Blind Placebo-Controlled trial in elderly citizens. *PLoS One* **10** (12):e0141641. doi:10.1371/journal.pone.0141641.

Alehagen, U., P. Johansson, M. Bjornstedt, A. Rosen, and U. Dahlstrom. 2013. Cardiovascular mortality and N-terminal-proBNP reduced after combined selenium and coenzyme Q10 supplementation: A 5-year prospective randomized double-blind placebo-controlled trial among elderly Swedish citizens. *International Journal of Cardiology* **167** (5):1860–6. doi:10.1016/j.ijcard.2012.04.156.

Alehagen, U., T. L. Lindahl, J. Aaseth, E. Svensson, and P. Johansson. 2015. Levels of sP-selectin and hs-CRP decrease with dietary intervention with selenium and coenzyme Q10 combined: A secondary analysis of a randomized clinical trial. *PLoS One* **10** (9):e0137680. doi:10.1371/journal.pone.0137680.

Ander, B. P., C. M. C. Dupasquier, M. A. Prociuk, and G. N. Pierce. 2003. Polyunsaturated fatty acids and their effects on cardiovascular disease. *Experimental & Clinical Cardiology* **8** (4):164–72.

Angkananard, T., T. Anothaisintawee, S. Eursiriwan, O. Gorelik, M. McEvoy, J. Attia, and A. Thakkinstian. 2016. The association of serum magnesium and mortality outcomes in heart failure patients: A systematic review and Meta-analysis. *Medicine (Baltimore)* **95** (50):e5406. doi:10.1097/md.0000000000005406.

Asselin, C., A. Ducharme, T. Ntimbane, M. Ruiz, A. Fortier, M.-C. Guertin, J. Lavoie, A. Diaz, É. Levy, J.-C. Tardif, and C. Des Rosiers. 2014. Circulating levels of linoleic acid and HDL-cholesterol are major determinants of 4-hydroxynonenal protein adducts in patients with heart failure. *Redox Biology* **2**:148–55. doi:10.1016/j.redox.2013.12.009.

Ayer, A.,. P. Macdonald, and R. Stocker. 2015. CoQ(1)(0) function and role in heart failure and ischemic heart disease. *Annual Review of Nutrition* **35** (1):175–213. doi:10.1146/annurev-nutr-071714-034258.

Barodka, V. M., B. L. Joshi, D. E. Berkowitz, C. W. Hogue, and D. Nyhan. 2011. Implications of vascular aging. *Anesthesia and Analgesia* **112** (5):1048–60. doi:10.1213/ANE.0b013e3182147e3c.

Belardinelli, R., A. Mucaj, F. Lacalaprice, M. Solenghi, G. Seddaiu, F. Principi, L. Tiano, and G. P. Littarru. 2006. Coenzyme Q10 and exercise training in chronic heart failure. *European Heart Journal* **27** (22):2675–81. doi:10.1093/eurheartj/ehl158.

Beyranvand, M. R., M. K. Khalafi, V. D. Roshan, S. Choobineh, S. A. Parsa, and M. A. Piranfar. 2011. Effect of taurine supplementation on exercise capacity of patients with heart failure. *Journal of Cardiology* **57** (3):333–7. doi:10.1016/j.jjcc.2011.01.007.

Bistola, V., and O. Chioncel. 2017. Inotropes in acute heart failure. *Continuing Cardiology Education* **3** (3):107–16. doi:10.1002/cce2.59.

Blankenberg, S., H. J. Rupprecht, C. Bickel, M. Torzewski, G. Hafner, L. Tiret, M. Smieja, F. Cambien, J. Meyer, and K. J. Lackner. 2003. Glutathione peroxidase 1 activity and cardiovascular events in patients with coronary artery disease. *The New England Journal of Medicine* **349** (17):1605–13. doi:10.1056/NEJMoa030535.

Bruyère, O., E. Cavalier, J.-C. Souberbielle, H. A. Bischoff-Ferrari, C. Beaudart, F. Buckinx, J.-Y. Reginster, and R. Rizzoli. 2014. Effects of vitamin D in the elderly population: Current status and perspectives. *Archives of Public Health = Archives Belges de Sante Publique* **72**(1): 32. doi:10.1186/2049-3258-72-32.

Burgoyne, J. R., H. Mongue-Din, P. Eaton, and A. M. Shah. 2012. Redox signaling in cardiac physiology and pathology. *Circulation Research* **111** (8):1091–106. doi:10.1161/circresaha.111.255216.

Caraba, A., V. Crişan, I. Romoşan, I. Mozoş, and M. Murariu. 2017. Vitamin D status, disease activity, and endothelial dysfunction in early rheumatoid arthritis patients. *Disease Markers* **2017**:1. doi:10.1155/2017/5241012.

Cooper, H. A., D. L. Dries, C. E. Davis, Y. L. Shen, and M. J. Domanski. 1999. Diuretics and risk of arrhythmic death in patients with left ventricular dysfunction. *Circulation* **100** (12):1311–5.

Csala, M., T. Kardon, B. Legeza, B. Lizák, J. Mandl, É. Margittai, F. Puskás, P. Száraz, P. Szelényi, and G. Bánhegyi. 2015. On the role of 4-hydroxynonenal in health and disease. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* **1852** (5):826–38. doi:10.1016/j.bbadis.2015.01.015.

Dandona, P., H. Ghanim, A. Chaudhuri, S. Dhindsa, and S. S. Kim. 2010. Macronutrient intake induces oxidative and inflammatory stress: Potential relevance to atherosclerosis and insulin resistance. *Experimental and Molecular Medicine* **42** (4):245–53. doi:10.3858/emm.2010.42.4.033.

Deichmann, R., C. Lavie, and S. Andrews. 2010. Coenzyme Q10 and statin-induced mitochondrial dysfunction. *The Ochsner Journal* **10** (1):16–21.

Drake, K. J., V. Y. Sidorov, O. P. McGuinness, D. H. Wasserman, and J. P. Wikswo. 2012. Amino acids as metabolic substrates during cardiac ischemia. *Experimental Biology and Medicine (Maywood, N.J.)* **237** (12):10. doi:10.1258/ebm.2012.012025.

Dzau, V. J., E. M. Antman, H. R. Black, D. L. Hayes, J. E. Manson, J. Plutzky, J. J. Popma, and W. Stevenson. 2006. The cardiovascular disease continuum validated: Clinical evidence of improved patient outcomes: Part I: Pathophysiology and clinical trial evidence (risk factors through stable coronary artery disease). *Circulation* **114** (25): 2850–70. doi:10.1161/circulationaha.106.655688.

Eaton, S. B., S. B. Eaton, 3rd, and M. J. Konner. 1997. Paleolithic nutrition revisited: A twelve-year retrospective on its nature and implications. *European Journal of Clinical Nutrition* **51** (4):207–16.

Ezekowitz, J. A. 2014. Time to energize coenzyme Q10 for patients with heart failure? *JACC Heart Fail* **2** (6):650–2. doi:10.1016/j.jchf.2014.07.007.

Fang, X., Han Wang, K. D., X. He, J. Wei, L. Zhao, M. U. Imam, Z. Ping, Y. Li, Y. Xu, J., et al. 2016. Dietary magnesium intake and the risk of cardiovascular disease, type 2 diabetes, and all-cause mortality: A dose-response meta-analysis of prospective cohort studies. *BMC Medicine* **14** (1):210.

Ferrari, R., and F. De Giuli. 1997. The propionyl-L-carnitine hypothesis: An alternative approach to treating heart failure. *Journal of Cardiac Failure* **3** (3):217–24.

Flores-Mateo, G., A. Navas-Acien, R. Pastor-Barriuso, and E. Guallar. 2006. Selenium and coronary heart disease: A Meta-analysis. *The American Journal of Clinical Nutrition* **84** (4):762–73.

Fotino, A. D., A. M. Thompson-Paul, and L. A. Bazzano. 2013. Effect of coenzyme Q(1)(0) supplementation on heart failure: A Meta-analysis. *The American Journal of Clinical Nutrition* **97** (2):268–75. doi:10.3945/ajcn.112.040741.

Gardner, D. G., S. Chen, and D. J. Glenn. 2013. Vitamin D and the heart. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* **305** (9):R969–77. doi:10.1152/ajpregu.00322.2013.

Green, J. J., D. A. Robinson, G. E. Wilson, R. U. Simpson, and M. V. Westfall. 2006. Calcitriol modulation of cardiac contractile performance via protein kinase C. *Journal of Molecular and Cellular Cardiology* **41** (2):350–9. doi:10.1016/j.yjmcc.2006.05.019.

Harris, R. A., J. Pedersen-White, D. H. Guo, I. S. Stallmann-Jorgensen, D. Keeton, Y. Huang, Y. Shah, H. Zhu, and Y. Dong. 2011. Vitamin D3 supplementation for 16 weeks improves flow-mediated dilation in overweight African-American adults. *American Journal of Hypertension* **24** (5):557–62. doi:10.1038/ajh.2011.12.

Hartupee, J., and D. L. Mann. 2017. Neurohormonal activation in heart failure with reduced ejection fraction. *Nature Reviews Cardiology* **14** (1):30–8. doi:10.1038/nrcardio.2016.163.

Hornig, B., N. Arakawa, C. Kohler, and H. Drexler. 1998. Vitamin C improves endothelial function of conduit arteries in patients with chronic heart failure. *Circulation* **97** (4):363–8.

Houston, M. 2014. The role of nutrition and nutraceutical supplements in the treatment of hypertension. *World Journal of Cardiology* **6** (2): 38–66. doi:10.4330/wjc.v6.i2.38.

Hunt, S. A., Abraham, W. T. M. H. Chin, A. M. Feldman, G. S. Francis, T. G. Ganiats, M. Jessup, M. A. Konstam, D. M. Mancini, K. Michl, J. A., et al. 2005. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: A report of the American college of cardiology/American heart association task force on practice guidelines (Writing committee to update the 2001 guidelines for the evaluation and management of heart failure): Developed in collaboration with the American college of chest physicians and the international society for heart and lung transplantation: Endorsed by the heart rhythm society. *Circulation* **112** (12):e154–235. doi:10.1161/circulationaha.105.167586.

Iliceto, S., D. Scrutinio, P. Bruzzi, G. D'Ambrosio, L. Boni, M. Di Biase, G. Biasco, P. G. Hugenholtz, and P. Rizzon. 1995. Effects of L-carnitine administration on left ventricular remodeling after acute anterior myocardial infarction: The L-Carnitine Ecocardiografia digitalizzata infarto miocardico (CEDIM) trial. *Journal of the American College of Cardiology* **26** (2):380–7.

Iyngkaran, P., S. R. Toukhsati, M. C. Thomas, M. V. Jelinek, D. L. Hare, and J. D. Horowitz. 2016. A review of the external validity of clinical trials with Beta-Blockers in heart failure. *Clinical Medicine Insights. Cardiology* **10**:163–71. doi:10.4137/CMC.S38444.

Jardine, M. J., A. Kang, S. Zoungas, S. D. Navaneethan, T. Ninomiya, S. U. Nigwekar, M. P. Gallagher, A. Cass, G. Strippoli, and V. Perkovic. 2012. The effect of folic acid based homocysteine lowering

on cardiovascular events in people with kidney disease: Systematic review and Meta-analysis. *BMJ* **344**:e3533. doi:10.1136/bmj.e3533.

Jeejeebhoy, F., M. Keith, M. Freeman, A. Barr, M. McCall, R. Kurian, D. Mazer, and L. Errett. 2002. Nutritional supplementation with MyoVive repletes essential cardiac myocyte nutrients and reduces left ventricular size in patients with left ventricular dysfunction. *American Heart Journal* **143** (6):1092–100.

Jing, Z.-C., Wu, B.-X. J.-Q. Peng, X.-L. Li, L. Pan, S.-P. Zhao, D.-Y. Li, Z.-X. Yu, J.-B. Gong, Q.-Y. Zhao, J.-N., et al. 2016. Effect of intravenous l-carnitine in Chinese patients with chronic heart failure. *European Heart Journal Supplements* **18** (Suppl A):A27–36. doi:10.1093/eurheartj/suw008.

Judy, W. V., W. W. Stogsdill, and K. Folkers. 1993. Myocardial preservation by therapy with coenzyme Q10 during heart surgery. *The Clinical Investigator* **71** (8 Suppl):S155–S61.

Keith, M. E., N. A. Walsh, P. B. Darling, S. A. Hanninen, S. Thirugnanam, H. Leong-Poi, A. Barr, and M. J. Sole. 2009. B-vitamin deficiency in hospitalized patients with heart failure. *Journal of the American Dietetic Association* **109** (8):1406–10. doi:10.1016/j.jada.2009.05.011.

Kell, R., A. Haunstetter, T. J. Dengler, C. Zugck, W. Kubler, and M. Haass. 2002. Do cytokines enable risk stratification to be improved in NYHA functional class III patients? Comparison with other potential predictors of prognosis. *European Heart Journal* **23** (1): 70–8. doi:10.1053/euhj.2001.28. 0.

Kkeveetil, C., Valiyakizha, G. Thomas, and S. J. U. Chander. 2016. Role of micronutrients in congestive heart failure: A systematic review of randomized controlled trials. *Tzu-Chi Medical Journal* **28** (4): 143–50. doi:10.1016/j.tcmj.2016.08.001.

Krim, S. R., P. Campbell, C. J. Lavie, and H. Ventura. 2013. Micronutrients in chronic heart failure. *Current Heart Failure Reports* **10** (1):46–53. doi:10.1007/s11897-012-0118-4.

Kunutsor, S. K., H. Khan, and J. A. Laukkanen. 2016. Serum magnesium and risk of new onset heart failure in men: The Kuopio ischemic heart disease study. *European Journal of Epidemiology* **31** (10): 1035–43. doi:10.1007/s10654-016-0164-4.

Lee, J. H., T. Jarreau, A. Prasad, C. Lavie, J. O'Keefe, and H. Ventura. 2011. Nutritional assessment in heart failure patients. *Congestive Heart Failure* **17** (4):199–203. doi:10.1111/j.1751-7133.2011.00239.x.

Leong, J. Y., J. van der Merwe, S. Pepe, M. Bailey, A. Perkins, R. Lymbury, D. Esmore, S. Marasco, and F. Rosenfeldt. 2010. Perioperative metabolic therapy improves redox status and outcomes in cardiac surgery patients: A randomised trial. *Heart, Lung and Circulation* **19** (10):584–91. doi:10.1016/j.hlc.2010.06.659.

Levitan, E. B., J. M. Shikany, A. Ahmed, L. G. Snetselaar, L. W. Martin, J. D. Curb, and C. E. Lewis. 2013. Calcium, magnesium and potassium intake and mortality in women with heart failure: The women's health initiative. *British Journal of Nutrition* **110** (01): 179–85. doi:10.1017/s0007114512004667.

Linnane, A. W., G. Kopsidas, C. Zhang, N. Yarovaya, S. Kovalenko, P. Papakostopoulos, H. Eastwood, S. Graves, and M. Richardson. 2002. Cellular redox activity of coenzyme Q10: Effect of CoQ10 supplementation on human skeletal muscle. *Free Radical Research* **36** (4): 445–53.

Lonn, E., J. Bosch, S. Yusuf, P. Sheridan, J. Pogue, J. M. Arnold, C. Ross, A. Arnold, P. Sleight, J. Probstfield, et al. 2005. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: A randomized controlled trial. *JAMA* **293** (11):1338–47. doi:10.1001/jama.293.11.1338.

Lonsdale, D. 2006. A review of the biochemistry, metabolism and clinical benefits of thiamin(e) and its derivatives. *Evidence-Based Complementary and Alternative Medicine* **3** (1):49–59. doi:10.1093/ecam/nek009.

Lopes, G., F. W. Ávila, and L. R. G. Guilherme. 2017. Selenium behavior in the soil environment and its implication for human health. *Ciência e Agrotecnologia* **41** (6):605–15.

Lourenco, R., and M. E. Camilo. 2002. Taurine: A conditionally essential amino acid in humans? An overview in health and disease. *Nutricion Hospitalaria* **17** (6):262–70.

Lubos, E., Sinning, C. R. R. B. Schnabel, P. S. Wild, T. Zeller, H. J. Rupprecht, C. Bickel, K. J. Lackner, D. Peetz, J. Loscalzo, T., et al. 2010. Serum selenium and prognosis in cardiovascular disease: Results from the AtheroGene study. *Atherosclerosis* **209** (1):271–7. doi:10.1016/j.atherosclerosis.2009.09.008.

Lundberg, A. M., and Z. Q. Yan. 2011. Innate immune recognition receptors and damage-associated molecular patterns in plaque inflammation. *Current Opinion in Lipidology* **22** (5):343–9. doi:10.1097/MOL.0b013e32834ada80.

Macdonald, J. E., and A. D. Struthers. 2004. What is the optimal serum potassium level in cardiovascular patients? *Journal of the American College of Cardiology* **43** (2):155–61.

Maladkar, M. 2016. Coenzyme Q10: The cardiac bio-energizer in cardiovascular diseases. *Journal of Cardiology & Cardiovascular Therapy* **1**(2):555560. doi:10.19080/jocct.2016.01.555560.

Mali, V., and S. S. Palaniyandi. 2013. Regulation and therapeutic strategies of 4-hydroxy-2-nonenal metabolism in heart disease. *Free Radical Research* **48**:251–63.

Mandarino, N. R., F. D C. M. Júnior, J. V. L. Salgado, J. S. Lages, and N. S. Filho. 2015. Is vitamin d deficiency a new risk factor for cardiovascular disease? *The Open Cardiovascular Medicine Journal* **9** (1):40–9. doi:10.2174/1874192401509010040.

McKeag, N. A., M. C. McKinley, M. T. Harbinson, R. L. Noad, L. H. Dixon, A. McGinty, C. E. Neville, J. V. Woodside, and P. P. McKeown. 2014. The effect of multiple micronutrient supplementation on left ventricular ejection fraction in patients with chronic stable heart failure: A randomized, placebo-controlled trial. *JACC Heart Fail* **2** (3):308–17. doi:10.1016/j.jchf.2013.12.008.

Mingorance, C., R. Rodriguez-Rodriguez, M. L. Justo, M. D. Herrera, and M. A. de Sotomayor. 2011. Pharmacological effects and clinical applications of propionyl-L-carnitine. *Nutrition Reviews* **69** (5): 279–90. doi:10.1111/j.1753-4887.2011.00387.x.

Morisco, C., B. Trimarco, and M. Condorelli. 1993. Effect of coenzyme Q10 therapy in patients with congestive heart failure: A long-term multicenter randomized study. *Clinical Investigation* **71** (8 Suppl.): S134–S6.

Mornos, C., L. Petrescu, D. Cozma, and A. Ionac. 2014. A new tissue doppler index to predict cardiac death in patients with heart failure. *Arquivos Brasileiros de Cardiologia* **102** (1):19–29. doi:10.5935/abc.20130222.

Mortensen, S. A., F. Rosenfeldt, A. Kumar, P. Dolliner, K. J. Filipiak, D. Pella, U. Alehagen, G. Steurer, and G. P. Littarru. 2014. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: Results from Q-SYMBIO: A randomized double-blind trial. *JACC Heart Fail* **2** (6):641–9. doi:10.1016/j.jchf.2014.06.008.

Mozaffarian, D., L. J. Appel, and L. Van Horn. 2011. Components of a cardioprotective diet: New insights. *Circulation* **123** (24):2870–91. doi:10.1161/circulationaha.110.968735.

Mozaffarian, D., and J. H. Wu. 2011. Omega-3 fatty acids and cardiovascular disease: Effects on risk factors, molecular pathways, and clinical events. *Journal of the American College of Cardiology* **58** (20):2047–67. doi:10.1016/j.jacc.2011.06.063.

Nair, S. S.D., J. W. Leitch, J. Falconer, and M. L. Garg. 1997. Prevention of cardiac arrhythmia by dietary (n-3) polyunsaturated fatty acids and their mechanism of action. *The Journal of Nutrition* **127** (3):383–93. doi:10.1093/jn/127.3.383.

Nolan, J., Batin, P. D. R. Andrews, S. J. Lindsay, P. Brooksby, M. Mullen, W. Baig, A. D. Flapan, A. Cowley, R. J. Prescott, J. M., et al. 1998. Prospective study of heart rate variability and mortality in chronic heart failure: Results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). *Circulation* **98**(15):1510–6.

Norman, P. E., and J. T. Powell. 2014. Vitamin D and cardiovascular disease. *Circulation Research* **114** (2):379–93. doi:10.1161/circresaha.113.301241.

O'Rourke, M. F., M. E. Safar, and V. Dzau. 2010. The cardiovascular continuum extended: Aging effects on the aorta and microvasculature. *Vascular Medicine* **15** (6):461–8. doi:10.1177/1358863x10382946.

Onur, S., P. Niklowitz, G. Jacobs, W. Lieb, T. Menke, and F. Doring. 2015. Association between serum level of ubiquinol and NT-

proBNP, a marker for chronic heart failure, in healthy elderly subjects. *Biofactors* **41** (1):35–43. doi:10.1002/biof.1198.

Packer, M., Colucci, W. S. J. D. Sackner-Bernstein, C. S. Liang, D. A. Goldscher, I. Freeman, M. L. Kukin, V. Kinhal, J. E. Udelson, M. Klapholz, S. S., et al. 1996. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE trial. Prospective randomized evaluation of carvedilol on symptoms and exercise. *Circulation* **94** (11):2793–9.

Panth, N., K. R. Paudel, and K. Parajuli. 2016. Reactive oxygen species: A key hallmark of cardiovascular disease. *Advances in Medicine* **2016**:1. doi:10.1155/2016/9152732.

Papandreou, D., and Z. T. Hamid. 2015. The role of vitamin D in diabetes and cardiovascular disease: An updated review of the literature. *Disease Markers* **2015**:1. doi:10.1155/2015/580474.

Paulus, W. J., and C. Tschope. 2013. A novel paradigm for heart failure with preserved ejection fraction: Comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *Journal of the American College of Cardiology* **62** (4):263–71. doi:10.1016/j.jacc.2013.02.092.

Pfeifer, M., B. Begerow, H. W. Minne, D. Nachtigall, and C. Hansen. 2001. Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. *Journal of Clinical Endocrinology and Metabolism* **86** (4):1633–7. doi:10.1210/jcem.86.4.7393.

Pfister, R., S. J. Sharp, R. Luben, N. J. Wareham, and K. T. Khaw. 2011. Plasma vitamin C predicts incident heart failure in men and women in European prospective investigation into cancer and Nutrition-Norfolk prospective study. *American Heart Journal* **162** (2):246–53. doi:10.1016/j.ahj.2011.05.007.

Ponikowski, P.,. Voors, A. A. S. D. Anker, H. Bueno, J. G. Cleland, A. J. Coats, V. Falk, J. R. Gonzalez-Juanatey, V. P. Harjola, E. A. Jankowska, M., et al. 2016. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the European society of cardiology (ESC)developed with the special contribution of the heart failure association (HFA) of the ESC. *European Heart Journal* **37** (27):2129–200. doi:10.1093/eurheartj/ehw128.

Ramadeen, A., and P. Dorian. 2012. How are n-3 LCPUFAs antiarrhythmic? A reassessment of n-3 LCPUFAs in cardiac disease. *Cardiology Research and Practice* **2012**:1. doi:10.1155/2012/746709.

Rees, K., L. Hartley, C. Day, N. Flowers, A. Clarke, and S. Stranges. 2013. Selenium supplementation for the primary prevention of cardiovascular disease. *Cochrane Database Systematic Reviews* (1):Cd009671. doi:10.1002/14651858.CD009671.pub2.

Rees, K., L. Hartley, C. Day, A. Clarke, and S. Stranges. 2012. Selenium supplementation for the primary prevention of cardiovascular disease. *The Cochrane Database of Systematic Reviews* **2012** (2):CD009671. doi:10.1002/14651858.CD009671.

Roger, V. L. 2013. Epidemiology of heart failure. *Circulation Research* **113** (6):646–59. doi:10.1161/CIRCRESAHA.113.300268.

Roig, E. 2006. Usefulness of neurohormonal markers in the diagnosis and prognosis of heart failure. *European Heart Journal Supplements* **8** (Suppl_E):E12–7. doi:10.1093/eurheartj/sul025.

Rosenfeldt, F., D. Hilton, S. Pepe, and H. Krum. 2003. Systematic review of effect of coenzyme Q10 in physical exercise, hypertension and heart failure. *Biofactors* **18** (1–4):91–100.

Rössig, L., J. Hoffmann, B. Hugel, Z. Mallat, A. Haase, J.-M. Freyssinet, A. Tedgui, A. Aicher, A. M. Zeiher, and S. Dimmeler, 2001. Vitamin C inhibits endothelial cell apoptosis in congestive heart failure. *Circulation* **104** (18):2182–7.

Said, HamidM. 2011. Intestinal absorption of water-soluble vitamins in health and disease. *Biochemical Journal* **437** (3):357–72. doi:10.1042/BJ20110326.

Saini, RAJIV. 2011. Coenzyme Q10: The essential nutrient. *Journal of Pharmacy and Bioallied Sciences* **3** (3):466–7. doi:10.4103/0975-7406.84471.

Sander, S., C. I. Coleman, A. A. Patel, J. Kluger, and C. M. White. 2006. The impact of coenzyme Q10 on systolic function in patients with chronic heart failure. *Journal of Cardiac Failure* **12** (6):464–72. doi:10.1016/j.cardfail.2006.03.007.

Schmidt, H. H., R. Stocker, C. Vollbracht, G. Paulsen, D. Riley, A. Daiber, and A. Cuadrado. 2015. Antioxidants in translational medicine. *Antioxidants & Redox Signaling* **23** (14):1130–43. doi:10.1089/ars.2015.6393.

Schnyder, G., and G. Rouvinez. 2003. Total plasma homocysteine and restenosis after percutaneous coronary angioplasty: Current evidence. *Annals of Medicine* **35** (3):156–63.

Schoenenberger, A. W., R. Schoenenberger-Berzins, C. A. der Maur, P. M. Suter, A. Vergopoulos, and P. Erne. 2012. Thiamine supplementation in symptomatic chronic heart failure: A randomized, double-blind, placebo-controlled, cross-over pilot study. *Clinical Research in Cardiology* **101** (3):159–64. doi:10.1007/s00392-011-0376-2.

Schroten, N. F., Ruifrok, W. P. L. Kleijn, M. M. Dokter, H. H. Sillje, H. J. Lambers Heerspink, S. J. Bakker, I. P. Kema, W. H. van Gilst, D. J. van Veldhuisen, H. L., et al. 2013. Short-term vitamin D3 supplementation lowers plasma renin activity in patients with stable chronic heart failure: An open-label, blinded end point, randomized prospective trial (VitD-CHF trial). *American Heart Journal* **166** (2):357–64.e2. doi:10.1016/j.ahj.2013.05.009.

Schuchardt, JanPhilipp, and ANDREAS Hahn. 2017. Intestinal absorption and factors influencing bioavailability of Magnesium-An update. *Current Nutrition and Food Science* **13** (4):260–78. doi:10.2174/1573401313666170427162740.

Sciatti, E., C. Lombardi, A. Ravera, E. Vizzardi, I. Bonadei, V. Carubelli, E. Gorga, and M. Metra. 2016. Nutritional deficiency in patients with heart failure. *Nutrients* **8** (7):442. doi:10.3390/nu8070442.

Shay, C. M., J. Stamler, A. R. Dyer, I. J. Brown, Q. Chan, P. Elliott, L. Zhao, N. Okuda, K. Miura, M. L. Daviglus, and L. Van Horn. 2012. Nutrient and food intakes of Middle-aged adults at low risk of cardiovascular disease: The international study of macro-/micronutrients and blood pressure (INTERMAP). *European Journal of Nutrition* **51** (8):917–26. doi:10.1007/s00394-011-0268-2.

Shenkin, A. 2006. Micronutrients in health and disease. *Postgraduate Medical Journal* **82** (971):559–67. doi:10.1136/pgmj.2006.047670.

Shimon, I., S. Almog, Z. Vered, H. Seligmann, M. Shefi, E. Peleg, T. Rosenthal, M. Motro, H. Halkin, and D. Ezra. 1995. Improved left ventricular function after thiamine supplementation in patients with congestive heart failure receiving long-term furosemide therapy. *American Journal of Medicine* **98** (5):485–90.

Sinatra, S. T. 2009. Metabolic cardiology: An integrative strategy in the treatment of congestive heart failure. *Alternative Therapies in Health and Medicine* **15** (3):44–52.

Sîrbu, E., R. Buzaș, R. Mihăescu, I. Suceava, and D. Lighezan. 2015. Influence of exercise training and eating behavior on arterial stiffness in young healthy students. *Wiener Klinische Wochenschrift* **127** (13–14):555–60. doi:10.1007/s00508-015-0799-2.

Soja, A. M., and S. A. Mortensen. 1997. Treatment of congestive heart failure with coenzyme Q10 illuminated by Meta-analyses of clinical trials. *Molecular Aspects of Medicine* **18** (Suppl):S159–S68.

Song, E. K., and S. M. Kang. 2017. Micronutrient deficiency independently predicts adverse health outcomes in patients with heart failure. *Journal of Cardiovascular Nursing* **32** (1):47–53. doi:10.1097/jcn.0000000000000304.

Song, E. K., D. K. Moser, S. M. Kang, and T. A. Lennie. 2015. Association of depressive symptoms and micronutrient deficiency with cardiac Event-Free survival in patients with heart failure. *Journal of Cardiac Failure* **21** (12):945–51. doi:10.1016/j.cardfail.2015.10.007.

Soukoulis, V., J. B. Dihu, M. Sole, S. D. Anker, J. Cleland, G. C. Fonarow, M. Metra, E. Pasini, T. Strzelczyk, H. Taegtmeyer, et al. 2009. Micronutrient deficiencies. An unmet need in heart failure. *Journal of the American College of Cardiology* **54** (18):1660–73. doi:10.1016/j.jacc.2009.08.012.

Stanley, W. C., and M. P. Chandler. 2002. Energy metabolism in the normal and failing heart: Potential for therapeutic interventions. *Heart Failure Reviews* **7** (2):115–30.

Steven, SEBASTIAN, THOMAS Münzel, and ANDREAS Daiber. 2015. Exploiting the pleiotropic antioxidant effects of established drugs in cardiovascular disease. *International Journal of Molecular Sciences* **16** (8):18185–223. doi:10.3390/ijms160818185.

van Heerebeek, L., and W. J. Paulus. 2016. Understanding heart failure with preserved ejection fraction: Where are we today? *Netherlands Heart Journal* **24** (4):227–36. doi:10.1007/s12471-016-0810-1.

Wald, D. S., M. Law, and J. K. Morris. 2002. Homocysteine and cardiovascular disease: Evidence on causality from a Meta-analysis. *BMJ (Clinical Research Edition)* **325** (7374):1202

Wende, A. R., M. K. Brahma, G. R. McGinnis, and M. E. Young. 2017. Metabolic origins of heart failure. *JACC Basic to Translational Science* **2** (3):297–310. doi:10.1016/j.jacbts.2016.11.009.

Wilke, R. A., R. U. Simpson, B. N. Mukesh, S. V. Bhupathi, R. A. Dart, N. R. Ghebranious, and C. A. McCarty. 2009. Genetic variation in CYP27B1 is associated with congestive heart failure in patients with hypertension. *Pharmacogenomics* **10** (11):1789–97. doi:10.2217/pgs.09.101.

Witham, M. D., L. J. Crighton, N. D. Gillespie, A. D. Struthers, and M. E. McMurdo. 2010. The effects of vitamin D supplementation on physical function and quality of life in older patients with heart failure. *Circulation: Heart Failure* **3** (2):195–201. doi:10.1161/circheartfailure.109.907899.

Witte, K. K., N. P. Nikitin, A. C. Parker, S. von Haehling, H. D. Volk, S. D. Anker, A. L. Clark, and J. G. Cleland. 2005. The effect of micronutrient supplementation on quality-of-life and left ventricular function in elderly patients with chronic heart failure. *European Heart Journal* **26** (21):2238–44. doi:10.1093/eurheartj/ehi442.

Witte, K. K., R. Byrom, J. Gierula, M. F. Paton, H. A. Jamil, J. E. Lowry, R. G. Gillott, S. A. Barnes, H. Chumun, L. C. Kearney, et al. 2016. Effects of vitamin D on cardiac function in patients with chronic HF: The VINDICATE study. *Journal of the American College of Cardiology* **67** (22):2593–603. doi:10.1016/j.jacc.2016.03.508.

Wong, A. P., A. L. Mohamed, and A. Niedzwiecki. 2015. The effect of multiple micronutrient supplementation on quality of life in patients with symptomatic heart failure secondary to ischemic heart disease: A prospective case series clinical study. *American Journal of Cardiovascular Disease* **5** (3):146–52.

Wong, A. P., A. Niedzwiecki, and M. Rath. 2016. Myocardial energetics and the role of micronutrients in heart failure: A critical review. *American Journal of Cardiovascular Disease* **6** (3):81–92.

Zenuk, C., J. Healey, J. Donnelly, R. Vaillancourt, Y. Almalki, and S. Smith. 2003. Thiamine deficiency in congestive heart failure patients receiving long term furosemide therapy. *Canadian Journal of Clinical Pharmacology* **10** (4):184–8.

Zibaeenezhad, M. J., M. Ghavipisheh, A. Attar, and A. Aslani. 2017. Comparison of the effect of omega-3 supplements and fresh fish on lipid profile: A randomized, open-labeled trial. *Nutrition & Diabetes* **7** (12):1. doi:10.1038/s41387-017-0007-8.

Zima, A. V., and L. A. Blatter. 2006. Redox regulation of cardiac calcium channels and transporters. *Cardiovascular Research* **71** (2):310–21. doi:10.1016/j.cardiores.2006.02.019.

Zittermann, A., Ernst, J. B. S. Prokop, U. Fuchs, J. Dreier, J. Kuhn, C. Knabbe, I. Birschmann, U. Schulz, H. K. Berthold, S., et al. 2017. Effect of vitamin D on all-cause mortality in heart failure (EVITA): A 3-year randomized clinical trial with 4000 IU vitamin D daily. *European Heart Journal* **38** (29):2279–2286. doi:10.1093/eurheartj/ehx235.

Zittermann, A., S. S. Schleithoff, and R. Koerfer. 2006. Vitamin D insufficiency in congestive heart failure: Why and what to do about it? *Heart Failure Reviews* **11** (1):25–33. doi:10.1007/s10741-006-9190-8.