Use of Alternative Pharmacotherapy in Management of Cardiovascular Diseases

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AUDIENCE

This activity is designed for healthcare professionals who provide care to patients with cardiovascular diseases

GOAL

To describe clinical trials on the use of alternative pharmacotherapy in patients with cardiovascular diseases.

OBJECTIVES

1. Discuss clinical trials on the use of alternative pharmacotherapy in cardiovascular disease management.
2. Explain potential interactions between alternative pharmacotherapy and cardiovascular medications.
3. Describe the role of the pharmacist in managing alternative pharacotherapy in patients with cardiovascular disease.

CONTINUING EDUCATION CREDIT

This course has been approved for a total of two (2) contact hours of continuing education credit (0.2 CEUs) by the University of Tennessee College of Pharmacy. The University of Tennessee College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. ACPE Program Number: 064-999-02-200-H-01. This course expires on March 31, 2004.

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Objectives: To review use of alternative pharmacotherapy (AP) in patients with cardiovascular disease (CVD) and significant drug interactions between AP and traditional CVD medications.

Study Design: A literature search of MEDLINE and the National Complementary and Alternative Medicine database was done using these search terms: supplements, vitamins, garlic, fish oil, *L*-arginine, soy, coenzyme Q10, herbs, phytosterols, chelation therapy, alternative medicine, and CVD.

Patients and Methods: English human clinical trials measuring surrogate and clinical end points.

Results: Antioxidants have not been consistently proven beneficial in reducing cardiovascular mortality. Fish oils may be beneficial in patients with hypertension and hypercholesterolemia, but therapeutic doses need to be defined. Use of coenzyme Q10 in patients with heart failure has not demonstrated consistent benefits. Garlic may lower blood pressure and cholesterol levels, but also may increase bleeding, so its use in CVD patients should be monitored. Clinical studies with small sample sizes have demonstrated that L-arginine may be useful to prevent and treat CVD. The Food and Drug Administration recommends 25 g/day of soy protein as part of a diet low in saturated fats for cholesterol reduction. Plant sterols are recommended by the American Heart Association and the National Cholesterol Education Program Expert Panel as adjunct therapy to reduce low-density lipoprotein. No data support use of chelation therapy. Some APs interact with common prescription CVD medications (eg, gingko and ginseng with warfarin, St. John's Wort with digoxin).

Conclusions: The benefits of APs as part of the treatment for CVD are controversial. Routine use is not recommended.

(Am J Manag Care 2002;8:270-285)

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Cardiovascular diseases represent the number one cause of death in the United States.[1] According to the 1998 statistics, approximately 41% of total mortality in the United States was attributed to cardiovascular causes.[1] Coronary heart disease (CHD) accounts for about half of those deaths. Fortunately, death rates from most of the cardiovascular diseases are declining due to longer life expectancy ascribed to improved medical treat-

ment and primary prevention strategies such as reduction of blood pressure and cholesterol. However, mortality due to congestive heart failure continues to increase. From 1979 to 1998, congestive heart failure deaths increased by 135%.[1]

Research into the prevention and treatment of cardiovascular diseases is progressive. Other than traditional medical and interventional treatment, several forms of alternative therapies—specifically, alternative pharmacotherapy (AP) such as vitamins, herbal remedies, and other dietary supplements—also have been studied in patients suffering from cardiovascular diseases. The manufacturing of AP is not currently controlled by the Food and Drug Administration (FDA). Most of the results of clinical studies on AP used in cardiovascular disorders remain controversial, and risk-versus-benefit ratios are not well defined. However, these considerations have not deterred patients from trying these agents.

Over the past decade, the medicinal use of AP has increased dramatically.[2] Consumers spend a significant amount of money purchasing these products.[2,3] In 1997, a conservative estimate for out-of-pocket expenditures for alternative therapy was $27 billion, a substantial increase from $10.3 billion in 1990.[2] In 1997, consumers spent $5.1 billion on herbal products alone,[4] and this figure was expected to exceed $12 billion by the end of the year 2000.[5]

In 1990, a national telephone survey of 1539 adults reported that 34% of the US population used at least 1 type of alternative therapy.[5] The use of alternative therapy was significantly higher ($P < .05$) in patients who were white, had incomes of more than $35,000 per year, were 25 to 49 years of age, and had some college education. Interestingly, alternative therapy was most commonly used to treat chronic conditions such as back problems, insomnia, headaches, anxiety, and depression. Almost 90% of patients who visited an alternative medicine practitioner did so without a recommendation from their physician. Additionally, 72% of patients who used alternative therapy did not report this to their physician.[5]

A follow-up survey of 2055 adults performed in 1997 compared the usage patterns of alternative therapy between 1990 and 1997.[2] Use of alternative therapy increased significantly ($P < .001$) from 34% in 1990 to 42% in 1997. Specifically, the use of herbal therapies escalated from 2.5% to 12.1% ($P < .001$) between 1990 and 1997. Alternative therapies continued to be used mainly by the white, educated, middle-class population, with the additional distinction of significantly greater ($P = .001$) use by women (49%) than men (38%). Like the 1990 survey, the 1997 survey indicated that alternative therapies were most commonly used to treat chronic conditions. Compared with 1990, in 1997 a significant increase in the use of alternative therapies was noted for back problems (48% vs 36%, $P < .01$), allergies (17% vs 9%, $P < .01$), arthritis (27% vs 18%, $P < .05$), and digestive problems (27% vs 13%, $P < .01$).[2] A point of concern noted in the 1997 survey was that approximately 20% of adults (estimated as 15 million adults in the US population) reported taking prescription medications concurrently with herbal products, but only 40% of these persons revealed this information to their physicians.[2] More recent surveys dealing with the usage patterns of herbal therapies indicate that up to 40% of the adult population in the United States uses 1 or more herbal products on a regular basis.[6,7]

Although these national surveys did not report on use of alterative therapy to treat cardiovascular disease, it also is considered to be a chronic medical condition, as it is among the most prevalent and fatal of diseases. Therefore, it is reasonable to believe that patients with cardiovascular disease may resort to alternative sources for prevention and treatment. Several limited investigations evaluated AP use among patients diagnosed with CHD, those with congestive heart failure,[8] and acute cardiac surgical candidates.[9]

The purpose of this review article is to critically evaluate the available evidence for the role of AP in prevention and treatment of cardiovascular diseases. Emphasis was placed on those APs for which researchers have the most extensive data, including vitamin E, vitamin C, β-carotene, fish oils, garlic, soy, coenzyme Q10 (Co-Q10), and *L*-arginine. In addition, patients with cardiovascular disease may consume other APs for other conditions. Some of these APs may significantly interact with the traditional medications that the patients take for their cardiovascular disease. Therefore, we will present available information on actual and potential AP-traditional medication interactions.

Information regarding alternative medicines is available from a wide variety of sources now (eg, the World Wide Web), some more credible then others. We are presenting information supported by clinical studies. To this end, we performed a MEDLINE search and a review of the National Complementary and Alternative Medicine database. Only English-language human studies with surrogate and clinical end points that were extracted from these 2 databases and published in peer-reviewed journals are discussed.

Antioxidants

A relationship between an elevated plasma level of low-density lipoprotein cholesterol (LDL-C) and the development of CHD is well established.[10] LDL-C undergoes oxidation in human circulation, and it has been suggested that oxidized LDL-C is primarily responsible for atherosclerosis through several mechanisms: (1) compared with nonoxidized LDL-C, it is believed to be easily taken up by the "scavenger" macrophages, leading to the development of foam cells; (2) it adversely affects endothelial cells and attracts more macrophages to the subintima; (3) it contributes to vascular smooth muscle proliferation; and (4) it increases vascular tone and blood coagulability.[11] Subsequently, modification of the oxidation of LDL-C by antioxidants has been suggested to prevent the development of atherosclerosis and CHD. Among the naturally occurring antioxidants are vitamin E, vitamin C, and carotenoids, all of which have been suggested to decrease LDL-C oxidation.[12]

Vitamin E is an antioxidant that exists as naturally occurring compounds, including α-, β, γ-, and δ-tocopherol and α-, β-, γ-, and δ-tocotrienol, of which α-tocopherol is the most potent antioxidant.[13] α-Tocopherol also is the form of vitamin E present in human plasma membranes, tissues, and LDL-C.[13] β-Carotene, a precursor to vitamin A, is another antioxidant.[14] Vitamin C, ascorbic acid, is an antioxidant vitamin known to regenerate α-tocopherol from the tocopheroxyl radical, resulting in preservation of lipophilic antioxidant within the LDL-C particles.[11] The antioxidants prevent the oxidation of polyunsaturated fatty acids that are bound to LDL-C.

Recently, there has been interest in using antioxidants to prevent and treat cardiovascular conditions, specifically coronary artery disease. More research efforts have focused on vitamin E because it produced the more consistent positive effects in early cohort studies.[15-23] One of the observational studies, the Nurses' Health Study, evaluated the relationship between vitamin E intake and major coronary disease events as well as overall mortality.[15] Every 2 years for a total of 8 years, the investigators collected questionnaires on dietary intake of vitamin E and other nutrients from 87,245 female nurses without cardiovascular disease at the beginning of the study. During the study period, 552 coronary events and 115 deaths from coronary disease were reported. After adjustment for age and smoking, women taking a median of 208 IU of vitamin E per day (range, 21.6-1000 IU/day), compared with those women taking a median of 2.8 IU/day of vitamin E (range, 1.2-3.5 IU/day), had a reduced risk of major coronary events. The relative risk (RR) was 0.66 (95% confidence interval [CI] = 0.50, 0.87; $P < .001$). The benefit of vitamin E intake in reducing CHD was associated with longer duration of dietary intake of vitamin E; specifically, women who took vitamin E for more than 2 years had an adjusted RR for development of CHD of 0.59 (95% CI = 0.38, 0.91; $P < .05$) compared with those subjects who took vitamin E for less than 2 years. However, no statistically significant benefit of vitamin E consumption was demonstrated for a reduction in cardiovascular mortality, ischemic stroke, coronary-artery bypass surgery, and overall mortality.[15]

A similar descriptive study evaluated the effects of vitamin E and other antioxidants on the development of CHD in 39,910 healthy male healthcare professionals in the Health Professionals Follow-up Study.[16] The participants reported their dietary and supplemental intake of antioxidants in the questionnaires completed every 2 years for a total of 4 years. During the study period, 667 coronary end points, including bypass grafts or angioplasties, nonfatal myocardial infarctions (MIs), and fatal coronary events, were reported. Adjusted for coronary risk factors and intake of other antioxidants, the RR for CHD in vitamin E consumers was calculated to be 0.60 (95% CI = 0.44, 0.81; $P = .01$) for men taking a median of 419 IU of vitamin E per day compared with those taking a median of 6.4 IU of vitamin E per day. Unlike the Nurses Health Study, this study did not demonstrate a significant relationship between duration of vitamin E consumption and risk of developing coronary artery disease. However, there was a trend of reduction in overall mortality in those who consumed high doses of vitamin E per day (RR = 0.78 [95% CI = 0.60-1.01; $P = .06$]).[16] In this study, β-carotene and vitamin C were not reported to reduce the risk of development of coronary artery disease.[16]

Another observational study evaluated vitamin E intake and the risk of CHD in postmenopausal women.[17] The study cohort consisted of 34,486 healthy women between 55 and 69 years of age. The duration of follow-up was 7 years. The vitamin E intake was measured through questionnaires evaluating participants' intake of antioxidants, including vitamin E. During the study period, 242 subjects died of CHD. The death rates from CHD among the highest median vitamin E intake group (≥35.59 IU/day) were not statistically different from those in the lowest vitamin E intake group (<5.68

IU/day); the adjusted RR was 0.96 (95% CI = 0.62, 1.51; P = .27). However, taking vitamin E (any amount) was protective against death from CHD among users compared with nonusers (P = .004). Consumption of vitamins A and C did not affect mortality and morbidity for coronary artery disease.

The longest follow-up cohort study of dietary intake of vitamin E and other antioxidants evaluating the relationship between antioxidant consumption and death from CHD is the Finnish study.[18] The study participants were healthy Finnish men (n = 2748) and women (n = 2385), 30 to 69 years of age. The duration of follow-up was 12 to 16 years. During the study period, 186 men and 58 women died of CHD. Compared with subjects who died from CHD, subjects without CHD consumed more vitamin E (men: 8.23 mg [1 mg = 1.4 IU] vs 8.57 mg; women: 5.98 mg vs 6.65 mg). Additionally, there was a significant inverse relationship between vitamin E intake and mortality from CHD in both men and women: P = .01 and P < .01, respectively.

As part of the Women's Health Initiative, a 40-disease prevention trial conducted by the National Institutes of Health, correlations between serum α- and γ-tocopherol concentrations and cholesterol levels were investigated in 1047 postmenopausal women.[19] Serum cholesterol (r = 0.6; P < .001) and triglyceride (r = 0.53; P < .001) levels were found to be highly correlated with serum α-tocopherol concentrations.

The primary limitations of these epidemiologic cohort and observational studies include the inability to control for all factors that could lead to development of coronary artery disease. In addition, the nurses and the physician studies both included only subjects who were healthcare professionals, a population who inherently may lead a healthier lifestyle than typical patients with coronary artery disease. Finally, results of dietary and vitamin supplementation questionnaires heavily rely on recall and may be inaccurate.

After the results of these observational studies were published, randomized, double-blind, controlled studies were designed to establish a more definitive role of vitamin E supplementation in primary or secondary prevention of CHD. In a primary-prevention, randomized, double-blind, controlled trial, Rapola and colleagues assessed the effects of α-tocopherol supplementation on the incidence of angina pectoris in healthy men.[20] The study sample was derived from the α-Tocopherol, Beta-Carotene Lung Cancer Prevention Study. The participants, 22,269 healthy Finnish male smokers age 50 to 69 years, were randomized to receive 1 of the 4 study regimens: α-tocopherol (50 mg/day), β-carotene (20 mg/day), both α-tocopherol and β-carotene, or placebo for 5 to 8 years. The incidence of angina pectoris was assessed by administering the World Health Organization Chest Pain Questionnaire, self-report of symptoms of chest pain, and a comprehensive health evaluation conducted yearly. During the follow-up period, 1983 new cases of angina pectoris were reported. In this study, participants taking vitamin E supplements did not have a significant reduction in the incidence of angina pectoris. However, looking at a subgroup of 1862 subjects with history of previous MI, vitamin E supplementation slightly decreased the risk of a second nonfatal MI (RR = 0.62; 95% CI = 0.41, 0.96), and β-carotene supplementation significantly increased the risk of fatal MI (RR = 1.75; 95% CI = 1.16, 2.64). It should be noted that this was a population of patients who smoked, which already increased their baseline risk of developing cardiovascular diseases and lung cancer. It also should be noted that the dose of α-tocopherol used was relatively low compared with other vitamin E supplement studies.

Another primary prevention study demonstrated similar results. The Collaborative Group of the Primary Prevention Project was a randomized, controlled, open-label, 2 × 2 factorial trial designed to look at low-dose aspirin (100 mg/day) versus vitamin E (300 mg/day) versus both in the prevention of cardiovascular events in 4495 subjects with 1 or more CHD risk factors (hypertension, hypercholesterolemia, diabetes, obesity, positive family history for CHD, and elderly age).[21] After a mean follow-up of 3.6 years, the trial was stopped due to the strong evidence for use of aspirin in primary prevention of CHD. Vitamin E did not demonstrate any effect in reducing fatal or nonfatal cardiovascular events. However, it is important to note that due to the early termination of the trial, the duration of follow-up was short. Thus, potential beneficial effects may not have become apparent.

In terms of secondary prevention of CHD, the Cambridge Heart Antioxidant Study was a randomized, double-blind, placebo-controlled trial that enrolled 2002 patients with established CHD for a median of 510 days.[22] Of these participants, 1035 were randomized to received α-tocopherol 800 IU (the first 546 patients) or 400 IU (the last 489 patients). Identical placebo was given to the remaining 967 patients. Treatment with vitamin E significantly reduced the number of cardiovascular deaths and nonfatal MIs compared with placebo (41 vs 61

cases; RR = 0.53 [95% CI = 0.34, 0.83; *P* = .005]). The results from this study generated much excitement when first published, as this was the first controlled trial looking at secondary longer-term cardioprotective effects of vitamin E supplements, and positive results were demonstrated in a relatively brief follow-up period (<2 years). However, many questions also were generated from the study. There was no stratification of results based on the 2 doses that the subjects received. It was not possible to determine whether the difference had an effect on outcome. In addition, most mortality observed in the study occurred early in the trial, and the onset of positive benefit was delayed. It was not known whether the higher dose of vitamin E contributed to the increased number of deaths earlier in the study. Recently published studies, including the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico Prevenzione trial (GISSI-prevenzione) and the Heart Outcomes Prevention Evaluation (HOPE) Study, did not show similar results.[23-27] The GISSI-prevenzione investigators designed a randomized, controlled trial looking at the effectiveness of n-3 fatty acids and α-tocopherol in reducing mortality in patients with prior myocardial infarction.[26] In this open-label, placebo-controlled study, subjects were randomly selected to receive 1 g of n-3 fatty acid (n = 2836), 300 mg of vitamin E (n = 2830), or a matching placebo (n = 2830). The primary end points of the trial were death, nonfatal MI, and stroke. After 2 years, the treatment with n-3 fatty acid resulted in an average 15% (2%-26%) decrease in combined incidence of death, nonfatal MI, and stroke. Administration of vitamin E did not produce similar results. Additionally, combined treatment with n-3 fatty acid and vitamin E produced results similar to those in subjects who received only the n-3 fatty acid.

The HOPE study, a double-blind, randomized trial with a 2×2 factorial design, was conducted to examine the effects of ramipril and vitamin E in 9541 patients at high risk of cardiovascular events (those who already had cardiovascular diseases or had diabetes).[27] They were randomized to received 400 IU of vitamin E daily from natural sources or matching placebo and either ramipril or placebo. Mean duration of treatment was 4.5 years. Vitamin E did not reduce the number of primary outcome events (death from cardiovascular disease, MI, or stroke). Vitamin E was, however, well tolerated in this study.

Results to date show controversies regarding the cardioprotective effects of vitamin E. The largest randomized, double-blind study (the HOPE study) did not demonstrate beneficial effects of vitamin E in the primary or secondary prevention of cardiovascular events. No effect was observed with vitamin C, and possibly negative effects were observed with β-carotene. Based on the information available to date, the American Heart Association recommends obtaining antioxidants from the diet by eating well-balanced meals consisting of fruits, vegetables, and whole grains rather than from dietary supplements.[12]

Fish Oils

Fatty acids are an integral component of all cellular membranes. They interact with membrane proteins, which affect receptor function, enzyme activity, signal transduction, and membrane excitability.[28] Recent evidence suggests that derivatives of omega-3 polyunsaturated fatty acids such as eicosapentaenoic acid and docosahexenoic acid, also known as n-3 fatty acids or fish oil, have been shown to have some effect on decreasing triglycerides and platelet and leukocyte reactivity, and can possibly decrease blood pressure in hypertensive subjects.[29-31]

Epidemiologic studies have suggested that increased consumption of cold-water fish or their oil can reduce the risk of mortality from cardiovascular disease by 44%.[32-38] The GISSI-prevenzione investigators demonstrated that treatment with n-3 fatty acid for 2 years resulted in an average 15% (2%-26%) decrease in combined incidence of death, nonfatal MI, and stroke. Fish oil was well tolerated in this study.

Other investigators examined the effect of fish oil on cardiovascular disease risk factors, in search of its mechanism of action in reducing cardiovascular mortality. However, most of these studies enrolled a relatively small number of patients, and doses and duration of fish oil used varied. Morris et al performed a meta-analysis on 31 placebo-controlled trials looking at the effect of n-3 fatty acid in lowering blood pressure.[39] The number of patients enrolled in these 31 trials was small (16-350 patients). All of these trials used encapsulated fish oil. The mean reduction in blood pressure caused by fish oil was 3 mm Hg for systolic blood pressure (95% CI = 1.5, 4.5 mm Hg) and 1.5 mm Hg for diastolic blood pressure (95% CI = 0.8, 2.2 mm Hg). There was a statistically significant dose-response effect. For an n-3 fatty acid dose of <3 g/day, reductions in systolic and diastolic blood pressure of 1.3 and 0.7 mm Hg, respectively, were observed. For doses from 3.3 g to 7 g per day, reductions of systolic and diastolic blood pressure of 2.9 and 1.6 mm Hg, respectively, were observed. For

doses of 15 g per day, reductions of 8.1 and 5.8 mm Hg in systolic and diastolic blood pressure, respectively, were observed. Blood pressure reduction was observed in hypertensive patients, but not in normotensive volunteers. Variations in length of treatment (3 to 24 weeks), type of placebo, and study design (crossover or parallel) did not appear to account for any inconsistent findings among studies. Fish oil supplementation was well tolerated in the studies reviewed by the meta-analysis.

In addition to its antihypertensive effects, n-3 fatty acid has been studied for its antiarrhythmic effects. Siscovick et al performed a population-based case-control study assessing whether dietary intake of n-3 fatty acid was associated with a reduced risk of primary cardiac arrest.[33] A total of 334 case patients with primary cardiac arrest between 1988 and 1994 and 493 population-based control cases were examined. All case and control subjects were free of prior clinical heart disease and other major comorbidity. Compared with no dietary intake of n-3 fatty acids, consumption of 5.5 g of n-3 fatty acids per month (the equivalent of one fatty fish meal per week) was associated with a 50% reduction in the risk of primary cardiac arrest (odds ratio = 0.5, 95% CI = 0.4, 0.8). Compared with an n-3 fatty acid level of 3.3% of total fatty acids in red blood cell membranes (the mean of the lowest quartile), an n-3 fatty acid level of 5% of total fatty acids in red blood cell membranes (the mean of the third quartile) was associated with a 70% reduction in the risk of primary cardiac arrest (odds ratio = 0.3; 95% CI = 0.2, 0.6). Another study of the antiarrhythmic effects of n-3 fatty acid was performed by Sellmayer and colleagues. This was a prospective, randomized, doubled-blind, placebo-controlled study examining the effects of dietary fish oil on the number of ventricular premature complexes.[40] Patients randomized to receive n-3 fatty acid consumed 0.9 g of eicosapentaenoic acid and 1.5 g of docosahexaenoic acid in fish oil daily. Twenty-four–hour Holter monitoring was performed at baseline and after 16 weeks of fish oil consumption. A positive response to treatment was defined as a reduction in premature ventricular complexes by more than 70%. Seventy-nine patients were enrolled (40 receiving fish oil and 39 receiving placebo). At baseline, the number of premature ventricular complexes did not differ significantly between the 2 groups. During the trial, premature ventricular complexes decreased by 48% in patients receiving fish oil versus 25% in those receiving placebo ($P = .052$). The proportion with a reduction in ventricular premature complexes by more than 70% was 44% in the fish oil group and 15% in the placebo group ($P < .01$). The results from this study indicated that dietary supplementation with a moderate dose of fish oil has antiarrhythmic effects. However, further studies are required to examine whether such results are reproducible, whether reducing ventricular premature complexes is directly related to benefits in mortality, and to define the therapeutic dose of fish oil as an antiarrhythmic agent.

In terms of other cardiovascular risk factors such as hyperlipidemia, despite being reported to reduce triglycerides by approximately 30%, n-3 fatty acid has consistently failed to demonstrate any beneficial effects in preventing coronary atherosclerosis.[41-43]

Fish oil appeared to be relatively well tolerated when used in clinical studies. The most common adverse reactions reported with fish oil products include fishy taste, belching, nosebleeds, nausea, and loose stools. Based on clinical trial information available to date, omega-3 fatty acid may be helpful in primary or secondary prevention of CHD. However, due to the potential increased risk of bleeding (3% to 9% reported in studies), the risk-versus-benefit ratio has to be carefully evaluated in each patient before it can be routinely recommended that patients consume extra supplements. Doses evaluated in different studies were not equivalent; therefore, the therapeutic dose remains to be determined.

Coenzyme Q10

Coenzyme Q10, also known as ubiquinone, primarily has been used for the treatment of congestive heart failure. Some evidence also suggests its use in angina, diabetes, hypertension, and cancer, and as a myocardium protectant in anthracycline-containing antineoplastic regimens.[44,45] Co-Q10 is a coenzyme found in all aerobic organisms[44] and plays a major role in mitochondrial oxidative phosphorylation and adenosine triphosphate production. It has a positive inotropic effect similar to that of digoxin, as well as free-radical scavenging ability. It also appears to have membrane-stabilizing properties and acts as an antioxidant in conjunction with vitamin E.[44]

There is evidence suggesting that a deficiency of Co-Q10 may exacerbate the poor contractility of myocardial cells seen in patients with heart failure.[46] The concentration of Co-Q10 is decreased in the myocardial cells of this patient population, and the extent of myocardial Co-Q10 deficiency seems to correlate with the clinical severity of heart failure.[46] Because the myocardium of patients with congestive

heart failure demonstrates oxidative stress and Co-Q10 prevents lipid peroxidation, this substance could conceivably prevent myocardial destruction.

Khatta and colleagues conducted a randomized, double-blind, placebo-controlled trial to determine the effect of Co-Q10 on peak oxygen consumption, exercise duration, and left ventricular ejection fraction.[47] Forty-six patients with congestive heart failure (New York Heart Association [NYHA] class III and IV symptoms) were randomly assigned to receive 200 mg per day of Co-Q10 or placebo for 6 months. In this study, left ventricular ejection fraction, peak oxygen consumption, and exercise duration did not change in either treatment arm. Coenzyme Q10 did not improve myocardial function in patients with congestive heart failure.

Baggio and colleagues, in a multicenter, postmarketing drug surveillance study, examined the safety and clinical efficacy of Co-Q10 as adjunctive treatment in patients with congestive heart failure who were treated with conventional therapy for at least 6 months.[48] A total of 2359 patients with stable congestive heart failure of NYHA class II and III were followed over a 3-month period. The daily dosage of Co-Q10 was 50 to 150 mg per day. Compared with the baseline measurements, significant reductions in respiratory rate (20.6 ± 3.5 breaths per minute [brpm] vs 21.2 ± 3.9 brpm at baseline; $P < .05$), systolic blood pressure (143.8 ± 14.9 mm Hg vs 149.4 ± 18 mm Hg at baseline; $P < .05$), diastolic blood pressure (82.0 ± 6.8 mm Hg vs 83.7 ± 7.6 mm Hg at baseline; $P < .05$), and heart rate (75.1 ± 8.2 beats per minute [bpm] vs 78.4 ± 9.6 bpm at baseline; $P < .05$) were observed at 3 months. Although these differences achieved statistical significance, the absolute magnitude of the changes was not clinically significant. Studies that focus on end points such as symptom improvement or increase in exercise tolerance may better define the role of Co-Q10 supplementation as adjunctive management for heart failure. In addition, this study was not placebo controlled; whether the beneficial effects truly resulted from Co-Q10 supplementation is not known.

In addition to a possible beneficial effect in patients with congestive heart failure, limited evidence also suggested that Co-Q10 might be useful in the treatment of patients with coronary artery disease and angina pectoris.[49,50] Some investigators suggest that administration of Co-Q10 may reduce myocardial injury due to ischemia, hypoxia, or other metabolic inhibitors.[49] Amikawa et al examined the effects of Co-Q10 on exercise tolerance in 12 patients with chronic stable angina.[49] The dose of Co-Q10 used was 150 mg per day. Co-Q10 therapy had no significant effect on angina symptoms, but its administration was associated with a significant increase in the treadmill exercise time (345 ± 102 seconds in the placebo group compared with 406 ± 114 seconds in the Co-Q10 group; $P < .05$). Furthermore, a delay in ischemic electrocardiogram changes was observed (time to 1 mm of ST-segment depression was 196 ± 76 seconds in the placebo group compared with 284 ± 104 seconds in the active group; $P < .01$). The small sample size of the study, however, did not allow a definite conclusion to be made.

Langsjoen et al further confirmed a beneficial effect of Co-Q10.[50] The investigators studied 424 patients with various cardiovascular diagnoses over an 8-year period (average follow-up time = 17.8 months) to determine the effect of Co-Q10 on cardiovascular diseases. Coenzyme Q10 was added to each patient's medical regimen. Patients were then monitored during regular clinic visits where various cardiologic studies were performed. The dosage range used in this analysis varied from 75 mg to 600 mg per day. Patients were subdivided into 6 categories for the purposes of the analysis: those with idiopathic dilated cardiomyopathy, primary diastolic dysfunction, hypertension, ischemic cardiomyopathy, valvular heart disease, and mitral valve prolapse. In general, the investigators observed symptomatic improvements in occurrence of chest pain, fatigue, dyspnea, and palpitations. Overall, 247 (58.2%) patients demonstrated improvements by 1 NYHA functional class, 120 (28.3%) patients by 2 NYHA classes, and 5 (1.2%) patients by 3 NYHA functional classes. Patients with hypertension ($P < .02$) and mitral valve prolapse ($P < .06$) also showed some improvement in the left ventricular end diastolic dimension (normal heart size of <5.7 cm) compared with baseline. Left ventricular wall thickness showed a significant improvement in all groups of patients except for patients with valvular heart disease ($P < .05$). This study, compared with others, enrolled a larger number of patients and had a longer follow-up period. However, the lack of control group and the wide range of doses administered did not allow a definitive role of Co-Q10 to be established.

Langsjoen et al also reported a significant decrease in the number of different cardiovascular drugs used: a 19% decrease in the use of digoxin, a 51% decrease in use of β-blockers, a 21% decrease in use of long-acting nitrates, a 61% decrease in the use of antiarrhythmic drugs, a 24% decrease in use

of calcium channel blockers, a 32% decrease in the use of angiotensin-converting enzyme inhibitors, and a 37% decrease in the use of other antihypertensive drugs.[50] Whether the decreased use of cardiovascular medications indicated an improvement in disease states could not be determined.

Overall, published literature on the use of Co-Q10 demonstrated trends in improvement of symptoms of congestive heart failure and ischemic heart disease. More rigorous studies are required to confirm these results due to the contradictory findings in some studies. The suggested dosage for patients with heart disease varied anywhere from 100 to 200 mg per day in clinical studies.[45] Side effects reported with Co-Q10 included some mild gastritis, nausea, and diarrhea; rash; photophobia; and irritability when taken at recommended doses.[44,45]

Garlic (*Allium Sativum*)

Garlic is indicated by the German Commission E for use in the support of dietary measures for treating hyperlipidemia and to prevent atherosclerosis.[51] Garlic also has been reported to have antiplatelet and antihypertensive effects.[51] Many reports have been published on the use of garlic in treatment of hyperlipidemia and hypertension. However, most of them enrolled small numbers of patients. Two groups of investigators performed meta-analyses on these small studies.

Silagy and Neil evaluated the effect of garlic on blood pressure.[52] In this meta-analysis, only prospective, randomized studies with 2 or more treatment group comparisons and a duration of at least 4 weeks were included (8 trials were included in total). Each of these studies included patients with elevated blood pressure. Six of the studies were placebo controlled. One study compared garlic with reserpine and a diuretic, and another compared garlic with benzofibrate. All but 1 of the studies were double blinded. All the studies used the same dried garlic powder preparation in dosages of 600 to 900 mg daily (equivalent to 1.8-2.7 g of fresh garlic per day) for 1 to 12 months. The pooled mean reduction in systolic blood pressure was 7.7 mm Hg more with garlic than placebo (95% CI = 5, 17.2 mm Hg). Similarly, the pooled mean reduction in diastolic blood pressure was 5 mm Hg more with garlic (95% CI = 3.4, 9.6 mm Hg). However, none of these studies assessed patient compliance with the garlic supplement. No significant increase in adverse effects was reported with garlic.

Warshafsky and colleagues performed another meta-analysis on studies that evaluated the effect of garlic on total serum cholesterol.[53] Trials were included if they were randomized and placebo controlled and if at least 75% of the study patients had total cholesterol levels greater than 200 mg/dL (5 studies were included in total). The studies used various oral garlic preparations (3 used Kwai powder tablets, 1 used a spray-dried powder, and 1 used an aqueous extract). Doses varied from 600 to 900 mg per day. Patients treated with garlic consistently showed a greater decrease in total cholesterol levels compared with those receiving placebo (net cholesterol decrease of 23 mg/dL [95% CI = 17, 29 mg/dL]). Results for individual lipoproteins were not reported.

Garlic odor on the breath and body is the most commonly reported side effect of garlic supplements. Odorless garlic formulations are available. However, odorless garlic is prepared either by adding other chemical substances to mask the odor or by cooking the garlic, which may destroy some of the active ingredients. Therefore, whether odorless garlic exerts the same therapeutic action as natural garlic is not known. Consumption of garlic also has been reported to be associated with decreased platelet aggregation and bleeding events.[54-59] Among the case reports describing adverse events associated with garlic consumption is an incident of spinal epidural hematoma diagnosed in an 87-year-old man after consumption of four cloves (~2 g) of garlic per day for an unknown period of time.[54] The bleeding episode was believed to be associated with platelet dysfunction that was reflected by prolonged bleeding time. Another episode of prolonged bleeding was reported in a woman undergoing mammoplasty who was a chronic "heavy garlic user."[55] Upon discontinuation of garlic, no further episodes of prolonged bleeding were reported. A hemorrhagic episode has been described in a 72-year-old man who underwent transurethral resection of the prostate.[56] The patient reported taking no medications before the procedure except for regular intake of garlic tablets for many years. The antiplatelet effects of garlic, however, have not been studied for therapeutic purposes.

Meta-analyses have demonstrated that garlic has potential beneficial effects in controlling blood pressure and reducing total cholesterol, and doses used in these studies were well tolerated However, in view of the potential side effects of heavy garlic consumption, patients who choose to consume extra garlic supplements need to be monitored, especially those who are concurrently taking antiplatelet agents and/or anticoagulants.

L-arginine

L-arginine has been studied extensively since 1988 as a natural metabolic donor of nitric oxide. Data from basic and clinical research demonstrate that intravenous supplementation of *L*-arginine augments endothelial function favorably by enhancing vasodilation (through nitric oxide) and reducing macrophage adhesion. Numerous experimental and clinical studies have demonstrated the therapeutic potential of *L*-arginine supplementation in relatively high doses for the prevention and treatment of a broad spectrum of cardiovascular disorders, as well as modification of cardiovascular risk factors. However, most studies published to date looked at the acute, single-dose effect with intravenous administration of *L*-arginine (doses varied from 0.5 g to 35 g). The results of these studies, although supporting the potential role of *L*-arginine, have little clinical application. However, several studies looked at the effect of oral *L*-arginine supplementation using doses of 3 g to 21 g per day for 3 days to 6 weeks in the management of patients who had hypertension, ischemic heart disease, heart failure, and peripheral vascular diseases, with clinical end points as their primary outcomes.

Because abnormalities in endothelium-dependent vasodilation may be involved in the pathogenesis of hypertension, *L*-arginine could have a blood pressure-lowering effect. Mehta et al demonstrated that intravenous administration of *L*-arginine 0.5 g/kg significantly reduced mean arterial blood pressure by 9.3 mm Hg ($P < .005$) in 10 healthy volunteers after an average of 32 minutes of *L*-arginine administration.[60] In an open-label study, Pezza et al evaluated the effect on blood pressure of oral *L*-arginine (2 g 3 times daily for 6 weeks) in 20 subjects with poorly controlled hypertension despite receiving 3 months of enalapril and hydrochlorothiazide therapy.[61] *L*-arginine significantly reduced systolic blood pressure by a mean of 14 mm Hg and diastolic blood pressure by a mean of 8 mm Hg compared with baseline ($P < .05$) at the end of 6 weeks. Studies of *L*-arginine for blood pressure control are among the few that utilized clinical end points (eg, reduction of blood pressure). However, only 1 study included hypertensive patients, the sample size was small, and there were many unspecified confounding factors that might have affected blood pressure. Therefore, a large, long-term randomized, controlled trial is needed before *L*-arginine can be recommended as adjunctive therapy for blood pressure control.

L-arginine also has been studied in patients with ischemic heart disease. In a randomized, double-blind, placebo-controlled study, Ceremuzynski et al examined the effect of oral *L*-arginine (1 g 3 times daily for 3 days) on exercise capacity in 22 patients with stable angina pectoris.[62] Compared with placebo, *L*-arginine supplementation significantly increased the mean exercise time to maximal ST-segment depression (from 501 seconds to 555 seconds for placebo and from 531 seconds to 700 seconds for *L*-arginine; $P < .04$). A significant increase in the maximum workload also was demonstrated in the *L*-arginine group (from 5 to 5.7 metabolic equivalents for placebo and from 6.2 to 7.4 metabolic equivalents for *L*-arginine; $P < .006$). It was concluded that oral *L*-arginine supplementation had a beneficial effect on exercise capacity in patients with stable angina.

Rector et al performed a randomized, placebo-controlled study evaluating the effects of 6 weeks of oral *L*-arginine therapy (5.6-12.6 g/day) on forearm blood flow in 15 heart failure patients with an average ejection fraction of 18%.[63] Compared with placebo, supplemental oral *L*-arginine significantly increased forearm blood flow during forearm exercise. Furthermore, *L*-arginine increased the 6-minute walk distance significantly (mean of 390 m to 422 m; $P < .05$). It also improved the Living with Heart Failure Questionnaire scores, which assess how heart failure affects a patient's quality of life, from a mean score of 55 to a mean score of 42 ($P < .05$). A lower score indicates fewer limitations in daily activities due to heart failure.

Maxwell et al did a study of *L*-arginine that utilized clinical end points. They investigated the effects of a commercially available *L*-arginine bar (HeartBar®) in enhancing the activity of endothelium-derived nitric oxide in patients with claudication from atherosclerotic peripheral arterial disease.[64] The study was a 2-week, double-blind, placebo-controlled trial of 41 subjects randomized to 3 groups: 12 subjects received 2 *L*-arginine bars per day (3 g of *L*-arginine per bar), 15 subjects received 1 *L*-arginine bar per day, and 14 subjects received placebo. Subjects were asked to continue their usual diet pattern. After 2 weeks of treatment, the pain-free walking distance increased by 66% ($P < .05$) and the total walking distance increased by 23% ($P = .05$) in the group consuming 2 bars per day, compared with baseline. Scores on the general and emotional functioning components of the Medical Outcome Survey (SF-36) also improved. *L*-arginine levels were not reported in this study. Significant effects were not observed in the group receiving 1 *L*-arginine bar per day or the control group. The

effects of the 2 weeks of *L*-arginine supplementation were maintained even after 10 weeks.

As with the other trials, generalization of these results is limited by the small sample size. In addition, HeartBar® contains other ingredients such as soy protein, DL-alpha-tocopherol, niacinamide, pyridoxine, folic acid, and cyanocobalamin. Whether any of these ingredients contributed to the observed effects of this supplement cannot be determined.

The most common reported side effects of *L*-arginine included nausea and diarrhea. However, because *L*-arginine therapy may be used chronically, more studies are required to evaluate potential long-term side effects. Patient compliance with the higher dose may be poor because of the slightly bitter taste of *L*-arginine. The average American diet provides about 5.5 g of arginine daily, mostly from meat and fish.[65] Therefore, vegetarians may be at higher risk of developing arginine deficiency and have a greater need for arginine supplementation.

Soy

There is increasing evidence that consumption of soy protein in place of animal protein lowers serum cholesterol levels and may provide other cardiovascular benefits. Epidemiologists have noted that Asian populations who consume soy food as part of their diet have a lower incidence of cardiovascular diseases.[66] Soy is the major food source of isoflavones. Isoflavones have a weak estrogenic effect and some antiandrogenic effect, which may lead to soy's beneficial effects in lowering cholesterol and increasing high-density lipoprotein cholesterol (HDL-C).[67]

A meta-analysis including 38 controlled clinical studies concluded that substituting soy protein for animal protein significantly lowered total cholesterol by 9.3%, LDL-C by 12.9%, and triglycerides by 10.5% without affecting HDL-C. These effects were greater in subjects with higher baseline cholesterol values.[68] The cholesterol-lowering effect of soy was in addition to the effect seen with a diet low in saturated fat and cholesterol (The National Cholesterol Education Program [NCEP] Step 1 diet). No difference was observed in terms of efficacy between different forms of soy protein.

In a recent study, postmenopausal women on the NCEP Step 1 diet consumed 40 g/day of soy protein with either 56 or 90 mg of isoflavones daily or casein (a protein found in milk of all mammals) for 6 months. Both soy groups had significantly better blood lipid profiles (average change from baseline was an 8.2% decrease in non-HDL-C and a 4.4% increase in HDL-C) than the casein group.[69]

Another 9-week human study comparing the effects of soy protein (25 g/day) containing various levels of isoflavones with the effects of casein[70] found that consumption of the highest isoflavone level (62 mg/day) results in significantly lower total and LDL-C values than those in the casein group. Subjects with the highest LDL-C levels (top 50%) also experienced significant reductions in total and LDL cholesterol with 36 mg/day of isoflavones. However, those consuming soy protein with lower isoflavone levels (<27 mg/day) did not have a significant change in their cholesterol profile.

Another dose-response study, however, demonstrated that consumption of soy protein in doses ranging from 20 to 50 g/day for 6 weeks led to significantly greater reductions in non-HDL-C compared to baseline (1.5%-4.5%), with higher levels being more effective.[71]

A more recent randomized, double-blind, controlled study looking at consumption of soy protein (50 g/day containing 165 mg of isoflavone for 6 weeks) in type 2 diabetic subjects also demonstrated that soy protein significantly reduced LDL-C by 10% ($P < .05$), the LDL/HDL ratio by 12% ($P < .05$), apolipoprotein B100 by 30% ($P < .01$), triglycerides by 22% ($P < .05$), and homocysteine by 14% ($P < .01$).[72]

The American Heart Association Dietary Guidelines for Healthy American Adults stated that although there was some evidence that when soy protein was substituted for animal protein, total and LDL cholesterol could be reduced, these findings were inconclusive. Therefore, although they did not discourage the use of soy protein, no recommendation was made to definitively include soy protein in the diet.[73] However, based on the same findings, the FDA recently published its food-labeling health claim for soy protein and cholesterol reduction, stating that 25 g/day (the lowest dose used in clinical studies) of soy protein, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease.[74] Soy foods have been a major part of Asian diets. If patients enjoy soy foods, there is no disadvantage to including these foods in their diet. However, because different clinical studies used different doses, the exact dose-response relationship needs to be further studied before an optimal amount can be determined.

Sterol Ester

Sterol is an essential constituent of cell membranes in animals and plants. Cholesterol is the sterol of mammalian cells, whereas phytosterols

(such as sitosterol, campesterol, and stigmasterol) are derived from plants. Since the 1950s, phytosterols, mainly sitosterol, have been added to patients' diets for the treatment of hypercholesterolemia.[75] Phytosterols inhibit cholesterol absorption; sitostanol, ingested in a soluble form, has been observed to have greater effects than other phytosterols.[76] Therefore, margarine rich in sitostanol ester has been developed (Benecol®) and has been shown to reduce cholesterol levels and to be well tolerated in preliminary short-term studies.[76-79]

Miettinen et al conducted a longer-term (1-year follow-up) double-blind study in 153 randomly selected subjects with mild hypercholesterolemia (total cholesterol ≥216 mg/dL and triglycerides <265 mg/dL), looking at the efficacy and tolerability of sitostanol-ester margarine.[80] These subjects replaced 24 g of their normal daily dietary fat intake with 3 portions per day of sitostanol-ester margarine containing 1 g of sitosterol per 8-g portion. The average 1-year reduction in serum cholesterol was 10.2% in the sitostanol ester group compared with an increase of 0.1% in the control group. The difference in the change in serum cholesterol concentration between the 2 groups was –24 mg/dL (95% CI = -17, –32 mg/dL; $P < .001$). The difference in the change in LDL-C concentration between the 2 groups was –21 mg/dL (95% CI = –14, –29 mg/dL; $P < .001$). No effect was observed on triglyceride and HDL-C concentrations.

Campesterol, a dietary plant sterol not synthesized in the body, is absorbed to such a small extent that its serum concentration is generally less than 1% of the cholesterol values. However, it was measured in the study by Miettinen et al because it reflected the intestinal absorption of cholesterol. Serum campesterol was decreased by 36% in the sitostanol group, and the reduction was directly correlated with the reduction in total cholesterol ($r = 0.57$; $P < .001$). The investigators concluded that substituting sitostanol-ester margarine for part of the daily fat intake in subjects with mild hypercholesterolemia was effective in lowering serum total cholesterol and LDL-C and was well tolerated even when administered long term up to 1 year.

Despite the fact that phytosterols seem to be well tolerated according to most case reports and studies, there are some observations that phytosterols can reduce the absorption of fat-soluble vitamins such as β-carotene, vitamin D, and vitamin E.[81-84] Because food supplements such as plant sterols are likely to be shared among family members, the long-term impact on children, pregnant women, or nonhypercholesterolemic individuals needs to be determined. Currently, the American Heart Association recommends that further studies and large-scale monitoring are needed to determine the long-term safety of phytosterol-containing foods in both normocholesterolemic adults and children. Based on current data, this type of product should be reserved for adults who require lowering of total and LDL cholesterol levels because of hypercholesterolemia or the need for secondary prevention after an atherosclerotic event.[85] The latest NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults guidelines concur with those of the American Heart Association and recommend the use of plant stanols/sterols (2 g/day) to enhance LDL-C reduction as part of therapeutic lifestyle changes.[86]

Chelation Therapy

Chelation therapy is defined as the use of repeated intravenous administration of ethylenediamine tetraacetic acid (EDTA), usually in combination with vitamins, trace elements, and iron supplements, as a treatment for a variety of diseases such as heavy metal poisoning.[87] As an AP, chelation therapy has been reported to be used for the treatment of vascular diseases.[87] Numerous case reports and results of uncontrolled trials have been published, with controversial results.[87] Only 1 controlled trial has been performed to date. Kitchell et al conducted a placebo-controlled, double-blind, crossover study on 9 patients with CHD.[88] Patients were assigned to receive 20 injections of placebo or EDTA over 3-month periods. Exercise tolerance on the treadmill was assessed. The results were not analyzed statistically, but it was mentioned that 2 of the 4 patients receiving EDTA benefited after 6 and 12 weeks of therapy, respectively. The side effects associated with chelation therapy include renal failure, arrhythmias, tetany, hypocalcemia, hypoglycemia, hypotension, bone marrow depression, prolonged bleeding time, convulsions, and respiratory arrest.[89-92] Therefore, until well-controlled studies are performed, chelation therapy is not recommended for management of cardiovascular diseases.

Potential Interactions Between Alternative Pharmacotherapy and Medications Commonly Used in Patients with Cardiovascular Diseases

In addition to resorting to APs that may help improve their cardiovascular conditions, patients with cardiovascular diseases may consume other APs not for the purpose of preventing or treating their heart disease. These other APs may be taken

for other concurrent health conditions or for general well-being. Some of them may have interactions with traditional prescription medications that the patients are taking for their cardiovascular conditions. Therefore, it is important to include these interactions as part of patients' therapeutic monitoring. Data regarding interactions of AP and medications commonly used in patients with cardiovascular diseases are sparse. Information reported here either is from published sources or is based on pharmacologic mechanisms indicating that certain agents might interact.

Garlic, Antiplatelets, and Anticoagulants. To date, no studies have been published reporting interactions between warfarin and garlic. However, as discussed previously, consumption of garlic has led to increased bleeding. Thus, the coadministration of garlic and antiplatelets (eg, aspirin) or garlic and anticoagulants (eg, warfarin) in patients with cardiovascular diseases has the potential to increase the risk of bleeding. Because the therapeutic range of garlic is not firmly established, routine consumption of garlic supplements for prevention and treatment of cardiovascular disease (in addition to regular dietary consumption) by patients who are taking antiplatelets or anticoagulants is not recommended. Those who consume garlic supplements should be closely monitored for bleeding.

Ginkgo biloba *and Warfarin.* Ginkgo is another popular alternative pharmacotherapy used for its potential beneficial effects in improving memory.[93] A case report describing a possible interaction between warfarin and ginkgo (*Ginkgo biloba*) has been published.[94] A 78-year-old woman, previously stabilized on warfarin therapy for 5 years, developed an intracerebral hemorrhage after 2 months of ginkgo consumption.[94] Upon discontinuation of ginkgo, anticoagulation reversed spontaneously to its previous stabilized values. Other case reports have been published describing hemorrhagic events associated with consumption of ginkgo alone. A 33-year-old woman developed bilateral subdural hematomas after consuming ginkgo 60 mg twice daily for 2 years.[95] Concomitant medications included acetaminophen, ergotamine, and caffeine. After discontinuation of ginkgo, her bleeding times returned to normal. Another case of subdural hematoma was described in a 72-year-old woman taking ginkgo 50 mg 3 times a day for 6 to 7 months.[96] A bleeding episode was described in a 70-year-old man who developed spontaneous anterior chamber hyphema 1 week after starting ginkgo extract 40 mg twice daily.[97] In addition to ginkgo, he had been taking aspirin 325 mg daily for 3 years before this incident. After discontinuation of ginkgo and continuation of aspirin therapy, bleeding resolved and no recurrences were reported. Another case of subarachnoid hemorrhage was reported in a 61-year-old man who had taken ginkgo 40 mg 3 or 4 times a day for more than 6 months.[98] Upon discontinuation of ginkgo, bleeding time returned to normal. A small study in 6 volunteers evaluated the effects of ginkgolide mixture BN 52063 on platelet-activating factor. The authors reported that the ginkgolide mixture resulted in inhibition of platelet-activating factor–induced platelet aggregation in vitro ($P < .001$).[99] Therefore, patients with cardiovascular diseases or bleeding disorders, especially those consuming antiplatelets and anticoagulants, should be advised against consuming ginkgo supplements.

Ginseng and Warfarin. Ginseng is yet another popular AP used for improving energy level and increasing concentration.[93] One case report identified a reduction in the international normalized ratio (anticoagulation effect) in a patient stabilized on warfarin after consumption of Asian ginseng (*Panax ginseng*).[100] A study in rats reported no effect of ginseng on the absorption and elimination of a single dose of warfarin.[101] There was no change in the effect on prothrombin time during warfarin administration with or without ginseng at steady state. In contrast, several reports have been published describing bleeding episodes associated with ginseng consumption alone.[102,103] Like garlic and ginkgo, the consumption of ginseng should be discouraged in patients with cardiovascular diseases who are receiving antiplatelets or anticoagulants.

Saint John's Wort and Digoxin. St. John's wort has been used for the treatment of anxiety and depression.[93] Johne and colleagues studied a potential interaction between St. John's wort (*Hypericum perforatum*) and digoxin.[104] In a single-blind, placebo-controlled, parallel study, 25 healthy volunteers received an oral loading dose of digoxin 0.25 mg twice a day for 2 days and then digoxin 0.25 mg orally daily for the remainder of the study period. On day 5 of the study, either St. John's wort extract LI160, 300 mg of dried hypericum extract 3 times a day, or identical placebo (also given 3 times daily) was introduced for the following 10 days. Pharmacokinetic parameters of digoxin were compared on days 5, 6, and 15 of the study period. A single dose of St. John's wort extract did not result in any statistically significant change in digoxin pharmacokinetic parameters. However, after 10 days of coadministration of digoxin and St. John's wort

extract, investigators reported significant decreases, compared with placebo, in the mean digoxin area under the concentration-time curve (12.9 ± 2.3 μg × h/L vs 17.2 ± 4.0 μg × h/L; $P = .0035$), the mean peak digoxin concentration (1.4 ± 0.4 μg/L vs 1.9 ± 0.5 μg/L; $P = .0095$), and the mean trough digoxin concentration (0.47 ± 0.1 μg/L vs 0.58 ± 0.13 μg/L; $P = .023$).[104] The mechanism of interaction was believed to be St. John's wort's ability to induce intestinal *P*-glycoprotein transporter, thus decreasing the bioavailability of digoxin. Therefore, coadministration of St. John's wort extract and digoxin should be avoided.

Summary

Different APs have been studied in patients who have risk factors for developing cardiovascular disease, as well as in those suffering from various cardiovascular conditions. Antioxidants, including vitamin E, vitamin C, and β-carotene, have not been consistently proven to be beneficial in reducing cardiovascular mortality; therefore, supplements of these antioxidants beyond regular dietary consumption are not routinely recommended to prevent or treat cardiovascular diseases. Fish oils have been proven to be beneficial in reducing triglyceride levels, blood pressure, and cardiovascular events and are relatively well tolerated. However, studies used a wide variety of doses and duration of treatment. Therefore, until a therapeutic dosage regimen is defined, patients should be encouraged to increase fish consumption in their diet but not to routinely consume an n-3 fatty acid supplement. Use of Co-Q10 in patients with congestive heart failure is controversial. Studies did not demonstrate consistent benefits. Again, routine recommendation is not warranted.

Garlic may lower blood pressure and total cholesterol levels. However, due to the potential risk for increased bleeding, the use of garlic in patients with cardiovascular diseases should be avoided, especially in patients concomitantly taking antiplatelets and anticoagulants. Clinical studies have demonstrated the therapeutic potential of *L*-arginine supplementation for the prevention and treatment of a broad spectrum of cardiovascular disorders, as well as modification of cardiovascular risk factors. However, most human studies currently available are small. Before oral supplementation of *L*-arginine can be recommended routinely, larger studies are required to confirm its effects and to better define the side-effect profile, especially with administration of higher doses and chronic therapy. There is increasing evidence that consumption of soy protein in place of animal protein lowers blood cholesterol levels and may provide other cardiovascular benefits. The FDA has stated that 25 g/day of soy protein as part of a diet low in saturated fat may reduce the risk of heart disease. However, the use of soy extracts of isoflavones as dietary supplements cannot be recommended because of lack of evidence.

Most AP compounds are currently available as food supplements and therefore are not regulated by the FDA. The Dietary Supplement Health and Education Act of 1994 did not subject dietary supplements to the premarket safety evaluations normally required for other new ingredients or for new uses of old food ingredients.[105] If APs are to be recommended for therapeutic use, better regulation and quality assurance in product content will be needed.

Recently, the United States Pharmacopeia (USP) developed a pilot program for quality assessment of ingredients in dietary supplements.[106] USP's certification program will address the need for a single national standards certification program for dietary supplements and botanicals. The program will be designed to complement the FDA's regulation of dietary supplements under the Dietary Supplement Health and Education Act. Manufacturers, trade associations, and other stakeholders are invited to participate. A manufacturer that successfully completes the pilot phase by demonstrating adherence to the criteria and passing the manufacturing audit will be granted the use of USP's certification mark upon launch and timely participation in the full program. The mark will communicate to healthcare practitioners, retail distributors, consumers, and all market stakeholders that USP has monitored the quality of a product's ingredient(s). With this information, more rigorous clinical studies can be performed with these agents, and the results from those studies can guide us to better define the role of AP in managing patients with cardiovascular diseases.

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CONTINUING PHARMACY EDUCATION

This course has been approved for a total of two (2) contact hours of continuing education credit (0.2 CEUs) by the University of Tennessee College of Pharmacy. The University of Tennessee College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. ACPE Program Number: 064-999-02-200-H-01. This course expires March 31, 2004.

Instructions

After reading the article "Use of Alternative Pharmacotherapy in Management of Cardiovascular Diseases," select the best answer to each of the following questions.

1. It is reasonable to expect patients with cardiovascular diseases to resort to alternative pharmacotherapy for prevention and treatment of their diseases because:

a) cardiovascular diseases are the number 1 cause of death in United States
b) there is a growing incidence of cardiovascular diseases
c) cardiovascular diseases are chronic medical conditions and patients with chronic medical conditions often resort to alternative pharmacotherapy
d) there is a tremendous amount of literature supporting the efficacy and safety of alternative pharmacotherapy in cardiovascular diseases

2. Which of the following explains the mechanism of antioxidants in preventing atherosclerosis?

a) they prevent low-density lipoprotein cholesterol (LDL-C) from undergoing an oxidation reaction and from being taken up by scavenger macrophages
b) they inhibit the formation of LDL-C, thus reducing the incidence of atherosclerosis
c) they decrease vascular tone and blood coagulability
d) they oxidize LDL-C, reducing its ability to form atherosclerosis

3. Results from clinical trials published to date strongly support the use of vitamin E but not vitamin C and β-Carotene for prevention of cardiovascular diseases.

a) true
b) false

4. Which of the following studies did not support the benefits of vitamin E in reducing cardiovascular mortality?

a) Heart Outcomes Prevention Evaluation (HOPE) study
b) the Finnish study
c) the Nurses Health study
d) all of the above

5. Which of the following is the current recommendation made by the American Heart Association regarding the use of antioxidants:

a) 400 IU of vitamin E daily
b) 800 IU of vitamin E daily
c) 400 IU of vitamin E and 1 g of vitamin C daily
d) consume well-balanced meals consisting of fruits, vegetables, and whole grains; no supplement necessary

(CPE questions continued on following page)

Use of Alternative Pharmacotherapy in Management of Cardiovascular Diseases

ACPE Program Number: 064-999-02-200-H-01

(PLEASE PRINT CLEARLY)

Name _____

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City _____

State/ZIP _____

Daytime Phone # _____

States in Which CE Credit is Desired _____

Please circle your answers:

1. **a b c d**	6. **a b c d**	11. **a b c d**	16. **a b c d**
2. **a b c d**	7. **a b c d**	12. **a b c d**	17. **a b**
3. **a b**	8. **a b c d**	13. **a b c d**	18. **a b c d**
4. **a b c d**	9. **a b c d**	14. **a b c d**	19. **a b**
5. **a b c d**	10. **a b c d**	15. **a b c d**	20. **a b c d**

Please complete the Program Evaluation on following page, and send with $15 fee, payable to University of Tennessee, to:

Glen E. Farr, PharmD
University of Tennessee College of Pharmacy
600 Henley Street, Suite 213
Knoxville, TN 37902

6. All of the followings are potential beneficial effects of fish oil EXCEPT:
a) decreased triglycerides
b) reduced platelet reactivity
c) increased HDL
d) decreased blood pressure

7. Which of the following statements best describe the physiological function of coenzyme Q10?
a) adenosine triphosphate (ATP) production, negative inotropes, and antioxidant
b) ATP production, positive inotropes, and antioxidant
c) adenosine diphosphate (ADP) production, negative inotropes, and oxidant
d) ADP production, positive inotropes, and oxidant

8. Coenzyme Q10 has been studied for which of the following indication(s)?
a) as a positive inotrope in systolic heart failure
b) for improvement of exercise tolerance in patients with angina
c) for reduction of left ventricular size in patients with left ventricular hypertrophy
d) all of the above

9. Which of the following is a reported side effect of coenzyme Q10?
a) peptic ulcer
b) dizziness
c) photophobia
d) fatigue

10. Garlic is indicated by the German Commission E for use as a dietary supplement for treatment of:
a) hypertension
b) hyperlipidemia
c) platelet hyperactivity
d) all of the above

11. Despite numerous published reports regarding the beneficial therapeutic effects of garlic, the problem shared by all these studies that prevents definitive conclusions from being drawn is:
a) they were not randomized, double-blind, or controlled
b) they used garlic cloves only
c) they had small sample sizes
d) they showed controversial results

12. Heavy consumption of garlic supplement should be discouraged in patients with cardiovascular diseases because of:
a) lack of definitive beneficial effects
b) production of strong garlic odor on body and breath
c) inhibition of the effects of other cardiovascular medications
d) decreased platelet aggregation and association with serious bleeding events

13. *L*-arginine exerts its potential beneficial cardiovascular effects by which of the following mechanisms?
a) acting as a natural donor of nitric oxide, which enhances vasodilation
b) acting as an antioxidant and preventing atherosclerosis
c) acting as an antiplatelet agent, which prevents acute thrombosis
d) acting as an inotrope, which enhances cardiac contractility

(CPE questions continued on following page)

CPE PROGRAM EVALUATION (064-999-02-200-H-01)

The University of Tennessee College of Pharmacy would like to have your opinion. Please fill out the questionnaire below, tear off along the dotted line, and mail along with your CPE test form. We thank you for your evaluation, which is most helpful.

Please circle your answers:

My pharmacy practice setting is:	Independent	Chain	Hospital	Consultant
The objectives of the lesson were achieved:	Yes	No		
The quality of presentation of the material was:	Excellent	Good	Fair	Poor
The information presented will be useful to me in my practice.	Strongly agree	Mildly agree	Mildly disagree	Strongly disagree

How long did it take you to read the material and respond to the Continuing Education questions: (Please specify the number of hours.)

_____

Please send this evaluation, along with your answer sheet and $15 check payable to University of Tennessee, to:

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14. *L*-arginine has been indicated for management of all the following indications EXCEPT:
a) peripheral vascular disease
b) hypertension
c) heart failure
d) diabetes

15. Soy is the major food source of _____, which have (has) _____ effects.
a) antioxidants, androgenic
b) isoflavones, estrogenic
c) riboflavones, androgenic
d) casein, estrogenic

16. The Food and Drug Administration (FDA) states that the consumption of ____ g/day of soy protein, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease.
a) 25
b) 35
c) 40
d) 90

17. The American Heart Association Dietary Guidelines for Healthy American Adults recommended the substitution of animal protein for soy protein for reduction of total and LDL cholesterol.
a) true
b) false

18. Which of the following alternative pharmacotherapies, when administered with warfarin, has been reported to cause intracerebral hemorrhage?
a) garlic
b) *ginkgo biloba*
c) ginseng
d) all of the above

19. Administration of St. John's wort with digoxin can potentially increase the risk of digoxin toxicity.
a) true
b) false

20. In addition to the lack of large-scale, well-controlled studies to define the role of alternative pharmacotherapies, another problem common to all these therapies is:
a) significant cost to the patients because alternative pharmacotherapies are not covered by health insurance
b) significant placebo effect
c) lack of regulation and quality assurance by the FDA
d) increased incidence of patient noncompliance with other prescription medications

Please fill out the University of Tennessee College of Pharmacy program evaluation that accompanies this quiz (page 287).