

Metabolic syndrome, nutritional deficits and heart failure

Nicoleta-Monica Popa-Fotea^{1,2*}, Miruna Mihaela Micheu², Maria Dorobantu^{1,2}

¹Cardiology Department, Carol Davila University of Medicine and Pharmacy, Clinical Emergency Hospital, Bucharest, Romania

²Cardiology Department, Clinical Emergency Hospital, Bucharest, Romania

Received: February 12, 2020, Accepted: March 9, 2020

Abstract

Heart failure (HF) is the most common cause of death in subjects over 65 years old. Despite the new pharmacological and non-pharmacological developments, HF remains a challenge for physicians world-wide. There is a high correlation between the components of metabolic syndrome (MS) and the incidence of HF, but the mechanisms through which these cluster of factors influence HF is still under debate; furthermore in chronic, advanced HF, obesity and arterial hypertension have paradoxical effects, being associated with better outcomes. In this article, will be revise the role of each individual risk factor for the development of HF with a focus on the therapeutic windows for major adverse cardiac events reduction. HF is also highly associated with various nutritional deficits that may influence the overall outcome; some of the most important nutritional deficits will be discussed related to the impact of diet supplementation in HF.

Keywords: heart failure; metabolic syndrome; nutritional defects; major adverse cardiac events

Introduction

Despite the development of pharmacological and non-pharmacological treatment in the last decade, the management of heart failure (HF) is still a challenge, reflected both in the high rate of rehospitalization for HF with increased mortality and morbidity, as well as in its prevalence, representing the most

common cause of death in individuals over 65 years of age [1]. Metabolic syndrome (MS), which includes in its definition a cluster of cardiovascular risk factors, such as insulin resistance, arterial hypertension (HT), lipid abnormalities and obesity, has a high prevalence in subjects with HF. Over time, the definition of MS knew various changes from the initial one formulated in 1998 by World Health Organization [2] little has been changed since that time. There is however considerable new knowledge regarding the aetiology of different forms of diabetes as well as more information on the predictive value of different blood glucose values for the complications of diabetes. A WHO Consultation has

*Correspondence to: Nicoleta-Monica POPA-FOTEA, MD, PhD Carol Davila University of Medicine and Pharmacy, Cardiology, Clinical Emergency Hospital, Bucharest, Romania, E-mail: fotea.nicoleta@yahoo.com
Phone: +40-724-381385

therefore taken place in parallel with a report by an American Diabetes Association Expert Committee to re-examine diagnostic criteria and classification. The present document includes the conclusions of the former and is intended for wide distribution and discussion before final proposals are submitted to WHO for approval. The main changes proposed are as follows. The diagnostic fasting plasma (blood sustaining that MS should be defined in subjects with type 2 DM or modified fasting glycemia or impaired glucose tolerance plus any two of the followings: high-density lipoprotein-cholesterol (HDL-C) <40 mg/dl in men and <50 mg/dl in woman and/or triglycerides \geq 150 mg/dl; body mass index $>$ 30 kg/m² or index waist-hip $>$ 0.9 in men and $>$ 0.85 in women; arterial hypertension (HT) $>$ 140/90 mmHg. From this initial definition, the criteria for MS were changed, in 2001 the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) [3] defined SM if three or more of the following criteria were met: HT $>$ 130/85, triglycerides $>$ 150 mg/dl, HDL $<$ 50 mg/dl in women and $<$ 40 mg/dl in men, waist circumference $>$ 40 inches in men, $>$ 35 inches in women and fasting glycemia $>$ 110 mg/dl. The NCEP-ATP III is one of the most widely used definition, as it incorporates all the central components of MS and does not require a specific criterion to be present. Also newer definitions from the Joint Interim Statement, require at least three criteria very similar with those from the NCEP-ATP III 2001 with one exception, the waist circumference thresholds were lowered both in men and women [4] which occur together more often than by chance alone, have become known as the metabolic syndrome. The risk factors include raised blood pressure, dyslipidemia (raised triglycerides and lowered high-density lipoprotein cholesterol. One remark should be made concerning the omnipresence of HT in all definitions over time.

The progression of HF as well as, fatal and non-fatal adverse cardiovascular events are highly correlated with MS, but the mechanisms relating MS with HF are unclear. It is still uncertain whether MS independently predicts cardiovascular prognosis or rather reflects the individual impact of each distinctive risk factor included in its definition. It is not surprising that 45-years-old subjects that did not have any of the following risk factors:

obesity, HT or diabetes mellitus (DM) lived on average 35 years longer with no signs and symptoms of HF compared to those having one or more of the risk factors mentioned [5]. In addition to MS, there are other metabolic factors that can influence or induce HF, such as: hemochromatosis, hyperuricemia, L-carnitine, taurine, coenzyme Q10 (CoQ10), vitamin B1 or vitamin D deficiency, etc.

Impact of metabolic syndrome components on the incidence and prognosis of HF

Insulin resistance, hyperglycemia and diabetes

Patients with DM type 2 have a high risk of developing HF, either with conserved or reduced left ventricular ejection fraction (LVEF), compared to the non-diabetic population. While the association between mortality and HbA_{1c} level in diabetic patients with HF seems to have a U-form in some studies, with the lowest mortality in those with HbA_{1c} of about 7%, in others it is associated with an increased risk of death and hospitalization for HF regardless of HbA_{1c}. If initially diabetic cardiomyopathy was used as a general term to describe LVEF dysfunction in the absence of coronary heart disease (CHD) or HT, today the term is used more broadly and refers to the description of myocardial vulnerability in individuals with DM. One study shows a 44% incidence of type 2 DM in patients with HF decompensations [6] we assessed temporal trends in diabetes prevalence among patients with HF and in subgroups with reduced ejection fraction (HFrEF; EF $<$ 40%. Twenty percentage of patients with DM will develop HF, independently of other causes, such as diastolic dysfunction, compared to only 10% of those without DM [7]. The risk of HF is increased even in minor alterations of glucose regulation; in a study that included over 18.000 patients without DM, but at high risk for cardiovascular events, one mmol/L increase in blood sugar was associated with a 1.23 rise of the risk for HF hospitalizations. Metabolic imbalances are closely related to the pathophysiology of HF, with insulin resistance occurring in 60% of patients with HF. DM can contribute by various mechanisms to the development

of HF: abnormalities of cardiac contractile proteins, relaxation dysfunction, modifications of energetic substrate, cellular injury, microvascular dysfunction and neurohormonal changes with hyper-activation of sympathetic tonus. Hyperglycemia increases the synthesis of hexosamines and polyols, formation of glycation products, overexpression of protein kinase C with increased oxidative stress and superoxide. Advanced glycation products increase arterial rigidity and reactive oxygen species leading to apoptosis and global cellular dysfunction [8]. Intracellular glucose transportation is reduced at myocardial level in DM due to the decrease of glucose transporters, GLUT 1 and GLUT 4, resulting in an increase of free fatty acids consumption and consequently, disproportionate demand for oxygen at mitochondrial level with decoupling of oxidative phosphorylation. Altered expression of myosin isoforms with predominance of fetal beta-myosin reduces myofibrillar adenosine-triphosphate (ATP)-dependent activities with abnormal calcium transportation and thus, calcium cell overloading. Abnormalities of microcirculation pinpointed by decreased endothelium-mediated flow reserve in DM patients can contribute to the development of HF by inducing repeated myocardial ischemia. Increased levels of G-protein-coupled receptor kinase 2, a protein that plays a role in cardiac beta-desensitization, have been identified in patients with HF and DM compared to non-diabetics [9].

Certain old classes of oral antidiabetics are not recommended for patients with HF and DZ, including: thiazolidinediones as these increase the risk of HF by hydro-saline retention and weight gain, dipeptidyl-peptidase inhibitors 4, which rises the risk of HF hospitalizations [10] or sulfonylureas, which increase mortality, probably through inhibition of myocardial preconditioning, hypoglycemia and HT [11]. Until recently, no drugs could destroy the paradox that although DM increased cardiovascular disease, its treatment was not associated with a reduction in risk, but nowadays there are oral antidiabetic drugs that have been shown to lower cardiovascular and HF risk in the same time with hyperglycemia. The two classes of anti-diabetic drugs that proved to have beneficial cardiovascular effects are: inhibitors of type 2 Na-glucose transporters (SGLT2i) inducing glycosuria with many beneficial effects on

cardiovascular system and glucagon-like peptide-1 receptor agonists (GLP-1R). Empagliflozin, one of the SGLT2i, reduced cardiovascular mortality and HF hospitalizations in the EMPA-REG trial [12], with similar effects being found in another class representative, canagliflozin [13] body weight, and albuminuria in people with diabetes. We report the effects of treatment with canagliflozin on cardiovascular, renal, and safety outcomes. **METHODS:** The CANVAS Program integrated data from two trials involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk. Participants in each trial were randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188.2 weeks. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. **RESULTS:** The mean age of the participants was 63.3 years, 35.8% were women, the mean duration of diabetes was 13.5 years, and 65.6% had a history of cardiovascular disease. The rate of the primary outcome was lower with canagliflozin than with placebo (occurring in 26.9 vs. 31.5 participants per 1000 patient-years; hazard ratio, 0.86; 95% confidence interval [CI], 0.75 to 0.97; $P < 0.001$ for non-inferiority; $P = 0.02$ for superiority. GLP-1R agonists are oral antidiabetic drugs that favor, among others, weight loss with reduced risk of hypoglycemia, but clinical trials had uncertain results referring to their usefulness in HF patients, although in patients with type 2 DM and high cardio-vascular, liraglutide may be a valid option for the prevention of cardio-vascular events [14].

Glucotoxicity and lipotoxicity

The metabolic disorders that occur in uncontrolled DM increase the number of ketones, fatty acids and glucose. The inability of the myocardium to process these substrates induces mitochondrial dysfunction, which ultimately leads to the accumulation of toxic intermediary products with myocardial injury by activation of aberrant signaling pathways [15]. Recent studies show that hyperglycemia modulates the expression of myocardial genes by epigenetic mechanisms or direct activation of transcription factors [16]. Through a similar mechanism, lipotoxicity exerts myocardial injuries, demonstrated both in vitro [17] and in vivo [18].

Arterial Hypertension

HT is the most prevalent modifiable risk factor of HF, favoring the development of LV hypertrophy and CHD. In the initial stages of HT, LV function is not affected, until mechanical stress following the increase of intraventricular pressure induces abnormal levels of cytokines and growth factors leading to LV hypertrophy and progression towards HF. The progression of HF is characterized by changes in the extracellular matrix, diastolic dysfunction and extensive myocardial fibrosis with remodeling, dilation and, finally, LV dysfunction. Cardiac remodeling during pressure overload consists of concentric LV hypertrophy, while remodeling in volume overload leads to eccentric hypertrophy. When the pressure overload is sustained, diastolic dysfunction develops with concentric remodeled LV and HF with preserved LVEF. The final stage of hypertensive heart disease, usually a combination of pressure and volume overload, is dilated cardiomyopathy with reduced LVEF, with the mention that diastolic dysfunction is far more common than systolic LV dysfunction. It is important to note that isolated diastolic dysfunction is a prevalent cause of acute cardiogenic pulmonary edema, even in the presence of a preserved LVEF [19]. A lot of studies have showed the benefic effects of antihypertensive treatment for the prevention of HF in the population of hypertensive subjects [20,21]. Although HT is a trigger for HF, the increased values of systolic arterial tension in those with HF are paradoxically associated with a protective effect and increased survival, numerous studies showing that increased systolic arterial tension is associated with fewer cardiovascular events. McAlister explained the beneficial effect of beta-blocker therapy in HF, as that the decrease of ventricular heart rate is associated with an increase of central arterial tension, a phenomenon also encountered in the case of ivabradine [22].

Lipid abnormalities

Decreased HDL-C and increased triglycerides are plasma abnormalities included in the definition of MS. Considering the protective effect of HDL-C for the cardiovascular system such as anti-inflammatory, anti-oxidant and maintaining normal endothelial function, it can be deduced that low HDL-C is

associated with increased risk of HF. However, the beneficial effect of all HDL-C molecules has been questioned by recent studies. Plasmatic HDL-C is a heterogeneous group of particles build on the surface of ApoA-I with different biological structure and activity, due to their different content in cholesterol transporters and receptors [23] to mere biomarker status. HDL is slowly emerging from these dark times due to the HDL flux hypothesis wherein measures of HDL cholesterol efflux capacity (CEC). Two studies, IDEAL and EPIC, showed that HDL-C levels ≥ 70 mg/dL and HDL-C particles greater than 9.53 nm were associated with a higher cardiovascular risk, while ApoA-I remained a protective factor that reflected more accurately the decrease in cardiovascular risk compared to HDL-C [24]. In fact, the nature of HDL-C components is essential to appreciate the detrimental or benefic effect. For example, ApoA-I containing the 2-OH-Trp72 group is associated with pro-atherogenic processes at the arterial level [25]. Furthermore, glycation end-products may affect the function of HDL-C, a factor contributing to atherosclerosis acceleration in type 2 DM [26], or in SM, due to the decreased antioxidant capacity, HDL-C become dysfunctional [27] atherogenic dyslipidemia, oxidative stress, and elevated cardiovascular risk and frequently involves subnormal levels of high-density lipoprotein (HDL). The myocardial accumulation of lipids in the form of intermediate products interferes with the anti-oxidative and reparative processes favoring HF development [28] as free intra-cardiac fatty acids deposit under the form of triglycerides is a source of toxic bio-products that impair myocardial beta-oxidation capacity [29]. Despite the fact that low HDL-C and increased high-density lipoprotein-cholesterol (LDL-C) are associated with increased cardiovascular disease, there is a “cholesterol paradox” as HF patients with low total cholesterol tend to have poorer outcomes compared with those with normal or higher cholesterol. Baseline cholesterol is pinpointed as a strong predictor of HF mortality and rehospitalizations [30]. Cholesterol lowering therapy is associated with HF reduction only in CHD, while there are no evidence that this have a role to prevent non-ischemic HF. 2019 European guideline for dyslipidemia does not recommend the initiation of statin therapy in those with chronic HF and no other indication for

their use, while in those already on statin treatment the continuation should be considered [31]. There are promising treatments arising such as proprotein-convertase subtilisin/kexin type 9 (PCSK-9) inhibitors, as one study finds a positive correlation between circulation PCSK-9 and worsening HF [32]. Future studies are needed to investigate if PCSK-9 inhibitors could lead to HF improvement.

Obesity

Although obesity is a recognized cardiovascular risk factor, there are meta-analyses showing that obesity can have a paradoxical protective effect in patients with HF. Although there is a temptation to explain this paradox only through the unfavorable association between severe HF and cardiac cachexia, this mechanism is not sufficiently comprehensive. In one study, subjects with HF and MS but without DM had the best survival rate compared with those with MS and DM or with DM, but without MS [33]. From this results that insulin resistance, but not obesity, is a risk factor for HF.

Impact of nutritional components on the incidence and prognosis of HF

Cardiac hemochromatosis

Cardiomyopathy by iron overload defined by systolic or diastolic dysfunction caused by increased iron deposition into cardiomyocytes, becomes a cause with increasing prevalence in patients with thalassemia and hereditary hemochromatosis. With the onset of HF, it has a rapid evolution towards dilated cardiomyopathy with severe systolic dysfunction. Constrictive pericarditis and cardiac tamponade caused by myocardial iron deposition progress to rapid clinical deterioration. Iron deposition also occurs at the level of the entire conduction system, especially at the level of the atrio-ventricular node with the appearance of complete atrio-ventricular blocks and permanent cardiac pacemaker implantation. Non-homogeneous iron deposition creates areas of electrical inhomogeneity within ventricular or atrial myocardium inducing tachy-cardiomyopathy. In patients with hemochromatosis and without anemic syndrome, therapeutic phlebotomy is the treatment of choice, starting from ferritin values greater than

300 µg/l in men and 200 µg/l in women. The therapeutic phlebotomy consists of eliminating of 450 up to 500 ml of blood per week to reach a ferritin level of 10-20 µg/l. In patients with anemia and severe HF phlebotomy is not a therapeutic option, in these patients the treatment of choice being iron chelation drugs, such as deferoxamine, deferiprone or deferasirox. Cardiac transplantation is the optimal treatment in cardiac hemochromatosis and severe refractory HF. In patients with iron deposits secondary to myelodysplastic syndrome, sickle cell anemia, beta-thalassemia or Diamond-Blackfan syndrome, hematopoietic stem cell transplantation reduces the need for blood transfusions and slows the rate of iron deposition, while in those without compatible donors, gene therapy is the ultimate, preferable therapy[34].

Vitamin B1 deficiency

Vitamin B1 acts as a coenzyme in the oxidation-reduction reactions of glucose and citric acid, as well as in the reactions with pyruvate dehydrogenase. Beri-beri syndrome caused by vitamin B1 deficiency is divided into wet beri-beri syndrome, when the heart and circulatory system are predominantly affected, and dry beri-beri syndrome affecting mainly the nerves which leads to hypotonia and in severe forms to paresis. When the cardiovascular system is affected, patients present with biventricular dysfunction, vasodilation, tachycardia and fluid retention. In developed countries, vitamin B1 deficiency is extremely rare and correlates with malabsorption, malnutrition or alcoholism, but a sub-clinical vitamin B1 deficiency is relatively common in HF, considering diuretic treatment, malnutrition or frailty. Vitamin B1 supplementation has beneficial effects on cardiac function in those with HF as shown in two randomized placebo-controlled studies where vitamin B1 administration improved LVEF, diuresis and quality of life [35,36]. But the existing studies do not demonstrate a prognostic role to favor the correction of vitamin B1 deficiency in HF, thus requiring larger, multicenter, placebo-controlled trials.

Coenzyme Q10 deficiency

CoQ10 is a natural antioxidant synthesized or supplemented by diet that acts at the level of the mitochondrial electron transport chain from complex 1 to complex 3 and from complex 2 to complex 3,

with three essential roles: cell membrane stabilization, antioxidant effect and ATP production. To these functions can be added that CoQ10 improves the bioavailability of nitric oxide and reduces myocardial fibrosis. A placebo-controlled, multicenter study- Q-SYMBIO-compared adjuvant treatment with CoQ10 with placebo in a HF population. CoQ10 did not modify short-term endpoints (NT-pro-BNP, NYHA class or 6-minute walk test), but significantly reduced composite endpoints: major adverse cardiovascular events, as well as the rate of HF rehospitalizations [37]. But this study should be interpreted with caution because of the reduced population and small number of events with an annual mortality of only 7%. Although there are numerous studies showing the benefits of CoQ10, meta-analyses with larger numbers of patients are needed to clarify the conflicting results on major endpoints in different studies. Regarding the doses of CoQ10, most of the studies used 60 to 300 mg per day, for a period of 3 months, with the longest administration of 2 years in the above mentioned Q-SIMBIO study. Few studies have investigated the role of CoQ10 in HF with preserved LVEF; one of these evaluated CoQ10 in patients with hypertrophic cardiomyopathy and diastolic dysfunction showing improvement in quality of life, NYHA class, 6-minute walk test and diastolic dysfunction [38] Coenzyme Q10 improves the systolic function in heart failure. The aim of this study was to see whether it benefits the diastolic dysfunction in hypertrophic cardiomyopathy (HCM, and other trial is still recruiting patients [39] the leading cause of morbidity and mortality in the US, affects 6.6 million adults with an estimated additional 3 million people by 2030. More than 50% of HF patients have heart failure with preserved left ventricular ejection fraction (HFpEF).

Vitamin D deficiency

Vitamin D plays an important role in bone mineralization and maintenance of optimal plasmatic calcium. At the cardiovascular level, vitamin D modulates LV hypertrophy and improves endothelial function by reducing atherosclerosis [40]. Observational studies have shown that vitamin D deficiency is common in HF, as well as hyperparathyroidism, regardless of kidney function or age. Another cause of reduced plasma vitamin D levels in HF is increased

level of TNF-alpha [41]. Different studies revealed the correlation between low levels of vitamin D and cardiovascular diseases [42,43]. Given the association with HF, randomized, placebo-controlled, double-blind studies were performed to evaluate the role of vitamin D supplementation in these patients. The results of the studies were contradictory, some of them showing no improvement of cardiac function at least on short term [44], while others have shown beneficial effects on LVEF function [45,46] which are both associated with poor prognosis. Vitamin D may inhibit renin transcription and lower PRA. We investigated whether vitamin D3 (VitD3). Although some of the aforementioned studies have shown improvement in LVEF, this was not associated with the reduction of long-term mortality, more precisely at 3 years, but instead, was associated with a higher need for ventricular assist devices [47]. In conclusion, vitamin D may be a target for improving functional decline in patients with HF, but there are insufficient arguments that it would have a definite benefit on cardiovascular mortality and morbidity.

Creatine

Creatine is a molecule found in muscle, skeletal or cardiac, with the ability to store and transfer large quantities of phosphates, its synthesis in liver or kidney relying on other amino-acids. There are few studies evaluating the role of creatine in HF [48,49], and none provide sufficient arguments for improving HF prognosis over standard therapy.

Amino acids

Amino acids are essential components of proteins with an important plastic role in the structure of muscles. In HF, the availability of amino acids is reduced by malabsorption, hyper-catabolism in the advanced stages and poor intake, which ultimately leads to cardiac cachexia. Amino acid deficiency favors the change of cardiac structure through the transition from red muscle fibers with higher utilization of ATP molecules, to white fibers, that are less efficient in terms of mitochondrial ATP utilization [50] 73.5 ± 4 years; BMI 22.5 ± 1.4 kg/m². Some amino acids supplemented in HF have shown beneficial effects on various cardiovascular parameters, such as taurine and carnitine. Taurine is a semi-essential amino acid that results from the

decarboxylation of cysteine. At the cardiac level it has an antioxidant role, regulating the function of two essential proteins involved in the process of coupling excitation with contraction: phospholamban and sarcoplasmic reticulum Ca^{2+} -ATPase. Some studies have shown a beneficial effect of taurine in HF by reducing NYHA class, improvement of exercise capacity and LVEF [51–53] they were mostly male (26 of 29). In some countries, such as Japan, supplementation with taurine is recommended as part of standard HF treatment, although there is no decrease of major adverse cardiovascular events such as HF mortality or hospitalization after taurine supplements. Carnitine derives from an amino acid and exists in two biologically active isomers, L- and D-carnitine, but only L-carnitine has a beneficial effect, as D-carnitine is toxic inhibiting the action of the other isomer. In vitro [54] and in vivo [55], L-carnitine supplementation resulted in improvement of NYHA class and exercise tolerance in congestive HF, mainly to the role of L-carnitine in muscle metabolism. In a meta-analysis of randomized control studies, L-carnitine ameliorated not only clinical symptoms, but also LVEF [56] and survival [57].

Conclusions

MS and nutritional deficits interact to influence the development or progression of HF. Only a broad treatment touching each of the factors involved in HF will assure a personalized, efficient care of the disease. A complex disorder such as HF still needs future research to answer the unsolved questions concerning the metabolic and nutritional imbalances.

Acknowledgments

This work was supported by a grant of the Romanian National Authority for Scientific Research and Innovation, CNCS/CCCDI UEFISCDI, project number PN-III-P2-2.1-PED-2016-1333, within PNCDI II.

Conflict of interest

The authors confirm that there are no conflicts of interest

References

1. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. *Card Fail Rev.* 2017 Apr;3(1):7–11.
2. Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabet Med.* 1998;15(7):539–53.
3. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.* 2002;106(25):3143–421.
4. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the Metabolic Syndrome. *Circulation.* 2009 Oct 20;120(16):1640–5.
5. Ahmad FS, Ning H, Rich JD, Yancy CW, Lloyd-Jones DM, Wilkins JT. Hypertension, Obesity, Diabetes, and Heart Failure-Free Survival: The Cardiovascular Disease Lifetime Risk Pooling Project. *JACC Heart Fail.* 2016;4:911–9.
6. Echouffo-Tcheugui JB, Xu H, DeVore AD, Schulte PJ, Butler J, Yancy CW, et al. Temporal trends and factors associated with diabetes mellitus among patients hospitalized with heart failure: Findings from Get With The Guidelines-Heart Failure registry. *Am Heart J.* 2016 Dec;182:9–20.
7. Klajda MD, Scott CG, Rodeheffer RJ, Chen HH. Diabetes Mellitus Is an Independent Predictor for the Development of Heart Failure: A Population Study. *Mayo Clin Proc.* 2020 Jan 1;95(1):124–33.
8. Stratmann B, Tschoepe D. Heart in diabetes: Not only a macrovascular disease. *Diabetes Care.* 2011;34:S138–144.
9. Rengo G, Pagano G, Paolillo S, de Lucia C, Femminella GD, Liccardo D, et al. Impact of diabetes mellitus on lymphocyte GRK2 protein levels in patients with heart failure. *Eur J Clin Invest.* 2015;45:187–95.
10. Margulies KB, Hernandez AF, Redfield MM, Givertz MM, Oliveira GH, Cole R, et al. Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: A randomized clinical trial. *JAMA - J Am Med Assoc.* 2016;316:500–8.
11. Li Y, Hu Y, Ley SH, Rajpathak S, Hu FB. Sulfonylurea use and incident cardiovascular disease among patients with type 2 diabetes: Prospective cohort study among women. *Diabetes Care.* 2014;37:3106–13.
12. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular

- Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015 Nov 26;373(22):2117–28.
13. Neal B, Perkovic V, Mahaffey KW, De Zeeuw D, Fulcher G, Erondou N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644–57.
 14. Howell R, Wright AM, Clements JN. Clinical potential of liraglutide in cardiovascular risk reduction in patients with type 2 diabetes: evidence to date. *Diabetes, Metab Syndr Obes Targets Ther*. 2019;12:505–12.
 15. Brunner Y, Schwartz D, Priego-Capote F, Couté Y, Sanchez J-C. Glucotoxicity and pancreatic proteomics. *J Proteomics*. 2009 Jan 30;71(6):576–91.
 16. Costantino S, Paneni F, Mitchell K, Mohammed SA, Hussain S, Gkolfos C, et al. Hyperglycaemia-induced epigenetic changes drive persistent cardiac dysfunction via the adaptor p66 Shc. *Int J Cardiol*. 2018;268:179–86.
 17. Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, et al. Efficacy and safety of degludec versus Glargine in Type 2 Diabetes. *N Engl J Med*. 2017;
 18. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, et al. Effect of a Mediterranean-Style Diet on Endothelial Dysfunction and Markers of Vascular Inflammation in the Metabolic Syndrome. *JAMA*. 2004 Sep 22;292(12):1440.
 19. Gandhi SK, Powers JC, Nomeir AM, Fowle K, Kitzman DW, Rankin KM, et al. The pathogenesis of acute pulmonary edema associated with hypertension. *N Engl J Med*. 2001;344:17–22.
 20. Furberg CD, Wright JT, Davis BR, Cutler JA, Alderman M, Black H, et al. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *J Am Med Assoc*. 2002;288(23):2981–97.
 21. Wing LMH, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GLR, et al. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med*. 2003;348(7):583–92.
 22. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: β -Blocker Dose, Heart Rate Reduction, and Death in Patients With Heart Failure. *Ann Intern Med*. 2009 Jun 2;150(11):784.
 23. Kajani S, Curley S, McGillicuddy FC. Unravelling HDL-Looking beyond the Cholesterol Surface to the Quality Within. *Int J Mol Sci*. 2018;19(7).
 24. van der Steeg A, Cannon CP. HDL cholesterol, HDL particle size, and apolipoprotein A-I: Significance for cardiovascular risk – The IDEAL and EPIC-norfolk studies. *ACC Cardiosource Rev J*. 2008;51:634–42.
 25. Huang Y, Didonato JA, Levison BS, Schmitt D, Li L, Wu Y, et al. An abundant dysfunctional apolipoprotein A1 in human atheroma. *Nat Med*. 2014;20(2):193–203.
 26. Hedrick CC, Thorpe SR, Fu MX, Harper CM, Yoo J, Kim SM, et al. Glycation impairs high-density lipoprotein function. *Diabetologia*. 2000;43(3):312–20.
 27. Hansel B, Giral P, Nobecourt E, Chantepie S, Bruckert E, Chapman MJ, et al. Metabolic syndrome is associated with elevated oxidative stress and dysfunctional dense high-density lipoprotein particles displaying impaired antioxidative activity. *J Clin Endocrinol Metab*. 2004;89(10):4963–71.
 28. van Herpen NA, Schrauwen-Hinderling VB. Lipid accumulation in non-adipose tissue and lipotoxicity. *Physiol Behav*. 2008;94:231–41.
 29. Djoussé L, Benkeser D, Arnold A, Kizer JR, Ziemann SJ, Lemaitre RN, et al. Plasma free fatty acids and risk of heart failure the cardiovascular health study. *Circ Hear Fail*. 2013;6:964–9.
 30. Greene SJ, Vaduganathan M, Lupi L, Ambrosy AP, Mentz RJ, Konstam MA, et al. Prognostic Significance of Serum Total Cholesterol and Triglyceride Levels in Patients Hospitalized for Heart Failure With Reduced Ejection Fraction (from the EVEREST Trial). *Am J Cardiol*. 2013 Feb;111(4):574–81.
 31. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020 Jan 1;41(1):111–88.
 32. Bayes-Genis A, Núñez J, Zannad F, Ferreira JP, Anker SD, Cleland JG, et al. The PCSK9-LDL Receptor Axis and Outcomes in Heart Failure: BIOSTAT-CHF Sub-analysis. *J Am Coll Cardiol*. 2017 Oct 24;70(17):2128–36.
 33. Perrone-Filardi P, Savarese G, Scarano M, Cavazzina R, Trimarco B, Minneci S, et al. Prognostic impact of metabolic syndrome in patients with chronic heart failure: Data from GISSI-HF trial. *Int J Cardiol*. 2015;178:85–90.
 34. Ribeil J-A, Hacein-Bey-Abina S, Payen E, Magnani A, Semeraro M, Magrin E, et al. Gene Therapy in a Patient with Sickle Cell Disease. *N Engl J Med*. 2017 Mar 2;376(9):848–55.
 35. Smithline HA. Thiamine for the treatment of acute decompensated heart failure. *Am J Emerg Med*. 2007 Jan;25(1):124–6.

36. Schoenenberger AW, Schoenenberger-Berzins R, Der Maur CA, Suter PM, Vergopoulos A, Erne P. Thiamine supplementation in symptomatic chronic heart failure: A randomized, double-blind, placebo-controlled, cross-over pilot study. *Clin Res Cardiol.* 2012;101:159-64.
37. Mortensen SA, Rosenfeldt F, Kumar A, Dolliner P, Filipiak KJ, Pella D, et al. The Effect of Coenzyme Q 10 on Morbidity and Mortality in Chronic Heart Failure. *JACC Hear Fail.* 2014 Dec;2(6):641-9.
38. Adarsh K, Kaur H, Mohan V. Coenzyme Q₁₀ (CoQ₁₀) in isolated diastolic heart failure in hypertrophic cardiomyopathy (HCM). *BioFactors.* 2008;32(1-4):145-9.
39. Pierce JD, Mahoney DE, Hiebert JB, Thimmesch AR, Diaz FJ, Smith C, et al. Study protocol, randomized controlled trial: reducing symptom burden in patients with heart failure with preserved ejection fraction using ubiquinol and/or D-ribose. *BMC Cardiovasc Disord.* 2018;18(1):57.
40. Weishaar RE, Simpson RU. Involvement of vitamin D3 with cardiovascular function. II. Direct and indirect effects. *Am J Physiol-Endocrinol Metab.* 1987;253:E675-E683.
41. Rauchhaus M, Doehner W, Francis DP, Davos C, Kemp M, Liebenthal C, et al. Plasma cytokine parameters and mortality in patients with chronic heart failure. *Circulation.* 2000;102(25):3060-7.
42. Roy A, Lakshmy R, Tarik M, Tandon N, Reddy KS, Prabhakaran D. Independent association of severe vitamin D deficiency as a risk of acute myocardial infarction in Indians. *Indian Heart J.* 2015;67:27-32.
43. Afshari L, Amani R, Soltani F, Haghighizadeh MH, Afsharmanesh MR. The relation between serum Vitamin D levels and body antioxidant status in ischemic stroke patients: A case-control study. *Adv Biomed Res.* 2015;4:213.
44. Boxer RS, Kenny AM, Schmotzer BJ, Vest M, Fiutem JJ, Piña IL. A randomized controlled trial of high-dose vitamin D3 in patients with heart failure. *JACC Hear Fail.* 2013;1(1):84-90.
45. Schrotten NF, Ruifrok WPT, Kleijn L, Dokter MM, Silljé HH, Lambers Heerspink HJ, et al. 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). *Am Heart J.* 2013;166:357-64.
46. Witte KK, Byrom R, Gierula J, Paton MF, Jamil HA, Lowry JE, et al. Effects of Vitamin D on Cardiac Function in Patients With Chronic HF: The VINDICATE Study. *J Am Coll Cardiol.* 2016;67:2593-603.
47. Zittermann A, Ernst JB, Prokop S, Fuchs U, Dreier J, Kuhn J, et al. Effect of vitamin D on all-cause mortality in heart failure (EVITA): a 3-year randomized clinical trial with 4000 IU vitamin D daily. *Eur Heart J.* 2017 Aug 1;38(29):2279-86.
48. Hemati F, Rahmani A, Asadollahi K, Soleimannejad K, Khalighi Z. Effects of complementary creatine monohydrate and physical training on inflammatory and endothelial dysfunction markers among heart failure patients. *Asian J Sports Med.* 2016;7(1):e28578.
49. Gordon A, Hultman E, Kaijser L, Kristjansson S, Rolf CJ, Nyquist O, et al. Creatine supplementation in chronic heart failure increases skeletal muscle creatine phosphate and muscle performance. *Cardiovasc Res.* 1995 Sep;30(3):413-8.
50. Aquilani R, Opasich C, Gualco A, Verri M, Testa A, Pasini E, et al. Adequate energy-protein intake is not enough to improve nutritional and metabolic status in muscle-depleted patients with chronic heart failure. *Eur J Heart Fail.* 2008;10:1127-35.
51. Beyranvand MR, Kadkhodai Khalafi M, Roshan VD, Choobineh S, Parsa SA, Piranfar MA. Effect of taurine supplementation on exercise capacity of patients with heart failure. *J Cardiol.* 2011 May 1;57(3):333-7.
52. Jeejeebhoy F, Keith M, Freeman M, Barr A, McCall M, Kurian R, et al. Nutritional supplementation with Myo-Vive repletes essential cardiac myocyte nutrients and reduces left ventricular size in patients with left ventricular dysfunction. *Am Heart J.* 2002;143:1092-100.
53. Azuma J, Sawamura A, Awata N. Usefulness of Taurine in Chronic Congestive Heart Failure and Its Prospective Application. *Jpn Circ J.* 1992;56:95-9.
54. Kobayashi A, Masumura Y, Yamazaki N. L-Carnitine Treatment for Congestive Heart Failure. Experimental and clinical study. *Jpn Circ J.* 1992 Jan;56(1):86-94.
55. Anand I, Chandrashekhyan Y, De Giuli F, Pasini E, Mazzeoletti A, Confortini R, et al. Acute and chronic effects of propionyl-L-carnitine on the hemodynamics, exercise capacity, and hormones in patients with congestive heart failure. *Cardiovasc Drugs Ther.* 1998;12:291-9.
56. Song X, Qu H, Yang Z, Rong J, Cai W, Zhou H. Efficacy and Safety of L-Carnitine Treatment for Chronic Heart Failure: A Meta-Analysis of Randomized Controlled Trials. *Biomed Res Int.* 2017;2017:1-11.
57. Rizos I. Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration. *Am Heart J.* 2000 Feb;139(2):s120-3.