Integrative Medicine for Cardiovascular Disease and Prevention

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KEYWORDS

• Cardiovascular disease • Prevention • Integrative medicine • Nutrition • Hypertension • Supplements • Alternative therapies • Stress

KEY POINTS

- Cardiovascular disease is traditionally treated through medications and lifestyle modifications, yet adherence to these treatments is often poor.
- The use of complementary therapies, such as nonprescription vitamins and herbs, is increasing, and patients are seeking information from their physicians about the safety and effectiveness of these therapies.
- When considering integrative therapies for cardiovascular disease, it is important to understand the underlying pathogenesis of the disease, which may be linked to chronic stress, inflammation, and altered gut microbiota.
- There is evidence for several promising integrative therapies for the treatment and prevention of cardiovascular disease, including specific nutritional approaches, meditation, yoga, acupuncture, and select supplements and herbal therapies.
- Physicians should be diligent in asking patients about any alternative therapies for cardiovascular disease that they may be using, and be capable of discussing the risk/benefit ratio of these options.

Cardiovascular disease (CVD) remains the number 1 cause of morbidity and mortality globally.[1] Early intervention with angiography and broad-based pharmaceutical therapies has contributed to a decline in deaths from CVD in the United States, yet the prevalence of risk factors and economic burden of CVD remain exceedingly high.

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Commonly, patients are placed on a minimum of 4 to 6 medications at any given time, which increases financial burden, worsens compliance rates, and increases rates of side effects and medication interactions. Expenditures on medications per capita in the United States in 2014 increased 10.3% to $373.9 billion from the year prior.[2] This increase is driven primarily by new treatment options, rising prices, and increased usage of medications.[3]

Traditional lifestyle measures for prevention of CVD include smoking cessation, maintaining a healthy body weight, regular exercise, and dietary changes involving reducing saturated fats, increasing fruits and vegetables, and limiting sugar intake. However, physicians are often unaware of what specific lifestyle changes to make, such as types of exercise regimens and targeted changes in the diet.[4]

The demand for integrative medicine is fueled by, among many things, patients' desires for nonpharmacologic options. However, guidelines and regulations of these therapies are not optimal, and there are issues with contamination of supplements and different potencies in different varieties. In addition, herb-drug interactions are often not fully recognized. It is imperative for physicians to start a discussion of complementary practices with patients to ensure safety and effective use of both traditional and integrative practices.

PATHOGENESIS OF CHRONIC DISEASE STATES, INCLUDING CARDIOVASCULAR DISEASE

Cardiovascular disease has been associated with an imbalance in the autonomic nervous system.[5] The sympathetic or "fight or flight" nervous system is activated in times of stress. As a result, cortisol and epinephrine levels are heightened. These hormones allow our blood pressures and heart rates to rise so we have adequate blood flow to essential organs for flight and allow the body to be alert. Our immune system also triggers an inflammatory cascade. The parasympathetic or "rest and digest" nervous system offsets the sympathetic nervous system. It brings the cortisol levels and epinephrine levels down. Blood flow goes back to nonessential processes, such as eating and bladder and bowel movements.

Often, our bodies are heavily shifted toward sympathetic overdrive, which leads to burnout. With this imbalance, there are chronically elevated hormone levels, which result in elevated blood pressures and heart rates on a long-term basis. In times of burnout, there is significant imbalance in the immune response and there is evidence of increased inflammatory markers, decreased wound healing, and poorer response to infection.[6] With chronic stress, there is overactivation of the hormonal systems and subsequent formation of disease-causing free radicals causing oxidative stress.[7] Inflammation and oxidative stress can then cause chronic fatigue, depression, and excessive weight gain. In addition, persistent elevation of cortisol can lead to insulin resistance, which can cause diabetes and CVD, such as hypertension, ischemic heart disease, congestive heart failure, and arrhythmias.[5]

The integrative treatment approach in cardiology focuses on bringing the "rest and digest" system into balance with the "fight or flight" system. Boosting the "rest and digest" nervous system often requires learning the art of meditation, yoga, and movement. It also involves understanding the impact of food on our bodies and putting healthful foods into our system to aid in proper digestion. It also requires us to understand about environmental exposures, such as pollution and heavy metal exposures.

HYPERTENSION

Hypertension affects almost one-third of our population, with 75% of those patients taking antihypertensive medication. However, only approximately half of this group

is considered well controlled. Often known as the "silent killer," hypertension is the culprit associated with end-organ damage in terms of stroke, kidney dysfunction, and vascular disease. Although hypertension is familial, obesity, smoking, and alcohol intake are well-known precipitating risk factors. Dietary changes are also essential for managing hypertension. The pioneer trial that examined the role of diet in the management of hypertension was the Dietary Approaches to Stop Hypertension (DASH) trial in 1997.

DASH was a large, prospective, multicenter trial that looked at lifestyle changes to affect blood pressure. The diet assigned to the intervention group was composed of fruits, vegetables, and low-fat dairy: a diet low in fat and cholesterol. Seventy-five percent of the US-recommended allowance of magnesium and potassium was advocated. The sodium consumption between the control and the intervention group was no different at approximately 3 g sodium per day. Within 2 weeks of the intervention, blood pressures reduced and the results sustained for another 6 weeks. Systolic blood pressure (SBP) reduced by 5.5 mm Hg and diastolic blood pressure (DBP) by 3.0 mm Hg more than the control diet.[8] This was a pivotal trial that demonstrated the effectiveness of dietary interventions in the treatment of hypertension.

Role of Sodium in the Diet for Hypertensive Patients

The role of sodium in the diet has come under controversy. For centuries, there has been a concern that excessive sodium intake triggers hypertension. The early Intersalt study[9] showed across various populations that those with a higher sodium urinary excretion rate had a higher blood pressure. Subsequently, the DASH study[8] gave patients a low-fat vegetarian diet that was high in fruits and vegetables with no sodium adjustment. Those who ate this diet were noted to have improved blood pressure. A DASH follow-up study[10] used the same diet randomizing to 3 different levels of sodium (high, medium, and low). After 30 days, patients on the lowest-sodium diet had the most significant blood pressure reduction. Thus, for a decade, the low-sodium diet was advocated. More recently, the Prospective Urban and Rural Epidemiological (PURE)[11] study evaluated more than 150,000 people and found a more moderate sodium intake was associated with the lowest overall mortality. That same year, a large meta-analysis was done corroborating this U-shaped relationship between salt intake and mortality; that is, too little and too much sodium was associated with higher mortality than usual sodium intake.[12] The Centers for Disease Control and Prevention and American Heart Association (AHA) continue to advocate a lower-sodium diet for the management of hypertension, recommending most Americans eat less than 1500 mg/d of sodium for "ideal" cardiovascular health. This recommendation continues to be controversial. We believe the most impact of sodium restriction is on patients with hypertension. Most Americans eat excessive sodium in their diet, 75% of which comes from processed, prepackaged, and restaurant foods.[13] Dietary changes, such as the DASH diet and the addition of potassium-rich foods, can counterbalance the deleterious effects of excess sodium, and should therefore be recommended.

Endothelial Dysfunction and Hypertension

One of the pathways associated with generation of essential hypertension is impaired endothelium-dependent vasodilation.[14] Healthy endothelium releases potent vasodilators in response to blood flow, which can lower vascular resistance directly. Nitric oxide (NO) is essential to causing vasodilatation of the arteries and is associated with antithrombotic and atheroresistant effects of the arterial wall.[15] Decreases in NO and increased vascular tone trigger sympathetic tone and increase sodium

retention.[14] Impaired endothelium is a well-established response to cardiovascular risk factors and is a precursor to CVD.

Nitrates

Dietary nitrates and their ability to increase NO levels has been studied and shown beneficial effects in clinical settings (**Table 1**). Data suggest fruits and vegetables provide a substrate for reduction of nitrate to nitrite and NO. This production leads to vasodilatation and a decrease in blood pressure.[16] Other studies have shown the production of NO has the ability to inhibit endothelial inflammatory cell recruitment and platelet aggregation.[17] By aiding in healthy endothelial function, NO production can aid in prevention of CVD, hypertension, atherosclerosis, and stroke.[18]

Although studies on intake of nitrate and nitrite through foods have shown cardiovascular benefits,[19] nitrates have also come under criticism as toxic and associated with increased gastric cancer.[20,21] Current data, however, suggest that there is an increased risk of gastric cancer with nitrate/nitrite ingestion from nitrate-preserved meats, whereas nitrites from vegetables are associated with reduced gastric cancer risk.[22] The most recent guidelines from The International Agency for Research for Cancer stated that processed meat does indeed cause cancer (level I evidence) and that red meat was probably carcinogenic (group IIa).

L-arginine In addition to functional foods, precursors to NO, such as L-arginine, have been studied. L-arginine uses the family of enzymes called NO synthases to convert to NO. Clinical trials have yielded mixed results.[23] Early studies on humans showed improved brachial artery flow-mediated dilation in patients with essential hypertension, but this effect did not translate into lower blood pressure.[24] A recent meta-analysis, however, looked at 11 randomized controlled trials (RCTs) and concluded that L-arginine supplementation did indeed lower both SBP and DBP.[25] Response to L-arginine may differ by subset of population. One study looked at 153 patients who had experienced myocardial infarction (MI) 6 months after their event and randomized them to either 3 g L-arginine 3 times per day versus placebo. No improvement in vascular stiffness or ejection fraction was noted in those who took L-arginine. Due to increased mortality in the post-MI group, the study was discontinued. Therefore, at this time, L-arginine is not advised for patients post MI but can be considered in hypertension.[26]

Nutrients/supplements Several nutrients are listed in the following sections with their supplement doses reported in the studies. However, following an AHA-recommended

Table 1
Vegetables according nitrate concentration

Nitrate Content (mg/100 g) of Fresh Food	Vegetables
Very low, <20 mg	Asparagus, garlic, onion, green bean, pepper, potato, sweet potato, tomato, and watermelon
Low, 20 to <50 mg	Broccoli, carrot, cauliflower, and chicory
Regular, 50 to <100 mg	Cabbage, turnip, and dill
High, 100 to <250 mg	Endive, sweet leaf, parsley, and leek
Very high, >250 mg	Celery, chard, lettuce, beetroot, spinach, arugula, and watercress

From d'El-Rei J, Cunha AR, Trindade M, et al. Beneficial effects of dietary nitrate on endothelial function and blood pressure levels. Int J Hypertens 2016;2016:6791519; with permission.

diet rich in fruits and vegetables, whole grains, low-fat dairy, and lean protein sources can allow for adequate sources of these nutrients often without supplementation.

Vitamin C

Vitamin C has been evaluated in many studies for its endothelium-dependent response. Several studies looking at humans have shown that blood pressure is inversely correlated with plasma ascorbate levels in epidemiologic, observational, cross-sectional, and controlled prospective clinical trials.[27] A recent meta-analysis in 2012 showed short-term benefits of reduced blood pressure with vitamin C at a median dose of 500 mg for 8 weeks, but long-term studies are needed.[28]

Flavonoids

Flavonoids are a group of more than 4000 antioxidants and are found in abundance in fruits, vegetables, wine, tea, and grains. Popular sources of flavonoids are in apples, cherries, onions, raspberries, citrus, broccoli, celery, and green tea. Many feel the benefits from the DASH diet are due to its increased fruits and vegetables, which would provide increased flavonoid content. Flavonoids have been shown to have anti-inflammatory and antiatherogenic properties.[29]

Tea

Black tea has been studied in patients with coronary artery disease (CAD) and was shown to reverse endothelial flow-mediated dysfunction.[30] A meta-analysis done in 2014 showed that there was a small but significant reduction in both SBP and DBP when black tea or green tea was ingested long-term for more than 12 weeks.[31] It is reasonable to recommend 450 to 900 mL of black tea or green tea per day.

Lycopene

Lycopene is one of the most powerful antioxidants and is found in abundance in tomatoes. It exerts its role by inhibiting oxidative stress, improving vascular function, and preventing CVD. A 2013 meta-analysis showed lycopene has potential to reduce SBP but was not conclusive for DBP.[32] Adding tomatoes and unprocessed tomato products is recommended for blood pressure reduction.

Coenzyme Q10

Coenzyme Q_{10} (CoQ10), also called ubiquinone because of its ubiquitous distribution in nature, is an antioxidant and an integral component of the mitochondrial respiratory chain for energy production. It is found in all tissues and organs of the body, but in highest concentration in the heart. With aging and CVD, CoQ10 levels decrease. There is evidence of CoQ10 deficiency in hypertension and heart failure, and in individuals on statins for hypercholesterolemia.[33,34] CoQ10 has been shown in many studies as early as 1975 to lower blood pressure in hypertensive patients. A meta-analysis in 2007 showed that CoQ10 can lower the SBP (−17 mm Hg) and DBP (−10 mm Hg) without causing side effects.[33] Although CoQ10 supplementation appears to be promising, a recent Cochrane review concluded there are no significant blood pressure reductions with the antioxidant.[35]

Magnesium

Magnesium is an essential nutrient that has a role in more than 300 reactions in the body. Magnesium lowers blood pressure by acting as a natural calcium channel blocker, competes with sodium for binding sites on vascular smooth muscle cells, and has been shown to induce endothelial-dependent vasodilation.[36] In a recent meta-analysis of 34 RCTs, magnesium at dosages of approximately 300 mg per day for 1 month helped raised intracellular levels of magnesium and helped reduce

both SBP (−2.0 mm Hg) and DBP (−1.98 mm Hg).[37] Although supplement doses may not be clear at this time, it is very reasonable to discuss food sources of magnesium with patients. Those foods with the highest levels are the dark, green leafy vegetables, unrefined grains, and legumes.

Potassium

Potassium is a critical nutrient needed to maintain total body fluid volume, electrolyte and acid balance, and many cellular functions. Although the recommended daily allowance is 4700 mg per day (120 mmol) for adults, most countries around the world report consumption of less than 70 to 80 mmol per day.[9] Processing foods lowers potassium content. Diets high in processed foods and low in fruits and vegetables contribute to low intakes.[38] Consumption of lower potassium is associated with elevated blood pressure, hypertension, and stroke.[39,40] In addition, potassium is often depleted with diuretic use for treatment of hypertension and congestive heart failure and therefore often needs to be supplemented. A meta-analysis looked at 22 RCTs and 11 cohort studies and found that increased potassium intake reduced SBP by 3.5 mm Hg (95% confidence interval 1.8–5.2) and DBP by 2.0 mm Hg (0.9–3.1) in adults, an effect seen in people with hypertension but not in those without hypertension. Most benefit in blood pressure was seen when potassium intake was up to 90 to 120 mmol per day. Higher potassium intake was associated with a 24% reduction in risk of stroke. No adverse effects on renal function, blood lipids, or catecholamine concentrations were found with higher potassium consumption.[41]

Zinc

Low zinc levels are implicated in hypertension.[42] The US Department of Agriculture lists animal proteins, nuts, whole grains, legumes, and yeast to be high in zinc. Zinc deficiency can be exacerbated by certain medications, poor intake, alcoholism, and digestive diseases such as inflammatory bowel disease. Higher dietary zinc intake results in a better taste acuity for salt. Thus, people with zinc deficiency tend to increase salt intake, which can lead to an increase in blood pressure. Although the exact mechanism is not clear, there is a correlation between zinc and the renin-angiotensin system with respect to its influence on blood pressure. Serum zinc level is the best way to assess zinc levels. Recommendations are to increase zinc through diet and supplement when needed.

Vitamin D

Vitamin D is a steroid prohormone, generated when skin is exposed to UV exposure, but also can be taken in through diet and supplements. Cross-sectional studies have shown vitamin D deficiency and increased risk of CVD: hypertension, heart failure, and ischemic heart disease.[43] Notable reasons for deficiencies are nonfortified products in the diet and obesity, which causes fat cells to bind to vitamin D and prevents the vitamin D from circulating. Due to the American Academy of Dermatology's view regarding excess UV radiation risk and premature aging and skin cancer, a safe amount of UV exposure to increase vitamin D without increasing cancer risk cannot be recommended. Therefore, due to lack of dietary sources fortified with vitamin D, supplementation is the preferred way to get levels into normal range. Findings from randomized trials of vitamin D supplementation are inconsistent. A meta-analysis in *JAMA* of 46 trials showed no effect of vitamin D supplementation on blood pressure.[44] Although vitamin D deficiency is associated with CVD and hypertension, using vitamin D for hypertension cannot be advocated at this time.

Calcium

Homeostasis of calcium has been associated with blood pressure regulation.[45] Dietary calcium appears to exert its benefits by lowering the activity of the renin-angiotensin system,[46] improve sodium-potassium balance,[47] and inhibit vascular smooth muscle cell constriction.[48] Earlier studies showed that calcium through dietary intake of whole foods showed blood pressure–lowering effects.[49] Most recently, the Multi-Ethnic Study of Atherosclerosis was a 10-year longitudinal cohort study to assess the role of calcium intake through diet and supplements and presence of atherosclerosis. Coronary artery calcification (CAC) using computed tomography was used. Using 5448 patients who had no evidence of heart disease, they found high calcium intake (average 1081 mg for women and 900 mg for men) was associated with reduced risk for CAC. However, the patients who used supplemental calcium instead of dietary calcium had a 22% increased risk of CAC. This study suggests that following the Recommended Dietary Allowance with dietary calcium may be cardioprotective, but supplements may not be the right option.[50]

Omega-3 fatty acids

Extensive literature has examined the benefit of eicosapentaenoic and docosahexaenoic acids (EPA + DHA) on blood pressure. A meta-analysis of food sources of EPA and DHA showed EPA + DHA reduced SBP (−1.5 mm Hg) and DBP (−1.0 mm Hg). The most profound effects of EPA + DHA were noted among untreated hypertensive subjects in whom SBP decreased by 4.5 mm Hg and DBP by 3.1 mm Hg. Blood pressure also decreased among normotensive subjects but to a smaller degree. Overall evidence from 70 RCTs showed doses of EPA + DHA from 1 to 5 g were associated with SBP reduction in hypertensive adults whereas greater than 2 g were needed for diastolic reduction.[51]

Amino acids

Taurine is a conditionally essential amino acid found in high concentrations in the brain, heart, and skeletal muscles. In animal and human models, taurine lowered blood pressure. Dietary sources of taurine are generally high in meat and fish and low in plant-based foods. A recent RCT with 120 patients with prehypertension showed taurine treatment upregulated the expression of enzymes associated with endothelium vasodilatation. Taurine supplementation at a dose of 1.6 g per day for 12 weeks showed a decrease in blood pressures, especially in those with high normal blood pressure. Mean SBP and DBP reduction for taurine was 7.2 and 4.7 mm Hg, respectively.[52] More studies are needed to further clarify its role in hypertension.

Apple cider vinegar

Although touted through data from animal studies, there is no evidence that vinegar reduces blood pressure in humans.

Herbs

Hawthorn

Current research suggests hawthorn may represent a safe, effective agent in the treatment of CVD and ischemic heart disease. One of the larger human studies looked at 80 patients with type 2 diabetes who had hypertension. They were randomized to receive a daily dose of either hawthorn extract (6 g dried flowering tops) or placebo. The study noted no significant change in SBP, but DBP was reduced significantly by 3.6 mm Hg over 16 weeks. No herb-drug interaction was noted.[53] Hawthorn extract appears to be a promising treatment for management of blood pressure. However, the exact dosage and formulation is not clear.

Pomegranate

Pomegranate also plays a role in reducing blood pressure, likely due to its polyphenol content. Hypertensive patients who drank pomegranate juice for as few as 2 weeks had a 36% decrease in angiotensin-converting enzyme activity and 5% reduction in SBP.[54] Although this effect was not noted in all studies, the transient increase in blood pressure after a meal high in fat was curtailed with the use of pomegranate juice.[55] It is reasonable to recommend drinking 300 mL pomegranate juice to aid in blood pressure.

Cocoa

Cocoa is a flavonoid that has been extensively studied for its blood pressure and cardiovascular benefits. The mechanism for its effects has been attributed to an increase in NO production. These effects are markedly reduced when cocoa is consumed with milk or ingested as milk chocolate.[56] High calorie load of commercially available chocolate may induce weight gain, but raw cocoa has low levels of sugar, which makes it reasonable to recommend.

Although herbs and spices may have benefits, many plants may potentially increase blood pressure, including arnica, bitter orange, ephedra, gingko, ginseng, licorice, senna, St John wort, capsicum, and yohimbine.

Exercise

Recommendations from the American College of Sports Medicine for exercise and hypertension are dynamic aerobic endurance training for at least 30 minutes per day supplemented by dynamic resistance exercise. Exact recommendations for types of exercise and reduction of blood pressure were examined in a recent meta-analysis showing that isometric resistance training showed the highest reductions in SBP.[57] The AHA recommends an average of 40 minutes of moderate to vigorous-intensity aerobic exercise 3 to 4 times per week for lowering blood pressure and cholesterol. They also define exercise as any activity that burns calories, such as walking, jogging, running, biking, playing sports, climbing stairs, weight training, and stretching.[58]

Stress and Its Role in Hypertension

Meditation has been shown to lower blood pressure and cortisol. Specifically, the AHA has deemed that behavioral therapies, such as transcendental meditation (TM), can be used in managing blood pressure (Class IIb level of evidence).[59] TM uses a mantra or chant to focus attention. It is a meditative practice recommended 20 minutes twice a day. The most recent meta-analysis in 2008 showed reduction in SBP (−4.7 mm Hg) and DBP (−3.2 mm Hg) over a median of 15 weeks. The mechanism may be associated with balancing the autonomic nervous system.[60] It is reasonable to advise patients to start a meditative practice to assist with blood pressure reduction without any potential side effects.

HYPERLIPIDEMIA

High cholesterol increases the risk of CVD and has been attributed to one-third of CAD around the world. Reduction of total cholesterol has been associated with decreased CVD and stroke.[61] Along with a large breadth of medication options, lifestyle changes, including proper diet and exercise, are important for management of hyperlipidemia.

Exercise

Studies show that there is some difference in the effect of exercise on lipids based on type of exercise. It appears that aerobic exercise decreases triglycerides and

low-density lipoprotein (LDL) cholesterol. Resistance training is more commonly associated with decreases in total cholesterol and LDL cholesterol. Notably, there is a dose-dependent relationship between amount of exercise and increases in high-density lipoprotein (HDL) cholesterol.[62] The AHA recommends 30 minutes of moderate to high-intensity exercise 5 times per week for overall cardiovascular health or 25 minutes of vigorous aerobic activity with moderate to high-intensity muscle strengthening exercise at least 2 days per week.[58]

Nutrition

Food preparation over the past several decades has shifted away from fresh food and cooking daily to more frequently ordering fast food and microwaving precooked and instant meals. Foods are filled with more oil, butter, and preservatives to increase their shelf life and refined products to increase speed of cooking. We have shifted away from eating fruits and vegetables and have become a heavy meat-eating society. Recent research has focused on the impact of the food we eat on the microbiome, and consequent effects on development of inflammation and CVD. Foods high in phosphatidyl choline, such as eggs, liver, beef, and pork, are processed in the gut and the metabolites trimethylamine and trimethylamine-*N*-oxide (TMAO) are formed. Recent studies show that people with high production of TMAO have increased risk of CVD.[63] In animal studies, a vegetarian and/or high-fiber diet has been shown to lower the amount of choline and therefore less TMAO production. Probiotics and antibiotics also are associated with reduced amounts of TMAO and will be the source of ongoing study. Although TMAO appears to be associated with CVD, it is also possible that it is a biomarker for gut microbiome differences rather than an independent risk factor or trigger.[64] Excess salt in meat serves as a preservative and may lead to high blood pressure. Nitrates, which are used as preservatives in meat, have been associated with endothelial dysfunction[65] and insulin resistance.[66] Studies show eating just 1 fatty meal can create endothelial dysfunction within 4 hours.[67]

The role of nutrition and its impact on heart disease has always been appreciated. In the early work by Dean Ornish and colleagues,[68] they directed 48 patients with moderate-severe CAD to eat a 10% fat vegetarian diet, do moderate aerobic exercise, undergo stress management training and smoking cessation counseling, and provided support groups. Over 1.5 years, plaque regression occurred in the treatment group and progression was observed in the control group.[68] Early studies on the Mediterranean diet, featuring an abundance of vegetables, fruit, and fiber, suggested this diet reduced heart disease risk. The large PREDIMED (Prevención con Dieta Mediterránea) study is the most recent study completed and is a primary prevention study. In this study, men (55–80 years) and women (60–80 years) either had diabetes mellitus or 3 other cardiovascular risk factors. A Mediterranean diet with olive oil or nuts was compared with a standard low-fat diet. The Mediterranean diet showed a 30% relative risk reduction of MI, stroke, or death from CVDs in both the olive oil and walnut groups. Importantly, the Mediterranean diet decreased TMAO production as well.[69] This was a significant study showing that dietary changes toward a plant-based diet with fruits, vegetables, legumes, nuts, fish, and white meat is effective in reducing CVD.

Regarding whole grains, the Iowa Women's Health Study showed higher consumption led to fewer cardiovascular events.[70] In the Nurses' Health Study, a 25% decrease in cardiovascular events was noted in women who ate more than 3 servings of whole grains per day versus those who ate less than 1 serving per day.[71] Hu and Colleagues[72] recommended the optimal diet for lowering risk of CAD was a diet with non-hydrogenated fats, whole grains, and an abundance of fruits and vegetables.

Saturated and Trans-fats

Saturated fats have long been associated with risk of CVD, and reduction is advocated as part of the American College of Cardiology (ACC)/AHA guidelines. Controlled studies have shown that trans-fats increase LDL and lower HDL cholesterol, compared with nonhydrogenated unsaturated fatty acids.[73] They also increase lipoprotein [a],[74] which is a proinflammatory marker that increases triglycerides,[75] may reduce the blood vessel's ability to dilate, and increases the risk of diabetes.[76] Clinical trials show the negative impact of trans-fats on the risk of coronary heart disease.[77] The Nurses' Health Study looked at 80,082 women and found that higher trans-fats (and, to a smaller extent, saturated fats) were associated with higher risk of heart disease compared with the polyunsaturated nonhydrogenated diet.[78]

Unsaturated Fats: Polyunsaturated and Monounsaturated Fats

Unsaturated fats are categorized into monounsaturated and polyunsaturated fats (MUFAs and PUFAs, respectively). Oleic acid is the most commonly consumed monounsaturated fat, found in canola and olive oil.[79] MUFAs are almost completely absorbed by the intestine and oxidized for energy production, converted into other fatty acids, or incorporated into tissue lipids. Polyunsaturated fats (PUFAs) include omega-3 and omega-6 essential fatty acids.

Omega-3 fatty acids, mostly from marine sources, have been studied extensively. Higher consumption has been associated with decreasing mortality associated with coronary heart disease.[72] Greater consumption also correlates with improved mood, greater insulin sensitivity, increased muscle growth, and better sleep. The mechanism for reducing CVD is likely multifactorial.[80] They may reduce triglycerides, aid in blood thinning, and cause vasodilation.[81] People consuming 2 or more servings of fish per week have increased lifespan during 20-year follow-up.[82] In the US Physicians Health Study, 1 serving of fish per week was inversely related to the risk of sudden cardiac death. However, there was no association between fish consumption and MI.[83] The GISSI-Prevenzione trial included 11,324 patients with a recent ($\leq$3 months) MI. At 3.5 years, participants taking 1 g per day of n-3 PUFA supplement had significantly less combined death, nonfatal MI, and stroke compared with the control group. This benefit resulted largely from a 45% reduction in sudden cardiac death.[84] Thus, the benefit of omega-3 fatty acids is likely related to decreased risk of sudden cardiac death rather than a reduction in MI.

Supplements of EPA and DHA widely vary in their potency. Using Web sites such as consumerlabs.com can be beneficial to find reliable supplement sources. The World Health Organization advocates 0.3 to 0.5 g of both DHA and EPA and 0.8 to 1.1 g of alpha linoleic acid (an omega-3 fatty acid primarily from seed sources) per day for all-comers.[85] For management of heart disease, doses of 1 to 4 g of omega-3 fatty acids are recommended. The proportion of EPA to DHA are variable. Overall, the ratio likely should be higher in EPA than DHA. The AHA focuses on eating fatty fish at least 2 times per week (3.5 oz) as the best source for omega-3 fatty acids.

Omega-6 fatty acids

The main omega-6 fatty acid is linoleic acid, found in corn, soy, sunflower, and safflower. Linoleic acid breaks down into eicosanoids, some of which promote inflammation,[86] platelet aggregation, and vasoconstriction. There are no clinical trials that specifically look at outcomes from adding omega-6 fatty acids to the diet. Overall, the AHA now suggests that 5% to 10% of our total energy intake should come from omega-6 fatty acids, which may bring about a decrease in coronary heart disease relative to lower intakes.[87] However, the average American diet has 14 to 25 times more

omega-6 than omega-3.[88] We recommend a 1:1 or 1:2 balance of omega-6 to omega-3 fats. Common oils used in cooking and their omega-6:3 ratios are shown in Fig. 1.

Monounsaturated fats

Analysis of food oils used in the Mediterranean diet led to the focus on olive oil as the "golden oil" and targeted its abundance of MUFAs. Olive oil is 72% monounsaturated fat. The remainder is linoleic acid. MUFAs lower triglycerides and LDL levels and elevate HDL compared with saturated fats. In some studies, they improve cardiovascular outcomes,[89] ease oxidative stress, and improve diabetes control. Olive oil is also rich in polyphenols, which may decrease oxidative stress.[79] In 2001, the Lyon Diet Heart Study prospectively investigated the effects of a Mediterranean diet. A benefit of increased MUFA intake in survivors of first-time MI was found.[90] The PREDIMED data discussed previously also shows compelling evidence for the benefit of olive oil consumption, with the Mediterranean diet significantly predicting reduced CVD and mortality when compared with a standard low-fat diet. The dose of extra-virgin olive oil needed to create maximum benefit versus risk is unclear and requires further study.[91]

Plant-Based Supplements for Hyperlipidemia

Red yeast rice

Red yeast rice is a traditional Chinese herbal supplement that can be used as a food additive and for its cholesterol-lowering benefits. The essential ingredient is monacolin K, which is chemically identical to the active ingredient in lovastatin. One study looked at 74 patients with high cholesterol and randomized them to statin versus red yeast rice and fish oil. After 12 weeks, there was a 42.4% reduction in the red yeast rice/fish oil group compared with 39.6% reduction in the statin group. Despite these data, variability in quality and potency of red yeast rice on the market limits clinical utility. By-products in production of red yeast rice, such as citrinin, have been shown in animal studies to cause renal failure.[92,93] Although the risk of red yeast rice for muscle and liver toxicity may be lower than equivalent-dosed statins, the risk persists. Ultimately, we suggest that patients and clinicians use Internet Web sources, such as

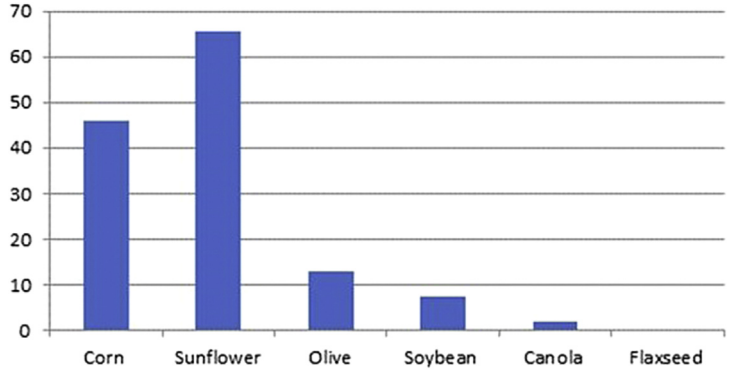

Fig. 1. Omega 6:3 ratio in oils. Note: Flaxseed oil cannot be used to cook with because it is potentially harmful when warmed. (*Data from* US Department of Agriculture, Agricultural Research Service. USDA National nutrient database for standard reference, release 28. Available at: https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/nutrient-data-laboratory/docs/usda-national-nutrient-database-for-standard-reference/. Accessed April 26, 2017.)

Consumer Labs, to check efficacy and potency of nutritional supplements, for example, levels of monacolin A and citrinin content.

Plant sterols (phytosterols) and stanols

Plant sterols block intestinal cholesterol absorption by competitively binding to cholesterol receptors. They are poorly absorbed and therefore result in overall reduction in cholesterol levels. Plant sterols are found in nuts, seeds, fruits, and legumes. In studies since the 1950s, plant sterols have been shown to reduce LDL cholesterol and therefore have long been added to foods and margarines to decrease cholesterol.[94] Although studies continued to show that plant sterols reduce cholesterol, it was unclear if this translated to reduction in CVD. Sitosterolemia, an inherited disorder characterized by increased absorption of plant sterols, is also associated with xanthomas and accelerated atherosclerosis.[95] This generated concern that plant sterols, at least in high doses, could increase risk of CVD. A meta-analysis of patients with moderate levels of plant sterol intake, however, did not show an association with increased CVD.[96]

Despite the meta-analysis, scientists continue to search for the lowest plant sterol dose that seemed to reduce cholesterol without doing any harm. They started experimenting with esterified plant stanols (the saturated form of sterols) that can be incorporated into other food sources without altering the taste or texture of the food. Plant stanol esters at the dosage of 2 to 3 g per day have been shown to decrease LDL cholesterol by 10% to 20% in many population subsets, such as elderly individuals, men, patients with CAD, and patients with diabetes. Notably, this benefit is in addition to statin medications.[97] Due to this trial data, many foods advertise added plant stanols, such as plant-based margarine, marketed as Benecol.

The ACC currently acknowledges that 1 to 3 g of plant sterols per day have a benefit in reducing cholesterol and can be obtained from natural food sources, such as legumes, nuts, and seeds. The benefit plateaus at 3 g per day.[98] Regarding plant stanol esters, using plant-based margarines, such as Benecol, are good options for bringing cholesterol down. A dosage of 1.7 g serving twice daily with a heart healthy diet is reasonable.

Fiber

Many experimental and observational studies have shown that increased fiber intake reduces cardiovascular risk factors.[99] Besides the phytosterol component of plant-based foods, soluble fibers and resistant starches (ie, insoluble fibers) are hypothesized to sit longer in the colon to form gels and allow the fiber to ferment. The formation of gels allows for satiety and decreases blood sugar and lipid levels.[100] The fermentation creates healthy short-chain fatty acids, which appear to also lower cholesterol levels.[101] An extensive meta-analysis showed an additional 7 g per day of dietary fiber decreased cardiovascular risk by 9%. Seven grams can be obtained from 1 serving of whole grains with beans or lentils. Alternatively, 2 to 4 servings of fruits and vegetables provide 7 g.[102] The consensus statement from the ACC, however, states that although there is a reduction in LDL cholesterol with 3 to 12 g of fiber per day, that improvement does not clearly translate into reduction in CVD.[98]

Polyphenols/phytonutrients/phytochemicals

These terms are often used interchangeably. They are naturally occurring nutrients in plants that possess antioxidant potential. Polyphenols can be broken down into carotenoids (beta-carotene, lycopene, lutein, and zeaxanthin), flavonoids (isoflavones, anthocyanidins, flavanols, quercetin), lignans, tannins, stilbenes (reservatrol), and others. Carotenoids and flavonoids are responsible for the color in our fruits and

vegetables. Much research is being devoted to clarify the biological activities of polyphenols. One study looked at older women's use of flavonoids retrospectively. Women with the most flavonoid-rich food intake had the lowest mortality.[103] One of the most impactful studies is the PREDIMED study subset analysis, which looked at polyphenol intake independently from omega-3 fatty acids and monounsaturated fats. Those with the highest polyphenol intake had the lowest cardiovascular mortality. Within the subsets of the polyphenols, the stilbenes and lignans had an inverse relationship with mortality.[104]

Stilbenes

The most common stilbene is resveratrol, found in grapes and red wine, and often attributed to the "French Paradox." One suggested mechanism of benefit is through increased NO levels in the vascular endothelium, thereby exerting a vasodilating effect.[105] Studies have also shown resveratrol to have beneficial effects to vascular aging by its effects of reducing inflammation, lowering oxidative stress, lowering platelet oxidation, and reducing thrombus formation.[106] In the Copenhagen City Heart Study[107] and the copenhagen city heart study and others,[108] 1 to 2 drinks of wine or other spirits significantly decreased cardiovascular mortality. There are insufficient data to recommend resveratrol supplements in clinical practice. However, the AHA does condone moderate alcohol intake but cautions against risks of abuse and alcoholism.[109]

Lignans

Lignans are phytoestrogens found in high quantities in flax, sesame seeds, and linseed. Benefits include lowering blood pressure, cholesterol, and C-reactive protein.[110] Supplementation at this time is not recommended, but food sources are reasonable.[111]

Coffee

Coffee beans contain polyphenols, namely lignans, caffeine, and vitamins. There appears to be a slight increase in blood pressure in coffee drinkers.[112] Coffee consumption, however, also appears to increase insulin sensitivity and decreases diabetes.[113] A meta-analysis done in 2013 found a U-shaped relationship between coffee intake and CVD. Moderate coffee consumption (3–5 cups of coffee per day) was associated with decreased CVD, whereas higher consumption was not associated with any effect.[114]

Tea

In a meta-analysis, tea consumption appeared to have a dose-dependent benefit in terms of decreasing stroke rate.[115] Results suggest a moderate improvement in LDL and total cholesterol with the addition of green tea catechins to the diet.[116] Although tea has potential, it cannot clearly be advocated for its benefits in lipid-lowering or cardiovascular benefit. It does not appear to cause harm, however, and therefore is a reasonable addition to a cardiovascular diet.

Soy

Soy has received substantial publicity because Asian countries that consume large amounts of soy have lower incidence of heart disease. Soy contains phytoestrogens called isoflavones. In early meta-analyses, when isolated soy protein with isoflavones was substituted for milk or animal fats, there was a notable decrease in LDL cholesterol concentrations. Fifty grams of soy seemed to potentiate the effect.[117] In 1999, the Food and Drug Administration approved labeling of soy proteins as cholesterol lowering and beneficial in reduction of CVD. The AHA issued a statement in 2000

that soy protein was beneficial in management of heart disease.[117] However, further studies and meta-analyses were reviewed and results were inconsistent. The AHA then put out a scientific advisory clarifying it is the soy itself and not necessarily the soy isoflavones that have showed benefit in reducing LDL cholesterol. No clear benefit of soy for improvement of HDL, triglycerides, or blood pressure was observed. Soy products in general have many potential benefits due to their high content of PUFAs, fiber, vitamins, and minerals, and low amount of saturated fat. Although soy is an estrogen mimetic, studies have not shown increased risk of breast cancer, a common concern among patients and clinicians.[118] Currently, a diet rich in plant-based foods and soy products is reasonable for all cardiovascular patients. Isoflavone supplements are not recommended, as their benefit is not clear and role in promoting cancer is unknown.

Pomegranate

In small human studies, patients who drank pomegranate juice for 3 months had decreased stress-induced ischemia compared with placebo.[119] Pomegranate juice may also decrease lipid oxidation (a precursor to atherosclerosis) and oxidative stress.[120] Benefits have been noted in patients with diabetes and patients with CAD, as well.[120,121]

Beta-carotene

Beta-carotene, a carotenoid polyphenol, has long been touted for its antioxidant effects. In 2 major RCTs, this claim was definitively refuted. Patients were given vitamin E, beta-carotene, both, or neither. With the addition of beta-carotene, there was not only no improvement, but rather an increase in cancer and ischemic heart disease.[122,123] Therefore, beta-carotene supplementation is not recommended for prevention of CVD.

Vitamin E

In a clinical trial, there was an increase in death from hemorrhagic stroke with vitamin E supplementation.[122] Subsequent studies did not show benefit from the addition of vitamin E into the diet in high-risk patients or for primary prevention. Therefore, vitamin E supplementation is not recommended for prevention of CVD. Some secondary prevention studies show a potential role for vitamin E that needs to be clarified.[124,125] The authors currently do not recommend vitamin E supplementation in CVD.

Vitamin D

Low vitamin D levels do appear associated with an increased incidence of CVD.[126] There is a potential U-shaped relationship between vitamin D and CVD in which high vitamin D levels in women were also associated with increased CVD.[127] Meta-analyses of the small trials available have not shown a benefit of supplementation in terms of a more favorable lipid profile.[128] The largest ongoing randomized trial of vitamin D in heart disease and cancer is The Vitamin D and Omega-3 Trial (VITAL). VITAL will look at differences in heart disease and cancer outcomes with the use of 2000 IU vitamin D per day with more than 25,000 participants.[129]

Chelation

Chelation to treat heavy metal burden is performed through intravenous administration of ethylene diamine tetraacetic acid (disodium EDTA) into the blood stream. Disodium EDTA then binds to heavy metals, such as cadmium and lead, and divalent minerals, such as calcium. The EDTA-metal/mineral complex is then excreted into the urine. Due to the notable calcium in CAD, interest by some investigators shifted to determining if chelation can be helpful for patients with CAD. The Trial to Assess Chelation

Therapy (TACT) trial in 2001 recruited patients older than 50 years, with a history of acute MI at least 6 weeks before enrollment and creatinine levels less than 2 mg/dL. The primary composite endpoint was all-cause mortality, MI, stroke, coronary revascularization, and hospitalization for angina. Chelation therapy showed an 18% reduction in the primary composite endpoint.[130] The reduction was sustained suggesting a long-term benefit to chelation. A multivitamin and a multimineral also were given in conjunction with chelation in a subset of patients and they demonstrated even more positive, powerful results. The most profound impact was seen in the diabetes subgroup and patients with previous history of an anterior wall MI subgroup in which hazard ratios were 0.61 and 0.63 favoring chelation, respectively.[131] Currently, TACT2 is enrolling specifically diabetic patients post MI and assessing chelation's effect on primary outcomes of all-cause mortality and other cardiovascular endpoints.[132] Chelation, therefore, has potential, but recommendations are deferred until further study.

Meditation and cardiovascular disease

In an RCT of African American men and women with CAD randomized to TM versus health education, TM showed a notable 48% relative risk reduction in the primary endpoint of all-cause mortality, stroke, or MI. These changes were associated with lower blood pressure and decreased stress.[133] In response to this pivotal article, the AHA advocates TM as part of secondary prevention. Although studies are not available, it is likely that moving meditation practices, such as tai-chi, yoga, and qi gong, have similar benefits. We believe that mind-body awareness exercises are important for decreasing stress with health benefits and should be advocated to our patients, along with other lifestyle changes.[58]

HEART FAILURE

Approximately 5 million Americans are currently living with heart failure and nearly 700,000 new cases are diagnosed each year.[134] Morbidity and mortality from heart failure remains high: 50% of patients newly diagnosed with heart failure will die within 5 years.[134] Hospital readmission rates have also been shown to be as high as 50% within 6 months after initial hospitalization.[135] Heart failure is also known to adversely affect quality of life and negatively impact day-to-day activities.[136] A potential strategy to reduce the burden of heart failure and improve symptom management is to leverage the use of evidence-based complementary and integrative therapies alongside traditional medical care.

Management of heart failure often necessitates a complex, coordinated care plan unique from other patients with a CVD diagnosis, including monitoring patients' limbs for signs of fluid retention, daily weight, and salt, alcohol, and fluid intake.[137] Adherence to lifestyle recommendations among patients with heart failure conspicuously low, despite well-established medical guidelines.[138] Dietary adherence in particular, including sodium restriction, is an important target because high sodium intake can often be a precipitating factor for hospitalizations.[139] This is an area in which primary care physicians may have substantial influence.

Sodium Intake in Patients with Heart Failure

Data on sodium restriction and outcomes among patients with heart failure is inconsistent. Sodium restriction has been associated with lower rates of symptom burden, readmission, and mortality in patients with heart failure in several studies.[140,141] However, in other larger studies, including RCTs, sodium restriction has been associated with higher mortality and readmission rates.[142–144] The current recommendation of the

AHA and ACC Foundation (ACCF) is 2000 mg of dietary sodium per day for patients with heart failure, which is notably higher than the AHA's proposed limit of 1500 mg per day for the general population.[145] The recommendation for sodium intake for patients with heart failure is based on level C evidence (expert consensus).

Translation of this recommendation is difficult in practice. Among a subsample of patients with heart failure participating in The Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure (COACH) trial, only 31% of those prescribed a sodium restriction of 2000 mg were compliant with the restriction.[146] Lack of adherence to prescribed levels of sodium is one reason that results are confounded in clinical trials attempting to discern the association between sodium intake and outcomes among patients with heart failure. In addition, the effects of sodium may significantly vary among patients with heart failure according to gender, race, or ethnicity.

The potential mechanism of action for the adverse effect of excess sodium in heart failure is decreased renal perfusion from decreased cardiac output, elevated systemic venous pressure, and/or shunting of blood from the kidney. This decreased perfusion leads to an increased sympathetic response and activation of the renin-angiotensin-aldosterone system, resulting in sodium and water retention even in the context of fluid overload.

Despite the conflicting evidence to date, sodium restriction to less than 2000 mg dietary sodium per day still should be recommended for most patients, consistent with AHA/ACCF guidelines for heart failure.[147] Diet education for patients with heart failure should include information specific to reading sodium values on food labels, high sodium foods to avoid, and suggested substitutions. Patients' personal sodium needs and fluid intake goals should be discussed and tailored to any coexisting conditions, such as diabetes.

Exercise

Walking capacity has been shown to be strongly associated with 10-year mortality and risk of heart failure among 2935 participants in the Health, Aging, and Body Composition Study.[148] Long-term RCTs have documented exercise training (ie, primarily walking) is associated with better functional capacity and improved quality of life. In turn, this improvement has resulted in a reduction in major cardiovascular events, hospitalizations, and cardiac mortality.[149] Supervised exercise training is generally recommended, provided patients are stable and without contraindications.[150] As an alternative to walking, a recent meta-analysis of 10 studies including 240 patients with heart failure found resistance training to increase muscle strength, aerobic capacity, and quality of life.[151] Resistance training may serve as a different approach to improve fitness among patients who are unable or unwilling to participate in aerobic activities. Although there is no AHA/ACC recommendation; studies typically used 45 to 60 minutes of aerobic exercise and resistance training 2 to 3 times per week.

Tai-chi exercise also may benefit patients with heart failure through improvements in their quality of life and capacity to exercise. Yeh and colleagues conducted a study in which 100 patients with systolic heart failure were randomized to either a tai-chi intervention for 60 minutes, twice per week, or an education-only control.[152] After 12 weeks, the tai-chi group experienced improved quality of life, exercise self-efficacy, and mood, with no observed adverse effects due to the intervention. There were no differential effects between groups in distance walked in 6 minutes or peak oxygen intake.

Mindfulness

The Support, Education, and Research in Chronic Heart Failure (SEARCH) study tested an 8-week mindfulness-based psychoeducational intervention on clinical

outcomes, depression, and quality of life in patients with heart failure. Results showed that the mindfulness-based intervention compared with control subjects reduced anxiety and depression and led to significantly fewer symptoms of heart failure after 1 year.[153] Proof of concept was demonstrated for the feasibility of a new 8-week program of integrative group medical care plus mindfulness training among patients with heart failure.[154] Patients participating in the Compassionate Approach to Lifestyle and Mind-Body (CALM) Skills for Patients with CHF, experienced improvements in depression, fatigue, and satisfaction with life. This intervention should be further evaluated in a controlled trial.

Meditation

A growing body of evidence is pointing toward the positive effects of meditation for patients with heart failure; however, it is somewhat limited by small sample sizes and studies of varying quality. Curiati and colleagues[155] randomly assigned 19 patients with heart failure to either usual care or usual care plus weekly meetings including meditation. The meditation component of the intervention consisted of a 30-minute audiotape for patients to listen to at their homes, twice a day for 12 weeks. At the end of 12 weeks, the meditation group showed improved measures of exercise performance, improved quality-of-life scores, and reduction in plasma norepinephrine.

Supplements

Dietary supplements are fairly common in patients with heart failure, with use ranging from 40% to 82%.[156] In contrast, physician awareness of patients' use of herbal or dietary supplements is approximately 60%.[157] The most common reasons for lack of awareness of use are the physician not asking or patient beliefs that the physician will be judgmental.[158] These data highlight the importance of systematically asking patients about any supplements, herbs, or other forms of treatment they may be using.

Coenzyme Q10

CoQ10 may reduce the toxic effects of reactive oxygen species that are seen in patients with heart failure. A systematic Cochrane review of 7 studies with 914 participants compared CoQ10 versus placebo. The investigators were unable to make a definitive conclusion regarding use of CoQ10 for heart failure.[159] Studies included in the Cochrane analysis led the ACC and the AHA to not recommend CoQ10 for management of heart failure. Following this statement, the Q-SYMBIO study, a 2-year prospective, randomized double-blind trial including 420 patients randomly assigned to either CoQ10 100 mg 3 times daily or placebo, showed short-term endpoints of New York Heart Association (NYHA) functional classification, 6-minute walk test, and levels of N-terminal pro-B type natriuretic peptide were not significantly different.[34] However, long-term endpoints of 2-year cardiovascular and all-cause mortality and heart failure hospitalizations were significantly decreased in the CoQ10 group. Additionally, there was a significant improvement in NYHA class after 2 years. Supplementation of CoQ10 may be considered as an adjunctive treatment in dosages of 100 mg, 2 to 3 times per day.

L-carnitine

A meta-analysis examining the role of L-carnitine in secondary prevention of CVD included 13 trials and concluded there were no protective effects for heart failure or myocardial reinfarction, despite reductions in all-cause mortality, ventricular arrhythmias, and angina attacks.[160] A large randomized multicenter trial is recommended

to confirm these results before suggesting supplementation specifically for patients with heart failure.

Selenium

Selenium deficiency is rare among individuals in United States and Canada, and limited clinical trial data do not support recommending supplementation for prevention or treatment of heart failure.[161]

Hawthorn

Although the mechanism of action is unclear, this herb may have vasodilatory properties, antioxidant activity, inotropic action, and lipid-lowering effects. A meta-analysis of hawthorn extract in 10 double-blind, placebo-controlled trials including 855 patients with heart failure showed symptomatic as well as functional benefits.[162] However, a randomized trial limited to patients with heart failure with reduced ejection fraction did not demonstrate any benefit.[163] Hawthorn extract may be considered as an adjunctive treatment for heart failure, at 900 to 1800 mg, divided over 2 to 3 doses per day. However, the potential for hawthorn to deleteriously interact with digoxin should be noted.[164]

ARRHYTHMIAS

Sudden cardiac death affects 180,000 to 450,000 persons per year in the United States, and accounts for more than 50% of all cardiovascular-related deaths. Most sudden cardiac deaths are attributable to arrhythmias.[165,166] Traditional medical treatment includes antiarrhythmic drugs, radiofrequency ablation, and implantable cardiac defibrillators. Potential downsides to traditional antiarrhythmic drugs may include cost and possible side effects, including triggering arrhythmias themselves in some cases.[167] Complementary and integrative medical treatments for arrhythmia with promising evidence for antiarrhythmic behavior or effectiveness with limited side effects include certain supplements, yoga, and acupuncture.[168]

Omega-3 Fatty Acids (See Also Hypertension Section)

Omega-3 PUFAs, such as EPA and DHA, may be effective in preventing and treating some types of arrhythmias.[169] The results of a 2013 meta-analysis (8 RCTs of 2967 patients) showed that preoperative supplementation with omega-3 PUFAs provided significant protection against atrial fibrillation in patients undergoing cardiac surgery.[170] Among patients who underwent coronary artery bypass graft (CABG) or valvular surgery, there was a 16% lower risk of atrial fibrillation for patients receiving omega-3 PUFAs compared with placebo. Among patients with CABG only, the risk reduction for atrial fibrillation was 34%. A different meta-analysis of a general population of 32,919 randomized patients (16,465 in the treatment group and 16,454 in the control group) found supplementation with omega-3 PUFAs compared with placebo did not affect the risk of sudden cardiac death or ventricular arrhythmias.[171] Thus, it appears that preoperative supplementation of PUFAs may decrease rates of atrial fibrillation, whereas PUFAs in the overall population may not affect incidence of ventricular arrhythmias. The AHA currently recommends 2 servings of oily fish per week for cardiac (including arrhythmic) benefits.

Magnesium and Potassium

Low concentrations of magnesium and potassium may increase risk of arrhythmia.[172] Magnesium supplementation has been shown to prevent arrhythmias after cardiac surgery. In a meta-analysis of 17 RCTs, the administration of magnesium postoperatively

reduced the risk of supraventricular arrhythmias by 23% (atrial fibrillation by 29%) and ventricular arrhythmias by 48%.[173] Oral administration of potassium with magnesium also was shown to be effective in reducing arrhythmias in a randomized, double-blind study of 232 patients with frequent ventricular arrhythmias.[174] Results showed that a 50% increase in the recommended minimum daily dietary intake of the 2 minerals for 3 weeks led to a moderate but significant antiarrhythmic effect. Supplementation of magnesium and potassium could be considered at 300 to 400 mg per day of magnesium and 2000 to 4700 mg of potassium per day. Usage of medications that could alter potassium levels, such as diuretics, should be taken into account before potassium administration. Good natural sources of magnesium are green leafy vegetables, nuts, legumes, and whole grains. Good sources of potassium include avocado, bananas, nuts, potatoes, citrus fruits, and green leafy vegetables.

Yoga

Yoga training could be beneficial for patients with arrhythmia because it incorporates breathing and relaxation exercises that significantly increase cardiac vagal modulation. In addition, it is easily implemented without serious adverse effects.[175] The YOGA My Heart Study examined the impact of twice-weekly, 60-minute yoga sessions for 3 months among patients with symptomatic paroxysmal atrial fibrillation on measures of arrhythmia burden, quality of life, depression, and anxiety scores.[176] The patients participated in an initial 3-month noninterventional observation period to serve as their own controls. Each yoga session consisted of 10 minutes of *pranayama* (breathing exercises), 10 minutes of warm-up exercises, 30 minutes of *asanas* (poses), and 10 minutes of relaxation exercises. After 3 months, yoga therapy significantly reduced symptomatic and asymptomatic atrial fibrillation burden. Further, patients had improvement in their heart rate, blood pressure, anxiety, and overall quality of life.

Acupuncture

A review synthesizing the evidence for acupuncture and cardiac arrhythmias concluded that 87% to 100% of participants converted to normal sinus rhythm after acupuncture. However, the review included case series or case studies, with only 1 RCT.[177] A 2011 controlled trial of 80 patients with atrial fibrillation found recurrence rates of atrial fibrillation lower in acupuncture compared with acupuncture-sham and control patients. Further studies are needed to better define the role of acupuncture in arrhythmia treatment.[178]

SUMMARY

Cardiovascular patients often desire an integrated approach, do not comply well with medical therapies, and complain of medication side effects. Thus, treating physicians need to be knowledgeable about the evidence for and against interventions such as diet, exercise, supplements, herbs, and mind/body techniques. A patient-centered evidence-based approach of discussing the risk/benefit profile of these complementary approaches will allow for a more open dialogue with our patients and hopefully improved compliance and outcomes.

REFERENCES

1. World Health Organization. Available at: www.who.int/mediacentre/factsheets. Accessed April 25, 2017.
2. Medicine use and spending shifts: a review of the use of medicines in the U.S. in 2014. Qunitiles IMS Institute; 2015.

3. Prescription drug costs [Internet] KFF. Menlo Park (CA): Kaiser Family Foundation; 2010 [December 26, 2011].
4. Haynes RB, McDonald HP, Garg AX. Helping patients follow prescribed treatment: clinical applications. JAMA 2002;288(22):2880–3.
5. Bairey Merz CN, Elboudwarej O, Mehta P. The autonomic nervous system and cardiovascular health and disease. JACC Heart Fail 2015;3(5):383–5.
6. Schneiderman N, Ironson G, Siegal SD. Stress and health: psychological, behavioral and biological determinants. Annu Rev Clin Psychol 2005;1:607–28.
7. Aschbacher K, O'Donovan A, Wolkowitz OM, et al. Good stress, bad stress and oxidative stress: insights from anticipatory cortisol reactivity. Psychoneuroendocrinology 2013;38(9):1698–708.
8. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med 1997;336(16):1117–24.
9. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. Intersalt Cooperative Research Group. BMJ 1988;297(6644):319–28.
10. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. N Engl J Med 2001;344(1):3–10.
11. O'donnell M, Mente A, Rangarajan S, et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. N Engl J Med 2014; 2014(371):612–23.
12. Graudal N, Jurgens G, Baslund B, et al. Compared with usual sodium intake, low-and excessive-sodium diets are associated with increased mortality: a meta-analysis. Am J Hypertens 2014;27(9):1129–37.
13. American Heart Association. Available at: https://sodiumbreakup.heart.org/sodium_and_your_health. Accessed April 25, 2017.
14. Brandes RP. Endothelial dysfunction and hypertension. Hypertension 2014; 64(5):924–8.
15. Martina V, Masha A, Gigliardi VR, et al. Long-term N-acetylcysteine and L-arginine administration reduces endothelial activation and systolic blood pressure in hypertensive patients with type 2 diabetes. Diabetes Care 2008;31(5):940–4.
16. Hord NG, Tang Y, Bryan NS. Food sources of nitrates and nitrites: the physiologic context for potential health benefits. Am J Clin Nutr 2009;90(1):1–10.
17. Lundberg JO, Weitzberg E, Gladwin MT. The nitrate–nitrite–nitric oxide pathway in physiology and therapeutics. Nat Rev Drug Discov 2008;7(2):156–67.
18. Bryan NS. Nitrite in nitric oxide biology: cause or consequence? A systems-based review. Free Radic Biol Med 2006;41(5):691–701.
19. D'El-Rei J, Cunha AR, Trindade M, et al. Beneficial effects of dietary nitrate on endothelial function and blood pressure levels. Int J Hypertens 2016;2016: 6791519.
20. Kapil V, Khambata RS, Robertson A, et al. Dietary nitrate provides sustained blood pressure lowering in hypertensive patients: a randomized, phase 2, double-blind, placebo-controlled study. Hypertension 2014;65(2):320–7.
21. Mcnally B, Griffin JL, Roberts LD. Dietary inorganic nitrate: from villain to hero in metabolic disease? Mol Nutr Food Res 2015;60(1):67–78.
22. Terry P, Terry JB, Wolk A. Fruit and vegetable consumption in the prevention of cancer: an update. J Intern Med 2001;250(4):280–90.
23. Gokce J. L-arginine and hypertension. J Nutr 2004;134(10 Suppl):2807S–11S.

24. Lekakis JP, Papathanassiou S, Papaioannou TG, et al. Oral l-arginine improves endothelial dysfunction in patients with essential hypertension. Int J Cardiol 2002;86(2–3):317–23.
25. Dong JY, Qin LQ, Zhang Z, et al. Effect of oral l-arginine supplementation on blood pressure: a meta-analysis of randomized, double-blind, placebo-controlled trials. Am Heart J 2011;162(6):959–65.
26. Schulman SP, Becker LC, Kass DA, et al. L-arginine therapy in acute myocardial infarction. JAMA 2006;295(1):58.
27. Houston MC, Fox B, Taylor N. What your doctor may not tell you about hypertension: the revolutionary nutrition and lifestyle program to help fight high blood pressure. New York: Warner Books; 2003.
28. Juraschek SP, Guallar E, Appel LJ, et al. Effects of vitamin C supplementation on blood pressure: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2012;95(5):1079–88.
29. Salvamani S, Gunasekaran B, Azmi Shaharuddin NA, et al. Antiartherosclerotic effects of plant flavonoids. Biomed Res Int 2014;2014:1–11.
30. Duffy S, Keaney J, Holbrook M, et al. Short- and long-term black tea consumption reverses endothelial dysfunction in patients with coronary artery disease. ACC Curr J Rev 2002;11(1):28.
31. Gang L, Xiaohong H. GW25-e0837 effects of tea intake on blood pressure: a meta-analysis of 21 randomized controlled trials. J Am Coll Cardiol 2014; 64(16). C112.
32. Li X, Xu J. Lycopene supplement and blood pressure: an updated meta-analysis of intervention trials. Nutrients 2013;5(9):3696–712.
33. Rosenfeldt FL, Haas SJ, Krum H, et al. Coenzyme Q10 in the treatment of hypertension: a meta-analysis of the clinical trials. J Hum Hypertens 2007;21(4): 297–306.
34. Mortensen SA, Rosenfeldt F, Kumar A, et al, Q-SYMBIO Study Investigators. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. JACC Heart Fail 2014; 2(6):641–9.
35. Ho MJ, Li EC, Wright JM. Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension. Cochrane Database Syst Rev 2016;(3):CD007435.
36. Houston M. The role of magnesium in hypertension and cardiovascular disease. J Clin Hypertens 2011;13(11):843–7.
37. Zhang X, Li Y, Del Gobbo LC, et al. Effects of magnesium supplementation on blood pressure novelty and significance. Hypertension 2016;68(2):324–33.
38. Cordain L, Eaton SB, Sebastian A, et al. Origins and evolution of the Western diet: health implications for the 21st century. Am J Clin Nutr 2005;81:341–54.
39. Dyer AR, Elliott P, Shipley M. Urinary electrolyte excretion in 24 hours and blood pressure in the Intersalt study. II. Estimates of electrolyte blood pressure associations corrected for regression dilution bias. Am J Epidemiol 1994;139(9): 940–51.
40. D'elia L, Barba G, Cappuccio FP, et al. Potassium intake, stroke, and cardiovascular disease. J Am Coll Cardiol 2011;57(10):1210–9.
41. Aburto NJ, Hanson S, Gutierrez H, et al. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. BMJ 2013;346:f1378.
42. Saltman P. Trace elements and blood pressure. Ann Intern Med 1983;98(5 Part 2):823–7.

43. Judd SE, Tangpricha V. Vitamin D deficiency and risk for cardiovascular disease. Am J Med Sci 2009;338(1):40–4.
44. Beveridge LA, Struthers AD, Khan F, et al. Effect of Vitamin D Supplementation on Blood PressureA Systematic Review and Meta-analysis Incorporating Individual Patient Data. JAMA Intern Med 2015;175(5):745–54.
45. Vaidya A, Forman JP. Vitamin D and hypertension: current evidence and future directions. Hypertension 2010;56(5):774–9.
46. Beierwaltes WH. The role of calcium in the regulation of renin secretion. Am J Physiol Ren Physiol 2010;298(1):F1–11.
47. Resnick L. The role of dietary calcium in hypertension: a hierarchal overview. Am J Hypertens 1999;12(1):99–112.
48. Bohr DF. Vascular smooth muscle: dual effect of calcium. Science 1963; 139(3555):597–9.
49. Mccarron DA, Reusser ME. Finding consensus in the dietary calcium-blood pressure debate. J Am Coll Nutr 1999;18(5 Suppl):398S–405S.
50. Anderson JJ, Kruszka B, Delaney JA, et al. Calcium intake from diet and supplements and the risk of coronary artery calcification and its progression among older adults: 10-year follow-up of the multi-ethnic study of atherosclerosis (MESA). J Am Heart Assoc 2016;5(10) [pii:e003815].
51. Miller PE, Van Elswyk M, Alexander DD. Long-chain omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid and blood pressure: a meta-analysis of randomized controlled trials. Am J Hypertens 2014;27(7):885–96.
52. Sun Q, Wang B, Li Y, et al. Taurine supplementation lowers blood pressure and improves vascular function in prehypertension. Hypertension 2016;67(3):541–9.
53. Walker AF, Marakis G, Simpson E, et al. Hypotensive effects of hawthorn for patients with diabetes taking prescription drugs: a randomized controlled trial. Br J Gen Pract 2006;56(527):437–43.
54. Aviram M, Dornfeld L. Pomegranate juice consumption inhibits serum angiotensin converting enzyme activity and reduces systolic blood pressure. Atherosclerosis 2001;158:195–8.
55. Mathew AS, Capel-Williams GM, Berry SE, et al. Acute effects of pomegranate extract on postprandial lipaemia, vascular function and blood pressure. Plant Foods Hum Nutr 2012;67:351–7.
56. Corti R, Flammer AJ, Hollenberg NK, et al. Cocoa and cardiovascular health. Circulation 2009;119(10):1433–41.
57. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. J Am Heart Assoc 2013;2(1):e004473.
58. Available at: www.heart.org. Accessed April 25, 2017.
59. Hudnut F. Comment on “beyond medications and diet: alternative approaches to lowering blood pressure: a scientific statement from the American Heart Association”. Hypertension 2014;63(1):e3.
60. Lackland DT, Townsend RR, Brook RD. Response to comment on “beyond medications and diet: alternative approaches to lowering blood pressure: a scientific statement from the American Heart Association”. Hypertension 2014;63(1):e4.
61. World Health Organization. Available at: www.who.int. Accessed April 25, 2017.
62. Aadahl M, Kjaer M, Jørgensen T. Associations between overall physical activity level and cardiovascular risk factors in an adult population. Eur J Epidemiol 2007;22(6):369–78.
63. Tang WH, Wang Z, Levison BS, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. N Engl J Med 2013;368:1575–84.

64. Cho CE, Taesuwan S, Malysheva OV, et al. Trimethylamine-N-oxide (TMAO) response to animal source foods varies among healthy young men and is influenced by their gut microbiota composition: a randomized controlled trial. Mol Nutr Food Res 2017;61(1).
65. Kleinbongard P, Dejam A, Lauer T, et al. Plasma nitrite concentrations reflect the degree of endothelial dysfunction in humans. Free Radic Biol Med 2006;40(2): 295–302.
66. Pereira EC, Ferderbar S, Bertolami MC, et al. Biomarkers of oxidative stress and endothelial dysfunction in glucose intolerance and diabetes mellitus. Clin Biochem 2008;41(18):1454–60.
67. Vogel R, Corretti M, Plotnick GD. Effect of a single high-fat meal on endothelial function in healthy subjects. Am J Cardiol 1997;79(3):350–4.
68. Ornish D, Scherwitz LW, Billings JH, et al. Intensive lifestyle changes for reversal of coronary heart disease. JAMA 1998;280(23):2001–7.
69. Hampton T. Ongoing research points to key role of gut microbes in cardiovascular health. Circulation 2016;134:1687–8.
70. Jacobs DR Jr, Meyer KA, Kushi LH, et al. Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: the Iowa women's health study. Am J Clin Nutr 1998;68:248–57.
71. Liu S, Stampfer MJ, Hu FB, et al. Whole-grain consumption and risk of coronary heart disease: results from the Nurses' Health Study. Am J Clin Nutr 1999;70:412–9.
72. Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. JAMA 2002;288(20):2569–78.
73. Mensink RP, Katan MB. Effect of dietary trans fatty acids on high-density and low-density lipoprotein cholesterols levels in healthy subjects. N Engl J Med 1990;323:439–45.
74. Nestel P, Noakes M, Belling B, et al. Plasma lipoprotein lipid and Lp [a] changes with substitution of elaidic acid for oleic acid in the diet. J Lipid Res 1992;33(7): 1029–36.
75. Katan MB, Zock PL, Mensink RP. Trans fatty acids and their effects on lipoproteins in humans. Annu Rev Nutr 1995;15:473–93.
76. Salmeron J, Hu FB, Manson JE, et al. Dietary fat intake and risk of type 2 diabetes in women. Am J Clin Nutr 2001;73(6):1019–26.
77. Kushi LH, Lew RA, Stare FJ, et al. Diet and 20-year mortality from coronary heart disease: the Ireland–Boston Diet–Heart Study. N Engl J Med 1985;312(13): 811–8.
78. Hu FB, Stampfer MJ, Manson JE, et al. Dietary fat intake and the risk of coronary heart disease in women. N Engl J Med 1997;337(21):1491–9.
79. Kris-Etherton PM. AHA Science Advisory. Monounsaturated fatty acids and risk of cardiovascular disease. American Heart Association. Nutrition Committee. Circulation 1999;100:1253–8.
80. Kang JX, Leaf A. Antiarrhythmic effects of polyunsaturated fatty acids: recent studies. Circulation 1996;94:1774–80.
81. Connor SL, Connor WE. Are fish oils beneficial in the prevention and treatment of coronary artery disease? Am J Clin Nutr 1997;66(4 Suppl):1020S–31S.
82. Kromhout D, Bosschieter EB, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. N Engl J Med 1985;312:1205–9.
83. Albert CM, Hennekens CH, O'Donnell CJ, et al. Fish consumption and risk of sudden cardiac death. JAMA 1998;279:23–8.

84. Dietary supplementation with N-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-prevenzione trial. Lancet 1999; 354(9177):447–55.
85. Available at: www.mayoclinic.org. Accessed April 25, 2017.
86. Steinberg D, Parthasarathy S, Carew TE, et al. Beyond cholesterol: modifications of low-density lipoprotein that increase its atherogenicity. N Engl J Med 1989;320:915–24.
87. Harris WS, Mozaffarian D, Rimm E, et al. Omega-6 fatty acids and risk for cardiovascular disease: a science advisory from the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention. Circulation 2009;119(6):902–7.
88. Omega-6 fatty acids, University of Maryland Medical Center. Available at: http://www.umm.edu/altmed/articles/omega-6-000317.htm. Accessed April 25, 2017.
89. Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368(14):1279–90.
90. Lorgeril M, De P, Salen JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation 1999;99(6):779–85.
91. Guasch-Ferré M, Hu FB, Martínez-González MA, et al. Olive oil intake and risk of cardiovascular disease and mortality in the PREDIMED Study. BMC Med 2014; 12:78.
92. Heber D, Lembertas A, Lu QY, et al. An analysis of nine proprietary Chinese red yeast rice dietary supplements: implications of variability in chemical profile and contents. J Altern Complement Med 2001;7(2):133–9.
93. Gordon RY, Cooperman T, Obermeyer W, et al. Marked variability of monacolin levels in commercial red yeast rice products: buyer beware! Arch Intern Med 2010;170(19):1722–7.
94. Lees AM, Mok HY, Lees RS, et al. Plant sterols as cholesterol-lowering agents: clinical trials in patients with hypercholesterolemia and studies of sterol balance. Atherosclerosis 1977;28:325–38.
95. Yoo EG. Sitosterolemia: a review and update of pathophysiology, clinical spectrum, diagnosis, and management. Ann Pediatr Endocrinol Metab 2016;21(1): 7–14.
96. Genser B, Silbernagel G, De Backer G, et al. Plant sterols and cardiovascular disease: a systematic review and meta-analysis. Eur Heart J 2012;33(4):444–51.
97. Cater NB. Plant stanol ester: review of cholesterol-lowering efficacy and implications for coronary heart disease risk reduction. Prev Cardiol 2000;3(3):121–30.
98. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2016;68(1):92–125.
99. Van Horn L, McCoin M, Kris-Etherton PM, et al. The evidence for dietary prevention and treatment of cardiovascular disease. J Am Diet Assoc 2008;108: 287–331.
100. James SL, Muir JG, Curtis SL, et al. Dietary fibre: a roughage guide. Intern Med J 2003;33:291–6.
101. Slavin JL, Martini MC, Jacobs DR Jr, et al. Plausible mechanisms for the protectiveness of whole grains. Am J Clin Nutr 1999;70(3 Suppl):459S–63S.

102. Threapleton DE, Greenwood DC, Evans CE, et al. Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. BMJ 2013;347: f6879.
103. Ivey KL, Hodgson JM, Croft KD, et al. Flavonoid intake and all-cause mortality. Am J Clin Nutr 2015;101(5):1012–20.
104. Tresserra-Rimbau A, Rimm EB, Medina-Remón A, et al. Polyphenol intake and mortality risk: a re-analysis of the PREDIMED trial. BMC Med 2014;12:77.
105. Wallerath T, Deckert G, Ternes T. Resveratrol, a polyphenolic phytoalexin present in red wine, enhances expression and activity of endothelial nitric oxide synthase. Circulation 2002;106(13):1652–8.
106. Delmas D, Jannin B, Latruffe N. Resveratrol: preventing properties against vascular alterations and ageing. Mol Nutr Food Res 2005;49(5):377–95.
107. Mukamal KJ, Conigrave KM, Mittleman MA, et al. Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men. N Engl J Med 2003; 348(2):109–18.
108. Hu FB, Willett WC. Prevention of coronary heart disease: findings from the Nurses' Health Study and health professionals' follow-up study. Coron Heart Dis Epidemiol 2005;654–68.
109. American Heart Association. Alcohol, wine and cardiovascular disease. Available at: http://www.americanheart.org/presenter.jhtml?identifier=4422. Accessed December 7, 2004.
110. Peterson J, Dwyer J, Adlercreutz H, et al. Dietary lignans: physiology and potential for cardiovascular disease risk reduction. Nutr Rev 2010;68(10):571–603.
111. Milder IE, Feskens EJ, Arts IC, et al. Intakes of 4 dietary lignans and cause-specific and all-cause mortality in the Zutphen Elderly Study. Am J Clin Nutr 2006;84(2):400–5.
112. Zhang Z, Hu G, Caballero B, et al. Habitual coffee consumption and risk of hypertension: a systematic review and meta-analysis of prospective observational studies. Am J Clin Nutr 2011;93:1212–9.
113. van Dam RM, Hu FB. Coffee consumption and risk of type 2 diabetes: a systematic review. JAMA 2005;294:97–104.
114. Ding M, Bhupathiraju SN, Satija A. Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies. J Vasc Surg 2014;59(5):1471.
115. Arab L, Khan F, Lam H. Tea consumption and cardiovascular disease risk. Am J Clin Nutr 2013;98(6 Suppl):1651S–9S.
116. Khalesi S, Sun J, Buys N, et al. Green tea catechins and blood pressure: a systematic review and meta-analysis of randomised controlled trials. Eur J Nutr 2014;53:1299–311.
117. Sacks FM, Lichtenstein A, Van Horn L, et al. Soy protein, isoflavones, and cardiovascular health. Circulation 2006;113:1034–44.
118. Shu XO, Zheng Y, Cai H, et al. Soy food intake and breast cancer survival. JAMA 2009;302(22):2437–43.
119. Sumner MD, Elliott-Eller M, Weidner G, et al. Effects of pomegranate juice consumption on myocardial perfusion in patients with coronary heart disease. Am J Cardiol 2005;96:810–4.
120. Aviram M, Dornfeld L, Rosenblat M, et al. Pomegranate juice consumption reduces oxidative stress, atherogenic modifications to LDL, and platelet aggregation: studies in humans and in atherosclerotic apolipoprotein E-deficient mice. Am J Clin Nutr 2000;71:1062–76.

121. Rosenblat M, Hayek T, Aviram M. Anti-oxidative effects of pomegranate juice (PJ) consumption by diabetic patients on serum and on macrophages. Atherosclerosis 2006;187:368–76.
122. Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group. The effect of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 1994;330:1029–35.
123. Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 1996;334:1150–5.
124. Stephens NG, Parsons A, Schofield PM, et al. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study. Lancet 1996;347:781–6.
125. Rapola JM, Virtamo J, Ripatti S, et al. Randomised trial of α-tocopherol and β-carotene supplements on incidence of major coronary events in men with previous myocardial infarction. Lancet 1997;349:1715–20.
126. Kendrick J, Targher G, Smits G, et al. 25-hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the third national health and nutrition examination survey. Atherosclerosis 2009;205(1):255–60.
127. Melamed ML, Michos ED, Post W, et al. 25-hydroxyvitamin D levels and the risk of mortality in the general population. Arch Intern Med 2008;168(15):1629–37.
128. Wang H, Xia N, Yang Y, et al. Influence of vitamin D supplementation on plasma lipid profiles: a meta-analysis of randomized controlled trials. Lipids Health Dis 2012;11(1):42.
129. Clinicaltrials.gov identified: NCT01169259.
130. Lamas GA, Goertz C, Boineau R, et al. Effect of disodium EDTA chelation regimen on cardiovascular events in patients with previous MI: the TACT randomized trial. JAMA 2013;309:1241–50.
131. Escolar E, Lamas GA, Mark DB, et al. The effect of an EDTA-based chelation regimen on patients with diabetes mellitus and prior myocardial infarction in the trial to assess chelation therapy (TACT). Circ Cardiovasc Qual Outcomes 2014;7:15–24.
132. Available at: https://clinicaltrials.gov/ct2/show/NCT02733185. Accessed April 25, 2017.
133. Schneider RH, Grim CE, Rainforth MV, et al. Stress reduction in the secondary prevention of cardiovascular disease randomized, controlled trial of transcendental meditation and health education in Blacks. Circ Cardiovasc Qual Outcomes 2012;5(6):750–8.
134. Writing Group Members, Mozaffarian D, Benjamin EJ, et al. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. Circulation 2016;133(4):e38–360.
135. Krumholz HM, Parent EM, Tu N, et al. Readmission after hospitalization for congestive heart failure among medicare beneficiaries. Arch Intern Med 1997; 157:99–104.
136. Juenger J, Schellberg D, Kraemer S, et al. Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. Heart 2002;87(3):235–41.
137. Horowitz JD. Home-based intervention: the next step in treatment of chronic heart failure? Eur Heart J 2000;21(22):1807Y1809.
138. van der Wal MH, van Veldhuisen DJ, Veeger NJ, et al. Compliance with non-pharmacological recommendations and outcome in heart failure patients. Eur Heart J 2010;31(12):1486–93.

139. Tsuyuki RT, McKelvie RS, Arnold JM, et al. Acute precipitants of congestive heart failure exacerbations. Arch Intern Med 2001;161(19):2337–42.
140. Son YJ, Lee Y, Song EK. Adherence to a sodium-restricted diet is associated with lower symptom burden and longer cardiac event-free survival in patients with heart failure. J Clin Nurs 2011;20(21–22):3029–38.
141. Philipson H, Ekman I, Forslund HB, et al. Salt and fluid restriction is effective in patients with chronic heart failure. Eur J Heart Fail 2013;15(11):1304–10.
142. Paterna S, Parrinello G, Cannizzaro S, et al. Medium term effects of different dosage of diuretic, sodium, and fluid administration on neurohormonal and clinical outcome in patients with recently compensated heart failure. Am J Cardiol 2009;103(1):93–102.
143. Paterna S, Gaspare P, Fasullo S, et al. Normal-sodium diet compared with low-sodium diet in compensated congestive heart failure: is sodium an old enemy or a new friend? Clin Sci (Lond) 2008;114:221–30.
144. Parrinello G, Di Pasquale P, Licata G, et al. Long-term effects of dietary sodium intake on cytokines and neurohormonal activation in patients with recently compensated congestive heart failure. J Card Fail 2009;15:864–73.
145. Jessup M, Abraham WT, Casey DE, et al. 2009 Focused Update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines developed in collaboration with the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 2009;53:1343–82.
146. Nieuwenhuis MM, van der Wal MH, Jaarsma T. The body of knowledge on compliance in heart failure patients: we are not there yet. J Cardiovasc Nurs 2011;26(1):21–8.
147. Molloy GJ, O'Carroll RE, Witham MD, et al. Interventions to enhance adherence to medications in patients with heart failure: a systematic review. Circ Heart Fail 2012;5(1):126–33.
148. Georgiopoulou VV, Kalogeropoulos AP, Chowdhury R, et al. Exercise capacity, heart failure risk, and mortality in older adults: the health ABC study. Am J Prev Med 2017;52(2):144–53.
149. Belardinelli R, Georgiou D, Cianci G, et al. 10-year exercise training in chronic heart failure: a randomized controlled trial. J Am Coll Cardiol 2012;60(16):1521–8.
150. Mant J, Al-Mohammad A, Swain S, et al. Guideline Development Group. Management of chronic heart failure in adults: synopsis of the National Institute for Health and Clinical Excellence guideline. Ann Intern Med 2011;155(4):252–9.
151. Giuliano C, Karahalios A, Neil C, et al. The effects of resistance training on muscle strength, quality of life and aerobic capacity in patients with chronic heart failure—a meta-analysis. Int J Cardiol 2017;227:413–23.
152. Yeh GY, McCarthy EP, Wayne PM, et al. Tai chi exercise in patients with chronic heart failure: a randomized clinical trial. Arch Intern Med 2011;171(8):750–7.
153. Sullivan MJ, Wood L, Terry J, et al. The support, education, and research in chronic heart failure study (SEARCH): a mindfulness-based psychoeducational intervention improves depression and clinical symptoms in patients with chronic heart failure. Am Heart J 2009;157(1):84–90.
154. Kemper KJ, Carmin C, Mehta B, et al. Integrative medical care plus mindfulness training for patients with congestive heart failure: proof of concept. J Evid Based Complement Altern Med 2016;21(4):282–90.
155. Curiati JA, Bocchi E, Freire JO, et al. Meditation reduces sympathetic activation and improves the quality of life in elderly patients with optimally treated heart

failure: a prospective randomized study. J Altern Complement Med 2005;11(3): 465–72.
156. Bin YS, Kiat H. Prevalence of dietary supplement use in patients with proven or suspected cardiovascular disease. Evid Based Complement Alternat Med 2011;2011:632829.
157. Chagan L, Bernstein D, Cheng JW, et al. Use of biological based therapy in patients with cardiovascular diseases in a university-hospital in New York city. BMC Complement Altern Med 2005;5:4.
158. Grant SJ, Bin YS, Kiat H, et al. The use of complementary and alternative medicine by people with cardiovascular disease: a systematic review. BMC Public Health 2012;12(1):1.
159. Madmani ME, Yusuf Solaiman A, Tamr Agha K, et al. Coenzyme Q10 for heart failure. Cochrane Database Syst Rev 2014;(6):CD008684.
160. DiNicolantonio JJ, Lavie CJ, Fares H, et al. L-carnitine in the secondary prevention of cardiovascular disease: systematic review and meta-analysis. Mayo Clin Proc 2013;88(6):544–51.
161. Institute of Medicine, Food and Nutrition Board. Dietary reference intakes: vitamin C, vitamin E, selenium, and carotenoids. Washington, DC: National Academy Press; 2000.
162. Pittler MH, Schmidt K, Ernst E. Hawthorn extract for treating chronic heart failure: meta-analysis of randomized trials. Am J Med 2003;114(8):665–74.
163. Holubarsch CJ, Colucci WS, Meinertz T, et al. The efficacy and safety of *Crataegus* extract WS® 1442 in patients with heart failure: the SPICE trial. Eur J Heart Fail 2008;10(12):1255–63.
164. Dasgupta A, Kidd L, Poindexter BJ, et al. Interference of hawthorn on serum digoxin measurements by immunoassays and pharmacodynamic interaction with digoxin. Arch Pathol Lab Med 2010;134(8):1188–92.
165. Kong MH, Fonarow GC, Peterson ED, et al. Systematic review of the incidence of sudden cardiac death in the United States. J Am Coll Cardiol 2011;57(7): 794–801.
166. Meissner MD, Akhtar M, Lehmann MH. Nonischemic sudden tachyarrhythmic death in atherosclerotic heart disease. Circulation 1991;84:905–12.
167. Podrid PJ, Lampert S, Graboys TB, et al. Aggravation of arrhythmia by antiarrhythmic drugs–incidence and predictors. Am J Cardiol 1987;59:38E–44E.
168. Brenyo A, Aktas MK. Review of complementary and alternative medical treatment of arrhythmias. Am J Cardiol 2014;113(5):897–903.
169. Jahangiri A, Leifert WR, Patten GS, et al. Termination of asynchronous contractile activity in rat atrial myocytes by n-3 poliun-saturated fatty acids. Mol Cell Biochem 2000;206:33–41.
170. Costanzo S, di Niro V, Di Castelnuovo A, et al. Prevention of postoperative atrial fibrillation in open heart surgery patients by preoperative supplementation of n-3 polyunsaturated fatty acids: an updated meta-analysis [review]. J Thorac Cardiovasc Surg 2013;146(4):906–11.
171. Khoueiry G, Abi Rafeh N, Sullivan E, et al. Do omega-3 polyunsaturated fatty acids reduce risk of sudden cardiac death and ventricular arrhythmias? A meta-analysis of randomized trials. Heart Lung 2013;42(4):251–6.
172. Maciejewski P, Bednarz B, Chamiec T, et al. Acute coronary syndrome: potassium, magnesium and cardiac arrhythmia. Kardiol Pol 2003;59(11):402–7.
173. Shiga T, Wajima Z, Inoue T, et al. Magnesium prophylaxis for arrhythmias after cardiac surgery: a meta-analysis of randomized controlled trials. Am J Med 2004;117(5):325–33.

174. Zehender M, Meinertz T, Faber T, et al. Antiarrhythmic effects of increasing the daily intake of magnesium and potassium in patients with frequent ventricular arrhythmias. Magnesium in cardiac arrhythmias (MAGICA) investigators. J Am Coll Cardiol 1997;29(5):1028–34.
175. Khattab K, Khattab AA, Ortak J, et al. Iyengar yoga increases cardiac parasympathetic nervous modulation among healthy yoga practitioners. Evid Based Complement Alternat Med 2007;4(4):511–7.
176. Lakkireddy D, Atkins D, Pillarisetti J, et al. Effect of yoga on arrhythmia burden, anxiety, depression, and quality of life in paroxysmal atrial fibrillation: the YOGA my heart study. J Am Coll Cardiol 2013;61(11):1177–82.
177. VanWormer AM, Lindquist R, Sendelbach SE. The effects of acupuncture on cardiac arrhythmias: a literature review. Heart Lung 2008;37(6):425–31.
178. Lomuscio A, Belletti S, Battezzati PM, et al. Efficacy of acupuncture in preventing atrial fibrillation recurrences after electrical cardioversion. J Cardiovasc Electrophysiol 2011;22(3):241–7.