

KEY ARTICLES

Key Articles Related to Complementary and Alternative Medicine in Cardiovascular Disease: Part 1

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Complementary and alternative medicine (CAM) therapy has gained popularity in America over the past several years, reflected in the increased utilization of these agents. Given the abundance of nontraditional products available to the public, clinicians should be made aware of the existing evidence relating to CAM therapy to better provide patient care in a meaningful manner. This bibliography article compiled key articles specific to CAM therapy and cardiovascular disease, which include primary literature, review articles, consensus statements, and abstracts of landmark studies. Based on the numerous published reports available on this topic, this bibliography, as part 1 of 2, focuses on the efficacy of CAM therapy in cardiovascular disease.

Key Words: cardiovascular disease, complementary medicine, alternative medicine, nutraceutical, key articles, consensus statements.
(*Pharmacotherapy* 2010;30(1):1e-49e)

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Complementary and Alternative Medicine (CAM) therapy has been traditionally used to define medical practices and approaches that did not conform to the standard beliefs of medical

practitioners. These therapies have been primarily used as adjuncts to conventional medicine in the past. In recent years, CAM therapy has gained popularity in America and the use of these agents is increasing. In fact, an estimated 38% of adults in the US were using CAM therapy in 2007. With this growing trend, clinicians should be well informed of the clinical evidence associated with these agents to better improve patient care in a more meaningful manner.

This compilation is part of a series of annotated bibliographies specific to CAM therapy and cardiovascular diseases compiled by members of the Cardiology Practice and Research Network of the American College of Clinical Pharmacy. The list of publications was compiled by 9 authors and reviewers who identified key articles and subtopics related to the efficacy of CAM therapy and cardiovascular diseases. The paper includes primary literature, review articles, consensus documents, and abstracts of landmark studies. Based on the numerous reports available on this topic, this bibliography will be published as part 1, out of a 2 part series. The first of the series (presented in this bibliography paper) focuses on the efficacy of CAM therapy in cardiovascular disease, whereas the second part of the series will emphasize CAM interactions and adverse effects.

Guideline and Reviews

Valli G, Giardina EV. Benefits, adverse effects, and drug-interactions of herbal therapies with cardiovascular effects. *J Am Coll Cardiol* 2002;39:1083–95.

This review article by Valli and Giardina does an excellent job of summarizing the epidemiology, historical background, and policies surrounding herbal therapies in the United States. The focus of the article is to provide the reader with evidence regarding the benefits, cardiovascular adverse effects, and drug-interactions for commonly used herbal supplements. The first section describes the indications and level of evidence for the following herbal therapies and their roles in cardiovascular medicine: danshen, dong quai, garlic, ginkgo, ginseng, hawthorn, hellebore, horse chestnut, and yohimbine. The second section highlights herbal agents with adverse cardiovascular effects including belladonna, danshen, dong quai, feverfew, garlic, ginger, ginkgo, ginseng, hellebore, kava, licorice, ma

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huang, oleander, and yohimbine. The final section reviews important cardiovascular drug-herbal interactions with warfarin, antiplatelet medications, digoxin, clonidine, tricyclic antidepressants, and serotonin agonists. The major advantages of this article lie in its evidence-based approach and comprehensive summary of the indication, mechanism, adverse effects, and drug interactions for each individual herbal product. Unfortunately, it does not provide the clinician with potential management strategies to avoid or handle particular side effects or drug-herbal interactions. Furthermore, the reader should note that the article was published in 2002, thus newer data surrounding these herbal remedies have been subsequently published. Nonetheless, despite these limitations, this review does provide a quick yet comprehensive overview of herbal supplements and their potential role in cardiovascular medicine.

Vogel JHK, Bolling SF, Costerllo RB, et al. Integrating complementary medicine into cardiovascular medicine. A Report of the American College of Cardiology Foundation Task Force on Clinical Consensus Documents. *J Am Coll of Card* 2005;46:185–21.

This document was initially commissioned by the American College of Cardiology Foundation (ACCF) Task Force on Clinical Expert Consensus Documents (CECDs) in 2005 to provide an evidence-based perspective on the current state of complementary, alternative, and integrative medical therapies specifically as they relate to cardiovascular diseases. Its overall purpose was to provide key information to practitioners, payers, and other interested parties on the clinical use of, and/or technologic advances with complimentary medicines that are widely available in the community. The topics covered consist of nutritional supplements, mind/body and placebo, acupuncture, bioenergetics, and spirituality and intentionality. General nutrition and dietary supplements including vitamins, minerals, and herbal therapies related to the prevention and reduction of risk for cardiovascular disease are discussed in excellent detail. More specifically, the document addresses food components that are recommended for lowering the risk of cardiovascular disease such as plant sterols, soluble fiber, omega-3 fatty acids, nuts, and soy. Additional foods such as garlic and teas, and moderate alcohol are also highlighted. As with

the Valli and Giardina review article, this document briefly provides an overview surrounding the current regulatory policies and their limitations on herbal supplements in the United States. Evidence and recommendations for vitamins and minerals (e.g., antioxidant vitamins, vitamin E, vitamin C, beta-carotene, folic acid and the B vitamins, magnesium, coenzyme Q10, L-carnitine, and L-arginine), as well as herbal preparations (e.g., hawthorn, ginkgo, horse chestnut, guggulipid, red yeast rice, policosanol, ephedra, and oleander) are provided. Unlike the Valli and Giardina review, this document gives the reader a more extensive list of herbal-drug interactions and evidenced-based recommendations for providers considering the use of these various agents. Overall, these recommendations from the ACCF and ACC/AHA are the most comprehensive guidelines addressing complementary therapies for clinicians practicing in cardiovascular medicine and should be considered an essential resource.

CAM Products

Alcohol

Arrhythmia

Albert CM, Manson JE, Cook NR, et al. Moderate alcohol consumption and the risk of sudden cardiac death among US male physicians. *Circulation* 1999;100:944–50

Previously it was well established that consumption of greater than 5 drinks per day was associated with an increased risk of sudden cardiac death (SCD). However, the relationship between lower amounts of consumption and SCD is unknown, with previous investigations providing mixed results. The current analysis describes a prospective assessment of the relationship between light to moderate drinking in 21,537 male participants from the Physicians Health Study (who were free from cardiovascular disease at baseline) and the incidence of sudden cardiac death. Over a follow-up period of 12 years, men consuming 2–4 drinks per week as well as 5–6 drinks per week had a lower risk of SCD as compared to individuals who rarely or never consumed alcohol (RR 0.41, 95% CI 0.22–0.75 and RR 0.21, 95% CI 0.08–0.56 respectively). The relationship between alcohol consumption and SCD followed a U shaped pattern, with the risk approaching unity when individuals consumed roughly 2 drinks per day.

These results to a certain extent correlate with results from the literature describing the relationship between moderate consumption of alcohol and the development of CAD, MI, as well as total mortality. They also provide further support for the recommendation of consuming 1-2 drinks per day to enhance cardiovascular health in patients who choose to consume alcohol.

Atherosclerotic Vascular Disease

Moore RD, Pearson TA. Moderate alcohol consumption and coronary artery disease. *Medicine* 1986;65:242-67

This comprehensive review article, which summarizes the information that existed to date on the relationship between alcohol intake and the development of coronary artery disease (CAD), serves as an excellent historical reference and a starting point regarding the nuances of alcohol intake and the impact on cardiovascular disease. Within the manuscript, the authors review, critique, and summarize results from various sources including autopsy studies, ecologic studies, case-control studies, clinical studies, data from alcoholics or heavy drinkers, and cohort studies. When considering the available evidence in total, it is clear that there is an inverse relationship between moderate alcohol consumption and CAD (defined as either anatomic measurement, clinical signs/symptoms of disease, or death due to CAD), with individuals classified as having moderate alcohol intake having the lowest risk of CAD. Furthermore, the relationship does not appear to be linear, with the risk of CAD lower in moderate drinkers (2-4 drinks/day) as compared to those who abstain from alcohol intake, or who are classified as heavy drinkers (> 4 drinks per day). The authors describe this as a "J" or "U" shaped relationship, a description that has been carried forward in the healthcare literature to this day. The authors also explore the biologic plausibility of the association, and review existing data to that point on the effect alcohol may have on HDL cholesterol, HDL subfractions, as well as apolipoproteins. However, the authors further state that much work remains to be done to correctly identify the biologic mechanisms whereby moderate consumption of alcohol protects against the development of CAD. Additional biologic mechanisms which are postulated to be involved, and hence remain to be investigated, include the effect of moderate

alcohol intake on blood pressure, platelet function, psychosocial stress, and coronary blood flow. Lastly, the authors call for further research to better determine the relationship between different types of alcoholic beverages and CAD.

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;348:109-18.

In recognizing the established benefit of moderate alcohol consumption on the incidence of coronary heart disease (CHD), the authors point out that some of the finer details of this relationship have yet to be determined. These would include whether: (1) different types of alcohol produce different effects; (2) does consuming alcohol with meals modify the effect on CHD; (3) does pattern of intake modify the effects on CHD; or (4) does varying amounts of consumption over time modify the effect on CHD? The authors sought to address these issues through a 12-year follow-up analysis of the Health Professions Follow-up Study, a prospective cohort including 51,529 U.S. male dentists, veterinarians, optometrists, osteopathic physicians, as well as podiatrists. Previous results published from this group with a 2-year follow-up established a J curve relationship with alcohol intake and MI. After 12 years of follow-up in 38,077 men, a graded inverse relationship between alcohol intake and the risk of myocardial infarction was once again established. This relationship was not affected by the type of alcohol consumed, the proportion of alcohol consumption that took place with meals, or the type of cardiac outcome. The frequency of alcohol intake throughout the week did modify the effects however, with patterns associated with binge drinking. While consumption of alcohol on only 1-2 days per week was still associated with a lower risk of MI compared to those who abstained from alcohol (RR 0.83, 95% CI 0.70-0.99), the magnitude of benefit was substantially less than in individuals who consumed alcohol 3-4 days/week (RR 0.66, 95% CI 0.50-0.85). These results are somewhat consistent with previous reports in the literature where episodic consumption of alcohol was associated with an increased risk of CHD. Although no significant differences were found in the association between different alcoholic beverages and risk of MI, the strongest positive associations in this population were for beer and spirits. The authors duly note that results for specific type of

beverage were significantly affected by the prevalence of consumption in the studied population, with the most prevalent beverage typically showing the greatest level of relative risk reduction. Therefore, this paper calls into question previous findings favoring one type of alcoholic beverage versus another. Lastly, an increase over time in the daily amount of alcohol consumed was associated with a lower risk of MI, a finding that deserves clarification in future studies.

Vlienghart R, Oei HHS, van den Elzen AP, et al. Alcohol Consumption and Coronary Calcification in a General Population. *Arch Intern Med* 2004;164:2355–2360

Although multiple investigations to date had shown a U shaped or J shaped relationship between alcohol consumption and cardiovascular endpoints, the underlying mechanism of benefit still remains to be determined. One potential mechanism that was investigated in this study is the inhibition of the atherosclerotic process. The development of electron beam computed tomography (EBCT) to identify the presence of coronary artery calcium allowed for a noninvasive assessment of the presence of CAD even in asymptomatic individuals. Although not a direct marker for the presence of CAD, the risk for CAD has been shown to correlate with increasing amounts of coronary calcium present. The Rotterdam Coronary Calcification study was a prospective population analysis in 1013 subjects without coronary artery disease at baseline who provided a detailed history of alcohol intake as well as underwent EBCT. The mean age of participants was 70.6 years. Reported intake of alcoholic beverages across the population studied was 15.8% consuming no alcohol, 46.5% consuming up to 1 drink per day, 16.9% 1–2 drinks per day, and 20.9% > 2 drinks per day. After adjusting for age, gender, and other potential confounders a U shaped relationship was demonstrated between alcohol consumption and coronary calcification. Coronary calcification was statistically lower for individuals consuming 2 alcoholic beverages per day as compared to non-drinkers and individuals consuming > 2 drinks per day. The strongest association for reduced risk was found in those with daily consumption of 1–2 drinks of port wine or sherry (OR 0.50, 95% CI 0.32–0.77) as compared to other types of alcoholic beverages. However, the authors warn not to over-interpret this finding as there were few beer drinkers in

the study as well as the potential that wine consumption may be confounded by drinking pattern (wine drinkers tend to consume with meals). This was the first trial confirming that alcohol intake significantly reduced the development of coronary atherosclerosis, as determined by the presence of coronary calcium. The authors note that these results correlate with previous results on reduction in peripheral arterial disease, carotid plaques, as well as the effect on HDL for alcohol.

Mukamal KJ, Ascherio A, Mittleman MA, et al. Alcohol and risk for ischemic stroke in men: The role of drinking patterns and usual beverage. *Ann Intern Med* 2005;142:11–19.

Despite the clear inverse association between moderate alcohol consumption and risk for MI or development of CAD, the risk between alcohol and ischemic stroke is not as clear. Previous studies were limited by not assessing beverage type, the pattern of drinking, distinguishing the type of stroke, as well as assessing the change in consumption over time. This prospective cohort analysis, utilizing the Health Professions Follow-up Study database, sought to better address the relationship between alcohol and ischemic stroke. Over a 14-year follow-up period evaluating over 38,000 men free of cardiovascular disease at baseline, those individuals consuming more than 2 drinks per day appeared to be at a higher risk for ischemic stroke as compared to non-drinkers (RR 1.42, 95% CI 0.97–2.09), although this did not reach statistical significance. Consumption of lower amounts of alcohol did not appear to be associated with increased risk, with the lowest risk seen in individuals consuming 3–4 drinks per week (RR 0.68, 95% CI 0.44–1.05), although this also did not reach statistical significance. A consistent drinking pattern and red wine consumption tended to be associated with a lower risk of ischemic stroke as well. While these results appear align to a certain degree with results for the development of CAD and MI, the current analysis lacked statistical power to formulate more firm conclusions. Characterization of the relationship between alcohol consumption and the risk for both ischemic and hemorrhagic stroke await future trials.

Mukamal KJ, Chiuve SE, Rimm EB. Alcohol Consumption and Risk for Coronary Heart Disease in Men with Healthy Lifestyles. *Arch Intern Med* 2006;166:2145–2150

Multiple prospective trials preceding this publication had demonstrated a J shaped relationship between alcohol consumption and risk for MI and total mortality. Despite the number of trials showing this association, concern still existed regarding the potential for confounding of other lifestyle habits such as level of exercise or dietary habits that may bias results in favor of moderate alcohol consumption. Given the ethical issues with conducting a randomized study of alcohol intake, the authors set out to conduct the most rigorous prospective cohort analysis to date, controlling for potential healthy lifestyle confounders, to assess the effect of alcohol consumption in a primarily healthy male population. This prospective cohort analysis used the database from the previously mentioned Health Professionals Follow-up Study. The authors selected for domains of healthy lifestyles, namely: (1) body mass index < 25; (2) 30 minutes of moderate to vigorous activity a day; (3) current abstinence from smoking; as well as (4) healthy dietary pattern through use of a validated dietary index. The study population for analysis was individuals who met all 4 criteria for a healthy lifestyle pattern in individuals with no previous reported cardiovascular disease, cancer, or diabetes. In this healthy population of 8867 male healthcare professionals, moderate alcohol intake up to 2 drinks per day was associated with a lower risk of MI (HR 0.86, 95% CI 0.36 – 2.05) as compared to nondrinkers and individuals consuming greater amounts of alcohol, although the results did not achieve statistical significance. However, the trend observed in results mirror results of previous studies in different populations including those with existing CHD as well as populations at high risk for CHD development. This indicates that it is unlikely the association between moderate alcohol intake and incidence of MI is inaccurate due to confounding with lifestyle habits. Drawbacks to this analysis certainly include the lack of analysis in females, as well as the relatively low number of actual events resulting in wide confidence intervals. However, given the concordance with previous published literature, one can be reasonably assured that consumption of 1-2 alcoholic beverages daily likely provides a cardiovascular benefit.

Chronic Heart Failure

Nicolas JM, Fernandez-Sola J, Estruch R, et al. The effect of controlled drinking in alcoholic

cardiomyopathy. *Ann Intern Med* 2002;136:192–200

Despite the findings of the previous article, the development of cardiomyopathy secondary to alcohol abuse has been well documented and is thought to relate to the total dose of alcohol consumed. In the background to this paper, the authors cite previous literature showing up to 1/3 of alcoholics without symptoms of heart failure nonetheless had left ventricular dysfunction. The general consensus in patients with heart failure, especially when secondary to alcohol consumption, is that abstinence from alcohol is the recommended course of action. However, as the authors point out, abstinence is often not feasible. In addition, it is unclear what the consequences of continued alcohol consumption may be, even at reduced levels, in patients with alcoholic cardiomyopathy. Therefore, the authors conducted a 4-year prospective cohort study in 55 alcoholics with cardiomyopathy to explore this issue. All patients were less than 60 years of age and consumed at least 100 grams or more of alcohol daily (6–7 drinks). All patients were recommended to follow total abstinence, although only 17 of the 55 patients did so in the first year. Fifteen others reduced their intake to between 20–60 grams per day (1–4 drinks), 7 consumed between 60–80 grams per day, while 16 others continued to drink more than 80 grams per day. While left ventricular function as assessed by ejection fraction (EF) improved in abstinent patients at 1 year (EF increased 13.1%, 95% CI 6.9–19.3%), surprisingly, patients who reduced their intake to 20–60 grams also had improvements in left ventricular function to a similar degree as abstinent patients (EF increased 12.5%, 95% CI 8.2–16.8%). Patients in the 60–80 grams per day range had mixed results, while those patients consuming greater than 80 grams per day continued to have deterioration in left ventricular function. While recommending abstinence is still likely the best course of action for patients with heart failure due to any cause, this study does indicate that patients with alcoholic cardiomyopathy may continue to consume low to moderate levels of alcohol and likely see improvements in left ventricular function. Whether this can be extrapolated to other forms of cardiomyopathy remains to be determined.

Walsh CR, Larson MG, Evans JC, et al. Alcohol consumption and risk for congestive heart failure in the Framingham Heart Study. *Ann Intern Med* 2002;136:181–191.

When considering the use of alcohol in the context of heart failure development or progression, the general consensus was that any alcohol consumption, potentially through direct toxic effects on the myocardium, the development of hypertension, as well as coexisting malnutrition may lead to impairment of left ventricular function and heart failure development. Conversely, moderate consumption has been associated with a protective effect against coronary artery disease. Since MI is an important cause of heart failure, the relation between consumption of alcohol and development of heart failure is not clear. As no previous investigations have specifically evaluated the relation between alcohol consumption and development of congestive heart failure, the current analysis was conducted to address this issue. The authors identified subjects from the Framingham Heart Study database for which there was adequate information regarding alcohol consumption as well as adequate follow-up (6–10 years) to assess for the development of congestive heart failure. In total 2796 men and 3493 women were included in the analysis. In men, all levels of alcohol consumption were associated with a reduced risk for developing congestive heart failure compared with non-drinkers. The hazard ratio (0.49, 95% CI 0.25–0.96) was lowest though in men who consumed 8–14 drinks per week. In women, consumption of alcohol was also associated with a reduced risk for heart failure, but only in those who consumed 3–7 drinks per week. While higher levels of consumption were not associated with a lower risk for heart failure, it was also not associated with an elevated risk either. When adjusting for known risk factors for heart failure such as hypertension, the associations did not change. Although there were differences in the nature of the association of alcohol consumption and development of heart failure between men and women, this community-based study surprisingly found that moderate levels of alcohol consumption did not lead to the development of heart failure. In addition, this level of alcohol consumption is consistent with current recommendations from the American Heart Association.

Djousse L, Gaziano JM. Alcohol consumption and risk of heart failure in the Physician's Health Study I. *Circulation* 2007;115:34–39

In a follow-up to the paper discussed above by

Walsh CR et al, the authors note that the literature still provides somewhat contradictory information regarding the relationship between alcohol and the development of heart failure. Again, several studies established the role of heavy drinking in the development of cardiomyopathy. However, the effect of moderate drinking remains to be well-defined, despite the findings from the paper discussed above and their analysis from the Framingham Heart Study. In addition, the effect of alcohol on the development of heart failure may be influenced by the presence of CAD. Therefore, the authors conducted this present analysis to try and provide clarity to these issues. The Physician's Health Study was a randomized, double-blind, placebo-controlled trial that assessed the role of low-dose aspirin and beta-carotene in the primary prevention of cardiovascular disease. Alcohol intake was established at baseline via a standard questionnaire, and the authors analyzed 21,601 patients from the original 22,071 randomized study population after excluding patients without baseline information on alcohol consumption, other covariates, as well as existing HF at study enrollment. Over an average of 18.4 years of follow-up, the consumption of 5–7 drinks per week reduced the incidence of HF as compared with individuals consuming < 1 drink per week (HR 0.80, 95% CI 0.68–0.94) in their multivariate Cox regression model. However, when assessing patients without either previous MI or previous CAD, the effect of 5–7 alcoholic drinks per week on the development of HF is less robust and loses statistical significance (HR 0.91, 95% CI 0.76–1.09 and HR 0.97, 95% CI 0.79–1.21 respectively). Although the data for individuals consuming > 7 drinks daily were similar to the results discussed above, caution must be employed in interpreting these results due to the small number of patients in this group (n=665 as compared with n=7449 for 5–7 drinks/week). These findings overall support the concept that moderate consumption of alcohol lowers the risk of developing HF, but that the effect may be confined to those individuals with CAD.

All-cause mortality

Gronbaek M, Becker U, Johansen D, et al. Type of alcohol consumed and mortality from all causes, coronary heart disease, and cancer. *Ann Intern Med* 2000;133:411–419.

At the time of publication it was well described in the literature that there was a J shaped relationship between intake of alcohol and death from all-causes. Potential mechanisms of benefit included the anti-platelet effect of alcohol, as well as increase in high-density lipoprotein (HDL) levels. Data indicated that potentially up to 4 drinks a day lowered the risk of all-cause mortality as compared to non-drinkers, but the risk increased when drinking was higher than this level. Certainly the intake of 1 to 2 drinks (typically described as 12 oz of beer, 4 oz of wine, or 1.5 oz of spirits) seemed to lower the risk of all cause mortality to a substantial degree as compared to non-drinkers. However, one area of controversy that remained unanswered was whether wine, beer, and spirits all produced the same effect, or did the consumption of wine have added benefits due to the presence of beneficial polyphenols and flavonoids. To address this issue the authors conducted a pooled analysis of multiple cohort studies in a Danish population in which the intake of beer, wine, spirits, smoking status, educational level, physical activity, and body mass index were assessed. In 257,859 years of follow-up, a J shaped relationship was confirmed between total alcohol intake and mortality. However, the effect was significantly more pronounced for wine compared with individuals consuming beer or spirits. In comparison to non-drinkers, those drinking 1 to 7 glasses of wine per week had a relative risk for all cause mortality of 0.80 (95% CI 0.67 to 0.86). The results for beer (RR 0.90, 95% CI 0.83–0.97) and spirits (0.94, 95% CI 0.87–1.01) were less robust. This would indicate that red wine has beneficial components beyond alcohol content. While the authors attempted to adjust for some confounders such as age, educational status, and smoking status, the results of this study must be interpreted with some caution since it was a cohort design and relied on self-reported rates of alcohol consumption. Despite potential limitations, this analysis represents the most reliable estimate of the differential effects of various alcoholic beverages on total mortality as they had sufficient numbers in each group evaluated, as well as sufficient numbers of endpoints from which to draw conclusions

Di Castelnuovo, Costanzo, Bagnardi V, et al. Alcohol dosing and total mortality in men and women. *Arch Intern Med* 2006;166:2437–2445

In presenting the rationale for the present analysis, the authors succinctly review present

knowledge regarding the relationship of alcohol intake and cardiovascular outcomes. They cite several potential mechanisms for the observed inverse relationship, including positive effects on HDL, anti-platelet and anti-inflammatory properties, as well as improving endothelial function. They also reviewed the complex relationship that exists with the potential benefits of alcohol intake, as well as the risks including cancer, cirrhosis, and accidental death. With this as the backdrop one question that remains unanswered is whether the J shaped relationship exists for both men and women. Previous investigations to date have tended to focus more on men. As such, the authors conducted an updated meta-analysis of available scientific data, including 10 articles published since the year 2000 that were not incorporated into previous meta-analyses, to address this specific question. In total, 34 studies were included involving 1,015,835 subjects and 94,533 deaths. The J shaped relationship was confirmed for both men and women with regard to total mortality in the analysis, although men and women differed with respect to the total amount of alcohol that provided a benefit. In men, up to 4 drinks per day was beneficial, while in women the upper boundary of benefit was only 2 drinks per day. However, the magnitude of benefit was similar in men and women, with an 18% relative reduction in women and 17% relative reduction in men for total mortality. Differences in the dose-response relationship between men and women may be explained by differences in body weight, metabolism, or the presence of estrogen in premenopausal women. Regardless, this present meta-analysis provides the healthcare practitioner with confidence that moderate alcohol intake is beneficial in men and women, and provides useful information regarding the maximum dose that could be recommended for each gender.

Coenzyme Q10

Chronic Heart Failure

Sander S, Coleman CI, Patel AA, Kluger J, White CM. The Impact of Coenzyme Q10 on Systolic Function in Patients with Chronic Heart Failure. *J Card Fail.* 2006;12:464–472.

Intracardiac levels of coenzyme Q₁₀ have been shown to increase with the use of coenzyme Q₁₀ supplementation in patients with severe heart failure. Several randomized studies have been

conducted comparing the effects of coenzyme Q₁₀ compared to placebo on systolic function and ventricular size. However, the results of these studies have been inconsistent. Due to the small nature of trials conducted to date and possible lack of power to demonstrate efficacy of coenzyme Q₁₀, this meta-analysis was conducted. Eleven randomized, controlled trials published between 1996 and 2001, evaluating the use of coenzyme Q₁₀ in heart failure were included. The primary outcome was ejection fraction. Secondary endpoints were cardiac output, cardiac index, stroke volume, and stroke index. The dose of coenzyme Q₁₀ utilized ranged from 60 mg to 200 mg daily. The treatment periods ranged from 1 to 6 months. The results demonstrated a 3.7% net improvement in ejection fraction (85% CI 1.59–5.77), $p < 0.00001$). In patients not receiving ACEI therapy, the effect on ejection fraction was more profound (6.74%, 95% CI 2.63–10.86). None of the secondary endpoints were found to be statistically significant. Based on these results, it appears that coenzyme Q₁₀ supplementation can significantly improve ejection fraction. However, this benefit may be diminished in patients already receiving standard heart failure medications, such as ACEI. Larger, longer-term trials are needed to confirm these results. Additionally, studies evaluating the effect of coenzyme Q₁₀ on different etiologies of heart failure are also necessary as some patients may respond better than others based on the type of heart failure present.

Molyneux SL, Florkowski CM, George PM, et al. Coenzyme Q10. An Independent Predictor of Mortality in Chronic Heart Failure. *J Am Coll Cardiol.* 2008;52:1435–1441.

A decreased level of myocardial coenzyme Q₁₀ has been demonstrated in patients with heart failure. Additionally, the levels of coenzyme Q₁₀ directly correlate to disease severity, with lower levels being associated with a worse functional class. However, no trials relating decreased levels of coenzyme Q₁₀ in heart failure to outcomes have been conducted. Therefore, this cohort study sought to investigate this hypothesis by evaluating coenzyme Q₁₀ levels in 236 patients admitted to the hospital for CHF. The primary endpoint was all-cause mortality. The majority of patients (65%) had NYHA class II with a median age of 77 years. The median ejection fraction was 37%. Patients were followed up at 3-month intervals and the median

follow-up period was 2.69 years. Plasma coenzyme Q₁₀ levels were measured with high-performance liquid chromatography with electrochemical detection. Receiver operator characteristic (ROC) curves were used for mortality prediction. Kaplan-Meier cumulative survival curves were constructed from date of admission with dichotomous data obtained with the cut-point from the ROC curve. The Kaplan-Meier curves for coenzyme Q₁₀, coenzyme Q₁₀ to total cholesterol ratios, and the coenzyme Q₁₀ to LDL-C ratio, showed a significant reduction in survival with lower coQ₁₀ levels and CoQ₁₀ to lipid ratios ($p < 0.01$). These findings demonstrate that plasma coenzyme Q₁₀ levels are an independent predictor of mortality and that long term deficiency may lead to a poorer prognosis. The event rate of this cohort was low; therefore, a large controlled intervention study is warranted.

Dyslipidemia

Caso G, Kelly P, McNurlan MA, et al. Effect of Coenzyme Q10 on Myopathic Symptoms in Patients Treated with Statins. *Am J Cardiol.* 2007;99:1409–1412.

The statin class of cholesterol lowering agents is well known for causing muscle symptoms of varying degrees. The inhibition of 3-hydroxy 3 methyl glutaryl coenzyme A (HMG-CoA) by statins is the same pathway shared by coenzyme Q₁₀. Coenzyme Q₁₀ is important for mitochondrial electron transport and decreased levels may affect oxidative phosphorylation and mitochondrial adenosine triphosphate production (ATP). Statin therapy may reduce coenzyme Q₁₀ levels and impair muscle energy metabolism resulting in myopathy or other muscle symptoms associated with these agents. This pilot study was conducted to determine if supplementation with coenzyme Q₁₀ would improve muscle symptoms in statin treated patients. This was a double-blind study involving 32 patients on statin therapy. Patients were enrolled if they had myopathic symptoms that had no other identifiable cause. Patients were randomly assigned to either 100 mg of coenzyme Q₁₀ or 400 international units of vitamin E for 30 days. Myopathic symptoms and their interference with daily activities were evaluated prior to and after the intervention using the Brief Pain Inventory Questionnaire. Pain intensity was evaluated using the Pain Severity Score (PSS). There was no significant

difference in the doses of statins used between the two treatment groups but the doses did vary. Patients treated with simvastatin received anywhere from 10 to 80 mg, atorvastatin 10 to 20 mg, pravastatin 10–40 mg, and lovastatin 40 mg. The results showed a significant decrease in pain intensity in the coenzyme Q₁₀ treated patients. Pain intensity decreased by $40 \pm 11\%$ ($p < 0.001$). Patients taking vitamin E showed no difference in pain intensity. In addition, the interference of pain with daily activities also significantly improved in the coenzyme Q₁₀ treatment group $30 \pm 14\%$ ($p < 0.02$) while there was no effect on daily pain in patients treated with vitamin E. However, there was no correlation between pain scores and the creatine kinase (CK) concentrations. These results indicate that supplementation with coenzyme Q₁₀ may decrease pain and improve patient's ability to perform daily activities without the need for an alteration in drug therapy or drug discontinuation. Of note, some of the limitations of this study were the lack of a placebo control arm and a lack of standardization of statin dose. Additional studies are warranted to more effectively assess the efficacy of coenzyme Q₁₀ on statin associated muscle symptoms. Furthermore, the evaluation of the optimal dose and duration of coenzyme Q₁₀ supplementation warrants evaluation as these parameters have varied greatly in studies conducted to date and remain unanswered.

Young JM, Florkowski CM, Molyneux SL, et al. Effect of Coenzyme Q₁₀ Supplementation on Simvastatin Induced Myalgia. *Am J Cardiol.* 2007;100:1400–1403.

Muscle symptoms associated with statin therapy are the most frequently reported adverse effect, occurring in up to 14% of patients. The exact etiology is unclear but focus has been placed on coenzyme Q₁₀ in part due to the fact that low density lipoprotein cholesterol (LDL-C) is a transporter of coenzyme Q₁₀ and lowering LDL-C, subsequently lowers coenzyme Q₁₀. The above mentioned study was a double-blind, placebo-controlled pilot study evaluating 44 patients with self-reported myalgia with resultant discontinuation of their statin. The primary outcome was the number of patients tolerating 40 mg of simvastatin at 12 weeks, as well as the number of patients remaining on statin therapy and the change in myalgia scores. Patients underwent a 2-week washout period of both lipid lower agents and coenzyme Q₁₀ prior to

randomization. They were also stratified based on level of severity of their muscle symptoms. Severe was defined as an inability to tolerate a dose of 20–40 mg of a statin within 1 month of initiation. Moderate was defined as the development of symptoms at a dose of ≥ 20 mg after 30 days following therapy initiation. Following the washout period, patients were then randomized to 200 mg per day of coenzyme Q₁₀ or placebo for 12 weeks in combination with open label simvastatin. The dose of simvastatin was titrated at 4 weekly intervals from 10–20 mg daily up to 40 mg daily. Total plasma coenzyme Q₁₀ levels were measured along with cholesterol levels, creatine kinase, renal and liver function. Myalgia assessment was conducted on a daily basis utilizing a visual analogue scale with intensity ranging from 0 to 100 mm. The results showed no difference in myalgia score in those treated with coenzyme Q₁₀ compared to those treated with placebo ($p = 0.63$). There was also no change in the number of patients who tolerated statin therapy or in the number or patients remaining on statin therapy at the end of the 12-week study period ($p = 0.34$, $p = 0.47$, respectively). Although this study did not demonstrate benefit with coenzyme Q₁₀ supplementation in those with myopathic symptoms on statin therapy, further long-term studies are needed to establish whether coenzyme Q₁₀ may have a role in this population or other specific subpopulations.

Marcoff L, Thompson PD. The Role of Coenzyme Q₁₀ in Statin-Associated Myopathy. *J Am Coll Cardiol.* 2007;49:2231–2237.

Given the inconsistencies in the data with regards to the benefit of coenzyme Q₁₀ on statin associated myopathy, this review was conducted to further examine the role coenzyme Q₁₀ deficiency may have in statin associated myopathy. Therefore a search for all English articles relating to statin therapy and coenzyme Q₁₀ was conducted via PUBMED through August 2006. This article provides an in depth review of statin associated myopathic pain and explores all the possible mechanisms. In addition, the role of coenzyme Q₁₀ in the body is also discussed. There is also an in depth review of the effect of statins on coenzyme Q₁₀ levels as well as the effect of statins on muscle coenzyme Q₁₀ levels. Finally the studies that have evaluated the role of coenzyme Q₁₀ are reviewed. While data suggests serum coenzyme Q₁₀ levels are reduced at moderate doses of statin, there is little evidence

to suggest that muscle coenzyme Q₁₀ levels are reduced. The conclusion of this review is that there is a general lack of consistency with respect to the efficacy of coenzyme Q₁₀ in clinical trials and the consensus is that the coenzyme Q₁₀ should not be routinely recommended. However, the supplement appears to be relatively safe and could be tried in patients who cannot tolerate other methods of treating their myopathic symptoms such as a change in dose or change in drug regimen.

Dark Chocolate

Coronary Artery Disease

Di Giuseppe R, Di Castelnuovo A, Centritto F, et al. Regular Consumption of Dark Chocolate Is Associated with Low Serum Concentrations of C-Reactive Protein in a Healthy Italian Population. *J Nutr.* 2008;138:1939–1945.

Cocoa seeds come from the cacao tree which contains high level of flavonoids, such as epicatechin and polyphenols, which may have beneficial cardiovascular effects. The pharmacologic property of cocoa such as antioxidation and anti-inflammatory activities may play role in the prevention of cardiovascular disease by decreasing oxidative stress and inflammation. In a cohort study of men and women ≥ 35 years of age, a total of 4849 subjects were selected to determine whether or not regular consumption of dark chocolate is associated with low serum concentrations of C-reactive protein (CRP) in a healthy Italian population. Out of the 4849 subjects, 2141 patients were extracted for the current study. Subjects were divided into two subpopulations: a test group of 824 subjects who regularly consumed dark chocolate and a control group of 1317 nonconsumers. The average intake of dark chocolate was 5.7 g/d for the experimental group. The results showed lower CRP levels in the group of chocolate consumers compared to control (1.10 vs. 1.32 mg/L, $p < 0.0001$). Furthermore, an inverse relationship between consumption of dark chocolate and CRP levels was observed ($p = 0.038$) after adjusting for age, sex, social status, systolic blood pressure, body-mass index, waist/hip ratio, food groups, and total energy intake. Although an initial decrease in serum CRP was demonstrated with consumption of 1 serving (20 g) of dark chocolate every 3 days, CRP levels showed a reverse relationship at the highest levels of

consumption, representing a J-shaped dose-response curve. This is a first study showing an association between regular consumption of dark chocolate and reduced CRP levels. The results of the study may have important prognostic implications, given the value of CRP as a biomarker for coronary artery disease. However, additional prospective randomized studies evaluating clinical outcomes are warranted.

Dyslipidemia

Allen RR, Carson L, Kwik-Urbe C, Evans EM, Erdman JW. Daily Consumption of a Dark Chocolate Containing Flavanols and Added Sterol Esters Affects Cardiovascular Risk Factors in a Normotensive Population with Elevated Cholesterol. *J. Nutr.* 2008;138:725–731.

The consumption of cocoa flavanol (CF) can improve endothelial function, and blood pressure whereas plant sterols have been shown to be safe and effective in reducing LDL cholesterol. This double-blind, placebo-controlled, cross-over study evaluated the efficacy of a CF containing dark chocolate bar with added plant sterols on serum lipids, blood pressure and other circulating cardiovascular health markers in a population with elevated cholesterol. A total 49 adults were recruited and randomized to either CF containing dark chocolate bars with plant sterols (180 mg CF and 1.1g sterol esters per bar) or CF alone. Each group received 1 dark chocolate bar twice daily for 4 weeks and crossed over to the alternative treatment group for an additional 4 weeks. Consumption of both plant sterols and CF significantly reduced serum total cholesterol levels by 2.0% and LDL cholesterol by 5.3%, ($p < 0.05$ for both), whereas there were no significant cholesterol reductions observed with CF alone. The presence of plant sterols had no significant effect on systolic or diastolic blood pressure; however, CF consumption reduced mean systolic blood pressure by -5.8 mm Hg at 8 weeks ($p < 0.05$). The authors conclude that regular consumption of CF containing chocolate bars with plant sterol may significantly improve lipid profiles and blood pressure. Because this was a short term study with a lack of wash out period between treatments, additional studies are needed to confirm these findings.

Hamed MS, Gambert S, Bliden KP, et al. Dark Chocolate Effect on Platelet Activity, C-reactive Protein, and lipid profile: A pilot Study. *South Med J* 2008;12(101):1203–1208.

In depth evaluation of the effects of dark chocolate consumption were examined in this pilot study. In addition to platelet reactivity that has been previously evaluated, this pilot study also evaluated the effects of dark chocolate consumption on C-reactive protein and lipid profiles. Twenty-eight healthy subjects (aged 18–60) were given dark chocolate (containing 70% cocoa that provided 700 mg of flavonoids) daily for seven days. All patients were nonsmokers. Individuals consuming other antioxidants such as vitamin C were excluded. In addition, the consumption of flavonoid-rich foods was not allowed for two weeks prior to the study. The primary outcome was to determine the effects of dark chocolate consumption on platelet activity. Blood samples were obtained pre and post treatment for analysis. The primary endpoint showed that dark chocolate consumption resulted in a significant reduction in platelet reactivity in (27.3 ± 27.8 versus 17.4 ± 20.5 mean fluorescence intensity) ($p < 0.006$). There was also a significant reduction in low-density lipoprotein cholesterol (LDL-C) by 6% (120 ± 38 versus 112 ± 37 mg/dL, $p < 0.018$). High-density lipoprotein cholesterol (HDL-C) rose by 9% (66 ± 23 versus 72 ± 26 mg/dL, $p < 0.0019$). High sensitivity C-reactive protein was also significantly reduced (1.8 ± 2.1 versus 1.4 ± 1.7 mg/dL, ($p < 0.04$). These results indicate that a daily consumption of dark chocolate containing 700 mg of flavonoids has a mildly favorable benefit on a number of parameters that affect cardiovascular health. Additional studies that include a control group would add valuable insight on the magnitude of benefits with dark chocolate on these outcomes.

Hypertension

Hermann F, Spieker LE, Ruschitzka F, et al. Dark chocolate improves endothelial and platelet function. *Heart* 2006;92:119–120.

Cigarette smoking is a well-known risk factor for the development of cardiovascular disease. Smoking induces several mechanisms that promote atherothrombosis. These include an increased oxidative stress, enhanced oxidation of low-density lipoproteins, and increased endothelial dysfunction by inactivation of endothelium derived nitric oxide and platelet hyperreactivity. Therefore, this study was conducted in 25 otherwise healthy male smokers to determine if the consumption of polyphenol rich dark chocolate improved endothelial

function and platelet hyperreactivity. Five study subjects followed a preliminary protocol in which endothelial function was assessed by high resolution ultrasound before and after ingesting 40 grams of dark chocolate (74%) following a 24-hour abstinence of polyphenol-rich foods. Endothelial function was reassessed at 2, 4, 8, and 24 hours following dark chocolate ingestion. The initial screen on these five subjects showed positive results so 20 additional subjects were randomly divided into two parallel groups. Endothelial function and platelet function were assessed at baseline and 2 hours after ingestion of dark chocolate (40 grams) or white chocolate (40 grams). In addition, both study groups were evaluated after a fasting period of 8 hours and a smoke free interval of at least 30 minutes. The results showed a significant improvement in flow mediated dilatation (FMD) after two hours 7.0 ± 0.7 % compared to baseline 4.4 ± 0.9 % in subjects who consumed dark chocolate compared to those who were consumed white chocolate ($p = 0.026$). This FMD effect lasted approximately 8 hours following ingestion. There was also a significant decrease in platelet reactivity in the dark chocolate group compared to the white chocolate group ($p = 0.03$). These findings demonstrate a direct effect of dark chocolate on vascular endothelium as well as platelet reactivity. All of these effects are likely mediated through antioxidant properties of the polyphenol content of dark chocolate. Further studies are needed to assess the long-term benefit of daily consumption of small amounts of polyphenol rich dark chocolate.

Flammer AJ, Hermann F, Sundano I, et al. Dark Chocolate Improves Coronary Vasomotion and Reduces Platelet Reactivity. *Circulation*. 2007;116:2376–2382.

There is an increasing amount of literature that flavonoid rich foods such as dark chocolate, may have a beneficial impact on cardiovascular events. This benefit is thought to be secondary to the antioxidant properties that flavonoids exert. Because oxidative stress can play a role in the development of atherosclerosis, the consumption of antioxidants may retard early atherosclerotic vascular disease progression. This was a randomized, double-blind study that evaluated the effect of flavonoid-rich dark chocolate compared to a cocoa-free control on coronary vascular reactivity and platelet function in 22 heart transplant recipients. Patients were randomized to either Nestle Noir Intense (70%

cocoa content) or flavonoid-free chocolate. All patients remained on their current medication regimen that included a statin, beta blocker, ACE inhibitor, or an ARB. Coronary vasomotion and platelet adhesion were assessed prior to and two hours after consumption of the dark chocolate. Coronary artery diameter was analyzed with quantitative coronary angiography and endothelium dependent vasomotion was evaluated using a response to cold pressor test. The results showed a significant increase in coronary artery diameter (2.36 ± 0.51 to 2.51 ± 0.59 , $p < 0.01$) as well as a significant increase in endothelium dependent coronary vasomotion (percent change of artery diameter compared to baseline) ($4.5 \pm 11.4\%$ to $-4.3 \pm 11.7\%$, $p = 0.01$) in the dark chocolate group compared to no change in the control group. Platelet adhesion was also significantly decreased in the dark chocolate group compared to the control group ($p = 0.04$). These results demonstrate that 2 hours after the consumption of dark chocolate, there is improvement in coronary vasodilation, decreased platelet adhesion, and improved coronary vascular function. It is important to note that the response on coronary vasomotion seen with dark chocolate was in addition to the effect that may have been caused by the patients' current drug therapy. Although this was a short-term study and the sample size was modest, the results provide support for additional evaluation.

Taubert D, Roesen R, Lehmann C, et al. Effects of Low Habitual Cocoa Intake on Blood Pressure and Bioactive Nitric Oxide. A Randomized Controlled Trial. *JAMA*. 2007;298(1):49–60.

Some small studies evaluating the effects of flavanol-rich cocoa have demonstrated a reduction in blood pressure and improvement in endothelial function. However, these studies were short in duration (2 weeks) and utilized fairly high doses of cocoa, (equivalent to 100 grams of chocolate a day). Therefore, this study was conducted to evaluate the effects of habitual cocoa intake on blood pressure in 44 adult patients with prehypertension or stage 1 hypertension over an 18-week period. Patients (ages 56–73 years) were randomized to 6.3 grams of dark chocolate per day containing 30 mg of polyphenols or matching polyphenol free white chocolate. In addition to the primary endpoint of change in blood pressure, secondary endpoints were changes in plasma markers of 8-isoprostane (a marker of oxidative stress), S-nitrosoglutathione (vasodilative nitric oxide), as

well as the bioavailability of cocoa phenols. The results showed a significant reduction in both systolic (-2.9 ± 1.6 mmHg $p < 0.001$) and diastolic (-1.9 ± 1.0 mmHg $p < 0.001$) blood pressure in patients who consumed the dark chocolate containing polyphenols compared to baseline values. The incidence of hypertension also decreased from 86% to 68%. In addition, there was a sustained increase in S-nitrosoglutathione ($P < 0.001$). No changes in body weight, glucose, 8-isoprostane, or plasma lipid levels were observed in the dark chocolate group. These results indicate that the consumption of daily doses of dark chocolate rich in polyphenols can help reduce blood pressure and improve the formation of S-nitrosoglutathione.

D-ribose

Chronic and Acute Heart Failure

Omran H, Illien S, MacCarter D, et al. D-ribose improves diastolic function and quality of life in congestive heart failure patients: a prospective feasibility study. *Eur J Heart Fail* 2003;5:615–619.

Heart failure is thought to be an energy deficient state, particularly during times of oxygen deprivation, such as during ischemia. D-ribose, a pentose monosaccharide, is hypothesized to restore myocardial ATP stores, and improve cardiac function. This randomized, double blind, crossover study investigated the effect of D-ribose on diastolic function and quality of life in 15 patients with chronic coronary artery disease and HF. Enrollees had known chronic stable coronary artery disease and NYHA functional class II or III HF. Each treatment phase was 3 weeks in duration, during which participants took D-ribose or placebo (5 grams of powder, mixed with water three times daily). Following a washout period of one week, participants were crossed over to the alternative arm for an additional 3 weeks. Outcome measures completed at baseline and at the end of each treatment phase included cardiac function by transthoracic echocardiography and exercise tolerance measured with an exercise ergometer, as well as quality of life (QoL) measured with the SF-36 questionnaire. Participants were NYHA functional classes II (N=7) and III (N=8) with a mean ejection fraction of $47.5 \pm 1\%$ (range 28–71%). Medications were not altered during the study. Echocardiography results revealed improvements in restrictive parameters associated with diastolic HF (a significantly

shorter deceleration time of the E wave ($p < 0.002$), a smaller left atrial volume ($p < 0.02$), and higher percentage of atrial contribution to left ventricular filling ($p < 0.02$) after the D-ribose arm, and no significant changes following the placebo arm. Peak exercise tolerance was not affected by either treatment. QoL scores improved in participants after the D-ribose arm (417 ± 118 to 467 ± 128 , $p < 0.01$) but were not changed significantly in the placebo arm. Comparisons of study outcomes (echocardiography, exercise, and QoL variables) between D-ribose and placebo groups were not reported. It is unclear whether a one week washout period is enough for outcome values to return to baseline if in fact there were benefits from D-ribose, or whether long term treatment would provide a sustained benefit.

MacCarter D, Vijay N, Washam M, et al. D-ribose aids advanced ischemic heart failure patients. *Int J Cardiol* 2008; in press. Doi: 10.1016/j.ijcard.2008.05.025. (Letter to the editor)

This open label study examined the effects of D-ribose on ventilation efficiency in 16 adults (mean age 72 ± 10 years) with NYHA functional classes III ($n=9$) and IV ($n=7$) HF. Participants underwent sub-maximal cardiopulmonary exercise testing at baseline and after 8 weeks, which involved 6 minutes of exercise using an 8 inch step platform. Investigators measured ventilation efficiency (VE_{eff}), oxygen uptake efficiency, oxygen pulse at anaerobic threshold (AT = the point at which lactate starts accumulating in the blood), maximal oxygen uptake (VO_2) at AT, VT/VCO_2 at AT, and HR/VT at AT. Inspired and expired air was measured directly with a monitor and accompanying software. D-ribose was dosed at 5 grams three times daily. Participants exhibited significant improvements in VE_{eff} (51.5 ± 9.7 to 43.2 ± 8.5 , $p < 0.005$; normal values 25-34), VO_2max (8.4 ± 1.5 to 10.0 ± 1.2 mL/kg/min, $p < 0.005$), as well as oxygen uptake efficiency (1.12 ± 0.38 to 1.4 ± 0.41 , $p < 0.02$). Adverse events were not reported by the investigators. Although interesting, study design issues should be considered when interpreting results, such as the lack of a placebo group. Additionally, patients' concomitant medications were not described and it was unclear if dose changes and titrations were allowed during the study.

Coronary Artery Disease

Pliml W, von Arnim T, Stablein A, et al. Effects of ribose on exercise-induced ischemia in stable coronary artery disease. *Lancet* 1992;340:507-510.

Post ischemic restoration of myocardial ATP concentrations may be impaired in the heart due to diminished availability of 5-phosphoribosyl-1-pyrophosphate (PRPP), one of the precursors of ATP in the salvage pathway. Based on this premise, investigators examined exogenous administration of D-ribose, which bypasses the rate limiting steps of PRPP formation. Twenty patients with coronary artery disease as evidenced by coronary arteriography and a positive treadmill exercise test on two successive days were included. Participants who did not demonstrate ST-segment depression were instructed to continue to exercise until the onset of angina of moderate severity. Participants meeting enrollment criteria were randomized by a table of random numbers on a 1:1 basis to D-ribose 60grams (powder, dissolved in water and given in 4 doses) or placebo daily for 3 days. A follow up treadmill test was performed on day 4. Participants in the D-ribose group exhibited increased mean walking time until ST depression compared to placebo (276 seconds [95% CI 220, 331] versus 223 seconds [95% CI 188, 259], $p=0.002$). There was no significant difference between groups in mean time to onset of moderate angina, which may be attributed to an increased time to onset of angina in the placebo group. Two of the D-ribose treated participants did not exhibit ST-segment elevations on follow up treadmill tests; therefore time to onset of angina was used in the analysis. Minor gastrointestinal discomfort was reported in 3 ribose-treated participants. It was unclear if the study was blinded, and treadmill tests are inherently subjective and based on patient effort, therefore appropriate blinding is crucial to make meaningful comparisons for this type of outcome. Additionally, the use of ECG to assess for ischemia has been largely replaced with stress echocardiography. Finally, as the study was powered based on feasibility, limited power existed for detecting significant differences between groups that were not based on chance.

Fish Oil (Omega-3 fatty acids)

Arrhythmias

Brouwer IA, Zock PL, Camm AJ, et al. Effect of

Fish Oil on Ventricular Tachyarrhythmia and Death in Patients With Implantable Cardioverter Defibrillators The Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) Randomized Trial. *JAMA* 2006;295:2613–9.

Very-long-chain n-3 PUFAs from fish are thought to reduce the risk of sudden death, possibly by reducing susceptibility to cardiac arrhythmia. The Study on Omega-3 Fatty acids and ventricular Arrhythmia (SOFA) was a randomized, double-blind, placebo-controlled, trial conducted across Europe to study the effect of supplemental fish oil (n-3 PUFA) vs. placebo on ventricular tachyarrhythmia or death in 546 patients with implantable cardioverter defibrillators (ICDs) and prior documented malignant ventricular tachycardia (VT) or ventricular fibrillation (VF). Patients were randomly assigned to receive 2 g/d of fish oil PUFAs (464 mg eicosapentaenoic acid, 335 mg docosahexaenoic acid, and 162 mg other omega-3 PUFAs; mean of 12 samples taken at regular intervals during the study) (n=273) or placebo (n=273) for a median period of 356 days (range, 14–379 days). There was no difference in the primary end point of ICD intervention for VT or VF, or all-cause death, which occurred in 81 (30%) patients taking fish oil vs. 90 (33%) patients taking placebo (hazard ratio [HR], 0.86; 95% CI, 0.64–1.16; P=.33) or in the prespecified subgroup analyses. This small study does not support the routine use of fish oil in patients with ICDs who do not have other indications.

Leon H, Shibata MC, Sivakumaran S, et al. Effect of fish oil on arrhythmias and mortality: systematic review. *BMJ* 2009;338:a2931.

This systematic review and meta-analysis was conducted to synthesise the literature on the effects of fish oil—docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) on mortality and arrhythmias and to explore dose response and formulation effects. The authors conducted a thorough, explicit and comprehensive literature search of major literature databases, without language restrictions of RCTs using fish oils as dietary supplements. The primary outcomes of interest were the arrhythmic end points of appropriate implantable cardiac defibrillator intervention (confirmed by electrogram) and sudden cardiac death. The secondary outcomes were all cause mortality and death from cardiac causes. Subgroup analyses included the effect of formulations of EPA and DHA on death from cardiac causes and effects of fish oil in patients

with coronary artery disease or myocardial infarction. A total of 12 studies totaling 32,779 patients met the inclusion criteria. Two blinded investigators reviewed and extracted the data systematically ($k=0.92$), and assessed the quality of each study using the Jadad criteria. Five of the 12 studies included scored 5 out of 5 on the quality score. Using a random effects model, a neutral effect was reported in three studies (n=1148) for appropriate implantable cardiac defibrillator (ICD) intervention (OR 0.90, 95% CI 0.55 to 1.46) and in six studies (n=31,111) for sudden cardiac death (OR 0.81, 95% CI 0.52 to 1.25). A total of 11 studies (n=32,439 and n=32,519) provided data that showed no difference on the effects of fish oil on all cause mortality (OR 0.92, 95% CI 0.82 to 1.03). These 11 studies did show a reduction in deaths from cardiac causes (OR 0.80, 95% CI 0.69 to 0.92), however, there was a partially skewed funnel plot suggesting some publication bias. The dose-response relation for DHA and EPA on reduction in deaths from cardiac causes was not significant. Significant heterogeneity using X^2 and I^2 was only present in the 3 studies for appropriate ICD intervention. Overall, fish oil supplementation was associated with a significant reduction in deaths from cardiac causes but had no effect on arrhythmias or all cause mortality. However, evidence to recommend an optimal formulation of EPA or DHA to reduce these outcomes is insufficient until further studies are conducted.

Chronic Heart Failure

GISSI-HF Investigators. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;372:1223–30.

Epidemiological and experimental studies have suggested that n-3 PUFAs can exert favourable effects on atherothrombotic cardiovascular disease, including arrhythmias. However, their effect in patients with HF is unknown. Therefore, the GISSI-HF study was a randomized, double-blind, placebo-controlled trial that investigated whether n-3 PUFA could improve morbidity and mortality in a large population of patients with symptomatic heart failure of any cause. A total of 7046 chronic heart failure patients in Italy primarily with New York Heart Association class II–III, were randomly assigned to n-3 PUFA 1 g daily (850–882 mg eicosapentaenoic acid and docosahexaenoic acid

as ethyl esters in the average ratio of 1:1.2) (n=3494) or placebo (n=3481) by a concealed, computerized telephone randomization system. Patients were well-treated with traditional heart failure medications (ACEI/ARB ~93%, β -blocker ~65%, spironolactone ~40%, diuretics ~90%, digoxin ~37%). The median follow-up was 3.9 years, with <0.05% lost to follow-up. The study had two primary endpoints: time to death, and time to death or admission to hospital for cardiovascular reasons. By intention to treat analysis, there was a 9% RRR and a 1.8% ARR in time to death in the n-3 PUFA group (27.3%) as compared with placebo (29.1%) (adjusted hazard ratio [HR] 0.91 [95% CI 0.833–0.998], p=0.041). The largest difference in cause of death between groups was in presumed arrhythmic death (8.7% for placebo vs 7.8% for n-3 PUFA). There was an 8% RRR and a 2.3% ARR in the composite endpoint of time to death or cardiac hospitalization in the n-3 PUFA group (57%) as compared with placebo (59%) (adjusted HR 0.92 [99% CI 0.849–0.999], p=0.009). In absolute terms, 56 patients needed to be treated for a median duration of 3.9 years to avoid one death or 44 to avoid one event like death or admission to hospital for cardiovascular reasons. The most commonly reported adverse reaction was gastrointestinal disorders at a rate of 3% in both groups. This study provides evidence that n-3 PUFAs provide a modest cardiovascular benefit in chronic heart failure patients.

Coronary Artery Disease

GISSI-Prevenzione Investigators* (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico). Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1999;354:447–55.

This was a landmark study, conducted from 1993–1995 in 11,324 patients surviving a recent (<3 months) myocardial infarction in Italy. Patients were randomly assigned supplements of n-3 polyunsaturated fatty acid (PUFA) [fish oil, containing 850–882 mg eicosapentaenoic acid (EPA) and docosahexaenoic acid

(DHA) as ethyl esters in the average ratio of EPA/DHA 1:2] (1 g daily, n=2836), vitamin E (300 mg daily, n=2830), both (n=2830), or none (control, n=2828) for 3.5 years. The primary combined efficacy endpoint was death, non-fatal myocardial infarction, and stroke. Intention-to-

treat analyses were done according to a factorial design (two-way) and by treatment group (four-way). This study found that treatment with n-3 PUFA, but not vitamin E, significantly lowered the risk of the primary endpoint from 14.6% in the control group to 12.3% in the fish oil group (RRR 10% [95% CI 1–18] by two-way analysis p=0.048, 15% [95% CI 2–26] by four-way analysis, p=0.023). Benefit was attributable to a decrease in the risk of death (14% [95% CI 3–24] two-way, 20% [95% CI 6–33] four-way) and cardiovascular death (17% [95% CI 3–29] two-way, 30% [95% CI 13–44] four-way). For every 44 patients treated with 1 g n-3 PUFA (approximately 2g of fish oil capsules) instead of nothing for 3.5 years, 1 patient will avoid a death, non-fatal myocardial infarction, or stroke. Gastrointestinal disturbances and nausea were the most frequently reported side-effects (4.9%, and 1.4% in the n3-PUFA group). This study has been used to support the American College of Cardiology/American Heart Association guidelines recommendation to increase ingestion of omega-3 fatty acids in fish or capsule form in post-myocardial infarction patients.

Kris-Etherton PM, Harris WS, Appel LJ, for the Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* 2002;106:2747–57.

Evidence from epidemiological studies and clinical trials are reviewed and recommendations are made that reflect the state of knowledge at the time regarding fish consumption and omega-3 fatty acid (plant- and marine-derived) supplementation. Potential mechanisms of action are also reviewed. This scientific statement considers guidance from the US Environmental Protection Agency and the Food and Drug Administration about the presence of environmental contaminants in certain species of fish. Three specific recommendations are provided: 1) Patients without documented CHD: Eat a variety of (preferably oily) fish at least twice a week. Include oils and foods rich in alpha-linolenic acid (flaxseed, canola, and soybean oils; flaxseed and walnuts). 2) Patients with documented CHD: Consume 1 g of EPA_DHA per day, preferably from oily fish. EPA_DHA supplements could be considered in consultation with the physician. 3) Patients needing triglyceride lowering Two to four grams of EPA_DHA per day provided as capsules under a physician's care.

Yokoyama M, Origasa H, Matsuzaki M, et al, for the Japan EPA lipid intervention study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet* 2007;369:1090–98.

The JELIS study aimed to test the hypothesis that long-term use of eicosapentaenoic acid (EPA) is effective for the prevention of major coronary events in hypercholesterolaemic patients in Japan who consume a large amount of fish. EPA is one of the two main long-chain n-3 PUFAs that have been linked to a reduction in cardiac mortality. Between 1996 and 1999, 18,645 patients in Japan with a total cholesterol of 6.5 mmol/L (251 mg/dL) or greater were enrolled in the open-label study and were randomly assigned to receive either 1800 mg of EPA daily with statin (EPA group; n=9326) or statin only (controls; n=9319) with a mean follow-up of 4.6 years. Only 1% of patients were lost-to-follow-up. The primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal myocardial infarction, and other nonfatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. Total cholesterol and LDL-C decreased by 19% and 25%, from 4.7 mmol/L (182 mg/dL) in both groups. Triglycerides decreased significantly by 9% from baseline in the EPA group and by 4% in the controls ($p<0.0001$ between groups). Intention-to-treat analysis showed a 19% RRR and a 0.7% absolute risk reduction (ARR) in the primary endpoint (2.8% patients in the EPA group; 3.5% in controls; $p=0.011$). The number needed to treat (NNT) for the primary endpoint is 143 patients. Sudden cardiac death and coronary death did not differ between the treatment groups. The lack of reduction in cardiac death observed is not entirely surprising since the Japanese population already consumes enough fish to exceed the threshold for preventing cardiac death. Therefore, one would expect minimal, if any further reduction in cardiac events with additional fish oil consumption. In patients with a history of coronary artery disease (secondary prevention) who were given EPA, major coronary events were reduced by 19% (158 [8.7%] with EPA vs 197 [10.7%] with control; $p=0.048$). In the primary prevention group, EPA treatment resulted in an 18% nonsignificant reduction in major coronary

events (104 [1.4%] with EPA vs 127 [1.7%] with control; $p=0.132$). Gastrointestinal disturbances (3.8% vs 1.7%), skin disorders (1.7% vs 0.7%) and bleeding (1.1% vs 0.6%) were more common in the EPA group ($p<0.001$ for all). This study shows that adding EPA to a low-risk population consuming a diet already rich in fish adds only minimal cardiovascular benefits, primarily to those patients with a history of cardiovascular disease. Further trials are required to investigate diverse PUFA formulations in populations of varying risk.

Folic Acid and B Vitamins

Coronary Artery Disease

Schnyder G, Roffi M, Flammer Y, et al. Effect of Homocysteine-Lowering Therapy With Folic Acid, Vitamin B12, and Vitamin B6 on Clinical Outcome After Percutaneous Coronary Intervention. The Swiss Heart Study: A Randomized Controlled Trial. *JAMA* 2002;288:973–9.

The Swiss Heart Study was the first large study evaluating folic acid with other B-vitamins (as a homocysteine-lowering regimen) to evaluate the impact on cardiovascular clinical outcomes. It was a randomized, double-blind placebo-controlled trial involving 553 patients after successful angioplasty of at least 1 significant coronary stenosis (>50%) in Switzerland in 1998–1999. Participants were randomly assigned to receive a combination of folic acid (1 mg/d), vitamin B₁₂ (cyanocobalamin, 400 µg/d), and vitamin B₆ (pyridoxine hydrochloride, 10 mg/d) (n=272) or placebo (n=281) for 6 months with a mean follow-up on 11 months, with about 10% lost to follow-up. Using intention to treat analysis, the primary composite end point of major adverse events defined as death, nonfatal myocardial infarction, and need for repeat revascularization was significantly lower at 1 year in patients treated with homocysteine-lowering therapy (15.4% vs 22.8%; relative risk [RR], 0.68; 95% CI, 0.48–0.96; $P=0.03$), primarily due to a reduced rate of target lesion revascularization (9.9% vs. 16.0%; RR, 0.62; 95% CI, 0.40–0.97; $P=0.03$). There was no statistical difference in the incidence of deaths (1.5% vs. 2.8%; RR, 0.54; 95% CI, 0.16–1.70; $P=0.27$) or nonfatal myocardial infarctions (2.6% vs 4.3%; RR, 0.60; 95% CI, 0.24–1.51; $P=0.27$) with homocysteine-lowering therapy. No medication side effects were reported. This small study

stimulated the interest in the use of homocysteine-lowering therapy in reducing cardiac events in patients with coronary artery disease. However, its unique results require confirmation in larger clinical trials.

The Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 2006;354:1567–77.

HOPE-2 was a randomized, double-blind, placebo-controlled study that assessed whether homocysteine lowering supplementation reduced the risk of major cardiovascular events in patients with vascular disease. A total of 5522 patients 55 years of age or older who had vascular disease or diabetes were randomized to daily treatment with either the combination of 2.5 mg of folic acid, 50 mg of vitamin B₆, and 1 mg of vitamin B₁₂ or with placebo. Average follow-up was five years. Only 0.7% were lost to follow-up and the compliance was reported as ~90%. Use of open-label folic acid was similar in both groups ranging from 2.2–5.5%. Mean plasma homocysteine levels decreased by 2.4 $\mu\text{mol/L}$ (0.3 mg/L) in the active-treatment group and increased by 0.8 $\mu\text{mol/L}$ (0.1 mg/L) in the placebo group. Using an intention to treat analysis, there was no difference in the primary outcome of a composite of death from cardiovascular causes, myocardial infarction, and stroke, which occurred in 18.8% in active therapy and 19.8% in placebo (RR 0.95; 95% CI, 0.84 to 1.07; $P=0.41$). As compared with placebo, active treatment did not significantly decrease the risk of death from cardiovascular causes (RR 0.96; 95% CI, 0.81 to 1.13), myocardial infarction (RR, 0.98; 95% CI, 0.85 to 1.14), or any of the secondary outcomes. While fewer patients assigned to active treatment than to placebo had a stroke (RR 0.75; 95% CI, 0.59 to 0.97; $P=0.03$), the number of strokes in the study was smaller than the number of cardiac events and the 95% CI around the risk estimate are wide. More patients in the active-treatment group were hospitalized for unstable angina (RR 1.24; 95% CI, 1.04 to 1.49). This study does not support the use of supplements combining folic acid and vitamins B₆ and B₁₂ to reduce the risk of major cardiovascular events in patients with vascular disease.

Bønaa KH, Njølstad I, Ueland PM, et al, for the NORVIT Trial Investigators. Homocysteine lowering and cardiovascular events after acute

myocardial infarction. *N Engl J Med* 2006;354:1578–88.

This randomized, double-blind, placebo-controlled trial of 3749 post-acute myocardial infarction (≤ 7 days) patients in Norway evaluated the efficacy of homocysteine-lowering treatment for secondary prevention was reported in the same issue as the HOPE-2 Study. Patients were randomly assigned, in a 2x2 factorial design, to receive one of the following four daily treatments: 0.8 mg of folic acid, 0.4 mg of vitamin B₁₂, and 40 mg of vitamin B₆; 0.8 mg of folic acid and 0.4 mg of vitamin B₁₂; 40 mg of vitamin B₆; or placebo with >90% compliance rates. The primary end point was a composite of recurrent myocardial infarction, stroke, and sudden death attributed to coronary artery disease. Median follow-up was 40 months, with no patients lost to follow-up for the mortality endpoint and 0.5% for the nonfatal endpoints. The mean total homocysteine level was lowered by 27% among patients given folic acid plus vitamin B₁₂, however, the treatment did not have a significant effect on the primary endpoint (RR 1.08; 95% CI, 0.93 to 1.25; $P=0.31$). This same finding was also observed in those treated with vitamin B₆ (RR 1.14; 95% CI, 0.98 to 1.32; $P=0.09$). Of concern, in the group given folic acid, vitamin B₁₂, and vitamin B₆, there was a trend toward an increased risk of the composite endpoint (RR 1.22; 95% CI, 1.00 to 1.50; $P=0.05$). Similar proportions of patients in all groups reported medication-related side effects (18–24%). Although high homocysteine has been shown in observational studies to be predictor of cardiovascular events, this prospective RCT showed lack of benefit and potential for harm in this population, similar to the HOPE-2 study findings.

Bazzano LA, Reynolds K, Holder KN, He J. Effect of folic acid supplementation on risk of cardiovascular diseases. A meta-analysis of randomized controlled trials. *JAMA* 2006;296:2720–6.

The objective of this meta-analysis was to evaluate the effects of folic acid supplementation on the risk of cardiovascular diseases and all-cause mortality in randomized controlled trials among persons

with preexisting cardiovascular or renal disease. The authors conducted an explicit, comprehensive literature search without language restrictions, and included review of bibliographies and contacted experts. A total of

12 RCTs including data from 16 958 participants (in addition to the HOPE and NORVT Trials discussed above) met the criteria of comparing folic acid supplementation with either placebo or usual care for a minimum duration of 6 months and with clinical cardiovascular disease events reported as an endpoint. Two investigators independently abstracted data (Kappa not reported). Both fixed and random effects models were used to calculate the pooled RR estimate. Heterogeneity was reported as not significant; however, statistical methods and results were not reported. There was no evidence of publication bias using funnel plots, rank correlation or regression testing. The overall RR (95% CI) of outcomes for patients treated with folic acid supplementation compared with controls were 0.95 (0.88–1.03) for cardiovascular diseases, 1.04 (0.92–1.17) for coronary heart disease, 0.86 (0.71–1.04) for stroke, and 0.96 (0.88–1.04) for all-cause mortality, all of which showed no significant difference. The RR was consistent among participants with preexisting cardiovascular or renal disease. This meta-analysis compiles the data to date, indicating that folic acid supplementation has not been shown to reduce the risk of cardiovascular diseases or all-cause mortality among participants with prior history of vascular disease. Several ongoing trials (as listed in the discussion and references) with large sample sizes might provide a definitive answer to this important clinical and public health question.

Albert CM, Cook NR, Gaziano JM, et al. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease. A randomized trial. *JAMA* 2008;299:2027–36.

Within an ongoing RCT of antioxidant vitamins, 5442 women who were US health professionals aged ≥ 42 years old, with either a history of CVD or 3 or more coronary risk factors, were enrolled in a randomized, double-blind, placebo-controlled trial to receive a combination pill containing folic acid 2.5 mg, vitamin B₆ 50 μ g, and vitamin B₁₂ 1 mg or a matching placebo. Median follow-up was 7.3 years, from April 1998 through July 2005. Average adherence was 83% and open-label folic acid was used from 2–11% in the active group and 2–13% in the placebo group. Morbidity and mortality data was complete for 98.9% and 98% of person-years of follow-up, respectively. Using intention to treat analysis, patients receiving

active vitamin treatment had similar risk for the composite CVD primary endpoint of myocardial infarction, stroke, coronary revascularization, or CVD mortality (226.9/10 000 person-years vs 219.2/10 000 person-years for the active vs. placebo group; RR 1.03; 95% CI, 0.90–1.19; $P=0.65$). There was also no difference between groups for the secondary outcomes (myocardial infarction, stroke, CVD mortality). In a blood substudy, geometric mean plasma homocysteine level was decreased by 18.5% (95%CI, 12.5–24.1%; $P<0.001$) in the active group ($n=150$) over that observed in the placebo group ($n=150$), for a difference of 2.27 μ mol/L (95% CI, 1.54–2.96 μ mol/L). Despite significant homocysteine lowering, this vitamin combination did not reduce clinical outcomes in women.

Ebbing M, Bleie O, Ueland PM, et al. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography. A randomized controlled trial. *JAMA* 2008;300:795–804.

In the Western Norway B Vitamin Intervention Trial (WENBIT), 3096 patients undergoing coronary angiography in Norway were randomized to 1 of 4 groups receiving daily oral treatment with folic acid, 0.8 mg, plus vitamin B₁₂, 0.4 mg, plus vitamin B₆, 40 mg ($n=772$); folic acid plus vitamin B₁₂ ($n=772$); vitamin B₆ alone ($n=772$); or placebo ($n=780$) in a double-blind manner using a 2x2 factorial design. Although the interim analysis on total mortality did not show a concern, the safety committee advised the steering committee to stop the trial since adherence could be severely compromised due to patients' concerns after the presentation of the NORVIT study (see above) in September 2005, with a median following of 38.4 months. A total of 692 patients had premature termination of the study intervention. Mean plasma total homocysteine concentration was reduced by 30% after 1 year of treatment in the groups receiving folic acid and vitamin B₁₂. Using intention to treat analysis, after a median follow-up of 38 months, there was no difference in the primary composite endpoint of all-cause death, nonfatal acute myocardial infarction, acute hospitalization for unstable angina pectoris, and nonfatal thromboembolic stroke, which was experienced by 14.2% receiving folic acid/vitamin B₁₂ vs. 13.1% not receiving such treatment (HR 1.09; 95% CI, 0.90–1.32; $P=0.36$) and 13.0% receiving vitamin B₆ vs. 14.3% not receiving vitamin B₆ (HR 0.90; 95% CI, 0.74–1.09; $P=0.28$). This trial does not support the use of

folic acid with B vitamins as secondary prevention in patients with coronary artery disease, and is consistent with the lack of effect demonstrated in several prior studies.

Garlic

Dyslipidemia

Gardner CD, Lawson LD, Block E, et al. Effect of raw garlic vs commercial garlic supplements on plasma lipid concentrations in adults with moderate hypercholesterolemia. *Arch Intern Med* 2007;167:346–353.

Studies of garlic (*Allium Sativum*) for its lipid lowering effects are largely inconsistent. Garlic's mechanisms for lowering cholesterol are incompletely understood, but hypothesized to involve reduced LDL oxidation and inhibition cholesterol synthesis. The goal of this parallel-design study was to compare the effects of raw garlic and 2 commercial garlic supplements of varying formulations on plasma lipid concentrations in 192 adults with dyslipidemia over 6 months of treatment. The primary outcome measure was LDL concentration. Participants were enrolled if their LDL concentration was between 130–190 mg/dL, their triglyceride levels were less than 250 mg/dL, and if their BMI was between 19 and 30. The study medication arms included placebo (4 or 6 tablets), raw garlic (4 grams blended, served in sandwiches), 4 tablets of powdered garlic (Garlicin, Nature's Way: twice the recommended dose) and 6 tablets of an aged garlic powder (Kyolic-100 Wakunaga of America Co: 1-1/2–3 times the recommended dose). The raw garlic and Garlicin formulation had a slightly less dry garlic matter content compared to the Kyolic. The consumed doses of Garlicin were considerably higher than those used in previous clinical trials. All participants received identical study sandwiches, and due to the characteristically strong taste of garlic, the group randomized to raw garlic was not blinded. Following a 2-week placebo sandwich run in phase, participants were randomized to 26 weeks of treatment. Lipid concentrations were measured at initiation of run in phase, prior to randomization, then monthly through month 5, and at the end treatment phase. Investigators were blinded to treatment groups until lipid analyses were completed. Diet was assessed by 3 day reviews of food records at the beginning of run in phase, at randomization, and mid-study,

and at end of treatment. Participants filled out weekly logs to document adherence, which was also assessed via pill count from returned bottles. Investigators also measured the stability of the garlic products throughout the study. After 26 weeks of treatment, there were no statistically significant differences in any of the fasting lipid concentrations by treatment group. LDL concentrations were not reduced significantly from baseline in any of the treatment arms (group by time p-value 0.54). No differences were detected between groups for physical activity, weight, or dietary intake of saturated fat, fiber, or calories. Adherence to tablet consumption was 91–94% among treatment arms, and to sandwiches was 96–97%. This study was well conducted and was powered to detect modest differences in LDL concentrations, which were not found. Moreover, higher doses than are recommended were used for the two commercial products. Nonetheless, discordant results from previous studies could be due to differing study designs.

Sobenin IA, Andrianova IV, Demidova ON, Gorchakova TV, Orekhov AN. Lipid-lowering effects of time-released garlic powder tablets in double-blinded placebo-controlled randomized study. *J Atheroscler Thromb* 2008;15:334–338.

The purpose of this study was to evaluate the effects of a new time-released garlic powder formulation in mildly hyperlipidemic men. This randomized, double-blind, placebo controlled trial included 42 men aged 35–70 with total cholesterol between 224–270 mg/dL, LDL 135–178 mg/dL, and HDL 25–75 mg/dL. Prior to randomization, participants underwent 4 weeks of treatment with a hypolipidemic diet, followed by a 4-week phase of hypolipidemic diet in addition to placebo (one tablet twice daily). Thereafter, they were randomized to either time released garlic powder tablets (Allicor) 600 mg twice daily or placebo for 12 weeks. Both tablets were coated in an identical fashion to exhibit a similar outlook, taste, and smell. Randomization was stratified by age, total and LDL cholesterol, fasting glucose values, systolic and diastolic blood pressure, smoking history, family history, BMI, alcohol consumption, and cardiovascular history. Fasting lipid levels were measured at baseline, following 4 weeks of diet, at randomization, and following 4, 8, and 12 weeks of study medication. After the 8-week run in phase, mean LDL values were mildly reduced (P=NS). Following 12 weeks of treatment, garlic

reduced LDL values more significantly compared to placebo (169 ± 8 mg/dL vs 196 ± 6 mg/dL, $p < 0.05$). HDL concentrations decreased significantly in the garlic group compared to baseline, but not compared to placebo. Total cholesterol values decreased by $7.6 \pm 2.4\%$ in the garlic group compared to at randomization (95% CI 2.7–12.5, $p = 0.004$), and were 11.5% lower than the placebo group ($p = 0.003$) at the end of the study. The use of a long acting garlic supplement in this study is noteworthy, considering known absorption problems with *Allium Sativum*, the active ingredient in garlic. As with previous studies with garlic supplements, it is unknown whether these lipid lowering effects would remain reduced after longer term treatment. Overall, discrepancies with garlic studies could be explained by inconsistent dosing, various garlic preparations with unpredictable pharmacokinetics, and different study populations studied.

Ginkgo Biloba

Peripheral Vascular Disease

Pittler MH, Ernst E. Ginkgo Biloba extract for the treatment of intermittent claudication: a meta-analysis of randomized trials. *Am J Med* 2000;108:276–281.

This meta-analysis assessed the efficacy of Ginkgo biloba for intermittent claudication by including randomized, clinical trials searched from MEDLINE, EMBASE, BIOSIS, AMED, CISCOR, and the Cochrane Library. Data were also gathered from bibliographies of studies and review articles, as well as from manufacturers of commercial Ginkgo products. When data were unsuitable for statistical pooling, the authors of the applicable publications were contacted to provide additional information. Studies were included if they were randomized, double blind, and placebo controlled. Studies using Ginkgo in combination with other medications or that did not assess walking distance were excluded. The common outcome measure was pain-free walking distance. The mean change compared to baseline was used to determine differences between Ginkgo and placebo. Eight trials were included for analysis. Seven of the 8 trials favored Ginkgo biloba compared to placebo for pain free walking distance, although only 4 noted statistically significant differences between groups. Nonetheless, statistical pooling showed a significant difference in pain free walking

distance with Ginkgo (weighted mean difference: 34 meters, 95% CI 26–43 meters). Three trials, which comprised 51% of the patients studied in this meta-analysis, had similar methodologies in Ginkgo biloba dose and study duration (24 weeks). Pooling of these studies also yielded significant differences with Ginkgo for pain free walking distance (weighted mean difference: 33 meters, 95% CI 22–43 meters). Of the 7 studies that reported maximal walking distance, six found significant differences in favor of Ginkgo; the range of improvement was wide, from 36 to 189 meters. There were too few studies to determine if publication bias influenced the overall results of this analysis. Of note, only one trial reported randomization procedures. Moreover, neither of the crossover studies reported a washout period. Overall, this analysis showed that pain free walking was statistically increased with Ginkgo, although whether these improvements are clinically significant is unclear.

Gardner CD, Taylor-Piliae RE, Kiazand A, et al. Effect of Ginkgo biloba on treadmill walking time among adults with peripheral artery disease. *J Cardiopulm Rehab Prev* 2008;28:28–265.

The active compounds in Ginkgo biloba, flavanoids and terpenes, have potential vasodilatory effects which may be beneficial in peripheral artery disease (PAD). The purpose of this study was to investigate the EGb 761 formulation, which contains 24% flavonoids and 6% terpenes, on pain free and maximal treadmill walking distance among patients with PAD. The primary endpoint was maximum walking time on a treadmill; investigators estimated that 30 participants were needed per group. This randomized, double-blind, placebo-controlled trial enrolled 62 adults with a resting ankle-brachial index (ABI) < 0.9 . Additionally, enrollees had to be able to walk on a treadmill at 2 mph at a 10% grade for at least a minute and less than 10 minutes, with at least a 25% drop in ABI within 1 minute after the treadmill test and less than 25% variability between 2 treadmill tests. In patients with DM, all ABI values were allowed provided participants met other inclusion criteria. The use of dietary supplements (except a multivitamin) was not allowed for at least a month within screening and during the study. Participants were instructed to take 3 tablets of EGb761 (60 mg each) or placebo with breakfast, and 2 with dinner daily for 4 months. At baseline and at 4 months, treadmill testing was performed, which was supervised by

a registered nurse. Participants were instructed to walk until they could no longer continue, and were asked to rate their leg pain every 30 seconds during exercise using a 4 point likert scale. Flow mediated vasodilation (FMVD) was measured via ultrasound at baseline and at the end of the study. Blood was drawn at baseline and at end of study for measurement of oxidized LDL markers. A Walking Impairment Questionnaire was completed by participants, which rates degree of difficulty of walking, and quality of life was assessed using the SF-36 questionnaire. Adherence was assessed by counting remaining tablets on returned study bottles. Overall adherence was 94% and 92% in the placebo and the Ginkgo groups, respectively. The time to onset of pain increased by 15 ± 31 seconds in the placebo group and 21 ± 43 seconds in the Ginkgo group ($p=0.28$). The average increase in walking time to maximum pain was increased by 40% in the Ginkgo group and by 10% in the placebo group ($p=0.12$). FMVD changes from baseline favored the Ginkgo group but the difference was short of statistical significance ($p=0.24$). Similarly, no significant changes were noted for oxidized LDL markers or for the Walking Impairment Questionnaire. However, for one of the SF-36 components, termed "role physical", the changes in scores between 4 months and baseline were higher for the Ginkgo group versus placebo (17 ± 29 vs. -6 ± 35 ; $p=0.009$, adjusted $p=0.03$). Although the primary endpoint results did not reach statistical significance, the trend was in favor of Ginkgo. Also noteworthy, there were a small number of individuals in both the Ginkgo and placebo groups ($N=6$ and 5 , respectively) with baseline walk times on the higher end of the inclusion criterion, between 5 and 10 minutes. Following treatment, those in the Ginkgo group increased their walking times dramatically, whereas those in the placebo group did not. It is plausible, therefore, that individuals with more severe PAD and shorter walking times at baseline would be less responsive to therapy. Moreover, investigators did not report adverse events, which could be useful to determine clinical utility of the Ginkgo formulation.

Guggulipid

Dyslipidemia

Szapary PO, Wolfe ML, Bloedon LT, et al. Guggulipid for the treatment of hypercholesterolemia. A randomized controlled trial. *JAMA* 2003;290:765–72.

Guggulipid is a tree resin extract containing purportedly active plant sterols and has been used in India to lower cholesterol. Recent research suggests that their active constituents may be involved with bile acid regulation and cholesterol metabolism. This study was designed to evaluate whether guggulipid could safely reduce low density lipoprotein-cholesterol (LDL-C) in a Western population with hyperlipidemia. This was a randomized, double-blind, placebo controlled trial comparing the short-term (8 week) safety and efficacy of 2 doses (1000 mg and 2000 mg) of a standardized guggul extract (guggulipid, containing 2.5% guggulsterones) to placebo. A total of 103 ambulatory healthy adults with hyperlipidemia, eating a typical Western diet were enrolled, with a 17% drop-out rate. The primary endpoint was percent change from baseline in directly measured LDL-C at 8 weeks, measured using intention to treat analysis. Compared with placebo, in whom LDL-C levels decreased by 5%, both standard dose guggulipid and high-dose guggulipid increased LDL-C by 4% ($p=0.01$) and 5% ($p=0.006$), respectively. In addition to the LDL-C increase seen with both guggulipid groups, there was also a concern raised regarding the development of a hypersensitivity rash in 6 participants (9%) treated with guggulipid, while there were none in the placebo group. Despite many preliminary studies published in the Indian medical literature supporting the use of guggulipid that are cited in the reference section of this article, this larger randomized clinical trial found no benefit on the cholesterol profile but rather a worsening, and also raised concerns for hypersensitivity reactions. Based on these findings, use of guggulipid for hypercholesterolemia is unwarranted.

Ulbricht C, Basch E, Szapary P, et al. Guggul for hyperlipidemia: a review by the Natural Standard Research Collaboration. *Complement Ther Med* 2005;13:279–90.

This article is a systematic review and evaluation of the scientific evidence on guggul for hyperlipidemia, including expert opinion, folkloric precedent, history, pharmacology, pharmacokinetics, pharmacodynamics, interactions, adverse effects, toxicology and dosing. The authors note that prior to the 2003 JAMA article, noted above, most scientific evidence suggested that guggulipid significantly reduced total cholesterol, LDL-C, triglycerides and increased high density lipoprotein-

cholesterol (HDL-C). However, two case reports have demonstrated similar results as those in the Szapary study. They conclude that at this time, there is not enough evidence to support the use of guggul for any medical condition, and that it may cause stomach discomfort, allergic rash, as well as other side effects and potential drug interactions, such as, decreasing absorption of propranolol and diltiazem.

Hawthorn

Chronic Heart Failure

Aaronson K. HERB-CHF (Hawthorn Extract Randomized Blinded Chronic HF Study). Late-Breaking and Recent Clinical Trials. Presented at the 8th Annual Scientific Meeting of the Heart Failure Society of America; September 12–15, 2004; Toronto, Ontario, Canada. *J Card Fail* 2004; 10(suppl): abstract 2832.

The small, fruit-bearing tree, hawthorn (*Crataegus monogyna*, *lanceolata*, *oxyacantha*, and others), found in East Asia, Eastern North America, and Europe, is used in Chinese, European, Japanese, and Native American traditional medicine and has been evaluated for the treatment of heart failure (HF) in conventional medicine. The active constituents in hawthorn leaves, flowers, and berries include two groups of polyphenolic compounds: flavonoids and oligomeric proanthocyanidins (OPCs). Pharmacologic activities attributed to the flavonoids and/or OPCs include: (1) angiotensin-converting enzyme (ACE) inhibition; (2) type-III/IV phosphodiesterase inhibition; (3) Na⁺/K⁺ ATPase activity; (4) antioxidant activity; and (5) decreased production and release of histamine, prostaglandins, leukotrienes, and inhibition of neutrophil elastase. Preliminary data with hawthorn have reported improved exercise measures, increased left ventricular ejection fraction (LVEF), and better hemodynamic parameters. However, these trials have been conducted in patients who were mainly New York Heart Association (NYHA) Class II, often with well-preserved LVEF, on background therapy consisting of a diuretic, sometimes digoxin, rarely an angiotensin converting enzyme (ACE) inhibitor, and never a beta-blocker. The HERB-CHF, a randomized, double-blind, placebo-controlled, parallel-group trial, was designed to determine the effect of hawthorn (WS^a 1442) 450 mg twice daily versus placebo,

each in addition to standard medical therapy (e.g., ACE inhibitor, β -blocker, digoxin, and diuretic as needed), in patients with chronic mild to moderately severe HF on changes in 6-minute walk distance, patient global assessment scores, Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores, and LVEF. A total of 57 and 54 patients, respectively with an LVEF \leq 40%, NYHA Class II-IV stabilized on background heart failure therapy for at least three months prior to randomization completed the six month study. Upon completion, no difference existed between groups in six-minute walk distance ($p=0.41$), MLHFQ scores ($p=0.48$), or patient global assessment scores. However, a modest relative benefit was seen with hawthorn compared to placebo for LVEF ($p=0.04$). Small, nonsignificant reductions were seen in systolic and diastolic blood pressure in the hawthorn group together with a small, nonsignificant increase in heart rate, contrary to findings of previous reports with hawthorn extract. The authors concluded that the results of HERB-CHF do not provide evidence that use of hawthorn extract is associated with functional improvement or symptomatic benefit in HF patients receiving contemporary concomitant medical therapy. Nonetheless, while not published, the HERB-CHF study was the first trial to specifically address study design limitations with earlier published investigations of hawthorn.

Pittler MH, Guo R, Ernst E. Hawthorn extract for treating chronic heart failure. *Cochrane Database Syst Rev* 2008; DOI: 10.1002/14651858.CD005312.pub2. Available at: <http://www.cochrane.org>.

In an attempt to determine the risk and benefit of hawthorn in patients with chronic HF, Pittler and colleagues through the Cochrane Collaborative conducted a systematic review of published and unpublished studies employing hawthorn extract for the management of patients with HF from 1952 to June 2006. Based on their inclusion criteria, which included randomized, placebo-controlled design, classification of all patients by NYHA class, appropriate clinical outcomes for HF and data reporting that allowed intention-to-treat analysis, a total of 1110 patients from 14 trials followed for up to 26 weeks were identified. Compared to placebo, administration of hawthorn extract appeared to significantly improve maximal workload (weighted mean difference ((WMD): +5.35 W,

95% confidence intervals (CI): 0.71 to 10.00, $p < 0.02$, $n = 380$) and exercise tolerance (WMD: +122 W x min (95% CI: 32.74 to 212.78, $p = 0.008$, $n = 98$) while reducing rate-pressure product (WMD: -19.22, 95% CI: -30.46 to -7.98, $p = 0.008$, $n = 264$) and symptom score (WMD: -5.47, 95% CI: -8.68 to -2.26, $p = 0.0008$, $n = 239$). Unfortunately, only one study reported deaths (three in active group versus one in the control group) without further details. The most common adverse effects reported were dizziness/vertigo and gastrointestinal intolerance. The authors concluded that based on their analyses hawthorn extract does have significant benefits when compared with placebo as an adjunctive treatment for patients with chronic HF. Unfortunately, data from the SPICE trial were not included in this systematic review as the study was still ongoing at time of analysis.

Holubarsch CJF, Colucci WS, Meinertz T, et al. The efficacy and safety of Crataegus extract WS 1442 in patients with heart failure: The Survival and Prognosis: Investigation of Crataegus Extract WS 1442 in CHF (SPICE) Trial. *Eur J Heart Fail* 2008;10:1255–63.

The SPICE trial conducted in 13 European countries randomized 2681 patients with NYHA class II-III HF and an LVEF $\leq 35\%$ to receive either hawthorn extract 900 mg daily (WS^a-1442) or placebo for two years. As with the HERB-CHF study, all participants received standard background HF drug therapy, which included diuretics in 85%, ACE inhibitors in 83%, beta blockers in 64%, glycosides in 57%, and aldosterone blockers in 39% of patients. The primary endpoint was time to first cardiac event defined as a composite of cardiac death (sudden death, death due to progressive HF, fatal myocardial infarction (MI)), non-fatal MI, or hospitalization due to progressive HF. Secondary endpoints consisted of all-cause mortality, death from cardiovascular causes, non-fatal MI, and hospitalization from progression of HF. Average time to first cardiac event was 620 days for those receiving hawthorn compared to 606 days for placebo (event rates: 27.9% versus 28.9%, respectively, hazard ratio (HR):0.95, $p = 0.476$). At 24 months, no significant difference was detected between groups with any of the secondary endpoints. However, in a subgroup of patients with LVEF between 25% to 35% ($n = 1139$), those patients receiving hawthorn did exhibit a reduction in sudden cardiac death by 39.7% when compared to placebo (event rate:

5.0% versus 8.3%, respectively, HR: 0.59, $p = 0.025$) at 24 months. This benefit was initially seen at 12 months and continued through 24 months of therapy. The rates of adverse events and of serious adverse events were about 68% and 40%, respectively, for both groups. While the SPICE trial was negative for its primary endpoint, it is noteworthy for reliably demonstrating that hawthorn can be safely added to background HF medication in patients with systolic dysfunction. Nonetheless, the role of hawthorn's efficacy is still debatable. Furthermore, analysis of the secondary outcomes may suggest that the supplement may reduce sudden cardiac death in patients with LVEF between 25 to 35%; however, it is difficult to draw any final conclusions on the basis of a subgroup analysis that was not a predetermined endpoint of the trial.

Horse Chestnut

Venous Insufficiency

Pittler MH, Ernst E. Horse chestnut seed extract for chronic venous insufficiency. *Cochrane Database Syst Rev* 2006; DOI: 10.1002/14651858.CD003230.pub3. Available at: <http://www.cochrane.org>.

The seed extract of horse chestnut (*Aesculus hippocastanum L.*) contains escin, a triterpenic saponin, as its active component. Escin had been shown to inhibit the activity of elastase and hyaluronidase, two enzymes involved in proteoglycan degradation. In patients with chronic venous insufficiency (CVI), activated leukocytes accumulate in affected limbs and release these two enzymes which in turn lead to pathophysiological damage. Oral horse chestnut seed extract (HCSE) has been suggested to curtail CVI through inhibition lysosomal enzymes from leukocyte activation. Current management of CVI consists of compression treatment which has been associated with discomfort and poor compliance, thus making oral therapies an attractive option. Pittler and colleagues through the Cochrane Collaborative conducted a systematic review of published and unpublished randomized controlled trials evaluating the safety and efficacy of oral mono-preparations of HCSE versus placebo or reference therapy for the treatment of CVI from 1966 to October 2005. From their literature, the investigators identified 14 trials consisting of 1501 patients with CVI. Compared to placebo,

administration of HCSE was associated with improvements in CVI related signs and symptoms, specifically edema (n=461, p<0.05), pruritus (n=407, p<0.05), and reduction in ankle (n=172) and calf (n=112) circumference and leg volume (n=502). Leg pain was assessed in seven placebo-controlled trials. Six studies (n=543) reported a significant reduction of leg pain through various measurement scales in patients taking HCSE compared to placebo, while another demonstrated an improvement compared with baseline. Regarding leg volume, one trial indicated that HCSE may be as effective as treatment with compression stockings. Of the 14 studies reporting adverse events, four studies found no treatment-related adverse events in those treated with HCSE, while six studies reported gastrointestinal complaints, dizziness, nausea, headache, and pruritus. Based on these data, the investigators found HCSE to be an effective and safe as a symptomatic short-term treatment for CVI; however, more rigorous large randomized controlled trials are needed.

L-Arginine

Chronic Heart Failure

Watanabe G, Tomiyama H, Doba N. Effects of oral administration of L-arginine on renal function in patients with heart failure. *J Hypertens* 2000;18:229–34.

Oral L-arginine (15g/day) was compared to placebo in this double-blind crossover trial to evaluate the supplements effects on renal function. NO, which may be produced by L-arginine supplementation, has been shown to regulate renal function. Seventeen HF patients (NYHA class II/III, mean EF 32%) were given 5 days of L-arginine or placebo then crossed over to the alternate therapy. Primary outcomes were 24-hour creatinine clearance and 24-hour urinary cyclic guanosine 5-monophosphate (GMP) excretion. Urinary sodium (UNa) and glomerular filtration rate (GFR) were also assessed before and after a saline load (1% saline 220 ml/h for 1 hour). Twenty-four hour GMP excretion (1.4 ± 1.1 vs 0.8 ± 0.5 mmol/day, p<0.01) and creatinine clearance (150 ± 43 vs 125 ± 42 ml/min, p<0.05) were significantly higher with L-arginine compared to placebo. Increase UNa (47 ± 12 % vs 34 ± 9 %, p<0.05) and GFR (44 ± 31 % vs 22 ± 29 %, p<0.01) after saline load was significantly higher in the L-arginine treatment group compared to placebo.

This reveals that L-arginine has beneficial effects on renal function in patients with chronic heart failure. These data are specifically important given the prognostic value of impaired renal function in acute and chronic HF and potentially offers a therapeutic option to improve kidney function in HF.

Hambrecht R, Hilbrich L, Erbs S, et al. Correction of endothelial dysfunction in chronic heart failure: Additional effects of exercise training and oral L-arginine supplementation. *J Am Coll Cardiol* 2000;35:706–13.

A randomized study of forty HF patients (Class II/III, mean EF 19%) compared the efficacy of 4 therapies on endothelium-dependent vasodilation. Patients were randomized to L-arginine (8 g/day) (L-arg), training with handgrips (T), L-arginine and handgrip training (L-arg + T), or inactive control (C) for 4 weeks. Mean internal radial artery diameter was measured at the beginning and end of the 4 week treatment period. To determine endothelial dependent versus endothelial independent vasodilation, acetylcholine (dependent) and nitroglycerin (independent) were administered. L-arg (8.8 ± 0.9 % increase, p<0.001), T (8.6 ± 0.9 % increase, p<0.001), and L-arg + T (12.0 ± 0.3 % increase, p<0.005) improved agonist-mediated endothelium dependent vasodilation compared to control. L-arg + T improved agonist-mediated endothelium dependent vasodilation compared to both L-arg and T alone (p<0.001). This provides further evidence that L-arginine may benefit patients with HF. It is still unclear why L-arginine is beneficial in HF, but not after MI. One mechanism may be that after MI, the body may be in a state of tetrahydrobiopterin deficiency. NOS then becomes a source of reactive oxygen species, which can be enhanced with L-arginine supplementation.

Coronary Artery Disease

Ceremuzynski L, Chamiec T, Herbaczynska-Cedro K. Effect of supplemental oral L-arginine on exercise capacity in patients with stable angina pectoris. *Am J Cardiol* 1997;80:331–3.

L-arginine is an amino acid substrate for nitric oxide synthase (NOS). NOS is the enzyme that produces nitric oxide (NO), a vasodilator. NO has been shown to reduce vascular stiffness. This randomized, double-blind, placebo controlled study investigated the acute effects of

L-arginine on exercise capacity. Twenty-two patients with stable angina were randomized to L-arginine 2 g three times daily for 3 days or placebo. An exercise test (treadmill with modified Bruce protocol) was performed at baseline and at day three. The primary endpoints were exhaustion, angina, or myocardial ischemia on ECG. Both placebo and L-arginine significantly increased mean exercise time to maximal ST-segment depression with the L-arginine increase being more prominent (placebo, 501 ± 101 sec to 555 ± 106 sec, $p < 0.004$; L-arginine, 531 ± 195 sec to 700 ± 173 sec, $p < 0.0002$). The maximum workload did not change significantly from baseline in the placebo group (5.0 ± 2 METs to 5.7 ± 2 METs, NS) whereas the L-arginine group significantly increased (6.4 ± 2 METs to 7.4 ± 3 METs, $p < 0.006$). This study demonstrates that L-arginine improves exercise tolerance in patients with stable angina and is a treatment option for those patients with chronic stable angina.

Blum A, Hathaway L, Mincemoyer R, et al. Oral L-arginine in patients with coronary artery disease on medical management. *Circulation* 2000;101:2160–64.

A double-blind, placebo controlled, crossover study was conducted in thirty patients with CAD to test the efficacy of L-arginine (3 g three times daily) on measures of vascular function. Serum nitrogen oxide levels (marker of nitric oxide release), flow-mediated brachial artery dilation, and serum cell adhesion molecules were measured at baseline and one month. Arginine serum levels (130 ± 53 versus 70 ± 17 mmol/L, $p < 0.001$) were elevated at follow-up compared to baseline, but nitrogen oxide levels (19.3 ± 7.9 versus 18.6 ± 6.7 mmol/L, $p = 0.546$), flow-mediated brachial artery dilation ($11.9 \pm 6.3\%$ versus $11.4 \pm 7.9\%$, $p = 0.742$), E-selectin (47.8 ± 15.2 versus 47.2 ± 14.4 ng/mL, $p = 0.601$), ICAM-1 (250 ± 57 versus 249 ± 57 ng/mL, $p = 0.862$), and VCAM-1 (567 ± 124 versus 574 ± 135 ng/mL, $p = 0.473$) were unchanged from baseline. This small study demonstrates that oral L-arginine did not improve these surrogate markers in CAD.

Maxwell AJ, Zapien MP, Pearce GL, MacCallum G, Stone PH. Randomized trial of a medical food for the dietary management of chronic stable angina. *J Am Coll Cardiol* 2002;39:37–45.

A randomized, double-blind, placebo controlled, crossover trial in thirty-six patients

with CAD and class II and III angina investigated the effects of L-arginine on flow-mediated brachial artery dilation, ECG measures of ischemia, exercise capacity, angina onset time on treadmill and measures of quality of life (SF-36 and Seattle Angina Questionnaire). L-arginine and placebo were given via a nutrient bar (2 bars per day) for two weeks then crossed over to the other therapy. Each active L-arginine nutrient bar contained 3.2 g of L-arginine and the placebo nutrient bar contained 0.59 g of L-arginine. The active nutrient bar also contained more vitamin C, vitamin E, niacin, vitamin B6, vitamin B12, folate, and soy isoflavones. The active group significantly improved flow-mediated dilation (5.5 ± 4.5 mm to 8.0 ± 4.9 mm, $p = 0.004$), treadmill exercise time (20% increase over placebo, $p = 0.05$), and quality of life scores (SF-36 68 ± 13 vs 63 ± 21 after placebo, $p = 0.04$; Seattle Angina Questionnaire 67 ± 10 vs 62 ± 18 , $p = 0.04$) compared to the placebo nutrient bar without significantly affecting the ischemic parameters on the ECG. These findings demonstrate that L-arginine improves several important endpoints in stable angina over a 2-week period and is a therapeutic option for class II/III angina.

Schulman SP, Becker LC, Kass DA, et al. L-arginine Therapy in Acute Myocardial Infarction: The Vascular Interaction with Age in Myocardial Infarction (VINTAGE MI) Randomized Clinical Trial. *JAMA* 2006;295:58–64.

This is the first clinical trial evaluating the effects of L-arginine in 153 patients with ST-segment elevation MI, VINTAGE MI. This double-blind, randomized, placebo controlled, single center study aimed to determine if L-arginine improves ejection fraction and decreases vascular stiffness over the 6 months after STEMI. L-arginine dosing was 1g three times a day for week 1, 2 g three times a day for week 2, then 3 g three times a day for the 6-month study period. The primary outcome of change in ejection fraction over 6 months in patients 60 years of age or older was no significantly different between the L-arginine group and placebo (-1.0% vs -1.0% , $p = 0.63$). Furthermore, there was no difference seen in ejection fraction or measures of vascular stiffness. The data safety monitoring committee stopped enrollment during the study because the L-arginine group had 6 participants die during the study period and no participants died in the placebo group. The mechanism of this is unknown. One potential explanation is

tetrahydrobiopterin, a cofactor for NOS. In the setting of tetrahydrobiopterin deficiency, NOS becomes a source of reactive oxygen species, which can be enhanced with L-arginine supplementation. Due to these findings, L-arginine should not be recommended following acute myocardial infarction.

L-Carnitine

Chronic Heart Failure

Rizos I. Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration. *Am Heart J* 2000;139:S120–S123.

L-carnitine performs a crucial role in myocardial energy production in the mitochondria and is a physiologic compound in humans. Eighty patients diagnosed with dilated cardiomyopathy and NYHA class III/IV symptoms were randomized to L-carnitine 2 g/day or placebo for a 3-month period (blinded). Then patients in the L-carnitine group and placebo group were unblinded but maintained on therapy and followed for a total of 3 years. The primary endpoint was a change in hemodynamic parameters at 3 months and death at three years. At 3 months, a significant difference in favor of L-carnitine was demonstrated in Weber classification, maximal time of cardiopulmonary exercise test, peak oxygen consumption, arterial and pulmonary blood pressure, and cardiac output. Survival at 3 years was lower in the L-carnitine group (3%) compared to the placebo group (18%) with the time to event analysis showing a significant difference between the two groups (Log-rank test, $p < 0.04$). L-carnitine was well tolerated in the study with only 3 patients with major gastrointestinal problems. This data suggests a clinical and survival benefit of L-carnitine in dilated cardiomyopathy with minimal side effects. The difficulty in interpreting these results is the small sample size, unblinding after 3 months, and lack of controlling for known factors that contribute to disease progression in HF. The use of L-carnitine in HF should be limited.

Coronary Artery Disease

Cherchi A, Lai C, Angelino F, et al. The effects of L-carnitine on exercise tolerance in chronic stable angina: a multicenter, double-blind, randomized, placebo controlled crossover study. *Int J Clin Pharmacol Ther Toxicol* 1985;23:569–72.

A multicenter, randomized, double-blind, placebo controlled crossover study investigated the effects of L-carnitine (2 g/day) on exercise tolerance. Forty-four men with chronic stable angina were randomized to L-carnitine or placebo for 4 weeks. The primary outcome was time to onset of angina, 1 mm of ST-depression, maximal work, and maximal workload during bicycle exercise test. Maximum exercise workload (102.7 ± 22.2 vs 97.1 ± 22.8 watts, $p = 0.001$), watts to onset of angina (95.7 ± 24.1 vs 87.4 ± 24.7 , $p < 0.0001$), and ST-depression at maximum common work (1.24 ± 0.9 mm vs 1.66 ± 0.8 mm, $p = 0.005$) was significantly improved in the L-carnitine group compared to placebo. This study demonstrates that L-carnitine improves exercise tolerance and decreases surrogate ECG markers of ischemia in chronic stable angina and is a potential treatment for chronic angina.

Iliceto S, Scrutinio D, Bruzzi P, et al, for the CEDIM investigators. Effects of L-carnitine administration on left ventricular remodeling after acute myocardial infarction: The L-carnitine Echocardiografia Digitalizzata Infarto Miocardico (CEDIM) trial. *J Am Coll Cardiol* 1995;26:380–7.

A randomized, double-blind, placebo controlled, multicenter trial was done to demonstrate the effects of L-carnitine on left ventricular remodeling after AMI. Four-hundred seventy-two patients were randomized to L-carnitine (9 g/day intravenously for 5 days, then 6 g/day orally) or placebo within 24 hours of onset of chest pain then continued for 12 months. Echocardiograms were performed on admission, at discharge, 3 months, 6 months and 12 months after the AMI. There were no significant differences found in the ejection fraction between the two groups at 12 months ($45.8 \pm 0.57\%$ vs $45.2 \pm 0.52\%$, $p = 0.46$). The percent increase in end-systolic (55.0 ± 1.63 ml vs 58.9 ± 1.75 ml, $p = 0.03$) and end-diastolic volumes (99.3 ± 2.06 ml vs 105.4 ± 2.37 ml, $p = 0.01$) were significantly reduced in the L-carnitine group compared to the placebo group at 12 months. No significant differences were seen in clinical endpoints (death, HF, unstable angina, or reinfarction) between the two groups. During the 12 months, there was no interruption in treatment from adverse events. This large clinical trial displayed a benefit of L-carnitine on some echocardiographic parameters after AMI, but further studies should be done before there is routine use of L-carnitine post-MI.

Singh RB, Niaz MA, Agarwal P, et al. A randomized, double-blind, placebo controlled trial of L-carnitine in suspected myocardial infarction. *Postgrad Med J* 1996;72:45–50.

This randomized, double-blind, placebo controlled trial evaluated the effects of L-carnitine for 28 days on infarct size. One-hundred and one patients with suspected MI were randomized to L-carnitine 2 g/day or placebo. Outcome measures were related to infarct size, measured by creatine kinase (CK), myoglobin CK (CKMB), and ECG QRS score. At the end of the 28 day follow-up, CK (95.5 ± 23.6 vs 116.2 ± 26.2 gram equivalents, $p < 0.01$), CKMB (58.6 ± 16.6 vs 73.3 ± 21.5 gram equivalents, $p < 0.01$), and ECG QRS score (7.4 ± 1.2 vs 10.7 ± 2.0 , $p < 0.01$) were significantly less in the L-carnitine group compared to placebo. Secondly, episodes of angina, NYHA class III/IV plus LV enlargement, and total arrhythmias were less in the L-carnitine group compared to placebo. These data demonstrate that L-carnitine reduces important post-MI surrogate markers and further studies should be done. Without large-scale clinical trials, the use of L-carnitine in MI should be limited.

Magnesium

Cerebrovascular accidents

Ascherio A, Rimm B, Hernan MA, et al. Intake of Potassium, Magnesium, Calcium, and Fiber and Risk of Stroke Among U.S. Men. *Circulation* 1998;98:1198–1204.

Animal studies as well as epidemiological studies have indicated that a diet high in potassium may reduce the risk of stroke. This benefit may be explained by a reduction in blood pressure but additional mechanisms have also been proposed. Some of these include inhibition of vascular smooth muscle proliferation, inhibition of free radical formation and a reduction in arterial thrombosis. However, the current body of evidence is inconclusive. Therefore, this study set out to test the hypothesis that a high level of potassium intake would reduce the risk of stroke. In addition to the association of potassium and stroke, associations between dietary magnesium, calcium and fiber related to stroke risk were also evaluated. A total of 43,738 men were eligible for the study and the stroke incidence was evaluated for 8 years. During the follow-up period, there were 328 cerebrovascular accidents

(50 fatal): 210 ischemic strokes, 70 hemorrhagic, and 48 unclassified. The results demonstrated that the multivariate relative risk of stroke of any type in men in the top fifth of potassium intake was significantly lower than compared to men in the bottom fifth ($p = 0.007$). The intake of fiber and magnesium were also inversely associated with stroke risk. However, this was not observed for calcium. These findings were stronger in men who were hypertensive than those who were normotensive. These data provide strong support for diets rich in potassium, cereal fiber, and magnesium, especially in hypertensive men.

Coronary Artery Disease

Abbott RD, Ando F, Masaki KH, et al. Dietary Magnesium Intake and the Future Risk of Coronary Heart Disease. (The Honolulu Heart Program). *Am J Cardiol* 2003;92:665–669.

A deficiency of magnesium is thought to play a role in some of the negative consequences of cardiovascular disease. Some studies have suggested that low magnesium may have effects on diabetes, hypertension, atherosclerosis, and sudden cardiac death. However, the relationship between magnesium deficiency and the risk of future cardiac events has not been fully evaluated. This study involving 7,172 men in the Honolulu Heart Program sought to examine this particular relationship. Magnesium intake was recorded at baseline at the time of study enrollment that took place between 1965 and 1968. The age of the subjects at the time of enrollment was between 45 and 68 years of age. Follow-up data was available on each subject for up to 30 years. Coronary Heart Disease (CHD) included fatal coronary events and nonfatal myocardial infarction. The relationship between magnesium intake (obtained by a dietitian based on a 24 hour dietary recall) and the incidence of future coronary heart disease, age-adjusted incidence of coronary heart disease was provided across quintiles of magnesium intake using standard analysis of covariance procedures and logistic regression. Proportional hazards regression models were used to provide estimates of the relative risk in each of the lowest 4 quintiles of magnesium intake versus the highest quintiles. The results showed that 1,431 developed coronary heart disease in the 30-year follow-up period with an average age of occurrence of 72. Overall, age-adjusted incidence of CHD decreased consistently with

increasing quintiles of magnesium intake. Within the first 15 years of follow-up, there was a 1.8 fold excess of CHD in the lowest quintile compared to the highest, even when adjusted for other cardiovascular risk factors ($p < 0.05$). However, the association beyond the 15-year follow-up period was less substantial. Based on these marginal results, it indicates that further study is still needed to determine if association between dietary magnesium and cardiovascular risk truly exists.

Omega-6 Polyunsaturated Fatty Acids

Cardiovascular Disease

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;119:902–7.

This document is a review of the evidence regarding the cardiovascular safety of omega-6 polyunsaturated fatty acids (PUFAs – primarily linolenic acid) intake. Current recommendations for dietary omega-6 consumption vary by region, but range from 3–10% of the total recommended caloric intake. Typically, Western diets contain much higher levels of omega-6 PUFAs as they are abundant in grain and protein sources. Recent nutritional and dietary societies have called for reductions in the consumption of linolenic acid as it serves as one of the principal sources for the production of arachidonic acid, a major substrate for reactive oxygen species in the body which may contribute to harmful proinflammatory and procoagulable conditions. However, arachidonic acid also produces a variety of anti-inflammatory, anti-aggregatory, and vasodilatory compounds. In addition, variations in linolenic acid dietary consumption have not been shown to alter arachidonic acid concentrations in the body as it appears this process is significantly regulated. Consistent with this, translational and clinical studies of arachidonic acid supplementation have actually demonstrated anti-inflammatory properties and neutral effects on platelet aggregation. Higher dietary intake of omega-6 PUFAs (up to 12%) is also associated with favorable effects on cholesterol levels, including LDL. In addition to mechanistic and biomarker studies, observational and cohort studies have

also demonstrated that higher consumption of omega-6 PUFAs is associated with lower rates of cardiovascular disease. Several randomized comparisons of higher omega-6 PUFA intake have also been conducted. While these trials are limited by the inability to utilize proper blinding techniques in addition to small sample sizes, a meta-analysis of 6 of these trials demonstrated a 24% RRR in the onset of coronary heart disease with higher omega-6 PUFA intake (ranging from 11% to 21% of the total daily caloric intake). While arguments to reduce the dietary intake of omega-6 PUFAs typically revolve around attempting to simultaneously increase levels of omega-3 PUFA consumption (known to be beneficial in cardiovascular disease), this advisory determined that reductions in omega-6 PUFAs to accomplish this goal may inadvertently increase cardiovascular events instead of producing a positive overall benefit on the world's cardiovascular health.

Policosanol

Dyslipidemia

Chen JT, Wesley R, Shamburek RD, et al. Meta-analysis of natural therapies for hyperlipidemia: Plant sterols and stanols versus policosanol. *Pharmacotherapy* 2005; 25: 171–83.

Policosanol is a mixture of aliphatic primary alcohols which are extracted from sugarcane (*Saccharum officinarum L*) wax, which has been used for reduction of low density lipoprotein cholesterol (LDL-C) concentrations in over 25 different countries, mainly the Caribbean and South America. Its major components consists of octacosanol (62.9%), tricothanol (12.6%), and hexacosanol (6.2%). Other plant-derived agents used for their LDL-C lowering abilities are the sterols, which are naturally occurring cholesterol derivatives from vegetable oils, nuts, soy, corn, woods, and beans, and the stanols, which result from the hydrogenation of plant sterols. Phytosterols is used to describe both sterols, stanols and their esters. Both stanols and sterols are believed to have comparable LDL-C - lowering efficacy and are endorsed by the National Cholesterol Education Program adult Treatment Panel (2 g/day) as an essential feature of therapeutic lifestyle modification in patients. Within this systematic review and meta-analysis, Chen and colleagues evaluated a total of 4,596 patients from 52 studies published between January 1967–June 2003. Study inclusion

consisted of the following: LDL-C concentrations were reported, treatment duration of four weeks or longer, and dosages of plant sterol and stanol equivalents of 2 g/day or greater or policosanol 5 mg/day or greater. [Based on 23 studies, phytosterols 3.4 g/day (range 2–9 g/day) reduced LDL by 11.0% in 893 patients versus a 2.3% reduction in 769 patients receiving placebo ($p < 0.0001$). In comparison, there was a 23.7% reduction for policosanol 12 mg/day (range 5–40 mg/day) in 1528 patients versus a 11% reduction in 1406 patients receiving placebo ($p < 0.0001$).] The net LDL reduction in the treatment groups minus that in the placebo groups was greater with policosanol than with phytosterols (24% vs 10%, respectively, $p < 0.0001$). While the authors concluded that both phytosterols and policosanol appear to be well-tolerated and safe, policosanol may be more effective at lowering LDL concentrations. This is the first systematic review to evaluate the potential role of policosanol in the management of hyperlipidemia.

Berhold HK, Uverdorben S, Degenhardt R, et al. Effect of policosanol on lipids levels among patients with hypercholesterolemia or combined hyperlipidemia: A randomized controlled trial. *JAMA* 2006; 2262–69.

As demonstrated in the meta-analysis by Cheng and colleagues, initial studies with policosanol appeared to have excellent efficacy in reducing LDL-C concentrations when compared to placebo and phytosterols with minimal side effects. Unfortunately, there are some limitations as (1) many of these earlier studies were authored by a single research group based in Havana, Cuba; (2) used a form of policosanol manufactured by a single company in Cuba; and (3) primarily included patients of Hispanic origin. With this in mind, there existed a need to independently verify these findings. Berthold and colleagues attempted to determine the lipoprotein lowering effects of policosanol and establish a possible dose-dependency effect of the agent. The study was a multi-center, randomized, double-blind, placebo-controlled, parallel-group trial conducted in Germans with hypercholesterolemia defined as an LDL-C concentrations of at least 150 mg/dl. Patients had either no or one cardiovascular (CV) risk factor other than coronary heart disease (CHD), or based line LDL-C concentrations between 150–189 mg/dl with two or more CV risk factors. The intervention consisted of an open-label six-

week placebo run-in phase followed by a double-blind 12-week treatment phase after randomization to one of five groups: 10 mg/day ($n=28$), 20 mg/day ($n=27$), 40 mg/day ($n=27$), or 80 mg/day ($n=32$) of policosanol or placebo ($n=29$). Upon completion of the study, no statistically significant difference existed between treatment groups regarding LDL-C, high density lipoprotein cholesterol (HDL-C), triglycerides, lipoprotein(a), and the ratio of total LDL and HDL. While the agent was well tolerated with no effects on weight, vital signs, or routine blood chemistry and hematological laboratory parameters, the investigators concluded that policosanol did not demonstrate a significant reduction in lipid levels when compared to placebo and that a dose-response did not exist. This was one of the first robust studies to demonstrate negative results with policosanol.

Cubeddu LX, Cubeddu RJ, Heimowitz T, et al. Comparative lipid lowering effects of policosanol and atorvastatin: A randomized, parallel, double-blind, placebo-controlled trial. *Am Heart J* 2006; 152: 982.e1–982.e5.

This study was the first U.S. trial to evaluate the efficacy of policosanol when given alone and in combination with atorvastatin in patients with dyslipidemia. In a randomized, parallel, double-dummy, placebo-controlled trial, Cubeddu and colleagues assigned patients with LDL-C concentrations from 140–189 mg/dl to receive either daily policosanol 20 mg ($n=25$), atorvastatin 10 mg ($n=25$), combination therapy ($n=25$), or placebo ($n=24$) for 12 weeks. As with the previous study, policosanol 20 mg daily did not significantly change total cholesterol, LDL-C, HDL-C, or triglyceride concentrations when compared to baseline values or with values of placebo-treated patients. Furthermore, the combination of policosanol with atorvastatin had no additional lipid-lowering effect when compared to atorvastatin alone. Policosanol was well tolerated and did not increase liver enzymes or creatinine phosphokinase concentrations. While the investigators concluded that additional rigorous studies are still needed, they commented that their data added to the current literature that policosanol appears to lack scientific validity for its use in the management of dyslipidemia.

Pomegranate

Atherosclerosis

Aviram M, Rosenblat M, Gaitini D, et al. Pomegranate juice consumption for three years by patients with carotid artery stenosis reduces common carotid intima-media thickness, blood pressure, and LDL oxidation. *Clin Nutr* 2004;23:423–33.

The fresh juice of the pomegranate fruit has been found to contain pectin, ascorbic acid and polyphenolic flavonoids, which consist of anthocyanins, catechins, ellagic tannins, and gallic acids. All of these components are believed to possess potent antioxidant activity that have been associated with antiatherogenic properties as well as inhibit cyclooxygenases and lipoxygenases in healthy human and animal models. Based on this preliminary pharmacological evidence, Aviram and colleagues in a placebo-controlled, observational cohort study investigated the effects of freshly squeezed and pasteurized pomegranate juice on progression of carotid lesions, changes in oxidative stress and blood pressure in 19 asymptomatic patients with severe carotid artery stenosis (CAS) defined as 70–90% stenosis in the internal carotid arteries. Ten patients consumed 50 ml per day of pomegranate juice for one year and five of the ten continued for up to three years. The remaining nine patients received placebo for one year. Compared to the control group, those receiving pomegranate juice for up to one year demonstrated a significant reduction in common carotid intima-media thickness (CIMT) (9% versus 30%, $p < 0.01$). Pomegranate juice consumption did not significantly affect serum glucose; HDL-C; LDL-C; homocysteine; total protein; lipoprotein(a); blood cell count, markers for coagulation, or markers for heart, kidney and liver function but did increase serum triglycerides by 16%. Compared to baseline, patients systolic blood pressure was significantly ($p < 0.05$) reduced after one (174 ± 8 mmHg vs 162 ± 9 mmHg), three (174 ± 8 mmHg vs 155 ± 9 mmHg), six (174 ± 8 mmHg vs 157 ± 8 mmHg), nine (174 ± 8 mmHg vs 157 ± 5), and 12 months (174 ± 8 mmHg vs 153 ± 7 mmHg) respectively. In contrast, no effect was seen in patients' diastolic blood pressure. Compared to baseline, those exposed to pomegranate juice had a significantly reduced serum LDL basal oxidative state and LDL susceptibility to copper ion-induced oxidation by 90% and 59% respectively

after one year. Furthermore, serum levels of antibodies against oxidized LDL were decreased by 19% and in parallel serum total antioxidant status was increased by 130% after one year in the treatment group. While no additional benefits were seen in CIMT after one year of pomegranate juice exposure, serum lipid peroxidation was further reduced by 16% after three years. The investigators concluded that continued consumption of pomegranate juice for up to one year could decrease CIMT and systolic blood pressure in patients with CAS. However, these data must be tempered by the large volume of juice that must be consumed, the increase in serum triglycerides, and the time necessary to prepare freshly squeezed juice.

Dyslipidemia

Esmailzadeh A, Garideh T, Gaieni I, et al. Concentrated pomegranate juice improves lipid profiles in diabetic patients with hyperlipidemia. *J Med Food* 2004; 7: 305–8.

In this eight-week quasi-experimental study, Esmailzadeh and colleagues administered 40 g/day of pomegranate juice to 22 patients with type 2 diabetes and dyslipidemia defined as a total cholesterol ≥ 200 mg/dl or triglycerides ≥ 204 mg/dl. The patients were followed for eight weeks before beginning the study so as to establish a baseline for normal dietary intake. In contrast to the study by Aviram and colleagues, significant reductions were seen in the following parameters compared to baseline: total cholesterol (4.94 ± 0.54 mmol/L vs 5.23 ± 0.71 mmol/L, $p < 0.006$), LDL-C (2.89 ± 0.66 vs 3.18 ± 0.81 , $p < 0.006$), LDL-C/HDL-C (5.09 ± 1.1 vs 5.5 ± 1.3 , $p < 0.001$), and total cholesterol/HDL-C (3.00 ± 0.9 vs 3.4 ± 1.2 , $p < 0.001$). No significant changes were seen in serum triglycerides or HDL-C concentrations. Anthropometric indices, physical activity, type and doses of oral hypoglycemic agents, and intake of nutrients and flavonoid-rich foods showed no change during the study period. The authors concluded that the addition of pomegranate juice could modify heart disease risk factors in patients with hyperlipidemia and diabetes. As these data are conflicting with the findings from the previous study, additional data from larger studies are needed to fully elucidate the impact of pomegranate juice on dyslipidemia and clinical outcomes. However, this is the first and only study evaluating the use of pomegranate juice in patients with diabetes.

Hypertension

Aviram M, Dornfeld L. Pomegranate juice consumption inhibits serum anigotensin converting enzyme acitivity and reduces systolic blood pressure. *Atherosclerosis* 2001;158:195–198.

Hypertension is a known risk factor for the development of atherosclerosis and in hypertensive patients with elevated plasma renin-angiotensin activity, a five-fold increase incidence of MI has been reported. Presently, some antioxidants such as vitamin C, vitamin E, beta-caroteone, and coenzyme Q have demonstrated antihypertensive properties. As pomegranate juice possess very potent antioxidants, Aviram and colleagues evaluated the effects of 50 ml/day of pomegranate juice consumption for two weeks on blood pressure and on serum ACE activity in ten patients with hypertension. Of the study participants, the mean blood pressure levels were $155 \pm 7/83 \pm 7$ mmHg. In seven of the ten patients, serum ACE activity was significantly reduced by 36% compared to baseline (p value not reported). The investigators attributed this effect secondary to pomegranate juice's antioxidant properties and/ or a possible direct inhibition of ACE activity. In an in vitro analysis, a dose-dependent inhibitor effect (up to 31%) on serum ACE activity was also observed. Regarding blood pressure, pomegranate juice exposure was associated with a 5% reduction in systolic blood pressure compared to baseline ($p < 0.05$). Based on these findings, the authors concluded that the significant inhibitory effect of pomegranate juice on serum ACE activity and the minor attenuation in blood pressure could offer a wide protection against cardiovascular disease. As these data along with Aviram and colleagues previous study are with naturally prepared pomegranate juice, it is difficult to extrapolate these findings to store bought pomegranate products.

Red Yeast Rice

Dyslipidemia

Wang J, Lu Z, Chi J, et al. Multicenter clinical trial of the serum lipid-lowering effects of a *Monascus purpureus* (red yeast) rice preparation from traditional chinese medicine. *Curr Ther Res.* 1997;58(12):964-78.

Red-yeast rice, a naturally fermented rice product originating from China, has been employed in alternative medicine practices for

centuries. It contains a wide variety of plant sterols and monacolin compounds which inhibit HMG-CoA reductase, including at least some percentage of the drug lovastatin.

This was the first human, multicenter study of the effects of red-yeast rice on lipid parameters. A total of 502 Chinese patients were randomized to receive either *M. purpureus* (n=324) formulation at 0.6 gm twice daily or to an alternate Chinese herbal medicine, Jiaogulan (*G. Pentophylla*) (n=122) at 1.2 gm/day for 8 weeks. Fifty-six patients did not complete the trial. Patients were eligible for inclusion if their total cholesterol was in excess of 230 mg/dL, LDL \geq 130 mg/dL, TG 200–400 mg/dL, or HDL was \leq 40 mg/dL for men or \leq 45 mg/dL for women. Patients underwent a 4 week wash-out period of any hyperlipidemic medications and received dietary advice 2-4 weeks prior to the study. Of note, these lipoparticle reductions were only measured in patients found to be hyperlipidemic according to the above inclusion criteria. After 8 weeks, patients randomized to receive the red-yeast rice formulation had a 22.7% reduction in TC relative to baseline (mean -62.8 mg/dL, $p < 0.001$) compared to a 7.0% reduction (mean -18.9 mg/dL, $p < 0.001$) in the Jiaogulan group. Beneficial effects on LDL (24.6% reduction, mean -45.9 mg/dL, $p < 0.001$), HDL (12.8% increase, mean +4.5 mg/dL, $p < 0.001$), and TG (34.1% reduction, mean -94.1 mg/dL, $p < 0.001$) were found after 8 weeks of treatment with red-yeast rice relative to baseline. With regard to safety, no patients in either group were found to have an increase in ALT greater than twice the upper limit of normal. One patient receiving red-yeast rice (0.3%) had an elevation in creatine kinase $>$ 2.5 times the upper limit of normal. These data support the ability of red-yeast rice to improve lipid profiles. However, the study was performed exclusively in a Chinese population, allowing no extrapolation of the benefits or safety to other populations. Additionally, the investigation was not blinded to investigators. There was also no assessment of the ability of red-yeast rice to reduce cardiovascular events or stroke, likely due to limited size and follow-up.

Heber D, Yip I, Ashley JM, et al. Cholesterol-lowering effects of a proprietary Chinese red-yeast-rice dietary supplement. *Am J Clin Nutr.* 1999;(2):231–6.

This study was a randomized, double-blind, placebo controlled trial examining the effects of red-yeast rice on lipid parameters in 83 U.S.

patients with hyperlipidemia. Subjects with an LDL cholesterol > 159.3 mg/dL and triglyceride levels < 260.0 mg/dL were eligible for inclusion and underwent a 1 week run-in phase to assess compliance. Dietary counseling was also provided to all subjects enrolled in the trial. Patients included in the trial were then randomized to receive either 2.4 gm per day of red yeast rice or placebo. Lipid profiles were drawn 8, 9, 11, and 12 weeks after randomization. The primary endpoint was change in total cholesterol at week 8 and week 12 relative to baseline and the control group. At week 8, patients randomized to receive red yeast rice (n=42) had significantly lower total cholesterol than those receiving placebo (208.0 ± 30.9 mg/dL vs. 254.1 ± 36.0 mg/dL, $p < 0.05$) which was maintained through week 12 (210.0 ± 30.9 mmol/L vs. 250.2 ± 40.0 , $p < 0.05$). Significant reductions were also detected in LDL cholesterol relative to placebo at week 8 (134.2 ± 27.1 vs. 179.0 ± 32.1 , $p < 0.05$, a 25.1% reduction) which also persisted through week 12. No serious adverse events were identified throughout the study. However, only liver function tests were analyzed; there was no assessment of creatine kinase levels. These data support the beneficial effects of red yeast rice on cholesterol. However, there is no data extrapolating these beneficial effects to clinical cardiovascular events. Given the strong data supporting the use of HMG-Co-A reductase inhibitors in this area, of which red yeast rice contains a significant number of similar compounds, this extrapolation may be reasonable. However, appropriately powered studies examining clinically meaningful endpoints are needed.

FDA Warns Consumers to Avoid Red Yeast Rice Products Promoted on Internet as Treatments for High Cholesterol Products Found to Contain Unauthorized Drug.
<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108962.htm>

While red-yeast rice contains a variety of compounds which may affect cholesterol homeostasis, commercially available products have also been found to contain variable amounts of the HMG-CoA inhibitor lovastatin (also known as monacolin K), which can be produced under certain fermentation conditions of the rice. On May 20th, 1998, the U.S. Food and Drug Administration (FDA) announced that since available dietary supplements were found to

contain lovastatin, they were therefore subject to regulation by the FDA and were being illegally marketed. While this decision was initially overturned by the 10th Circuit Court of Appeals on July 21, 2000, it was later upheld by the U.S. District Court on March 30th, 2001. Following this decision, a reformulation of red yeast rice took place which removed monacolin K and the supplement continued to be available. However, the FDA has since released this statement calling for the removal of certain red-yeast rice products which were found to contain more than 5 mg of lovastatin per dose due to potential for muscle related side effects such as rhabdomyolysis and concern over drug interactions with existing therapies. While the efficacy of statins in the prevention of cardiovascular disease is unquestioned, the effectiveness of a reformulated red-yeast rice supplement with only trace amounts of lovastatin has not been established and should not be used routinely as an alternative to statin therapy.

Lu Z, Kou W, Du B, et al. Effect of Xuezhikang, an extract from red yeast Chinese rice, on coronary events in a Chinese population with previous myocardial infarction. *Am J Cardiol.* 2008;101(12):1689–93.

While the lipid lowering effects of red yeast rice have been well documented along with the reduction in cardiovascular events associated with statin therapy, the effects of red yeast rice on clinical outcomes have not been determined. This study was a randomized, double-blind, placebo controlled, multicenter trial in China investigating the use of Xuezhikang (XZX), a purified extract of red-yeast rice containing lovastatin, lovastatin hydroxyl acid, and ergosterol, among other components. Subjects were eligible for enrollment if they had a documented myocardial infarction in the previous 60 months, with a total cholesterol concentration of 170-250 mg/dl and triglycerides of ≤ 400 mg/dl. A total of 4,870 patients (age 18-70) were included in the trial and randomized to receive XZX (300 mg twice daily) or placebo following 4 weeks of washout from previous lipid lowering therapy and a diet control period. The primary endpoint of the trial was the occurrence of a major coronary event (nonfatal MI, or death from coronary or cardiac causes). After a mean duration of treatment of 4.5 years, the trial was terminated after the second interim analysis. This was due to a highly significant reduction in the primary endpoint for patients randomized to

receive XZX (5.7% vs. 10.4%, $p < 0.001$). Additionally, multiple secondary endpoints favored the use of XZX, including reductions observed in death from cardiac causes (4.3% vs. 6.1%, $p=0.005$), all-cause mortality (5.2% vs. 7.7%, $p=0.0003$), coronary revascularization (2.8% vs. 4.2%, $p=0.004$), and cancer-related mortality (5.2% vs. 7.7%, $p=0.0003$). Detailed discussion on adverse events was not presented beyond the fact that both treatments were well tolerated and that mild increases in creatine kinase and serum transaminases were observed in both groups. While the results of this trial strongly mirror those of secondary prevention trials with statin drugs, some questions remain regarding the use of red-yeast rice in cardiovascular prevention. First, while the purified extract used in this trial contains at least some concentration of lovastatin, it is unknown what percentage of benefit observed in this trial can be partially or wholly attributed to the statin drug alone. Second, as the trial was performed in a Chinese population, the results can not necessarily be extrapolated to Western or other ethnic populations. Lastly, the results observed with a purified form of red-yeast rice in this trial may not generalize to all formulations of red-yeast rice.

Resveratrol

Coronary Artery Disease

St. Leger AS, Cochrane AL, Moore F. Factors associated with cardiac mortality in developed countries with particular reference to the consumption of wine. *Lancet* 1979;1:1017–20.

This landmark ecologic study attempted to explain the “French paradox” of low mortality combined with a high cholesterol diet in France. The relationship between population-based, age-specific ischemic heart disease-related mortality in men from 18 developed countries and wine consumption per country was examined. This study found a significant, strong and specific negative association between wine consumption and ischemic heart disease deaths, with France having the highest wine consumption and the lowest mortality per one-thousand men. This study led researchers to find a specific compound in wine that would be protective against cardiovascular mortality. Since this study, compounds isolated from wine, particularly, resveratrol and more recently, procyanidins have been investigated for their potential therapeutic benefits.

Opie LJ, Lecour S. The red wine hypothesis: from concepts to protective signaling molecules. *Eur Heart J* 2007;28:1683–93.

Resveratrol is a polyphenol found principally in the skin of grapes. Red wine is a rich source of resveratrol and it is proposed that benefits of red wine may be achieved by ingesting resveratrol.

This article reviews the evidence for and against the “red wine hypothesis”. Although its main purpose is to compare the evidence of red versus white wine in conferring cardiovascular benefits, it contains an extensive review of the scientific literature on resveratrol. Most of the resveratrol literature is based on small animal or cellular studies and this is reviewed and summarized. This article also reviews specific beneficial mechanisms and pharmacokinetics of resveratrol that have been evaluated to date, which will assist the reader with better understanding of its potential pharmacological effects and possible links to positive clinical outcomes.

Soy Protein and isoflavones

Coronary Artery Disease and Dyslipidemia

Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med* 1995;333:276–82.

Prior to the publication of this meta-analysis in 1995, it was well accepted that replacement of animal protein with vegetable protein in the diet was associated with a lower risk of coronary heart disease. Reasons for this association focused on a decrease in cholesterol levels with this dietary switch. In particular, animal data demonstrated a significant cholesterol lowering effect of soy protein intake. However, clinical trial data in humans at this time demonstrated a mixed effect on serum lipid concentrations with substantial soy protein intake. Therefore the authors conducted a meta-analysis of current available controlled human trials to increase statistical power in evaluating the effects of soy protein on serum lipid concentrations. Thirty-eight clinical studies were included in the meta-analysis. Average soy protein intake was 47 grams per day with a variety of sources used to deliver the daily protein supplement. Most studies attempted to standardize intake of total and saturated fat. Soy protein intake resulted in a 9.3% reduction in total cholesterol, a 12.9% reduction in LDL cholesterol, and a 10.5% decrease in serum triglyceride levels.

HDL and VLDL cholesterol were not affected significantly. Interestingly the level of reduction seen with soy protein intake was directly related to the baseline levels of lipid fractions, with larger reductions seen when baseline levels were more elevated. However, there was no dose response noted with soy protein intake. This investigation was important as it crystallized for the first time the effect of soy protein intake on lipoprotein fractions, and was part of the rationale for the 1999 FDA approval that soy protein containing foods are protective against coronary heart disease. Specifically, the FDA stated that the ingestion of 25 grams a day of soy protein, as part of a healthy diet, may lower the risk of heart disease.

Weggemans RM, Trautwien EA. Relation between soy-associated isoflavones and LDL and HDL cholesterol concentrations in humans: a meta-analysis. *Eur J Clin Nut* 2003;57:940–946

While the Anderson meta-analysis from 1995 did establish overall benefits of soy protein, no dose response was detected. One possible explanation put forward was the variable levels of isoflavones contained in the various soy preparations used in clinical trials. It was postulated that soy protein supplements that contain high levels of isoflavones would lower cholesterol levels, thereby implicating isoflavones as the active cholesterol-lowering ingredient. The authors conducted this meta-analysis with the intent to specifically address whether variations in isoflavone content in soy protein preparations was directly correlated to the level of cholesterol reduction in clinical trials. The authors identified 10 well-controlled studies to be included in their analysis. The main finding of the trial found that the LDL decreases or HDL increases observed in clinical trials were independent of isoflavone content in the soy protein administered. Overall, the conclusions of this analysis coincided with findings from individual trials, as well as similar combined analyses that isoflavone content has no effect on the magnitude of cholesterol reduction. Furthermore, the active component responsible for the lipid lowering effects of soy still remain to be identified. However, this analysis did reinforce the overall concept that soy protein intake can have favorable effects on cholesterol levels although the magnitude of effect was substantially smaller than what was seen in the 1995 meta-analysis by Anderson, et al. (approximately 3% average reduction of LDL cholesterol within a wide range of intake).

Sacks FM, Lichtenstein A, Van Horn L, et al. Soy Protein, Isoflavones, and Cardiovascular Health. An American Heart Association Science Advisory for Professionals From the Nutrition Committee. *Circulation* 2006;113:1034–1044

This AHA Scientific Advisory released in 2006 was a pivotal document in forming the current perspective on soy protein intake for health promotion. The authors recount the history of soy by revisiting the 1999 FDA recommendation for 25 grams of soy protein intake daily, as well as a subsequent recommendation from the AHA Nutrition Committee in the year 2000 in favor of soy protein intake for CVD prevention. Subsequent to these recommendations, many well-controlled studies were conducted that improved the knowledge base regarding soy protein supplementation. As such the authors of this analysis were able to conduct a revised overview of existing clinical data which drove an updated recommendation regarding the use of soy for cardiovascular health promotion. In incorporating newer clinical trial data into the assessment of the effect of soy protein on cholesterol levels, the authors found that LDL concentrations were reduced when soy protein with isoflavones were used, but that the average treatment effect was only 3%. This value was substantially lower than previous estimates of 12.9%. A likely explanation of these discordant results is the lack of quality controlled trials upon which the 1995 meta-analysis was based. In addition there was no difference in effect when considering the isoflavone content of soy products, or when considering the baseline cholesterol levels, which was different from the Anderson meta-analysis in 1995. There were no significant effects noted on HDL, triglycerides, lipoprotein(a), or blood pressure. In addition to noting no beneficial effects for other disease states, such as postmenopausal bone loss prevention, the current analysis led the AHA to change their previous recommendation. Here the specific use of isoflavone supplements in food or pills is not recommended for health promotion. However, they do state that soy products overall may be beneficial due to the high content of polyunsaturated fats, high fiber content, as well as the presence of beneficial vitamins and minerals. A beneficial effect on health may especially be noted if soy protein intake is used to replace animal protein sources high in saturated fat and cholesterol.

Kokubo Y, Iso H, Ishihara J, et al. Association

of dietary intake of soy, beans, and isoflavones with risk of cerebral and myocardial infarctions in Japanese populations. The Japan Public Health Center-Based (JPHC) Study Cohort I. *Circulation* 2007;116:2553–2562

Previous investigations with soy protein have primarily focused on their effect on cardiovascular risk factors, specifically, lipid levels. However, few investigations have looked at the effect on the development of CAD, or prevention of hard cardiovascular outcomes. In the case of soy protein, due to the presence of beneficial constituents such as high fiber, vitamins, and unsaturated fatty acids, it is possible that beneficial effects on cardiovascular outcomes may be seen without large changes in cholesterol levels. This prospective cohort study of 40,462 Japanese men and women assessed the effect of soy and isoflavone intake on the incidence of both stroke and myocardial infarction. As compared to individuals who self-reported soy intake only 0 to 2 times per week, those who ingested soy ≥ 5 times per week had a reduced risk of stroke (HR 0.64, 95% CI 0.43–0.95), cardiovascular disease mortality (HR 0.31, 95% CI 0.13–0.74), as well as a downward trend for the incidence of MI (HR 0.55, 95% CI 0.26 – 1.09). In addition, there was an inverse association between the level of isoflavone intake and the incidence of MI and stroke, in other words a dose-response was observed. However, the benefit in women was confined to those who were postmenopausal, and there were no observed benefits in men regardless of age. Potential mechanisms of benefit in postmenopausal women include antioxidant effects of isoflavones, polyunsaturated fatty acid intake, as well as estrogen-like effects. Despite the benefits observed in this cohort analysis, further research is needed to better quantify the effects of soy protein or isoflavone intake on hard cardiovascular outcomes.

Stanols/sterol esters

Dyslipidemia

Katan MB, Grundy SM, Jones P, et al. for the Stresa Workshop Participants. Efficacy and Safety of Plant Stanols and Sterols in the Management of Blood Cholesterol Levels. *Mayo Clin Proc.* 2003;78:965–978.

Therapeutic lifestyle changes including diet, exercise, and weight loss are considered the backbone of therapy for the management of

patients with lipid abnormalities or those at risk for the development of coronary heart disease. A modification to diet that incorporates foods that contain plant sterols and stanols can significantly modify cardiovascular risk and can enhance low density lipoprotein cholesterol (LDL-C) lowering even in patients already on LDL-C lowering agents such as the HMG-CoA reductase inhibitors. This review article is considered the commensurate reference for plant sterols and stanols. The deliberations of 32 thought leaders in lipids, nutrition, and heart disease are summarized in this document. It provides an excellent background on the sterols and stanols, including their absorption, where they are hydrolyzed, and their proposed mechanism for how they lower cholesterol. The article discusses the efficacy of stanols and sterols based on 41 trials that were identified through a MEDLINE search. A comprehensive reference list of these studies is also provided. Additional aspects covered in this section include; frequency of dosing, portion sizes needed, if the effect is additive to those of diet and cholesterol lowering agents, and if plant sterols and stanols reduce CHD risk. The safety of plant stanols and sterols as well as where future research is needed are also discussed in detail. Based on available data, the panel recommended the consumption of 2 grams daily of sterols and stanols for a 10% LDL-C reduction, and a 20% reduction in lifetime risk of CHD. In addition, the incorporation of stanols and sterols into the daily diet are recognized as safe and the risk of adverse effects extremely low. It is the feeling of these experts that there is sufficient evidence exists to support these recommendations.

De Jong A, Plat J, Mensink RP. Metabolic effects of plant sterols and stanols (Review). *J Nutri Biochem.* 2003;362–369.

Lowering LDL-C is known to be associated with a decrease in cardiovascular events. In addition, lower LDL-C can be achieved through therapeutic lifestyle changes such as diet. One such dietary modification can be the incorporation of plant sterols and stanols. Plant sterols and stanols cannot be synthesized by humans and the only way to obtain them is through dietary consumption. This review article initially describes a different aspect of cholesterol metabolism including cholesterol absorption and lipoprotein metabolism. It further describes plant sterol and stanol metabolism, their effects on intestinal cholesterol

absorption and lipid and lipoprotein metabolism as well as their effect on atherosclerosis development and regression. The final segment of this article discusses the role of plant sterols and stanols on many other metabolic processes in the human body. These include effects on fat soluble antioxidants, membrane properties, the immune system, and their effects on colon and prostate cancer.

Cater NB, Garcia-Garcia AB, Vega GL, Grundy SM. Responsiveness of Plasma Lipids and Lipoproteins to Plant Stanol Esters. *Am J Cardiol.* 2005;96(Suppl):23D–28D.

The incorporation of plant stanols and sterols into the daily diet has been shown to reduce LDL-C cholesterol. The addition of these substances is an attractive alternative, especially in those unable to tolerate cholesterol lowering agents or who want to try and reduce their levels through diet prior to initiating drug therapy. This study set out to answer three questions, 1) if higher doses of plant sterols/stanols (> 2 grams/day) would provide additional LDL-C lowering, 2) if a substantial reduction in LDL-C can be obtained in postmenopausal women with hypercholesterolemia, 3) if adding plant stanol esters would help high risk patients achieve their LDL-C goal despite current statin therapy. Additionally, the effect of plant stanol esters on lipoprotein subfractions, apolipoprotein B (APO B) levels, and C-reactive protein were examined. In order to evaluate these three points, three separate studies were conducted. All studies included lipid, lipoprotein, and APO B levels. The first study was a crossover, double-blind, placebo controlled study involving 8 patients with a baseline LDL-C of 130 mg/dL. Patients were randomly assigned to 4 periods of 6 weeks each. The 4 different periods required the consumption of varying amounts of plant stanols that included 0 grams, 2 grams per day, 3 grams per day, or 4 grams per day. Study 2 involved 13 postmenopausal women with LDL-C concentrations of > 150 mg/dL. This was a randomized placebo controlled trial with a crossover design for stanol esters (3 grams per day). The women were treated for a period of 6 weeks in each phase. The final segment included the open label addition of 10 mg of simvastatin added to the stanol ester for an additional 6 weeks. Study 3 involved 10 men with a fasting LDL-C of 100 to 129 mg/dL already taking a stable dose of statin monotherapy for at least 2 months. This was a randomized, placebo

controlled, double-blind crossover study for with plant stanols. The men were randomly assigned to consume 3 grams per day of plant stanols for 2 months after which they were switched to placebo for the alternate 2 months. The consumption of the plant stanol esters was in addition to their current statin regimen. The results of study one revealed that there was no difference in LDL-C concentrations between the 2 grams, 3 grams, and 4 grams per day of plant stanol esters. However, when compared to placebo, the 2 grams per day serving resulted in a 12% reduction in LDL-C. The results of study 2 showed that compared to placebo, the stanol esters alone significantly reduced LDL-C concentrations by 13%. In addition, there was a 10% decrease in total cholesterol, and a 13% reduction in both non-HDL-C and APO B. When open label simvastatin was added to plant stanol esters following the initial crossover portion of the study, LDL-C was reduced by an additional 28%, total cholesterol by 16%, and non-HDL cholesterol by 23%. In addition, APO B concentrations were reduced by 21%. There was no significant difference in C-reactive protein concentrations. Study 3 showed a 15% reduction in LDL-C with plant stanols esters compared to placebo when added to statin therapy. There was also a mean reduction in total cholesterol of 9%, non-HDL cholesterol by 14%, APO B by 14%, and HDL increased by 7%. Additionally, C-reactive protein decreased by 42% in the plant stanol phase. The National Cholesterol Expert Treatment Panel III currently recommends the consumption of 2 grams of plant stanol/sterols daily to reduce LDL-C and cardiovascular risk. The results suggest that the incorporation of plant stanols/sterols can have a positive impact in a variety of settings.

Tea (Green and Black)

Coronary Artery Disease

Mukamal KJ, Maclure M, Muller JE, Sherwood JB, Mittleman MA. Tea consumption and mortality after acute myocardial infarction. *Circulation.* 2002;105(21):2476–81.

The beneficial effects of tea are largely attributed to its strong antioxidant effects, particularly from flavonoid compounds, which are abundant in green and black tea. This was a prospective, multicenter, cohort subanalysis of the Determinants of Myocardial Infarction Onset Study (Onset Study) examining the effects of tea

consumption on cardiovascular mortality after acute myocardial infarction. Previous studies have inconsistently linked tea consumption to reductions in cardiovascular events at the population level, but no studies exist in patients with high cardiovascular acuity. A total of 1935 patients were interviewed regarding caffeinated tea consumption (all types), with 1900 patients containing complete data included in the analysis. Cardiovascular mortality was assessed using the National Death Index and examination of death certificates for cardiovascular causes of death. Tea consumption was divided into groups, including no tea consumption, moderate use (tea consumption of < 14 cups per week), and heavy use (\geq 14 cups per week). Of the 1900 patients, 1019 consumed no tea (nondrinkers), 615 consumed < 14 cups per week (moderate tea drinkers), and 266 consumed 14 or more cups per week (heavy tea drinkers). After adjustment for age and sex, moderate and heavy tea consumption was associated with lower incidence of cardiovascular death relative to patients consuming no tea (HR 0.69 [95% CI 0.53 to 0.89] and HR 0.61 [95% CI 0.42 to 0.86], respectively, $p < 0.001$). After further adjustments with a variety of socioeconomic factors, moderate and heavy tea consumption remained beneficial (HR 0.79 [95% CI 0.58-1.08], and HR 0.54 [95% CI 0.33-0.87], respectively, $p=0.005$). While these results suggest that tea is beneficial for patients suffering acute myocardial infarction, they do not completely imply causality despite adjustment for known socioeconomic factors. Prospective, randomized, placebo controlled investigation is warranted.

Kuriyama S, Shimazu T, Ohmori K, et al. Green tea consumption and mortality due to cardiovascular disease, cancer and all causes in Japan. The Ohsaki Study. *JAMA* 2006;296:1255–1265.

Green tea polyphenols have been extensively studied as cardiovascular preventative agents *in vitro* and in animal models. However, the effects of green tea in humans had not been conclusively demonstrated to this point, as previous studies were too limited to draw adequate conclusions. The Ohsaki Study was a prospective, observational, cohort study of 40,530 Japanese adults from 40-79 years of age with no history of cardiovascular disease (including stroke) or cancer. Patients were followed for up to 11 years after enrollment and completed questionnaires

regarding various lifestyle parameters and food consumption, including green tea. Green tea consumption was categorized into never, occasional, 1–2 cups/day, 3–4 cups/day, or 5+ cups/day. Subjects consuming green tea tended to be older and were more likely to be unemployed, engage in sports or exercise, have a history of hypertension and diabetes mellitus and were less likely to walk, for both men and women. Green tea consumption of all frequencies was found to be significantly associated with a reduction in all-cause mortality over study follow up (see table). After adjustment for baseline demographic, socioeconomic, and dietary information, green tea use continued to be associated with lower rates of death over the follow-up period. Interestingly, this finding was more pronounced in women compared to men ($p=0.03$ for interaction by sex). When individual outcomes were examined, green tea significantly reduced the rates of cardiovascular disease related mortality and stroke. Cancer rates were not affected by green tea consumption. While the results of this study suggest the association of green tea consumption with lower rates of cardiovascular disease and stroke, these results do not prove causality, despite adjustment for a variety of medical and socioeconomic factors. In addition, the type of green tea used by participants was not controlled for in this trial.

Table: Effects of Green Tea Consumption on Outcomes

Outcome	Green Tea Consumption (cups/day)				p-value
	< 1	1–2	3–4	\geq 5	
All-Cause Mortality - Adjusted HR (95% CI)					
All Subjects	1.00	0.96	0.90	0.84	< 0.001
Men	1.00	0.93	0.95	0.88	0.03
Women	1.00	0.98	0.82	0.77	< 0.001
Cardiovascular Mortality – Adjusted HR (95% CI)					
All Subjects	1.00	0.87	0.77	0.74	< 0.001
Stroke Mortality - Adjusted HR (95% CI)	1.00	0.84	0.78	0.63	< 0.001

Stephoe A, Gibson EL, Vuononvirta R, et al. The effects of chronic tea intake on platelet activation and inflammation: A double-blind placebo controlled trial. *Atherosclerosis*. 2007;193(2):277–82.

Tea consumption has been shown to have beneficial, albeit inconsistent, effects on the development of cardiovascular disease in population and cohort based studies. This was a

prospective, randomized, double-blind, placebo controlled trial designed to examine whether consumption of black tea had beneficial effects on platelet activation and inflammation. Following a 4-week washout phase of tea and other caffeinated beverages, 75 healthy volunteers were enrolled and randomized to four sachets of black tea (1050 mg each, dissolved in 250 ml of hot water) per day or placebo for 6 weeks. Each sachet contained 6.4% flavonols. Following the conclusion of the study, platelet aggregation was assessed with flow cytometry, examining platelet-leukocyte interaction, and C-reactive protein, antioxidant capacity, and P-selectin levels were analyzed. After 6 weeks, platelet-monocyte, platelet-neutrophil, and total platelet-leukocyte aggregates were significantly reduced by approximately 9% each relative to placebo ($p=0.027$, 0.017 , and 0.027 respectively). In addition, mean C-reactive protein levels were significantly reduced versus placebo (0.76 vs. 0.97 mg/L, $p=0.05$). However, no difference was detected in total antioxidant capacity (1.58 vs. 1.52 mmol/L, $p=0.26$) or in P-selectin (54.0 vs. 54.9 mg/mL, $p=0.69$) relative to placebo. All post-treatment values were adjusted for pre-treatment values by using analysis of covariance. These data provide mechanistic evidence by which black tea may reduce cardiovascular events in affecting platelet activation and inflammation.

Mukamal KJ, MacDermott K, Vinson JA, et al. A 6-month randomized pilot study of black tea and cardiovascular risk factors. *Am Heart J.* 2007;154(4):724.e1–6.

While tea consumption has been linked to reductions in a variety of cohort and population based studies, no prospective trial has proven the benefit of black tea consumption with a long-term follow up. This was a prospective, randomized, controlled, parallel trial with 31 patients with either diabetes or 2 cardiovascular risk factors (HTN, smoking, LDL cholesterol > 130 mg/dL, HDL < 40 mg/dL, or family history of premature CAD). Patients were randomized to 3 sachets of black tea (2.0 gm) per day whereas control patients were asked to consume 3 glasses of water per day. After 6 months, a variety of markers of cardiovascular risk were measured, including lipids, inflammatory markers (CRP, IL-6, TNF- α), blood pressure, hemoglobin, adhesion molecules (ICAM, VCAM), lipoprotein oxidizability, and prothrombotic and fibrinolytic parameters (vWF, tPA antigen, PAI-1 activity).

After 6 months, treatment with black tea did not have a significant effect on any measure of cardiovascular risk. While the results of this trial do not show beneficial effects of black tea on known cardiovascular biomarkers, the dose comparative to other trials may have been inadequate. In addition, although the study was likely underpowered to detect a difference, it is the only randomized clinical trial examining the effects of tea on surrogate markers of cardiovascular risk.

Thiamine

Chronic and Acute Heart Failure

Seligmann H, Halkin H, Rauchfleisch S, et al. Thiamine deficiency in patients with congestive heart failure receiving long-term furosemide therapy: a pilot study. *Am J Med.* 1991 Aug;91(2):151–5.

Long-term diuretic therapy has been shown to contribute to urinary thiamine deficiency in patients with chronic heart failure (CHF). In this pilot trial, 23 patients with heart failure on chronic furosemide therapy (3–14 months) and 16 age matched healthy controls were examined for thiamine deficiency. Twenty-one of 23 furosemide patients, compared with 2 of 16 controls, were found to have high thiamine pyrophosphate effect (TPPE), indicating thiamine deficiency. Of the 21 thiamine deficient heart failure patients, 6 were treated with a 7-day course of intravenous thiamine (100 mg twice daily). TPPE improved in all six patients (mean $27.0 \pm 3.8\%$ to $4.5 \pm 1.3\%$, $p<0.001$) and increases in ejection fraction were identified in four of the five patients who underwent echocardiography (mean change from baseline $+0.13 \pm 2.7$, no statistical analysis performed). Although the results of this study encouraging, the small size and lack of placebo control preclude any assessment of the benefit of thiamine in diuretic treated patients with heart failure.

Shimon I, Almog S, Vered Z, et al. Improved left ventricular function after thiamine supplementation in patients with congestive heart failure receiving long-term furosemide therapy. *Am J Med.* 1995;98(5):485–90.

This follow-up to the previous trial randomized 30 patients with CHF (NYHA Class II-IV) on long-term, moderate to high dose diuretic therapy (80 mg/day or more for at least 3 months) to 1 week of double-blind intravenous

thiamine (200 mg/day, n=15) or placebo (n=15). Following discharge, all 30 patients received oral thiamine (200 mg/day) for 6 weeks. The primary endpoint of the trial was change in left ventricular ejection fraction (LVEF) at Day 7. At Day 7, LVEF was improved in patients receiving thiamine relative to baseline (0.28 ± 0.11 to 0.32 ± 0.09 ; $p < 0.05$), and further improved in all 27 participants who completed the remaining six week study medication course relative to baseline (0.27 ± 0.10 to 0.33 ± 0.11 , $p < 0.01$). No significant changes in LVEF were observed in participants receiving placebo. Additionally, no significant differences in LVEF at Day 7 were observed between the thiamine and placebo groups (mean increase $+0.044 \pm 0.090$ vs. $+0.020 \pm 0.060$, $p = \text{NS}$). Mild, although statistically significant, changes in diuresis rates and sodium excretion were also observed in patients randomized to thiamine replacement relative to baseline ($1,731 \pm 800$ mL/d to $2,389 \pm 752$ mL/d; $p < 0.02$ and 84 ± 52 mEq/d to 116 ± 83 mEq/d, respectively) whereas no significant increases were observed in patients randomized to placebo. However, no significant change was noted in left ventricular end diastolic volume with thiamine supplementation. The results of this study are encouraging, although the change in ejection fraction is of questionable clinical significance, given the small number of patients enrolled in the trial. However, given the unlikely potential for harm, patients with CHF on moderate to chronic high dose loop diuretic therapy may be periodically monitored for thiamine deficiency and/or routinely supplemented.

Smithline HA. Thiamine for the treatment of acute decompensated heart failure. *Am J Emerg Med.* 2007;25(1):124–6.

In this trial, 50 patients admitted to the emergency department with acute decompensated heart failure were randomized to receive 100 mg of intravenous thiamine (n=25) or placebo (n=24). The primary outcome of the trial was the percentage of patients admitted from the emergency department to the hospital, indicating worsening of clinical status or failure to improve in the emergency department. Secondary outcomes measured were in-hospital length of stay, and change in dyspnea according to a 6-point scale after 4 hours. The percentage of patients hospitalized was not different between the thiamine group and the placebo group (92% vs. 96%, $p = 0.99$). In addition, no significant differences were identified between thiamine and

placebo with respect to median length of stay (4 days [range 2–5] vs. 3 days [range 1.5–4], $p = 0.11$), or 4 hour change in dyspnea score (1 [range 1–2] vs. 1 [range 0–1], $p = 0.09$). These data do not support the routine use of thiamine in decompensated heart failure patients. However, the endpoints chosen for investigation in this trial can be significantly confounded by other variables and may not represent the complete therapeutic futility of thiamine in this area.

Vitamin C

Chronic Heart Failure

Mak S, Overgaard CB, Newton GE. Effect of Vitamin C and L-NMMA on the inotropic response to dobutamine in patients with heart failure. *Am J Physiol Heart Circ Physiol* 2005;289:H2424–H2428.

These investigators previously observed that vitamin C augments inotropic response to dobutamine in patients with preserved left ventricular function, but not in patients with HF, which they hypothesized was due to excessive levels of nitric oxide. The purpose of this study was to examine the interaction between redox environment (the oxidizing/reducing state of a cell) and the nitric oxide synthase (NOS) pathway on cardiac function stimulated by dobutamine in patients with HF. Investigators hypothesized that vitamin C may augment the inotropic response to dobutamine in the setting of nitric oxide synthase (NOS) inhibition. Eleven participants had stable heart failure (NYHA functional class II or III) and were studied after undergoing elective heart catheterization. Ten participants were taking ACE inhibitors and beta adrenergic blockers. Study measurements included ECG, femoral artery pressure, LV pressure, and peak positive rate of change of LV pressure (LV +dP/dt) and were acquired during infusions of vehicle (control), dobutamine (rates of 2.5, 5, and 7.5 mg/kg/min), N-monomethyl-L-arginin (L-NMMA) — a NOS inhibitor, and the combination of L-NMMA, dobutamine, and vitamin C (500mg). The L-NMMA alone did not affect any of the variables measured. Dobutamine (mean dose 5.5 ± 0.8 $\mu\text{g/kg/min}$) resulted in a mean increase in LV +dP/dt of $25 \pm 5\%$. When combined with L-NMMA, dobutamine resulted in a significantly greater elevation in mean arterial pressure and compared

to dobutamine alone, however LV +dP/dt was not changed significantly with the combination (+203 ± 46 mmHg/s versus 193 ± 40 mmHg/s, $p=NS$). When vitamin C was added to L-NMMA and dobutamine, a significant rise in LV +dP/dt resulted (+284 ± 51 mmHg/s, $p<0.05$ when compared to dobutamine and combination of dobutamine + L-NMMA). While interesting, investigators did not examine the combination of vitamin C with dobutamine in the absence of L-NMMA, and the differences between dobutamine with and without L-NMMA on LV +dP/dt were not significant. It is therefore difficult to prove that NOS negates the effect of vitamin C on responses to dobutamine with this study design.

Shinke T, Shite J, Takaoka , et al. Vitamin C restores the contractile response to dobutamine and improves myocardial efficiency in patients with heart failure after anterior myocardial infarction. *Am Heart J* 2007;154:645e1–645e8.

This is another study investigating the effects of vitamin C on responsiveness to dobutamine in patients with HF. Nineteen individuals with HF (NYHA functional class II) and 4 weeks following an MI were enrolled. All were taking ACE inhibitors but were not on beta adrenergic blockers until after study completion. Ten participants were in the vitamin C arm and 9 were in the control group, and there were no differences in baseline characteristics between groups. After routine cardiac catheterization, hemodynamic and mechanoenergetic measurements were completed, taken from the coronary sinus and coronary artery, which included: hemodynamic variables, pressure-volume loops, coronary sinus blood flow (CSF), and blood gases. End diastolic pressure volume relation was obtained during inferior vena caval occlusion. The treatment phases were: baseline study, dobutamine (4 µg/kg/min) for 10 minutes, and dobutamine + vitamin C (2 grams diluted in vehicle solution) for 10 minutes. For controls, the vitamin C was replaced with vehicle. Participants received atrial pacing at 90 beats/min for the duration of the study. Dobutamine + vitamin C increased +dP/dt by additional 15% ± 5, and left ventricular contractility by 21 ± 6% over dobutamine alone ($p<0.05$). This occurred without changes in arterial afterload, LV end-diastolic pressure, or end-diastolic volume. Additionally, vitamin C caused a further 20% ± 4% increase in stroke work ($p<0.05$) without an increase in myocardial energy consumption compared to dobutamine alone. Significant

differences were also noted between the vitamin C and control group for stroke work (1.27 ± 0.18 joules/beat vs. 0.91 ± 0.13 joules/beat, $p<0.05$). No significant differences above that of dobutamine were observed for any variables in the control group. It is encouraging that these results corroborated those of previous investigators (see Mak et al above) for +dP/dt with patients with less severe HF. Additionally, the fact that participants were not taking beta blockers lead to a clearer assessment of a beta agonist. However no differences were noted between vitamin C and control groups for +dP/dt.

Coronary Artery Disease

Salonen RM, Nyyssonen K, Kaikkonen J, et al. Six-year effect of combined vitamin C and E supplementation on atherosclerotic progression: The Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) Study. *Circulation* 2003;107:947–953.

This study examined the use of vitamin C and E and their combination on carotid atherosclerosis in high-risk men and women with hypercholesterolemia. Following an 8 week dietary counseling and placebo run in phase, participants (n=520) were randomized to 3 years of placebo, vitamin E 136 IU, vitamin C 250mg, or their combination twice daily. Randomization strata included smoking men, nonsmoking men, smoking postmenopausal women, and nonsmoking postmenopausal women. Thereafter, participants continued on open label study medication for an additional 3 years. Atherosclerosis was determined with high-resolution ultrasonography, and the primary outcome measure was carotid intima-media thickness (IMT) over all points of follow-up time, which were every 6 months for 36 months, following by one measurement at 72 months. Additionally, plasma tocopherol and F2-isoprostane concentrations were measured throughout the study. The mean annual increase of the mean common carotid artery (CCA) IMT (estimated as a linear slope across all time points) for unsupplemented participants was 0.0156 mm/yr ± 0.0182 and 0.0118 mm/yr ± 0.0136 in the supplemented individuals, a 25% reduced rate of change ($p=0.007$). Compared to baseline, CCA-IMT increased by 0.0134 ± 0.016 mm/yr at 72 months in nonsupplemented participants, and by 0.0103 ± 0.014 mm/yr in supplemented participants ($p=0.007$). When

men and women were analyzed separately for comparisons of end of study to baseline CCA-IMT, the results for men remained statistically significant, whereas results were not significant for women. Covariance analyses confirmed these differences in results between men and women in the study. Interestingly, results for the individual supplement components, vitamin E and C, were not reported separately so it is unknown whether treatment effect was due to one or both agents. This study suggested that antioxidant treatment with concomitant vitamin E and C may slow down progression of atherosclerosis as measured by the surrogate outcome CCA-IMT. The reasons for the differences noted in treatment effect between men and women are unclear, and the result would require validation in additional studies.

Cook NR, Albert CM, Gaziano JM, et al. A randomized factorial trial of vitamins C and E and beta carotene in the secondary prevention of cardiovascular events in women. *Arch Intern Med* 2007;167(15):1610–1618.

This is one of the first clinical trials to examine the effects of vitamin C on cardiovascular disease (CVD) as a single agent instead of in combination with other antioxidants. The Women's Antioxidant Cardiovascular Study (WACS) was a randomized, double-blind, placebo controlled, 2 x 2 x 2 factorial trial investigating the effects of vitamin C (500 mg daily), vitamin E (600 IU every other day), and beta carotene (50 mg every other day). The primary outcome was a combination of CVD morbidity and mortality, including MI, stroke, coronary revascularization, and cardiovascular mortality. Participants were women (N=8171) over 40 years old with either self-reported CVD or at least 3 self-reported cardiac risk factors. A folic acid/vitamin B₆/vitamin B₁₂ combination arm was added later on for the fourth factorial of the study, the results of which are not reported here. Following randomization, participants were sent packs containing placebo or active agents, as well as questionnaires assessing adherence (defined as taking at least 2/3 of study medication), adverse effects, and medical events. The mean follow up time was 9.4 years (range 8.3–10.1 years), and mortality and morbidity information was complete for 99% and 93% of participants, respectively. The only difference in adherence between vitamin C and placebo occurred at the 8 year mark (70% vs. 67%, p=0.01). Mean age was 60.6 ± 8.8 years, and

mean BMI was 30.3 ± 6.7. No differences in the primary outcome were noted for vitamin C users (RR 1.02, 95% CI 0.92–1.13, p=0.71). Results were similar when corrected for non-adherence (RR 0.95, 95% CI 0.83–1.09, p=0.47). There was a non-significant trend for improvement in ischemic stroke with vitamin C (RR 0.83, 95% CI 0.66-1.06, p=0.13), otherwise individual components were not different for vitamin C. Overall this was a well-designed study, although it is noteworthy that authors did not discuss the study's power when describing its methodology. However, participant self report of adherence and cardiovascular endpoints could have been subject to bias. Due to the large sample size and concordance with previous studies showing lack of benefit of vitamin C on primary or secondary CVD prevention, enthusiasm for use of vitamin C in this setting is limited.

Sesso HD, Buring JE., Christen WG, et al. Vitamins C and E in the prevention of cardiovascular disease in men. *JAMA* 2008;300(18):2123–2133.

Due to inconsistent results shown with CVD prevention for both vitamin E and C, this study, named the Physician Health Study II (PHS II), was designed to examine the effect of these agents on cardiovascular prevention in men at lower risk for CVD. The trial was a randomized, double-blind, placebo-controlled, 2 x 2 x 2 x 2 factorial study evaluating vitamin C (500 mg daily), vitamin E (400 IU every other day), a multivitamin, and beta carotene (50 mg every other day). Participants were either part of the first PHS study (N=7641), or recruited through invitational letters (N=7000). The primary endpoint was a composite of nonfatal MI, nonfatal stroke and cardiovascular mortality. Randomization was stratified based on age, prior diagnosis of cardiovascular disease, and prior diagnosis of cancer (block sizes = 16). Participants received monthly calendar packs every 6 months for the first year, then annually along with questionnaires assessing adherence (defined as taking at least 2/3 of study medication supply), adverse events, occurrence of new endpoints, and updated risk factors. Median follow up was 8 years, and mean participant age was 64.3 ± 9.2 years. Morbidity and mortality follow up were 95.3% and 97.7%, respectively. Adherence at the end of follow up was 71% for the vitamin C and its matching placebo group. There was no effect of vitamin C on the primary endpoint. Moreover, vitamin C had no effect on

individual component cardiovascular endpoints. Adjustment for non-adherence with vitamin C did not significantly change study findings (HR 0.98, 95% CI 0.86–1.13, $p=0.81$). Separate analyses of the sample with and without participants with a history of CVD did not yield significant benefits of vitamin C, thus vitamin C did not affect primary or secondary prevention of CVD. Overall, this study corroborated results from the WACS. Both studies used the same dose of vitamin C of 500 mg daily. It is possible that higher doses and longer duration of treatment are necessary to portend CVD protection; but the above studies do not support the use of vitamin C for CVD prevention.

Vitamin D

Chronic Heart Failure

Schleithoff SS, Zitterman A, Tenerich G, et al. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr.* 2006;83:754–9.

In this double-blind, randomized, placebo-controlled trial the investigators sought to investigate the effects of vitamin D supplementation (cholecalciferol 2000 IU/day) on cytokines known to be predictors of HF disease severity. HF patients (mean EF ~32%) were randomized to cholecalciferol or placebo for 9 months. The main outcomes were change in cytokine profile, clinical laboratories, or diagnostic tests from baseline. At the 9 month time point, 25(OH)D levels significantly increased in those patients taking the supplementation ($p=0.001$). The cytokine profile was the only significant outcome to respond to vitamin D supplementation over time, with the change in TNF- α levels lower ($p=0.006$) and the change in IL-10 levels higher ($p=0.042$) in those patients randomized to vitamin D therapy compared to placebo. The survival rate did not differ between the 2 groups. Vitamin D supplementation with cholecalciferol (2000 IU/day) does improve some of the cytokines that are known to be predictors of HF disease severity. Further prospective studies are needed to fully understand the effects of vitamin D in HF.

Dobnig H, Pilz S, Scharnagl H, et al. Independent association of low serum 25-hydroxyvitamin D and 1,25 dihydroxyvitamin D levels with all-cause and cardiovascular mortality. *Arch Intern Med* 2008;168:1340–9.

The association of vitamin D levels with all-cause and cardiovascular mortality was investigated in the Ludwigshafen Risk and Cardiovascular Health (LURIC) prospective cohort study. LURIC was originally designed to investigate the effects of genetics and biomarkers on cardiovascular outcomes in patients presenting to for angiography in a tertiary care medical center in Germany. Of the 3316 patients in the trial, 3258 patients were followed for a median of 7.7 years and received 25(OH)D and 1,25(OH)2D levels. After adjustment, patients in the two lowest quartiles (median 7.6 and 13.3 ng/mL) 25(OH)D levels had significantly higher all-cause mortality (HR 2.08 and 1.53, respectively) and significantly higher cardiovascular mortality (HR 2.22 and 1.82, respectively) when compared to the highest quartile (median 28.4 ng/mL) (log-rank test $p<0.001$). Comparable effects were seen with the 1,25(OH)2D levels and when adjusted by presence of CAD, Charlson Comorbidity Index, variables of mineral metabolism, and NYHA functional class. This data supports an independent association between low vitamin D levels and higher all-cause and cardiovascular mortality, but it is unclear if routine supplementation of vitamin D would decrease these events.

Pilz S, Marz W, Wellnitz B, et al. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. *J Clin Endocrin Metab* 2008;93:3927–35.

One analysis from the LURIC study (as described above) examined the association of vitamin D deficiency with death due to heart failure and sudden cardiac death (SCD). 25(OH)D levels were negatively correlated with N-terminal pro-BNP and inversely associated with impaired LV function. When comparing patients with 25(OH)D levels <10 ng/mL to patients with 25(OH)D levels ≥ 30 ng/mL, those with the lower 25(OH)D levels had increase death due to HF and SCD (HR 2.84, 95% CI 1.20–6.74 and 5.05 95% CI 2.13–11.97, respectively) after adjustment of cardiovascular risk factors. Similar results were obtained with 1,25(OH)2D levels. These results demonstrate that vitamin D has a role in the progression of HF and SCD, but it is unclear if routine supplementation of vitamin D will reduce HF progression and SCD.

Zitterman A, Schleithoff SS, Gotting C, et al. Poor outcomes in end-stage heart failure patients with low circulating calcitriol levels. *Eur J Heart Fail* 2008;10:321–7.

Three-hundred eighty-three patients listed for cardiac transplant (mean EF ~28%) in The Netherlands between May 2004 and April 2006 had calcitriol (1,25(OH)₂D) levels measured. These patients were then followed after transplant listing for the outcome of one-year freedom from death or transplantation. When patients were classified by urgent listing (UL) or elective listing (EL), calcitriol was independently associated with UL compared to EL ($p < 0.001$). Calcitriol concentrations were also significantly lower in those patients with an event at one year than those that survived. Patients with the highest tertile of calcitriol concentrations (>73 pmol/l) had a significantly lower number of events (HR 0.50, $p = 0.005$) compared to the lowest tertile of calcitriol concentrations (<43 pmol/l). This represents an association between low calcitriol concentrations and poor outcomes in end-stage HF.

Coronary Artery Disease

Hsia J, Heiss G, Ren H, et al. Calcium/vitamin D supplementation and cardiovascular events. *Circulation* 2007;115:846–54.

The Women's Health Initiative (WHI) was a prospective, randomized, double-blind, placebo controlled trial evaluating the risks and benefits of hormone replacement therapy in postmenopausal women. At their first or second annual visit the main participants were invited to join a substudy of this trial investigating the cardiovascular benefits of calcium 500 mg plus vitamin D3 200 IU (CaD) 2 tablets twice daily. The CaD portion of the trial enrolled 36,282 women and was also prospective, randomized double-blind, and placebo controlled, but given the age of the women open label CaD supplementation was allowed. During the 7 years of follow-up, the incidence of CAD and or MI were not different between the 2 groups (HR 1.04 95% CI 0.92–1.18). The incidence of stroke was also no different between the 2 groups (HR 0.95 95% CI 0.82–1.10). The authors conclude that calcium and vitamin D supplementation does not decrease the risk for coronary heart disease or stroke in post menopausal women. This study, however, had several limitations that may have affected the results. Participants assigned to the calcium and vitamin D group

only received 400 IU of vitamin D daily, a dose that may not be adequate for the prevention of cardiovascular diseases and is well below the recommended daily intake of 800 IU for postmenopausal women. Women in the placebo arm were permitted to take vitamin D supplements and may have resulted in similar vitamin D intakes in each group, nullifying the differences that may have been seen between the two groups. Finally, baseline 25-hydroxyvitamin D levels were measured in this study. The benefit of supplementing only deficient individuals could not be assessed since treatment assignment was determined irrespective of vitamin D status. Large prospective trials assessing adequate doses of vitamin D supplementation in truly deficient individuals are needed to understand the role of vitamin D in cardiovascular disease prevention.

Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 2008;117:503–11.

The Framingham Offspring Study participants without cardiovascular disease were used to evaluate an association between vitamin D levels and incident cardiovascular disease. This cohort began in 1971 and enrolled 5124 offspring from the original Framingham Heart Study population. Cardiovascular events were defined as MI, coronary insufficiency, angina, stroke, transient ischemic attack, peripheral claudication, or heart failure. After follow-up of over 5 years in 1739 participants between 1996 and 2001, those with 25(OH)D levels <15 ng/mL had 1.6 (95% CI 1.11 to 2.36, $p = 0.01$) times the odds of having an incident cardiovascular event compared to those with 25(OH)D levels ≥ 15 ng/mL, when adjusted for conventional risk factors. There was a linear trend in risk of cardiovascular events with 25(OH)D levels ($p = 0.01$, for linear trend). The effect of 25(OH)D levels on risk of incident cardiovascular events was only seen in those with HTN but not those without HTN. This cohort provides support for an inverse association of 25(OH)D levels with incident cardiovascular events, but is only evident in those with HTN.

Hypertension

Forman JP, Giovannucci E, Holmes MD, et al. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. *Hypertension* 2007;49:1063–9.

Vitamin D has been shown to decrease renin expression and vascular smooth muscle cell

proliferation, which may be essential in preventing HTN. The vitamin D receptor is also expressed on the heart and in the vasculature. The Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NHS) were combined in this analysis to investigate the association of vitamin D levels and incident HTN. After 4 years of follow-up, men with 25-hydroxyvitamin D [25(OH)D] levels <15 ng/mL had 6.13 (95% CI 1.00 to 37.8) times the risk of developing incident HTN than those men with 25(OH)D levels \geq 30 ng/mL. In women, then same comparison lead to 2.67 (95% CI 1.05 to 6.79) times the risk of incident HTN. When pooled relative risk of men and women was performed, the association remained with 3.18 (95% CI 1.39 to 7.29) times the risk of incident HTN in those with 25(OH)D levels <15 ng/mL compared to 25(OH)D levels \geq 30 ng/mL. In conclusion, this analysis provided evidence that 25(OH)D levels are inversely and independently associated with the risk of incident HTN, but it is unclear if routine supplementation of vitamin D reduces the incidence of HTN.

Margolis KL, Ray RM, Van Horn L, et al, for the Women's Health Initiative Investigators. Effect of calcium and vitamin D supplementation on blood pressure: The Women's Health Initiative Randomized Trial. *Hypertension* 2008;52:847–55.

As described above, the Women's Health Initiative (WHI) was a prospective, randomized, double-blind, placebo controlled trial evaluating the risks and benefits of hormone replacement therapy in post-menopausal women. At their first or second annual visit the main participants were invited to join a substudy of this trial investigating the cardiovascular benefits of calcium 500 mg plus vitamin D3 200 IU (CaD) 2 tablets twice daily. The CaD portion of the trial enrolled 36,282 women and was also prospective, randomized double-blind, and placebo controlled, but given the age of the women open label CaD supplementation was allowed. This analysis of the WHI study investigated the effects of CaD on incident HTN. Over the 7 years of follow-up, there was no significant difference in the mean change of systolic (0.22 mmHg; 95% CI -0.05 to 0.49 mmHg, $p=0.14$) or diastolic (0.11 dmmHg; 95% CI -0.04 to 0.27 mmHg, $p=0.2$) blood pressure between the CaD group and placebo. In the women that were nonhypertensive at study enrollment the incidence of HTN was not different between the

CaD group and placebo (HR 1.01 95% CI 0.96 to 1.06, $p=0.69$). This study demonstrated that CaD supplementation does not reduce either blood pressure or the incidence of blood pressure in postmenopausal women. This study, however, had several limitations that may have affected the results. Participants assigned to the calcium and vitamin D group only received 400 IU of vitamin D daily, a dose that may not be adequate for the prevention of cardiovascular diseases and is well below the recommended daily intake of 800 IU for post-menopausal women. Women in the placebo arm were permitted to take vitamin D supplements and may have resulted in similar vitamin D intakes in each group, nullifying the differences that may have been seen between the two groups. Finally, baseline 25-hydroxyvitamin D levels were not measured in this study. The benefit of supplementing only deficient individuals could not be assessed since treatment assignment was determined irrespective of vitamin D status. Large prospective trials assessing adequate doses of vitamin D supplementation in truly deficient individuals are needed to understand the role of vitamin D in cardiovascular disease prevention.

Vitamin E

Coronary Artery Disease

Stephens NG, Parsons A, Schofield PM, et al. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). *Lancet* 1996;347:781–86.

Prior to the publication of the CHAOS study, there were numerous epidemiologic reports, as well as cohort studies, which provided evidence that vitamin E may have beneficial effects on the development and progression of coronary artery disease (CAD). Epidemiologic studies focused on the intake of vitamin E within the diet, while cohort studies assessed the use of vitamin E supplements. The primary mechanism of benefit was believed to be inhibition of low-density lipoprotein (LDL) oxidation and prevention of atherosclerotic lesion progression. The CHAOS study at the time represented one of the first randomized investigations on the effect of vitamin E supplementation on cardiovascular outcomes. Two thousand and two patients with angiographically proven CAD were randomized in a double-blind fashion to either 400 or 800 IU of alpha-tocopherol or placebo. Patients were

followed up for a median of 510 days and the primary endpoint was a combination of cardiovascular death and non-fatal MI. Patients receiving vitamin E had significant elevations in plasma alpha-tocopherol concentrations as compared to placebo. The primary endpoint was significantly reduced in patients receiving vitamin E (RR 0.53, 95% CI 0.34-0.83), with the primary benefit seen in a reduction in non-fatal MI (14 vs 41 events in vitamin E and placebo, respectively). However, there was a non-significant increase in the rate of cardiovascular death as well as all-cause mortality in the vitamin E group. Despite overall favorable results with the primary endpoint, there was concern with the higher number of cardiovascular and all-cause deaths in the vitamin E group. The authors correctly pointed out that the trial lacked statistical power to assess the disparity in results, and postulated that there may be differences in effect depending on when vitamin E intake was initiated in relation to the atherosclerotic process. While generally viewed as favorable, the CHAOS study set the stage for several larger, randomized trials that followed.

GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of GISSI-Prevenzione trial. *Lancet* 1999;354:447-55.

The GISSI-Prevenzione Investigators undertook this investigation to assess the effects of both n-3 polyunsaturated acids, as well as vitamin E, on various cardiovascular endpoints in myocardial infarction survivors. Only the results of only vitamin E supplementation will be discussed here (n-3 polyunsaturated acids are discussed under fish oil section). At the time of publication, there were mixed results for vitamin E in randomized trials in patients with cardiovascular disease with the previously discussed CHAOS trial showing a potential benefit in non-fatal MI, while the Alpha-tocopherol Beta Carotene Cancer Prevention (ATBC) trial published in 1994 found no cardiovascular benefit for vitamin E when taken for cancer prevention in smokers. In this trial 11,324 patients who had survived a recent MI in the last 3 months were randomized to one of four treatment groups: (1) n-3 polyunsaturated fatty acids; (2) vitamin E 300 mg; (3) both supplements; (4) or neither. The trial utilized an open-label design. Patients also received other medications considered standard of care for post-

MI treatment at the time. The primary endpoint consisted of death, non-fatal MI and stroke. Secondary endpoints consisted of mainly the individual components of the primary endpoint. Over an average follow-up of 3.5 years, vitamin E supplementation did not result in any statistically or clinically significant difference in the primary endpoint (12.9% vitamin E, vs 13.6% placebo, 95% CI 0.86-1.05). Similar results were observed for each individual endpoint as the primary composite endpoint. There was no interaction in the results based on the presence or absence of n-3 polyunsaturated acids. Overall this large randomized, appropriately powered trial did not find a benefit for vitamin E supplementation in patients with recent MI. The authors speculated that the lack of benefit for vitamin E might be due to timing of administration (vitamin E may only be beneficial in the early stages of atherosclerosis), or that beneficial effects might only be seen with longer durations of administration such as ≥ 5 years.

Vivekananthan DP, Penn MS, Sapp MS, et al. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomized trials. *Lancet* 2003;361:2017-23.

The authors of this meta-analysis noted that despite the lack of supporting evidence from large randomized trials, there was generally strong support in the healthcare community, as well as the general public, for the use of antioxidant vitamins to promote health. The likely source of this disconnect was the preclinical evidence available demonstrating that antioxidant supplementation can inhibit the atherosclerotic process. To help reconcile this issue, the authors set out to conduct a meta-analysis on trials involving both beta-carotene and vitamin E to provide a more robust estimate of their impact on all cause mortality and cardiovascular death. Only the results for vitamin E will be discussed here. In total, 5 secondary prevention and 2 primary prevention vitamin E trials were included in the analysis, including the ATBC, CHAOS, GISSI-Prevenzione, as well as HOPE study which will be discussed in more detail below. In total 81,788 patients were included in the analysis which showed that vitamin E had no effect on either all-cause mortality (11.3% vitamin E vs 11.1% placebo, 95% CI 0.98-1.06) or cardiovascular death (6.0% vitamin E vs. 6.0% placebo). Additionally there was no difference in the incidence of total stroke. The results did not differ when analyzed by

either primary prevention or secondary prevention as well. The results of this meta-analysis further solidified results from randomized clinical trials that vitamin E supplementation has no demonstrable effect on cardiovascular outcomes. The authors postulated that vitamin E intake may only be important when consumed as part of a healthy diet in which other antioxidants and vitamins are present. In addition, they discuss published data showing that vitamin E may blunt the formation of HDL as well as may not have an appreciable effect on LDL oxidation in vivo as explanations for a lack of benefit.

Miller ER, Pastor-Barriuso R, Dalal D, et al. Meta-analysis: High-dose vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 2005;142:37–46.

Prior to the publication of this important analysis, 3 previous meta-analyses had been published (one of which was previously discussed), all showing similar results in that vitamin E supplementation had no appreciable effect on cardiovascular outcomes. However, each of these investigations had not looked at the issue from a dose-response perspective. Part of the rationale for undertaking such an investigation was that previous trials with high-dose supplementation had indicated a statistically non-significant increase in all-cause mortality. In this meta-analysis, the authors identified 135,967 patients across 19 trials. Some criteria for trial inclusion consisted of trials that (1) had random allocation; (2) used of vitamin E supplementation alone or in combination with other antioxidants; (3) used of a placebo control; (4) duration of supplement use greater than 1 year; and (6) at least 10 deaths to evaluate. Of the 19 trials, 9 tested vitamin E alone and the doses used ranged from 16.5 to 2000 IU per day (median 400 IU/day). Overall, vitamin E did not affect all-cause mortality, but a dose-dependent effect for vitamin E was found, with doses greater than 150 IU/day associated with an increased risk of death. Potential mechanisms discussed for the increased risk include a possible pro-oxidant effect for vitamin E at high doses, displacement of other beneficial fat soluble vitamins, as well as anticoagulant effects. In fact, the previously mentioned ATBC trial found an increased risk for hemorrhagic stroke with vitamin E. These results were important and a paradigm shift. Previously it was thought that while there was no good evidence from clinical trials that high-dose

vitamin E had any favorable benefits, it was thought that there was no harm from it. This trial challenged that line of thinking and likely changed how healthcare practitioners informed patients about vitamin E supplementation.

The HOPE and HOPE-TOO Investigators. Effects of long-term vitamin E supplementation on cardiovascular events and cancer. *JAMA* 2005;293:1338–1347.

The original HOPE study was a 2 x 2 factorial investigation on the effects of both ACE inhibition and vitamin E supplementation on cardiovascular outcomes in patients with previous cardiovascular disease and preserved left ventricular function, or patients with diabetes and multiple risk factors for cardiovascular disease. In the original HOPE publication addressing vitamin E supplementation in 2000, the use of 400 IU a day for an average of 4.5 years, had no effect on the composite primary endpoint of MI, stroke, and death from cardiovascular disease (16.2% vitamin E vs 15.5% placebo, $p=0.33$). In this follow-up publication, the authors attempted to address one of the postulated reasons for the lack of benefit for vitamin E in previous trials, namely the duration of exposure to the intervention. As discussed previously, there was some speculation that exposure to vitamin E supplementation would need to be at least 5 years or longer in order to show a benefit on cardiovascular outcomes. In this follow-up investigation, 3994 of the original 7030 study enrollees continued on their initial randomized therapy for a total mean follow-up of 7.2 years. After a longer duration of exposure, vitamin E supplementation had no effect on the composite outcome of cardiovascular death, non-fatal MI and stroke (21.5% vitamin E vs 20.6% placebo, RR 0.71–1.09). Results were also consistent when analyzed by each individual endpoint. Of particular note and reported for the first time in the literature, the patients receiving vitamin E had a significant increase in the rate of both the development of heart failure (RR 1.13, 95% CI 1.01–1.26), as well as heart failure hospitalization (RR 1.21, 95% CI 1.00–1.47). The results of this investigation do not support the notion that long term administration of vitamin E beneficial effects on cardiovascular outcomes.

Cook NR, Albert CM, Gaziano M, et al. A randomized factorial trial of vitamins C and E

and beta carotene in the secondary prevention of cardiovascular events in women. *Arch Intern Med* 2007;167(15):1610–1618

While previous clinical trials and meta-analyses had not supported the concept that antioxidant supplementation improved cardiovascular outcomes, there had been little in the way of assessing the effect of antioxidant vitamin combinations, as well as the individual effect of vitamin C. The Women's Antioxidant Cardiovascular Study (WACS) was conducted to address these specific issues. Only results pertaining to vitamin E supplementation in this study will be discussed here (vitamin C effects are discussed under vitamin C section). The WACS was a randomized, double-blind, placebo-controlled trial evaluating the effects of vitamin C 500 mg a day, vitamin E 600 IU every other day, and beta carotene 50 mg a day in a 2 x 2 x 2 factorial design. Women who were greater than 40 years of age or postmenopausal that had self-reported cardiovascular disease were considered eligible. Women without cardiovascular disease could also be included if they had 3 cardiovascular risk factors. The primary composite endpoint consisted of MI, stroke, coronary revascularization, and cardiovascular mortality. Eight thousand one hundred and seventy one women with an average age of 60.6 years were randomized. Vitamin E supplementation over an average of 9.4 years had no effect on the primary endpoint (RR 0.94, 95% CI 0.85–1.05), with no difference in effect over the duration of the trial. No difference in all-cause mortality was noted. However, there were non-significant reductions in total and ischemic stroke with vitamin E. Other interesting findings that merit further investigation were results that were censored for noncompliance. In evaluating only patients deemed compliant (73% of total study group were taking 2/3 of study pills by self-report throughout study duration), there was a statistically significant reduction in the primary endpoint, a 22% reduction in MI, a 27% reduction in stroke. However, overall this trial must be taken to reinforce the concept that vitamin E supplementation has no beneficial effect on cardiovascular outcomes, even over a long duration of exposure such as 9 years. However, this study did not confirm the dose-dependent increase in mortality noted in previous meta-analyses.

Bjelakovic G, Nikolova D, Gluud LL, et al. Mortality in randomized trials of antioxidant

supplements for primary and secondary prevention. Systemic review and meta-analysis. *JAMA* 2007;297:842–857.

The authors of this investigation, using the Cochrane Collaboration method, set out to investigate through meta-analysis the effects of antioxidant supplements vitamin A, C and E, selenium, as well as beta-carotene on all-cause mortality in primary and secondary prevention trials. In total, the authors identified 68 randomized trials with 232,606 participants giving them robust statistical power to assess the effects of anti-oxidant vitamins. Only the results related to vitamin E will be presented here. Whether given alone as a single agent. or in combination with other anti-oxidants, vitamin E did not affect mortality in either direction. In addition, there was no effect on mortality when analyzed by either high dose supplementation (> 1000 IU per day) or low dose supplementation (< 1000 IU per day), although one could reasonably question the authors definition of low dose given previous results in the literature. However, after excluding low methodological quality trials, as well as trials where selenium was also administered (results of trials with selenium have generally been favorable), vitamin E supplementation significantly increased total mortality (RR 1.04, 95% CI 1.01–1.07). Overall, while not specifically evaluating the effects of vitamin E on cardiovascular outcomes, this analysis lends further weight to the concept that healthcare practitioners should not be recommending vitamin E for health promotion.

Sesso HD, Buring JE, Christen WG, et al. Vitamins E and C in the prevention of cardiovascular disease in men. The Physicians' Health Study II Randomized Controlled Trial. *JAMA* 2008;300(18):2123–2133.

Despite the large body of evidence on vitamin E and cardiovascular outcomes prevention prior to this study, there has been little in the way of investigating the effects of vitamin E supplementation in men initially at low risk of developing cardiovascular disease. In addition, there is scant information on the role vitamin C may play in the prevention of cardiovascular disease. In addition, the authors note that in the year 2008, despite the body of evidence regarding vitamin E and cardiovascular outcomes, the use of vitamin E supplementation to enhance overall health is still very prevalent. This randomized, double-blind, placebo-controlled trial using a factorial design assessed the effect of both

vitamin C (500 mg daily) as well as vitamin E (400 IU every other day) on cardiovascular events (primary endpoint combination of nonfatal MI, nonfatal stroke, and cardiovascular death) in 14,641 US male physicians. The average age of participants was 64.3 years and mean follow-up was 8 years. Ten percent of participants had a history of MI, with the incidence of hypertension, hypercholesterolemia, and diabetes 42%, 36%, and 6% respectively. Vitamin E had no effect on the incidence of the primary endpoint (HR 1.01, 95% CI 0.75–1.07). There was no difference in total mortality with Vitamin E, however, it was associated with an increased risk of hemorrhagic stroke (HR 1.74, 95% CI 1.04–2.91). The results of this recent investigation adds to the large body of evidence that vitamin E has no role in reducing cardiovascular events. In addition, specifically as seen in this trial, vitamin E did not prevent the development of CAD and increased the risk of hemorrhagic stroke.

Zinc

Cardiovascular disease

Pilz S, Dobnig H, Winklhofer-Roob BM, et al.
Low serum zinc concentrations predict mortality

in patients referred to coronary angiography. *Br J Nutr* 2008 Oct 24:1–7 [Epub ahead of print].

Zinc is an antioxidant and alters immune function, which could be important in cardiovascular disease. Zinc concentrations were evaluated in the LURIC prospective cohort study in Germany. LURIC was originally designed to investigate the effects of genetics and biomarkers on cardiovascular outcomes in patients presenting to for angiography in a tertiary care medical center in Germany. The objective of this analysis is to investigate an association between zinc concentrations and mortality with a median follow-up of 7.7 years after entry into the cohort. When comparing the lowest zinc quartile (<780 mg/l) with the highest quartile (>960 mg/l) cardiovascular mortality (HR 1.10 95% CI 1.01 to 1.21, $p=0.038$), non-cardiovascular mortality (HR 1.32 95% CI 1.16 to 1.50, $p<0.001$), and total mortality (HR 1.15 95% CI 1.07 to 1.24, $p<0.001$) was increased in the lower zinc quartile when controlling for common cardiovascular risk factors. This data represents a possible association between zinc concentrations and cardiovascular mortality. Until larger clinical trials are performed, zinc supplementation is not recommended.