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ACCF COMPLEMENTARY MEDICINE EXPERT CONSENSUS DOCUMENT

Integrating Complementary Medicine Into Cardiovascular Medicine

A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents (Writing Committee to Develop an Expert Consensus Document on Complementary and Integrative Medicine)

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The recommendations set forth in this report are those of the Writing Committee and do not necessarily reflect the official position of the American College of Cardiology Foundation.

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PREAMBLE

This document was commissioned by the American College of Cardiology Foundation (ACCF) Task Force on Clinical Expert Consensus Documents (CECDs) to provide a perspective on the current state of complementary, alternative, and integrative medical therapies specifically as they relate to cardiovascular diseases (CVDs). It is intended to inform practitioners, payers, and other interested parties of many evolving areas of clinical practice and/or technologies associated with this topic that are widely available or new to the practice community. Topics chosen for coverage by CECD are so designated because the evidence base and experience with technology or clinical practice are not considered sufficiently well developed to be evaluated by the formal American College of Cardiology/American Heart Association (ACC/AHA) Practice Guidelines process. Often, the topic is the subject of considerable ongoing investigation.

The Task Force on CECDs recognizes that considerable debate exists regarding the clinical utility of alternative medicine practices. By their nature, alternative medicine practices differ widely in their scientific support. Despite this varying evidence base, these practices are widely employed by patients, including those with CVD. Many practitioners are not familiar with many alternative medicine techniques. Thus, the reader should view this CECD as the best attempt of the ACCF to inform and guide clinical practice in an area where rigorous evidence is not yet available or the evidence to date is not widely accepted. Where feasible, CECDs include indications or contraindications. The ACC/AHA Practice Guidelines Committee may subsequently address some topics covered by CECDs.

The Task Force on Clinical Expert Consensus Documents makes every effort to avoid any actual or potential conflicts of interest that might arise as a result of an outside relationship or personal interest of a member of the writing panel. Specifically, all members of the writing panel are asked to provide disclosure statements of all such relationships that might be perceived as real or potential conflicts of interest. These statements are reviewed by the parent task force and updated as changes occur. Please see Appendix I for the relationship with industry information pertinent to this document.

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I. INTRODUCTION

Organization of Committee and Evidence Review

The Writing Committee consisted of acknowledged experts in the field of complementary, alternative, and integrative medicine. Both the academic and private sectors were represented. The document was reviewed by five official reviewers nominated by the ACCF, representatives from the American Association of Critical Care Nurses, AHA, American Nurses Association, Preventive Cardiovascular Nurses Association, and the Society of Thoracic Surgeons, as well as 20 content reviewers nominated by the Writing Committee. This document will be considered current until the Task Force on CECDs revises or withdraws it from publication.

Background

Alternative medical therapies encompass a broad spectrum of practices and beliefs (1). From a historical standpoint, they may be defined as, " . . . practices that are not accepted as correct, proper, or appropriate or are not in conformity with the beliefs or standards of the dominant group of medical practitioners in a society" (2). The Institute of Medicine (IOM) has recently reviewed complementary and alternative medical practices in the U.S. from a general viewpoint (3). This document will focus on cardiac aspects of complementary medicine. From a functional standpoint, alternative (also known as "complementary" or "integrative") therapies may be defined as interventions neither taught widely in medical schools nor generally available in hospitals (4). Ernst et al. (5) contend that "complementary medical techniques [complement] mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual frameworks of medicine." The terminology currently in use to describe these practices remains controversial. Many commonly used labels (e.g., "alternative," "unconventional," or "unproven") are judgmental and may inhibit the collaborative inquiry and discourse necessary to distinguish useful from useless techniques (6). Complementary and alternative medicine (CAM) is the language currently used by the National Institutes of Health (NIH) to describe this field of inquiry. The term "integrative medicine" has been used with increased frequency. Several recently published studies and editorials wrestle with the challenges of properly labeling and describing this field of inquiry (7–12). Herbs, vitamins, and non-herbal dietary products, as well as therapies conducted around issues such as spirituality, bioenergetics (i.e., acupuncture and energy fields), and mind/body, are all considered to be forms of complementary, alternative, or integrative medicine.

Purpose of This CECD

The purpose of this CECD is to put the emerging area of CAM treatment and investigation into focus in order to enable the physician to provide better patient care in a meaningful and safe manner. The document will be concerned with the most recent advances and utilization of CAMs and therapies in a traditional cardiovascular practice.

In 2000, nearly 50% of all Americans sought the help of an alternative health care practitioner. This represents over 600 million visits (13). Nearly $30 billion was spent in the year 2001 on CAM (13,14). Many CAM interventions, including numerous herbal supplements, have been employed in an attempt to treat CVD. Of prime importance is putting CAM into perspective with its potential benefits and knowledge of important interactions with traditional cardiovascular medicines. In response to an enormous involvement in CAM, medical facilities have developed specialized CAM centers to investigate the potential benefits and integrate those benefits into routine care and lifestyle management.

The most complete and comprehensive findings to date on Americans' use of CAM were released on May 27, 2004, by the National Center for Complementary and Alternative Medicine (NCCAM) and the National Center for Health Statistics (NCHS, part of the Centers for Disease Control and Prevention) (15). The new data came from a detailed survey on CAM included for the first time in 2002 in the National Health Interview Survey (NHIS). The NHIS, a survey done annually by the NCHS, interviews people in tens of thousands of American households about their health- and illness-related experiences.

The findings are yielding (and will continue to yield, through future analyses) a wealth of information on who uses CAM, what they use, and why. In addition, researchers can examine CAM use as it relates to many other factors such as age, race/ethnicity, place of residence, income, educational level, marital status, health problems, and the practice of certain behaviors that impact health (such as smoking cigarettes or drinking alcohol).

The survey showed that a large percentage of American adults are using some form of CAM—36% (15). When prayer specifically for health reasons is included in the definition of CAM, that figure rises to 62%. Dr. Stephen E. Straus, NCCAM Director, said, "The survey data will provide new and more detailed information about CAM use and the characteristics of people who use CAM. One benefit will be to help us target NCCAM's research, training, and outreach efforts, especially as we plan NCCAM's second five years, 2005 through 2009."

There is little doubt that CAM represents a revolution within our health care delivery system. Nevertheless, our traditional views of the medical establishment do not fully support CAM. There is a lack of significant instruction of CAM in medical schools, there is a paucity of CAM in most major hospitals, and there is little solid research published in peer-reviewed journals. Compensation by insurance companies for CAM is also an issue.

A recent report of the IOM entitled "Complementary and Alternative Medicine in the U.S." (3) described and characterized CAM therapies used by the American public. Additionally, the IOM sought to identify major scientific policy and practice issues related to CAM research and to the translation of validated therapies into conventional practice. In short, the report recommended that the same principles and standards of evidence of treatment effectiveness apply to all treatments, whether currently labeled as conventional medicine or CAM. Although randomized controlled trials (RCTs) remain the "gold standard" of evidence for treatment efficacy, the IOM noted that other study designs can be used to provide information about the effectiveness when RCTs cannot be done or may not be generalizable to CAM practice. Other acceptable clinical research designs included: preference RCTs (trials that include both randomized and non-randomized treatment

arms); observational and cohort studies; case-control studies; studies of bundles (combinations) of therapies; studies that specifically incorporate, measure, or account for placebo or expectation effects; and attribute-treatment interaction analyses. Prioritization criteria were also proposed to assist researchers regarding which CAM therapies might warrant further investigation.

Integrating CAM into medicine must be guided by compassion, but enhanced by science, and made meaningful through solid doctor-patient relationships. Most importantly, CAM involves a commitment to the core mission of caring for patients on a physical, mental, and spiritual level. This document attempts to enable us to fulfill these objectives. A glossary of terms is contained in Appendix II. For additional information on CAM, please refer to www.acc.org for Appendix III: Internet Sources for Complementary Medicine Information and Appendix IV: Review of the Literature for Cardiovascular-Related Integrative Medicine.

II. NUTRITION AND SUPPLEMENTS

This section provides a discussion of general nutrition and dietary supplements, including vitamins, minerals, and herbs that are related to the prevention and reduction of risk of CVD. Please see Appendix V at www.acc.org for a sample dietary supplement intake form.

Nutrition

Diet is a major determinant of cardiovascular health. General nutrition affects body weight, lipoproteins, blood pressure, blood glucose, endothelial function, inflammation, and coagulation. Dietary modification is an important component of primary and secondary prevention of coronary heart disease (CHD) and hypertension. The essentials of proper nutrition include appropriate caloric intake and consumption of the essential macronutrients (carbohydrate, proteins, and fats) and micronutrients (vitamins, minerals). Specific nutrients can either accelerate or retard the development of CVD.

Obesity. Obesity contributes to CHD, diabetes, and hypertension (16). Obesity (body mass index [BMI] greater than 30 kg/m^2) increased 50% in this country from 1991 to 1998 (17). Almost one-third of Americans are now obese and another one-third are overweight (BMI 25 to 30 kg/m^2). The major cause of this recent increase in obesity is a 150 to 200 kcal increase in our daily caloric intake, mainly from snacks (18). A decrease in physical activity associated with more television viewing has also contributed. A third factor has been an increase in sugar consumption, which now averages 150 lbs per person per year (19). The latter factor has also contributed to an increased prevalence of type 2 diabetes.

Weight loss is often an important part of the management of CHD, diabetes, and hypertension (20). Excess weight increases low-density lipoprotein (LDL) cholesterol, triglycerides, and markers of inflammation, such as C-reactive protein; and decreases high-density lipoprotein (HDL) cholesterol. Even modest weight reduction can improve these atherogenic markers (20). Weight loss only occurs when caloric intake is less than caloric expenditure. The daily caloric requirement for sedentary and physically active individuals, respectively, is about 12 and 15 kcal per lb of ideal weight. A 3,500 kcal deficit results in approximately 1 lb of weight loss. On the average, a deficit or excess of 500 calories a day brings about weight loss or gain at the rate of 1 lb a week. Increasing physical activity also results in weight loss. One mile walked or jogged is equivalent to about 100 calories burned. The most successful weight loss programs use calorie restriction, exercise, counseling, and group support.

Extremely low-carbohydrate or ketotic diets have become popular for weight loss (21). Some randomized trials have found that obese individuals lose more weight on low-carbohydrate diets than on low-fat diets, although the difference is not uniformly significant (22,23). The mechanisms by which extremely low-carbohydrate diets facilitate weight loss include osmotic diuresis, glycogen and associated water depletion, anorexia due to ketosis, and exclusion of foods. Although LDL cholesterol decreases during the weight loss phase of low-carbohydrate dieting, levels return to baseline in the long term. Two benefits of extremely low-carbohydrate diets are a decrease in triglycerides and an increase in insulin sensitivity. The long-term cardiovascular effects of low-carbohydrate/high-fat diets are unknown, but epidemiologic data suggest that they would increase atherosclerosis (24).

Extremely low-fat diets have been used to treat established coronary artery disease (CAD) (25). One small study has demonstrated modest CAD regression (26). Extremely low-fat diets are difficult to apply widely. Low-fat diets are consistent with the general epidemiologic finding that atherosclerosis prevalence correlates with saturated fat intake, and more specifically, with trans fat intake. However, low-fat diets can increase small LDL particles. These diets also do not recognize the cardiovascular benefits that can be derived from omega-3 fatty acids. They also may increase triglyceride levels and decrease insulin sensitivity.

Macronutrients. Fatty acids can be generally characterized into saturated, trans, monounsaturated, and polyunsaturated classes depending on the number and configuration of double bonds. Saturated and trans fatty acids increase serum LDL cholesterol and directly impair endothelial function (27,28). Trans fatty acids also decrease HDL cholesterol (29). Considerable data suggest an association between dietary saturated and trans fats and CHD (24). Dietary cholesterol is also associated with CHD, but elevations in serum cholesterol are individually variable with dietary intake. Monounsaturated fatty acids have neutral effects on serum LDL and HDL cholesterol (30). Polyunsaturated fatty acids reduce HDL cholesterol, but their use in randomized trials is associated with decreased cardiovascular events (27).

Omega-3 fatty acids have three to six double bonds, the first one occurring between the third and fourth carbon from the methyl end. The omega-3 fatty acids have triglyceride-reducing, membrane-stabilizing, antiplatelet, and anti-inflammatory properties (31). Omega-3 fatty acids include alpha-linolenic, eicosapentaenoic, and decosahexaenoic acids. The former is contained in plant oils, whereas the latter two are contained in fish oils. Prospective randomized trials have demonstrated that consuming plant and fish omega-3 fatty acids reduces cardiovascular events, sudden death, and overall mortality (32).

Carbohydrates include monosaccharides, such as sugars, oligosaccharides, and polysaccharides or starches. Complex carbohydrates consist of starches and indigestible fiber. Fiber adds bulk to food and slows carbohydrate digestion. Soluble fiber in the form of psyllium, guar gum, and oat bran reduces serum LDL cholesterol (33). The blood glucose raising property of a food per 50 g of carbohydrate and per portion is measured by its glycemic index and load, respectively (34). High glycemic load foods such as cookies, rice, and potatoes increase serum triglycerides, decrease insulin sensitivity, and probably facilitate obesity.

Dietary recommendations. There are two types of dietary guidelines. The first type recommends specific quantities of macronutrients, such as less than 200 mg of cholesterol per day and less than 7% of calories as saturated fat, as in the AHA Step 2 diet (1). A second type recommends consumption and exclusion of specific foods, often in combination. An example is the recommendation to eat stanol/sterol ester margarines, soy products, soluble fiber, and walnuts or almonds to lower LDL cholesterol (33,35,36). The latter specific food portfolio recommendation has been found to lower LDL cholesterol more (29%) than an AHA Step 2 approach (8%) (37). In general, diets containing unsaturated fats, whole grains, fruits, vegetables, fish, and moderate alcohol are optimal for preventing heart disease (38,39). In October 2000, the AHA revised its dietary guidelines for Americans (1). The new guidelines retain the principles of the Step 1 and Step 2 diet but place emphasis on foods and an overall eating pattern (see the following text) rather than on percentages of food components such as fat.

The National Cholesterol Education Program (NCEP) has issued new practice guidelines on the prevention and management of high cholesterol in adults (40). The Third Adult Treatment Panel (ATPP III) of the NCEP further modified its dietary recommendations to include a more intense and effective eating plan than previously advocated. The new Therapeutic Lifestyle Changes (TLC) treatment plan complements that of the AHA guidelines and recommends less than 7% of calories from saturated fat and less than 200 mg of dietary cholesterol daily. Total allowed fat ranges from 25% to 35% of total daily calories provided that saturated fats and trans fatty acids are kept low. The ATP III encourages the use of foods that contain plant stanols and sterols or are rich in soluble fiber, to achieve greater LDL cholesterol-lowering power.

Mediterranean diet. The prevalence of CVD is considerably less in Mediterranean and Pacific Rim countries than in the U.S. at equivalent cholesterol levels (41). Common to such societies is a diet high in fruits, vegetables, beans, whole-grain carbohydrates, nuts, fish, and monounsaturated and polyunsaturated oils. Dairy products are consumed in low-to-moderate amounts and little red meat is eaten. Alcohol is consumed in moderation. The Lyon Diet Heart Study (42,43) tested the effectiveness of a Mediterranean-type diet, modified by substitution of an alpha-linolenic acid-enriched canola oil margarine for olive oil, on cardiovascular risk after a first myocardial infarction. After an average follow-up of 46 months, subjects following the modified Mediterranean-style diet had 72% fewer cardiovascular events and 60% lower all-cause mortality. Findings from the Lyon Diet Study have been reproduced recently using an Indo-Mediterranean diet in subjects with CHD (44). The intervention diet recommending increased consumption of fruits, vegetables, nuts, whole grains, and mustard and soybean oils reduced cardiovascular events by 45% and sudden cardiac death by 66%. Additionally, recommendations to increase fruit, vegetables, and low-fat dairy product consumption has been found to lower blood pressure in the Dietary Approaches to Stop Hypertension (DASH) study (45).

Summary of general nutritional recommendations.

- Achieve and maintain ideal body weight by limiting foods high in calories and low in nutrient density, including those high in sugar, such as soft drinks and candy.
- Eat a variety of fruits, vegetables, legumes, nuts, soy products, low-fat dairy products, and whole grain breads, cereals, and pastas.
- Eat baked or broiled fish at least twice per week.
- Choose oils and margarines low in saturated and trans fat and high in omega-3 fat, such as canola, soybean, walnut, and flaxseed oils, including those fortified with stanols and sterols.
- Avoid foods high in saturated and trans fats, such as red meat, whole milk products, and pastries.
- If you drink alcohol, limit consumption to no more than 2 drinks per day for a man or 1 drink per day for a woman.
- Eat less than 6 g of salt or less than 2,400 mg of sodium per day.
- Be physically active. Get 30 min of exercise daily.

Bioactive Components in Foods

Food components recommended for lowering the risk of CVD include plant sterols, soluble fiber, omega-3 fatty acids, nuts, and soy. Additional foods, such as garlic and teas, and moderate alcohol use will be discussed.

Omega-3 fatty acids. Individual fatty acids have remarkably diverse effects on coronary risk factors and vascular biology (41–45). Omega-3 and -6 fatty acids are essential

nutrients. Dietary fatty acids affect eicosanoid products (e.g., thromboxanes, leukotrienes, prostaglandins) responsible for vasoregulation, inflammation, and coagulation. Omega-3 fatty acids may also affect CHD outcomes by decreasing triglyceride levels, ventricular arrhythmias, decreasing fibrinogen levels and platelet counts, modestly reducing blood pressures, and decreasing cell proliferation. Improvements in arterial compliance and endothelial function have also been documented with fish oil, a major supply of dietary omega-3 fatty acids. There are changes in autonomic tone (as observed by improvement in heart rate variability measures) and in mood (depression) (46).

Epidemiologic studies (47–51) have generally shown an inverse correlation between consumption of fish or other sources of dietary omega-3 fatty acids and cardiovascular events. Conversely, other epidemiologic studies (52–55) have failed to document the benefits of fish consumption. Good plant sources of the 18 carbon omega-3 fatty acid, alpha-linolenic acid, include flaxseed, canola, pumpkin seed, walnut, and soybean oil.

Omega-3 fatty acids have been tested in several secondary prevention trials. Four prospective, controlled intervention trials with either oily fish (56) or omega-3 fatty acid capsules (42,57,58) have demonstrated reduced cardiovascular events. However, in the DART trial, fish consumption reduced overall mortality early after myocardial infarction (MI) (56), but was associated with higher risk over the subsequent three years of the study (53). The GISSI-Prevenzione study is the largest of the controlled trials investigating omega-3 fatty acid supplements (1 g per day) and CHD risk. In this trial, total mortality was reduced by 20% and sudden death by 45% in an intention-to-treat analysis. Mortality was reduced through a decreased incidence in sudden death.

Studies published to date are mixed regarding a role for dietary omega-3 fatty acids in the prevention of restenosis after percutaneous coronary angioplasty (59–62). They have not been found to reduce coronary atherosclerosis progression to a significant extent (58,63). One study demonstrated that occlusion of aortocoronary venous bypass grafts was reduced after one year by daily ingestion of 4 g of fish-oil concentrate (64).

Stanol/sterol esters. Plant sterols or phytosterols have been known to have a cholesterol-lowering effect since the 1950s. The esterification of plant stanols renders them soluble in dietary fat, an effective vehicle for delivering plant stanols and sterols to the site of cholesterol absorption in the small intestine. Commercially available margarines that provide 3.4 to 5.1 g a day of plant stanol esters can significantly reduce serum total and LDL cholesterol levels without affecting HDL cholesterol or triglycerides (65–67). A decrease in LDL cholesterol levels of 9% to 20% can be achieved with consumption of approximately 2 g per day of plant sterol esters (36). In a randomized, eight-week placebo-controlled trial in 167 subjects, using plant stanol esters incorporated into an oil-based margarine, there was a significant reduction in serum total (12%) and LDL (17%) cholesterol levels in individuals taking a stable dose of a statin drug (68). No trials have studied the effects of stanol/sterol esters on cardiovascular risk. Stanol and sterol esters should be avoided by the rare individual with familiar sitosterolemia.

Garlic (*Allium sativum*). Garlic is an herb that has been used for thousands of years as a food and spice. Garlic potentially affects plasma lipids, fibrinolytic activity, platelet aggregation, blood pressure, and blood glucose (69). Various formulations/preparations of garlic and different study designs have led to contradictory results. The Agency for Healthcare Research and Quality (AHRQ) (70) noted on review of 36 randomized trials modest, short-term effects of garlic supplementation on lipid and antithrombotic factors. Various garlic preparations led to small but significant reductions in total cholesterol at one month and at three months (range of average pooled reductions 11.6 to 24.3 mg/dl). Eight six-month controlled trials showed no significant reductions. Effects on clinical outcomes are not established, and effects on glucose and blood pressure are none to minimal. A similar meta-analysis conducted by Stevinson et al. (71) that included 13 randomized, placebo-controlled trials concluded that the use of garlic for hypercholesterolemia was of questionable value. Superko and Krauss (72) demonstrated in a randomized, placebo controlled trial in hypercholesterolemic subjects that garlic has no effect on major plasma lipoproteins and that it does not impact HDL subclasses, Lp(a), apolipoprotein B, postprandial triglycerides, or LDL subclass distribution.

Soy. Soy-based foods have cholesterol-lowering, estrogenic, and antioxidant properties. The mechanism underlying the cholesterol-lowering effect of soy is likely multifactorial. Soy-based foods reduce lipid oxidation, promote increased vascular reactivity, and improve arterial compliance (73). Favorable effects of soy phytoestrogens on lipid profiles, vascular reactivity, thrombosis, and cellular proliferation have been reported (74). Dietary intake of foods containing phytoestrogens is associated with a favorable cardiovascular risk profile as was demonstrated in 939 postmenopausal women participating in the Framingham Off-Spring Study (75). The consumption of soy protein can improve lipid profiles in hypercholesterolemic individuals above a background NCEP Step I diet. Soy decreases LDL cholesterol more in hypercholesterolemic individuals. Soy supplementation may also increase the levels of HDL cholesterol regardless of whether an individual is hypercholesterolemic or not. A meta-analysis of 38 trials of soy protein demonstrated reductions in total cholesterol of 9.3%, LDL cholesterol of 12.9%, and triglyceride levels of 10.5%, accompanied by an increase of 2.5% in HDL cholesterol (76). However, more recent studies in postmenopausal women fail to show improvements in plasma lipids (77). A recent placebo-controlled study in 108 men and 105 postmenopausal women randomized to either soy protein isolate or casein placebo for three months demon-

strated an increase in levels of Lp(a) on soy supplementation with no improvement in indices of arterial function (78). Extracts of soy isoflavones given to human subjects do not result in cardiovascular benefits except for improvements in systemic arterial compliance (79).

The clinical benefit of isoflavones is unclear. In light of the recent findings about estrogen from the Women's Health Initiative, the U.S. Preventive Services Task Force has stated that the evidence is inconclusive to determine whether phytoestrogens, such as soy isoflavones, are effective for reducing the risk of CVD (80).

Soluble fiber. Soluble or viscous fibers, such as oat bran, psyllium, guar, and pectin, are thought to reduce heart disease by lowering total and LDL cholesterol levels without affecting serum triglycerides. Conversely, insoluble wheat fiber and cellulose have no cholesterol-lowering effects unless used in the diet to replace foods supplying saturated fats or cholesterol (81). Increasing dietary fiber has been recommended as a safe and practical approach to cholesterol reduction. Large epidemiologic studies (82–84) have demonstrated a reduced risk for MIs and death from CHD in both men and women who consume higher amounts of dietary fiber. These studies provide strong support linking dietary fiber intake to protection from CHD. These data are supported by numerous ecological, cohort, case-comparison, population-based, and, most recently, clinical trials demonstrating an inverse relationship between dietary fiber consumption and atherosclerotic CVD (85).

The hypocholesterolemic effects of psyllium (86), guar gum (87), and oat bran (88) are documented by meta-analyses (89). A meta-analysis of 67 controlled trials studying the cholesterol lowering effect of four types of soluble fiber (oat, psyllium, pectin, and guar gum) reported small but significant reductions in total cholesterol (1.7 mg/dl per g soluble fiber) and LDL (cholesterol (1.9 mg/dl per g soluble fiber) (81). Hypercholesterolemic subjects with initially higher cholesterol levels experienced the most significant reductions. Triglycerides and HDL cholesterol were not significantly influenced by soluble fiber. The magnitude of lipid lowering was found to be similar for oat, psyllium, or pectin-based fibers.

Because of the favorable effect of soluble fiber on LDL cholesterol levels, the ATP III panel recommends that the diet be enriched by foods that provide a total of at least 5 to 10 g of soluble fiber daily (90). Dietary fiber also reduces blood pressure, obesity, insulin resistance, and clotting factors—all independent risk factors for CHD (85).

Nuts. The few studies that have looked at the consumption of whole nuts in relation to CHD have reported a consistent and substantial protective effect. Three of the largest nutritional epidemiologic prospective studies evaluating multiple population groups, ages, races, and gender have found a consistent inverse relationship between nut consumption and coronary risk (91–93).

The improvement in serum lipids associated with the consumption of nuts does not explain the magnitude of the CHD risk reduction of approximately 40% to 50% found in the epidemiologic studies. Nuts, especially walnuts and almonds, are high in arginine, magnesium, folate, plant sterols, and soluble fiber. Some nuts contain high levels of omega-3 essential fatty acids (e.g., walnuts), and they are an excellent source of vitamin E. In a prospective study of 86,016 women between the ages of 34 to 59 years, without previously diagnosed CHD, eating 5 oz of nuts per week was associated with a relative risk (RR) of 0.66 (95% confidence interval [CI] 0.47 to 0.93, p for trend = 0.005) of coronary events adjusted for risk factors and independent of fiber, fruit, and vegetable supplements (92). Recent prospective data from the Physicians' Health Study demonstrated consumption of nuts two or more times a week significantly reduced the risk of sudden cardiac death (RR) of 0.53 (95% CI 0.30 to 092, p for trend = 0.01) and a RR of 0.70 (95% CI 0.50 to 0.98, p for trend = 0.06) for total CHD deaths compared with men who rarely or never consumed nuts (93). The association between nut consumption and sudden cardiac death became stronger after adjustment for lifestyle, cardiac risk factors, and diet. Like some nuts, canola oil and flaxseed oil are the richest known source of alpha-linolenic acid, an omega-3 fatty acid.

Tea. Tea drinking appears to be protective against CHD in a number of epidemiologic studies (94–97). In the older cohort of the Rotterdam Study, an inverse association was demonstrated between tea drinking and advanced aortic atherosclerosis (98). Data from a more recent follow-up of the Rotterdam Study highlighted a strong inverse relation between tea intake (greater than 375 ml/day) and MI with the relation being stronger in women than in men. The inverse association with tea drinking was stronger for fatal events than for nonfatal events. For flavonoid (quercetin + kaempferol + myricetin) intake, a strong association with MI was observed only in women (99). Results are inconclusive for clinical and case control studies. However, a recent prospective cohort study of 1,900 patients hospitalized with an acute MI followed for 3.8 years found a significantly reduced hazard ratio for subsequent total and cardiovascular mortality of 0.56 (95% CI 0.37 to 0.84) for heavy tea drinkers (more than 14 cups/week) compared to non-tea drinkers (100). A recent clinical study has shown that consumption of black tea improves brachial artery flow-mediated dilation in patients with CAD (101). Despite the favorable epidemiology and mechanistic investigations, no studies have prospectively documented a reduction in cardiovascular risk with tea drinking.

Alcohol. Epidemiologic studies have shown that the incidence of MI, angina pectoris, and coronary-related deaths are inversely related to moderate alcohol intake, as defined by 1 to 3 drinks daily. Although many mechanisms for this effect have been suggested, the best documented effect is an increase in HDL cholesterol by alcohol (102). Recent studies have shown that moderate drinkers are less likely to suffer ischemic stroke (103,104), peripheral vascular disease (105), and death following an acute MI (106). Cooper et al.

(107) found that light-to-moderate drinkers with left ventricular systolic dysfunction had fewer adverse outcomes. In the Framingham Heart Study, Walsh et al. (108) found that the incidence of congestive heart failure was lower in subjects who consumed moderate amounts of alcohol. Abramson et al. (109) were able to demonstrate that subjects who consumed moderate levels of alcohol had a significantly lower risk of developing heart failure.

Moderate consumption of alcohol-containing beverages does not appear to result in significant morbidity; however, heavy alcohol consumption can result in cardiomyopathy, hypertension, hemorrhagic stroke, cardiac arrhythmia, and sudden death. Alcohol ingestion poses such a number of health hazards with irresponsible consumption that the AHA recommends that physicians and patients discuss the adverse and potentially beneficial aspects of moderate drinking (39).

Overview of dietary supplements. The Dietary Supplement Health and Education Act (DSHEA) of 1994 defined dietary supplements as a product (other than tobacco) intended to supplement the diet for such ingredients as vitamins, minerals, herbs, or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites. Whatever their form, the DSHEA places dietary supplements in a special category under the general umbrella of "foods," not drugs, and requires that every supplement be labeled a dietary supplement. The establishment of dietary supplements as foods limited the Food and Drug Administration (FDA)'s premarketing regulatory authority and placed the FDA in a reactive, postmarketing role. Thus, for the FDA to remove a supplement from the market it most prove that the supplement presents a significant or unreasonable risk of injury or illness when used as recommended on the label. Recently, the IOM has urged that the U.S. Congress and federal agencies, in conjunction with industry, research scientists, consumers, and other stakeholders, amend DSHEA and the current regulatory practices for dietary supplements in an effort to improve product consistency and reliability (IOM, 2005). Just prior to the release of the IOM report on Complementary and Alternative Medicine in the U.S., the FDA announced three major regulatory initiatives designed to further implement DSHEA (http://www.cfsan.fda.gov/~lrd/fr04119a.html, docket no. 2004N-0458). These initiatives serve to inform the dietary supplement industry on a regulatory strategy involving the monitoring and evaluation of product and ingredient safety, assurance of product quality via good manufacturing practice (CGMP regulations), and monitoring and evaluation of product labeling. At the same time these new initiatives will give consumers a higher level of assurance about the safety of dietary supplement products and the reliability of their labeling.

Vitamin and Mineral Supplements

Antioxidant vitamins. Antioxidant therapies are potentially useful in preventing both atherosclerosis and its complications by retarding LDL oxidation and by inhibiting the proliferation of smooth muscle cells, platelet adhesion and aggregations, the expression and function of adhesion molecules, and the synthesis of leukotrienes (110). Antioxidants may improve endothelial function, reduce ischemia, and stabilize atherosclerotic plaques to prevent plaque rupture (110).

VITAMIN E. *Primary Prevention Trials.* A potential benefit of vitamin E in CHD is suggested by two large prospective epidemiologic trials, which found lower event rates in subjects who took at least 100 units of vitamin E per day (111,112). However, 50 mg of vitamin E in the Alpha-Tocopherol, Beta-Carotene (ATBC) cancer prevention trial of male smokers did not decrease nonfatal MIs, and increased hemorrhagic stroke (113,114). Vitamin E use was not associated with decreased stroke in the Health Professionals Follow-Up Study (115), the Nurses Health Study (112), and the Iowa Women's Health Study (116). Most recently, the Collaborative Group of the Primary Prevention Project (PPP) found no decrease in cardiovascular events in 4,495 subjects with one or more risk factors after 3.6 years of synthetic vitamin E (300 units) therapy compared to none (117). These data have been confirmed by a recent pooled analysis of nine cohort studies (Pooling Project of Cohort Studies on Diet and Coronary Disease) in 293,172 subjects free of CHD. A lower CHD risk at higher intake of dietary vitamin E was present when adjusted for age and energy intake. However, supplemental vitamin E intake was found not to be significantly related to a reduced risk of CHD (118).

Secondary Prevention Trials. Only one of several controlled trials of vitamin E has shown a reduction in some aspect of cardiovascular risk. In the Cambridge Heart Antioxidant Study (CHAOS) (119) vitamin E reduced the risk of nonfatal MI, but not of fatal MI. The Heart Outcomes Prevention Evaluation (HOPE) study found no effect of vitamin E for several of primary and secondary CVD end points, including disease progression monitored by carotid ultrasound (120). The GISSI-Prevenzione trial (42) failed to show benefit from vitamin E supplementation on CHD or stroke in almost 8,000 patients. The Vitamin E Atherosclerosis Prevention Study (VEAPS) provided additional evidence that vitamin E supplementation (400 units) did not reduce the progression of atherosclerosis as evaluated by change in intimal medial thickness (121). A meta-analysis of seven randomized trials of vitamin E (50 units to 800 units) in 81,788 patients confirmed that vitamin E did not reduce mortality, decrease cardiovascular death, or cerebrovascular accident (122). A more recent and larger (135,967 participants in 19 clinical trials) meta-analysis that considered the dose dependent effects of vitamin E supplementation noted that at high dosage (400 units/day or more) a pooled risk difference of 34 per 10,000 persons (95% CI 5 to 63 per 10,000 persons, $p = 0.022$). However, it is unclear whether the investigators isolated the effects of

vitamin E from those of other supplements. Most of the evidence for an elevated mortality risk came from two trials that administered vitamin E together with beta-carotene. It is uncertain whether an increased risk for death from high-dose vitamin E based on this most recent analysis of RCTs exists (123).

VITAMIN C. *Primary Prevention.* When examined individually, most observational and prospective cohort studies do not demonstrate a relationship between vitamin C intake and CVD (124,125) and there have been no RCTs specifically examining the effects of vitamin C supplementation on cardiovascular end points (115,126). In the Iowa Women's Health Study, women in the top quintile of vitamin C intake versus the lowest quintile had a nonsignificant increased risk for CHD mortality and a borderline significant trend toward increased stroke (127). Long-term use of vitamin C in a large prospective investigation was not associated with a reduced risk of stroke, as well (115). However, a more recent analysis from the Nurses' Health Study indicates that women in the highest quintile of intake for vitamin C (greater than 360 mg per day from diet and supplements) compared with the lowest quintile (less than or equal to 93 mg per day), had a 27% lower risk for CHD, and women taking supplemental vitamin C had a 28% lower risk of nonfatal MI and fatal CHD compared with women who took no vitamin C (128). In the recent pooled analysis from the Pooling Project of Cohort Studies on Diet and Coronary Disease (118), those subjects with higher supplemental vitamin C intake (greater than 700 mg/day) had a 25% reduced risk of CHD. Nevertheless, the current consensus does not find a value for supplemental vitamin C in preventing heart disease (129).

BETA-CAROTENE. Trials of beta-carotene have demonstrated no cardiovascular benefit, and one demonstrated an adverse clinical outcome. An increased incidence of lung cancer and CVD mortality were observed in the ATBC cancer prevention study (130). Beta-carotene supplementation was also associated with a slight increase in the frequency of angina pectoris (131). A meta-analysis of eight trials evaluating beta-carotene in 138,113 patients revealed a small but significant increase in all-cause mortality and cardiovascular death (128). Thus, beta-carotene supplementation is discouraged (1).

Combination Vitamin Trials. The Heart Protection Study (HPS) randomized 20,536 subjects at high risk for CHD to 40 mg simvastatin daily or placebo and vitamin E (600 mg), vitamin C (250 mg), and beta-carotene (20 mg) or placebo. After 5.5 years of study, no benefit from combination vitamin therapy was evident (132). A small RCT, the HDL Cholesterol Atherosclerosis Treatment Study (HATS), found that vitamin C (1 g), vitamin E (800 units), beta-carotene (50 mg), and selenium (100 mcg) reduced the benefit of simvastatin plus niacin therapy on CAD progression and cardiovascular events (133) suggesting a potential drug/supplement interaction affecting the efficacy of statin therapies. Lack of benefit for combination vitamin E (400 units) and vitamin C (500 mg) was also documented in 423 postmenopausal women with CAD participating in the Women's Angiographic Vitamin and Estrogen (WAVE) trial (134).

In contrast to the aforementioned negative trials, the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study of 440 hypercholesterolemic patients randomized to vitamins E and C, reported that combination therapy decreased the rate of atherosclerosis progression (especially in men) over a six-year period as measured by carotid artery intima-media thickness. This study selected subjects with high oxidative stress and maximized absorption of the antioxidants by giving them with meals (135).

In summary, aside from the recent pooled analysis of vitamin C cohort studies, the consensus of antioxidant vitamin study results do not support a cardiovascular benefit related to the use of vitamins E and C and beta-carotene (129).

FOLIC ACID, VITAMIN B_6, AND VITAMIN B_{12}. Elevated homocysteine levels are associated with increased risk of coronary artery and vascular disease. The mechanisms by which elevated homocysteine impairs vascular function are not completely understood, but may involve the stimulation of vascular smooth muscle cell growth and collagen synthesis, oxidative-endothelial injury and dysfunction, lipid peroxidation and platelet activation, and hypercoagulability (136). Intakes of folate, vitamins B_6, and B_{12} are inversely related to homocysteine levels as all three vitamins are directly involved in the metabolism of homocysteine. Beginning in 1996 and mandatory in 1998, the FDA issued a regulation requiring all enriched grain products be fortified with folic acid (140 mcg/100 g serving portion), primarily for the reduction of congenital neural tube defects. The fortification of enriched grain product with folic acid has been associated with an improvement in the folate status of middle-aged and older adults (137). In the Framingham Offspring Study cohort, mean homocysteine levels decreased from 10.1 to 9.4 μmol/l with the introduction of fortified products (138).

Initial retrospective case-control studies (139–141) and prospective studies (142–147) suggested an inverse relationship between homocysteine and CVD. A recent meta-analysis, combining 30 prospective and retrospective studies, concluded that elevated homocysteine is less strongly related to ischemic heart disease and stroke risk in healthy populations than has been suggested (148). A meta-analysis of 14 prospective cohort studies, using the inclusion criterion of time to first cardiac or cerebrovascular event, found that elevated homocysteine levels moderately increased the risk of a first cardiovascular event, regardless of age and duration of follow-up (149).

In secondary prevention studies, two nonrandomized trials in patients with vascular disease found an inverse relationship between the intake of folic acid and vitamin B6 and vascular events (150). One study conducted in open-

label fashion in 593 patients with coronary artery disease on statin therapy showed no benefit of folic acid in reducing cardiovascular events despite an 18% lowering in homocysteine levels (151–153).

Most recently, a trial of folic acid (1 mg), vitamin B_{12} (400 units), and pyridoxine (B_6) (10 mg) found a significantly reduced homocysteine levels, rate of restenosis, and need for revascularization in a group of 553 CAD patients at one year of follow-up (151,152). A similar RCT of 626 patients treated with B-vitamin therapy following coronary stenting procedures, however, found increased rates of restenosis, particularly in patients receiving bare-metal stents and major adverse cardiac events in the vitamin treated group after one year of follow-up. The rate of restenosis in the homocysteine-lowering group was 35% compared with 27% in the group receiving placebo (154). Although striking differences exist between the study populations, it raises the potential of possible harm from use of high-dose B-vitamins. Strong evidence for a benefit for B vitamins in CVD is pending; there remain a number of ongoing trials, including WACS, SEARCH, PACIFIC, NORVIT, and CHAOS-2 (155).

Minerals. MAGNESIUM. Magnesium metabolism is involved in insulin sensitivity and blood pressure regulation, and magnesium deficiency is common in both diabetes and hypertension. The links among magnesium, diabetes, and hypertension suggest the possibility that magnesium can affect CVD (156,157). Magnesium depletion is associated with electrocardiographic changes, arrhythmias, and increased sensitivity to cardiac glycosides (158). Epidemiologic studies have suggested that ingesting hard water that contains magnesium, consuming a diet higher in magnesium, or using magnesium supplements decreases CVD (159). The Honolulu Heart Program found a 1.7- to 2.1-fold excess risk of CHD among those subjects in the lowest versus highest quintile of magnesium intake after 15 years of follow-up (160). Similarly, epidemiologic evidence suggests that magnesium may play a role in regulating blood pressure (161–165). A recent meta-analysis of 20 randomized studies including both normotensive and hypertensive subjects detected a dose-dependent blood pressure reduction with magnesium supplementation (166). The DASH intervention study demonstrated that a diet of fruits and vegetables, which increased magnesium intake from an average of 176 to 423 mg per day, significantly lowered blood pressure in adults who were not classified as hypertensive (167). However, studies in hypertensive patients have led to conflicting results. Ascherio et al. (168) found an inverse correlation between the intake of magnesium and the risk of stroke.

Magnesium intake has been found to be inversely associated with carotid artery thickness in women but not in men (163). Oral magnesium therapy (365 mg twice daily for 6 months) in 187 patients with CAD demonstrated a 14% improvement in exercise duration combined with a decrease in exercise-induced chest pain compared to no change in the placebo group (169). In patients with congestive heart failure (CHF), a population at high risk for magnesium deficiency, oral magnesium replacement decreases the frequency of ventricular arrhythmias (170).

Dietary intakes of magnesium are suboptimal in the U.S. as evidenced by recent NHANES survey intake data (171). Diets rich in magnesium and magnesium supplementation may be helpful in preventing CVD, especially hypertension.

Other bioactive supplements. COENZYME Q10. Coenzyme Q10 (CoQ10) is involved in oxidative phosphorylation and the generation of adenosine triphosphate (ATP). The CoQ10 acts as a free radical scavenger and membrane stabilizer. There have been over 40 controlled trials of the clinical effect of CoQ10 on CVD, a majority of which show benefit in subjective (quality of life, decrease in hospitalizations) and objective (increased left ventricular ejection fraction, stroke index) parameters. A recent review (172) and meta-analysis (173) have shown benefit of CoQ10 as adjunctive treatment in patients with CHF. The largest trial to date was a one-year, placebo-controlled study of CoQ10 in 651 New York Heart Association (NYHA) functional class III or IV CHF patients (174). These investigators found a significant decrease (38% to 61%) in the number of hospitalizations, incidences of pulmonary edema, and episodes of cardiac asthma. No differences in death rates were documented. However, two of the most recent placebo-controlled trials found that the addition of 100 to 200 mg/day of oral CoQ10 to conventional medical therapy did not result in significant improvement in left ventricular ejection fraction, peak oxygen consumption, exercise performance, or quality of life in patients with advanced heart failure (175,176).

A mortality benefit for CoQ10 has not been established in contrast to angiotensin-converting enzyme inhibitors, beta-blockers, and aldosterone antagonists. Case reports associate CoQ10 therapy with decreased internation normalized ratio (INR) in patients taking warfarin (177); however, CoQ10 had no effect on the INR in patients on warfarin in a randomized, double-blind, placebo-controlled, crossover trial (178). Caution is advised if patients are taking CoQ10 and warfarin. The HMG-CoA reductase inhibitors may inhibit the natural synthesis of CoQ10, and reduced levels of CoQ10 have been documented in small controlled clinical trials in patients on statin therapies (179). Reduced levels of CoQ10 may place the patient at increased risk for myopathy (180–183); however, studies of CoQ10 for decreasing myalgias and myositis are not definitive. One unique formulation of CoQ10 has received FDA Orphan Drug status for treating mitochondrial disorders. The value of CoQ10 in CVD and with statin use has not been clearly established.

L-CARNITINE. In 1986, the FDA-approved L-carnitine for use in primary carnitine deficiency, which manifests as a disruption in the transport of free fatty acids across the mitochondrial membrane for energy production. In myo-

pathic carnitine deficiency, muscle weakness is paramount (184). Convincing evidence is lacking for the use of carnitine in patients without carnitine deficiency undergoing cardiac surgery, in patients with angina pectoris, acute myocardial infarction, shock, and peripheral vascular disease (185). Urinary carnitine excretion is known to be increased in patients with heart failure (186). Several clinical RCTs have evaluated the addition of L-carnitine to standard medial therapy for heart failure with mixed results (187–189). Significant improvements in maximum exercise times and ejection fractions were reported by Mancini et al. (190) in 60 patients with NYHA functional class II or III CHF who were randomized either to propionyl-L-carnitine (50 mg t.i.d.) or placebo for 180 days. Two other small trials reported similar results, and one trial showed improvement at a higher dose. In a double-blind randomized trial in 155 patients with claudication, a significant improvement in exercise treadmill performance (54% increased walking time) and functional status was achieved with oral propionyl-L-carnitine 2 g/day for 6 months (191). Differences in effect may be due to the dose and formulation of carnitine. In contrast, the investigators of the Study on Propionyl-L-Carnitine in Chronic Heart Failure did not show improved exercise tolerance on L-carnitine supplementation (187).

At present, it is unclear whether L-carnitine provides any benefit beyond well-established therapies. A more definitive answer will come from the Carnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM-2) trial, which will assess the efficacy of L-carnitine in approximately 4,000 patients with acute MI over six months (192). Supplements containing D- or DL-carnitine, often present in over the counter preparations and dietary supplements, should not be substituted for L-carnitine. Carnitine frequently causes nausea, pyrosis, dyspepsia, and diarrhea. Concomitant use of carnitine with warfarin may potentiate warfarin's anticoagulant effects.

L-ARGININE. L-arginine is the precursor of nitric oxide (NO) and has been shown to improve coronary and brachial artery endothelial function and reduce monocyte/endothelial cell adhesion (193–195). In patients with recurrent chest pain, improvements in coronary blood flow in response to acetylcholine have also been documented. In hypercholesterolemic subjects, dietary supplementation with L-arginine over two weeks has been shown to normalize the adhesiveness of mononuclear cells (196) and reduce platelet aggregability (197). However, in a study in 30 patients with CAD, supplemental L-arginine did not affect measures of NO bioactivity and NO-regulated markers of inflammation (198).

There are a few documented reports of adverse effects from oral use of L-arginine. Several patients with hepatic impairment and a recent history of spironolactone use were reported to develop severe hyperkalemia upon initiation or arginine hydrochloride for management of metabolic alkalosis (199). Oral L-arginine appears to have potential benefit in CHD, but hard evidence for its value is currently not available.

Herbal Preparations

In the U.S. today, herbs may be marketed as dietary supplements providing their intended use is not to diagnose, treat, cure, or prevent disease. A number of approved drug substances have their origin in plants, such as digoxin, atropine, reserpine, and amiodarone. However, only a few herbal products available in the U.S. have been tested for cardiovascular purposes: hawthorn (heart failure and coronary insufficiency), garlic (atherosclerosis), ginkgo (arterial occlusive disease), and horse chestnut (chronic venous insufficiency) (200). Few U.S. products benefit from rigorous characterization and standardization necessary for clinical study.

Hawthorn (*Crataegus*). Hawthorn has positive inotropic effects and is a peripheral vasodilator. It increases myocardial perfusion and stroke volume and reduces afterload. Antiarrhythmic effects have been reported in an ischemia-reperfusion model. Orally, hawthorn leaf extract has been used for CHF, cor pulmonale, ischemic heart disease, arrhythmias, blood pressure reduction, atherosclerosis, and cerebral insufficiency (200). Preparations made from flowers with leaves are sold as a prescription medication in parts of Europe and Asia. For example, in Germany, hawthorn can be prescribed for "mild cardiac insufficiency."

Several double-blind clinical studies of patients diagnosed with heart failure have shown objective improvement in cardiac performance using bicycle ergometry (201,202) or spiroergometry. In one study, hawthorn was found to be as effective as captopril in improving exercise tolerance. Based on ergometric performance parameters, the minimum effective daily dose of hawthorn extract is 300 mg. In most trials, the maximum benefit was seen after 6 to 8 weeks of therapy. Weikl et al. (203) demonstrated an improvement in exercise performance in 136 stage II CHF subjects receiving 160 mg hawthorn special extract WS 1442 (leaves and flowers). The efficacy and safety of hawthorn extract WS 1442 (900 and 1,800 mg) were evaluated in a 16-week randomized, controlled trial in 209 patients with NYHA functional class III heart failure. The investigators found a dose-dependent effect of WS 1442 on enhancing exercise capacity and reducing heart failure-related signs and symptoms. The preparation was shown to be well-tolerated and safe (204). A recent pharmacokinetic study was conducted in 8 healthy subjects consuming 0.25 mg digoxin alone or with hawthorn extract WS 1442, which demonstrated no significant alterations in the pharmacokinetic parameters for digoxin (205). Clinical trials are underway in the U.S. to evaluate further the safety and efficacy of hawthorn in patients with heart failure.

Hawthorn may offer some advantages over digoxin in mild heart failure. Compared to digitalis, hawthorn has a wider therapeutic range, lower risk in case of toxicity, has

less of an arrhythmogenic potential, is safer to use in renal impairment, and can be safely used with diuretics and laxatives (200). However, hawthorn can markedly enhance the activity of digitalis (206), and care should be taken when combining it with beta-blockers and class III antiarrhythmics.

Ginkgo biloba (ginkgo leaf extract). Ginkgo has been used for relief of intermittent claudication in patients with peripheral arterial occlusive disease. Ginkgo leaf, obtained from the *Ginkgo biloba* tree, and its extracts, or GBE, contain several bioactive constituents including flavonoids, terpenoids, and organic acids. As with other phytomedicines, several constituents of ginkgo extracts may contribute to its therapeutic effect. The mechanism of benefit is unknown. Two meta-analyses of the efficacy of ginkgo leaf extract for the treatment of intermittent claudication concluded that only modest benefits resulted from its use (207,208). In the meta-analysis performed by Pittler and Ernst (207), eight randomized, placebo-controlled, double-blind studies involving a total of 415 participants were evaluated. All of the studies used pain-free walking distance as the primary outcome measure. Several different formulations of ginkgo were used with doses ranging from 120 to 160 mg a day. The majority of trials lasted 24 weeks. Statistical pooling of the results from the eight trials showed that ginkgo significantly increased pain-free walking distance by 34 m. The clinical relevance of this increase is unclear.

Ginkgo is considered relatively safe, with a few documented adverse effects being mild gastrointestinal upset and headache. Ginkgo has been reported to increase the risk of bleeding. The concomitant use with aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and anticoagulants, such as warfarin and heparin, is not advised. Ginkgo can increase blood pressure in patients taking thiazide diuretics (209). Ginkgo does not appear to interact or adversely affect concomitant therapy with cardiac glycosides, and it appears to provide a small benefit in the treatment of peripheral arterial disease.

Horse chestnut (*Aesculus hippocastanum*). Horse chestnut seed extract (HCSE) contains escin, a triterpene glycoside, and the toxic glycoside aesculin, a hydroxycoumarin derivative that is used to treat venous insufficiency (210). A systematic review of 14 randomized, placebo-controlled trials (a total of 1,071 subjects) was recently completed evaluating the efficacy of HCSE for the treatment of chronic venous insufficiency. The HCSE was found to be superior to placebo and as effective as compression therapy in decreasing lower leg volume and leg circumference at the calf and ankle. Symptoms such as leg pain, pruritus, and feeling of fatigue and tenseness were also reduced (211). Side effects are uncommon, but gastrointestinal irritation and toxic nephropathy may occur (212).

Contraindications to use include hypersensitivity to escin or horse chestnut and renal or hepatic impairment (213). At present there is no human drug interaction data available, but the increased risk of bleeding due to the naturally occurring coumarin constituents is possible. Also, HCSE has been suspected of causing hypoglycemic effects (209). The German Commission E has approved the use of HCSE in chronic venous insufficiency. It may be effective in that role.

Guggulipid (guggul gum). Guggulipid has a long history of use in Ayurvedic medicine, which is an ancient Indian system that uses an integrated approach (diet, lifestyle, herbs, exercise, and meditation) to the prevention and treatment of illness by maintaining harmony among the mind, body, and forces of nature. Both guggul and its purified extracts have been used as hypolipidemic agents in patients with ischemic heart disease, hypercholesterolemia, and obesity (214). Clinical studies performed in India have demonstrated that 25 mg of guggulsterone extracts t.i.d. may be an effective treatment for hypercholesterolemia and hypertriglyceridemia. Reductions in total cholesterol levels of approximately 24% and reductions in triglycerides of 16% to 23% have been reported (215,216). The majority of these trials were not randomized.

In one randomized, controlled study of 125 hyperlipidemic patients, a standardized extract of guggulsterone was compared with clofibrate with mean reductions in serum cholesterol and triglycerides of 11% and 16%, respectively (217). In the first randomized, controlled trial of guggulipid outside of India, 103 healthy adults with hypercholesterolemia given 1,000 or 2,000 mg guggulipid containing 2.5% guggulsterones experienced no improvement in their lipid levels. A hypersensitivity rash was reported in a small number of subjects (218). Effects of guggulipids on HDL were mixed. A standard dose is 75 to 100 mg of guggulsterones daily divided into three doses. Guggulipids can cause gastrointestinal upset, headache, mild nausea, belching, hiccups (209), and rash (218). Concomitant oral administration can reduce propranolol and diltiazem bioavailability and might reduce the therapeutic effects of these drugs (219). Although in vitro studies suggest a plausible mechanism of action for guggulipid as a cholesterol-lowering agent (220), definitive safety and efficacy data are lacking.

Red yeast rice (*Monascus purpureas*). Red yeast is the rice fermentation product of a mixture of several species of *Monascus fungi*, principally *Monascus purpureas*. It contains monacolin K (lovastatin, mevinolin) and other HMG-CoA reductase inhibiting compounds. Red yeast has been used to reduce cholesterol levels (221,222). In a 12-week placebo-controlled study conducted in the U.S. in 83 healthy subjects with hyperlipidemia (222), 2.4 g of red yeast rice significantly reduced total cholesterol by 16%, LDL cholesterol levels by 22%, and total triglycerides by 7% compared with placebo. No serious side effects were reported, but additional longer-term studies are needed.

Red yeast should be treated as an HMG-CoA reductase inhibitor, with all the possible side effects, drug interactions, and precautions associated with this class of drugs. Red yeast rice is no longer marketed with standardized lovastatin

Table 1. Herbs Containing Stimulants

Ingredient	Use	Adverse Cardiac Effects
Bitter orange (Citrus aurantium)	Weight loss, nasal congestion	Cardiovascular toxicity, hypertension
Cola nut (1% to 3.5% caffeine)	Short-term relief of mental and physical fatigue	Arrhythmias, increased heart rate, palpitations
Country mallow (Heartleaf) (0.8 to 1.2% ephedrine)	Weight loss to burn fat, increase energy, impotence, sinus, allergy, asthma, bronchitis	Arrhythmias, increased blood pressure, palpitations, tachycardia
Ephedra (Ma huang) alkaloid constituents contain ephedrine and pseudoephedrine	Diseases of respiratory tract (bronchospasm, asthma, bronchitis, nasal congestion), appetite suppressant	Increased heart rate, diastolic and systolic blood pressure
Green tea (2% to 4% caffeine)	Improves cognitive performance, diuretic, lower cholesterol and triglycerides	Arrhythmias, increased heart rate, palpitations
Guarana (2.5% to 7% caffeine)	Central nervous system stimulant, weight loss, enhance athletic performance, reduces fatigue	Increased heart rate, central nervous system stimulant
Khat	Depression, fatigue, obesity	Increased blood pressure, palpitations, tachycardia
Wahoo root bark (Euonymus atropurpiuretus) (2% to 4% caffeine)	Indigestion, stimulates bile production	Shortness of breath, circulatory problems, large quantities affect the heart
Yerba mate (0.2% to 2.0% caffeine) (contains theophylline and theobromine)	Appetite suppressant, mental stimulant	Arrhythmias, increased heart rate

Reprinted with permission from Nykamp DL, et al. Ann Pharmacother 2004;38:812–6 (227).

levels in U.S. owing to legal issues, and it is now sold without lovastatin levels declared. Because of the availability of statins, its use is not recommended.

Policosanol. Policosanol is a sugar cane extract that contains a mixture of aliphatic alcohols. Lipid-lowering effects of policosanol have been shown in a variety of animal species; however, little is known about its mechanism of action or its exact composition. Over 1,000 subjects have been studied for periods of six weeks to one year in 15 randomized, placebo-controlled trials using policosanol (5 to 20 mg per day) for lipid lowering. At doses of 10 to 20 mg per day, significant reductions were observed for total cholesterol (17% to 21%) and LDL cholesterol (21% to 29%) with increases in HDL cholesterol (8% to 15%) (223). There are no data on efficacy determined by clinical end points. Although policosanol appears to be well-tolerated, caution should be exercised when combining policosanol with antiplatelet or anticoagulant agents, including garlic, ginkgo, and high doses of vitamin E (224), as policosanol has been shown to inhibit platelet aggregation in both healthy and diseased patients (225). The majority of the existing studies have been conducted in Cuba, and independent verification is needed before its use can be recommended.

Ephedra (Ma huang). Ephedra, together with its principal alkaloid ephedrine, was one of the first of the Chinese herbal medicines to be used in Western medicine. Ephedra is used to treat bronchospasm, asthma, bronchitis, allergic disorders, and nasal congestion, or as a central nervous system stimulant (209). Ephedrine acts by stimulating alpha, beta-1, and -2 adrenergic receptors, and indirectly by releasing norepinephrine from body stores. The cardiovascular effects of ephedrine last 10 times longer than those of epinephrine and consist primarily of increased heart rate and peripheral vascular resistance. Ephedrine and related alkaloids have been associated with adverse cardiovascular events, including acute MI, severe hypertension, myocarditis, and lethal cardiac arrhythmias. Dietary supplements that contain ephedra alkaloids were widely promoted and used in the U.S. for weight loss and increased energy. Their use was associated with a number of adverse events, including MI, stroke, arrhythmias, and death (226), and in December 2003 the FDA announced a ban on the sale of ephedra products in the U.S. Of developing concern is the herbal *Citrus aurantium*, or bitter orange, which contains similar stimulant amines as ephedra and is now being marketed in weight loss products. The Joint National Committee (JNC)-7 guidelines list it as a possible cause of resistant hypertension (227). One case report of acute MI has been associated with its use as contained in a multi-ingredient weight loss product. Table 1 provides a list of herbs containing stimulants.

Oleander (*Nerium oleander/Thevetia peruviana*). Oral oleander was once used for treating mild heart failure, but is now considered too dangerous for medicinal use (209). All parts of the oleander plant contain the cardiac glycosides oleandrin, oleandroside, nerioside, and digitoxigenin, which have positive inotropic and negative chronotropic actions. Oleander poisoning resembles digitalis toxicity, with predominant symptoms of nausea and vomiting, and cardiac toxicity with conduction delays that may last up to three to six days. Reports suggest that yellow oleander toxicity can be reversed by infusion of antidigoxin Fab fragments. Use of this herb is contraindicated in patients on digoxin and should not be used with other cardiac glycoside-containing herbs (209). In view of the availability of digoxin, its use is not recommended.

Herb-Drug Interactions: What We Need to Know

The increased use of herbal and phytomedicines by both health professionals and consumers has raised questions about herb-supplement and herb-drug interactions because herbs are making a resurgence in the U.S. market. Kaufman

Table 2. Loss of Serum Potassium, Which May Potentiate the Effects of Cardiac Glycosides and Antiarrhythmics

(Potassium deficiency increased by the simultaneous use of thiazide diuretics, corticosteroids, or licorce root)
Laxatives containing anthraquinone glycosides with laxative effects:
Senna fruit and leaf (*Cassia senna*)
Aloe latex (aloe vera or aloe ferox)
Buckthorn bark and berry
Cascara sagrada bark (*Rhamnus purshiana*)
Rhubarb root

et al. (228) described the patterns of prescription and nonprescription drugs in the U.S. population, noting that:

- 14% of the population took supplements and herbals over the prior week
- 16% of prescription drug users also took herbs or supplements
- 40% of the population used one or more mineral or vitamin supplements

In 1997, an estimated 15 million adults took prescription medications along with herbal remedies and/or high dose vitamins (229). These individuals are potentially at risk for adverse herb-supplement or herb-drug interactions. The following tables delineate possible drug interactions with herbal or botanical products. Table 2 lists herbs that may potentiate the effect of cardiac glycosides and antiarrhythmics. Table 3 lists the potential adverse effects of herbal remedies and their major constituents. Table 4 lists potential interactions between some herbal medicinal products and cardiovascular drugs. Table 5 lists the interference of herbal products in therapeutic drug monitoring.

Summary of recommendations for bioactive food components and dietary supplements. Supplements/interventions that can be recommended

1. Omega-3 supplements 1 to 2 g per day if insufficient omega-3 intake from fish
2. Stanol/sterol ester margarines (2 g per day)
3. Soluble fiber (5 to 20 g per day)
4. Soy foods and soy protein (equivalent to 25 g soy protein daily

Possibly useful for indications noted

1. Moderate alcohol intake (1/2 to 2 drinks per day—a drink is 5 oz of wine, 12 oz of beer or 1.5 oz of 80 proof whiskey) for cardiovascular risk reduction
2. Tea (1 to 2 cups daily) for cardiovascular risk reduction
3. Recommended dietary intake of magnesium (RDA adult men 420 mg; women 320 mg daily). Consider supplementation for those at risk (poor dietary intake or conditions that increase renal magnesium losses).
4. Folic acid supplementation (plus vitamins B_6 and B_{12}) if homocysteine is elevated.

Cannot recommend at this time (for some individuals in some situations, probably not harmful)

Table 3. Potential Adverse Effects of Herbal Remedies and Their Major Constituents*

Cardiotoxicity	**Neurotoxicity or Convulsions**
Aconite root tuber	Aconite root tuber
Herbs rich in cardioactive glycosides	*Alocasia macrorthiza* root tuber†
Herbs rich in colchicine	Artemisia species rich in santonin
Leigongteng	Essential oils rich in ascaridole
Licorice root	Essential oils rich in thujone
Ma huang	Ginkgo seed or leaf‡
Pokeweek leaf or root	Herbs rich in colchicine
Scotch broom†	Herbs rich in podophyllotoxin
Squirting cucumber†	Indian tobacco herb
	Kava rhizome†
Hepatotoxicity	Ma huang
Certain herbs rich in anthranoids	Nux vomica
Certain herbs rich in protoberberine alkaloids	Pennyroyal oil
Chaparral leaf or stem	Star fruit
Germander species	Yellow jessamine rhizome
Green tea leaf†	**Renal Toxicity**
Herbs rich in coumarin	Beta-aescin (saponin mixture from horse-chestnut seed)
Herbs rich in podophyllotoxin	Cape aloes†
Herbs rich in toxic pyrrolizidine alkaloids	Cat's claw†
Impila root	Certain essential oils
Kava rhizome	Chaparral leaf or stem†
Kombucha	Chinese yew
Ma huang	Herbs rich in aristolochic acids
Pennyroyal oil	Impila root
Skullcap pennyroyal oil	Jering fruit
Soy phytoestrogens†	Squirting cucumber†
	Star fruit

*The full version of this table is available from the National Auxiliary Publications Service (NAPS). (See NAPS document no. 05609 for 33 pages of supplemental material. To order, contact NAPS, c/o Microfiche Publications, 248 Hempstead Tpke., West Hempstead, NY 11552.) Adverse effects of multiple-herb therapies are not included. Case reports do not always provide adequate evidence that the remedy in question was labeled correctly. As a result, it is possible that some of the adverse events reported for a specific herb were actually due to a different, unidentified botanical or another adulterant or contaminant. †A single case was reported without reference to previous cases. ‡Convulsions have been observed after large doses of yinguo (ginkgo seed), a traditional Asian food and medicine, which contains the convulsive agent 4′-O-methylpyridoxine (MPN) (230,231). Recently, anecdotal reports have associated ginkgo-containing preparations available on the Western market with seizures (232), and these adverse events have also been reported in patients with seizure disorders stabilized by valproate (233). How Western ginkgo preparations might induce seizures is still unclear. MPN has been detected in ginkgo leaf and preparations that contain ginko, but usually at subtoxic levels (234). Reliable information concerning herb-drug interactions can be obtained from the following Web sites: www.Naturaldatabase.com, www.herbmed.org. and www.herbalgram.org.

1. Folic acid supplementation if homocysteine is not elevated for vascular disease
2. Garlic for lipid lowering
3. Soy isoflavones for lipid lowering
4. L-arginine supplementation for nutritional support
5. CoQ10 for nutritional support
6. Hawthorn for mild heart failure
7. Ginkgo biloba for peripheral vascular disease
8. HCSE for peripheral vascular disease

Supplements/interventions not recommended (possibly harmful)

1. Levels exceeding the upper tolerable limits (IOM, 2001) for vitamins C (2,000 mg/day) and E (1,000 mg/day);

Table 4. Potential Interactions* Between Some Herbal Medicinal Products and Cardiovascular Drugs

Herbal Medicine†	Usage or Relevant Pharmacological Effect‡	Potential Interaction
Adonis (*Adonis vemalis*)	Digitalis-like	Contains cardiac glycosides and may enhance other such drugs; increases (adverse) effects of quinodine, calcium saluretics, laxatives, glucosteroids, beta-blockers, calcium channel blockers, and digitalis
Aloe vera (*Aloe barbadensis*)	Various, e.g., wound healing (topical) or antidiabetic (oral)	With chronic use, potentiation of cardiac glycosides or antiarrhythmic drugs due to loss of potassium
Arnica (*Arnica montana*)	Wound healing	Decreases effects of antihypertensives and anticoagulants
Bearberry (*Arctostaphylos uva ursi*)	Diuretic	Increases effects of cardiac glycosides through potassium depletion: may alter blood level of drugs metabolized in the liver due to hepatic enzyme induction
Bilberry (*Vaccinium myrtillus L*)	Circulatory disorders	Increases effects of anticoagulants
Black cohosh (*Cimicifuga racemosa*)	Estrogenic	Increases effects of antihypertensives
Blue cohosh (*Caulophyllum*)	Smooth muscle stimulant	Decreases effects of antihypertensives
Bogbean (*Menyanthes trifoliate*)	Diuretic, analgesic	Increases effects of anticoagulants
Boldo (*Bolodo folium*)	Diuretic	Increases effects of cardiac glycosides (potassium depletion)
Broom (*Cystisus scoparius*)	Antiarrhythmic, diuretic	Increases effects of antidepressants, beta-blockers, and cardiac glycosides: induces circulatory collapse with quinidine, haloperidol, or moclobemide
Buchu (*Barosma betulina*)	Diuretic	Increases effects of anticoagulants and cardiac glycosides (potassium depletion)
Buckthorn (*Rhamnus cathartica*)	Laxative, cathartic	Causes loss of potassium with chronic use; potentiates cardiac glycosides or antiarrhythmic drugs
Butchers broom (*Busus aculeatus*)	Venoconstriction	Decreases effects of alpha-blockers
Capsicum (*Capsicum anuum L*)	Appetite stimulant	May interfere with antihypertensives and MAO inhibitors; can stimulate the hepatic metabolism of drugs
Cascara (*Rhamnus purshiana*)	Laxative, cathartic	Causes loss of potassium with chronic use; potentiates of cardiac glycosides or antiarrhythmic drugs
Cats claw (*Uncaria tomentosa*)	Anti-inflammatory	Increases effects of anticoagulants and antihypertensives; can interfere with protein-based drugs and chemotherapy
Chamomile (*Matricaria chamomilla*)	Spasmolytic. anti-inflammatory	May potentiate effects of anticoagulants through its coumarin content
Cinchona (*Cinchonae cortex*)	Dyspepsia	Increases effects of anticoagulants
Coltsfoot (*Tussilaga farfara*)	Asthma, bronchitis	May antagonize antihypertensives: increases hepatotoxicity of other drugs
Cordyceps (*Cordyceps sinensis*)	Tonic, stress management	Increases effects of anticoagulants and MAO inhibitors
Cowslip (*Primula veris*)	Sedative	Increases effects of diuretics and antihypertensives
Dandelion (*Taraxatum officinale*)	Laxative, diuretic	Increases effects of antihypertensives, diuretics, and hypoglycemics
Feverfew (*Tanacetum parthenium*)	Migraine prevention	Increases effects of warfarin
Fenugreek (*Trigonella foenum-graecum*)	Hypocholesterinemic	Increases effects of anticoagulants and hypoglycemics: may decrease absorption of other drugs
Figwort (*Scrophularia nodosa*)	Antibacterial, anti-inflammatory	Increases effects of beta-blockers, calcium channel blockers, and cardiac glycosides
Fumitory (*Fumaria officinalis*)	Antibacterial, diuretic, laxative	Increases effects antihypertensives, beta blockers, calcium channel blockers, and digoxin
Ginseng, Siberian (*Eleutherococcus senticosus*)	Stimulant	May interact with cardiac drugs, hypo- and hypertensives, and antihypoglycemics
Goldenseal (*Hydrastis canadensis*)	Anti-inflammatory, antimicrobial	Increases effects of antihypertensives, calcium channel blockers, and digoxin; may decrease anticoagulant effects; many herbalists believe that goldenseal generally enhances the activity of other drugs
Gossypol (*Gossypium hirsutum*)	Antifertility drug	May lead to potassium depletion with diuretics; can enhance renal toxicity of other drugs
Hawthorn (*Crataegus laevigata*)	Digitalis-like	Can increase hypotensive effects of nitrates, antihypotensives, cardiac glycosides, and CNS stimulants
Horse chestnut (*Aesculus hippocastanum*)	Anti-inflammatory	Increases effects of anticoagulants
Horsetail (*Equisetum arvense*)	Diuretic	Increases effects of CNS stimulants and diuretics
Ilex (*Ilex paraguarensis*)	Diuretic, analgesic	Can increase effects of diuretics; hepatic microsomal enzyme inhibitors may decrease clearance and cause toxicity
Indian snake root (*Rauwolfia*)	Hypotensive	Cardiac glycosides, bradycardiabarbiturates (and other CNS depressants); potentiation; levodopa; neutralization; extrapyramidal symptoms; sympathomimetics; hypertension
Irish moss (*Chondrus crispus*)	Demulcent for ulcers or gastritis	Increases effects of anticoagulants and antihypertensives
Kelp (*Laminaria digitata*)	Antitumour effects, antiobesity	Increases effects of anticoagulants and antihypertensives

Continued on next page

Table 4 Continued

Herbal Medicine†	Usage or Relevant Pharmacological Effect‡	Potential Interaction
Khella (*Ammi visnaga*)	Spasmolytic	Increases effect of anticoagulants, calcium channel blockers, and other antihypotensive drugs
Lily of the valley (*Convallaria majalis*)	Congestive heart failure	Increases effects of quinodine, calcium, salureties, laxatives, glucosteroids, beta-blockers, calcium channel blockers, and digitalis
Lovage (*Levisticum officinale*)	Diuretic	May potentiate effects of anticoagulants
Nettle (*Urtica dioica*)	Diuretic	May potentiate effects of other diuretics
Night-blooming cereus (*Selenicereus grandiflorus*)	Digitalis-like	Increases effects of hypoglycemics; may enhance effects of cardiac glycosides, angiotensin-converting enzyme inhibitors, antiarrhythmics, beta-blockers, and calcium channel blockers
Parsley (*Petroselinum crispum*)	Hypotensive	Increases effects of antihypertensives; enhances toxicity of MAO inhibitors
Pau d'arco (*Tabebuia impetiginosa*)	Aphrodisiac	Increases effects of anticoagulants; decreases effects of iron supplements
Pineapple (*Anannas comosus*)	Constipation, jaundice, obesity, antiulcer	Overanticoagulation through coumarin contents; may antagonize effects on bradykinin with angiotensin-converting enzyme inhibitors (bromelain)
Plantains or psyllium (*Plantago lanceolata*)	Bulk laxative	Can delay absorption of other drugs (e.g., lithium); increases effects of cardiac glycosides
Poplar (*Populus alba*)	Anti-inflammatory	Increases effects of anticoagulants
Prickly ash (*Zanthoxylum americanum*)	Antiflatulent	Increases effects of anticoagulants
Pumpkin seed (*Curcubita*)	Anthelmintic, diuretic	Can increase effect of diuretics
Red clover (*Trifolium partense*)	Estrogen-like	Increases effect of anticoagulants on digoxin; interferes with oral contraceptives
Sarsaparilla (*Sarsaparilla aristochiifolia*)	Diuretic, psoriasis	Increases absorption of digitalis, glycosides, bismuth; accelerates elimination of hypnotics
Senna (*Cassia*)	Laxative	Causes loss of potassium with chronic use; increases effects of cardiac glycosides, antiarrhythmic drugs, calcium channel blockers, clamodium antagonists, and indomethacin; may decrease effects of senna preparations
Sorrel (*Rumex acetosella*)	Antiseptic, diuretic	Increases effects of other diuretics; increases hepatotoxicity of other medications
St John's wort (*Hypericum perforatum*)	Antidepressant	Hepatic enzyme inducer; increases activity of P-glycoprotein, thereby reducing plasma levels of many drugs
Strophantus (*Strophantus kombe*)	Digitalis-like	Contains cardiac glycosides and may enhance effects of other such drugs
Sweet clover (*Meliloti herba*)	Venous insufficiency	Contains coumarins, which may enhance effects of anticoagulants
Tonka bean (*Dipteryx odorata*)	Aphrodisiac	Increases effects of anticoagulants; increases hepatotoxicity of other drugs
Turmeric (*Curcuma longa*)	Cancer prevention	Enhances effects of antiplatelet drugs; decreases effects of immunosuppresants
Vervain (*Verbena officinalis*)	Antirheumatic	Increases effects of anticoagulants and hypnotics
Willow (*Salix alba*)	Analgesic	Causes transient potentiation of phenytoin; increases effects of anticoagulants
Woodruff (*Asperula odorata*)	Diuretic	Contains coumarins, which may enhance effects of anticoagulants
Yarrow (*Achillea millefolium*)	Antispasmodic, anti-inflammatory	Increases effects of anticoagulants, antihypertensives and CNS depressants; increases hepatotoxicity of other drugs

Cardiovascular adverse effect of herbal medicines: a systematic review of the recent literature. Reprinted with permission from Ernst E. Can J Cardiol 2003;19:818–27 (235). Data extracted from Fugh-Berman A. Lancet 2000;355:134–8 (236). *Not all effects are true interactions (some are, for instance, additive effects). †Plant source in parentheses. ‡Not comprehensive.

CNS = central nervous system; MAO = monoamine oxidase.

and beta-carotene supplementation not recommended; limit to food sources.

2. Ephedra, oleander, and other herbs/botanicals with well-defined contraindications to cardiovascular drug and/or CVD conditions.

Related Alternative Therapy

Chelation. Chelation therapy is a form of alternative medicine utilized in the treatment of atherosclerotic CVD. Over 800,000 patient visits were made for chelation therapy in the U.S. in 1997. Chelation therapy consists of a series of intravenous infusions containing disodium ethylene diamine tetraacetic acid (EDTA) in combination with other substances, such as vitamins. Use of EDTA has been found to be effective in chelating and removing toxic heavy metals from the blood (238). It is purported that the removal of polyvalent cations, notably calcium ions, can lead to the regression of atherosclerotic plaques by a yet undefined mechanism. Use of EDTA chelation therapy is FDA-approved in treating lead poisoning and toxicity from other

Table 5. Laboratory Analysis and Treatment Guidelines for Specific Herbal Preparation and Their Critical Contaminants

Herbal Preparation	Suggested Laboratory Analysis	Antidote
Cardiac toxins		
Ch'an Su	Serum digoxin, potassium	Digoxin Fab
Foxglove	Serum digoxin, potassium	Digoxin Fab
Oleander	Serum digoxin, potassium	Digoxin Fab
Squill	Serum digoxin, potassium	Digoxin Fab
Central nervous system toxins		
Henbane	None	Physostigmine
Jimsonweed (Datura)	None	Physostigmine
Mandrake	None	Physostigmine
Gastrointestinal toxins		
Aloe	Serum electrolytes	Potassium repletion
Buckthorn	Serum electrolytes	Potassium repletion
Cascara	Serum electrolytes	Potassium repletion
Fo-Ti	Serum electrolytes	Potassium repletion
Senna	Serum electrolytes	Potassium repletion
Heavy metals	Ag, As, Au, Cd, Cr, Cu, Hg, Pb, Th, or Zn Abdominal radiograph	Metal chelator
Hematologic toxins		
Dong Quai	INR	Vitamin K_1
Tonka bean	INR	Vitamin K_1
Woodruff	INR	Vitamin K_1
Hepatotoxins		
Pennyroyal oil	AST/ALT	*N*-acetylcysteine
Pyrrolizidine alkaloids	AST/ALT	None available
Salicylates		
Medicated oils, etc.	Serum salicylate	Sodium bicarbonate, multiple dose activated charcoal, hemodialysis
Cellular toxins		
Apricot pits (cyanide)	Lactate	Cyanide antidote kit
Autumn crocus (colchine)	WBC, BUN	? Glutamic acid
Elder (cyanide)	Lactate	Cyanide antidote kit
Periwinkle (vincristine)	WBC, BUN	? Glutamic acid
Pododphyllum (podophylline)	WBC, BUN	? Glutamic acid
Miscellaneous		
Licorice	Serum potassium	Potassium repletion
Quinine	None	Sodium bicarbonate, magnesium

Reproduced with permission from Toxicologic Emergencies, 7th edition, Goldfrank LR, et al. McGraw-Hill Medical Publishing Division (237).
ALT = alanine aminotransferase; AST = aspartate; BUN = blood urea nitrogen; INR = international normalized ratio; WBC = white blood cell.

heavy metals. The FDA has not approved the use of chelation therapy to treat CAD.

The bulk of the evidence supporting the use of EDTA chelation therapy is in the form of case reports and case series. A systematic review on chelation therapy for peripheral arterial occlusive disease has shown that chelation therapy is not superior to placebo and is associated with considerable risks (239). At present, the benefit of chelation therapy remains controversial as highlighted by a recent Cochrane Review (240) of five randomized controlled studies in small numbers of subjects evaluating outcomes of disease severity and subjective measures of improvement.

The ACC position statement reapproved in 1990 states "that there is insufficient scientific evidence to justify the application of chelation therapy for atherosclerosis on a clinical basis. At the present time, therefore, chelation therapy for atherosclerosis should be applied only under an investigation protocol."

In an effort to advance the evidence base for the use of chelation therapy, the NCCAM and the National Heart, Lung, and Blood Institute (NHLBI) have launched the first large-scale clinical trial to determine the safety and efficacy of EDTA chelation therapy in individuals with coronary artery disease. The five-year Trial to Assess Chelation Therapy (TACT) will involve over 2,300 patients at more than 100 research sites across the country. The study will determine whether EDTA chelation and/or high-dose vitamin supplements improve event-free survival, whether these are safe for use, improve the quality of life, and are cost-effective. The primary end point in the trial will be a composite of death, MI, stroke, hospitalization for angina, and coronary revascularization.

III. MIND/BODY AND PLACEBO

The Mind/Body Relationship and its Correlation to CVD

Reviewing the mind/body relationship and its clinical correlates to CVD is a union of both the social and biological. Although physicians easily grasp measurable physiological phenomena (e.g., the concept of acid production, blood pressure elevation, and the angiographic narrowing of a

coronary artery), it is much more difficult to understand social relationships, isolation, anger, depression, and their manifestation in disease. Sterling and Eyer (241) have illustrated how the development of modern society is associated with a disruption of human relationships. These disruptions cause chronic psychological arousal, which is defined as stress. The body's physiological mechanisms are altered by chronic psychological arousal and this leads to pathology and disease.

The function of arousal is to help the individual "cope" with environmental demands. Coping may be defined as "contending" or "struggling." This behavior frequently requires excess physical or emotional energy to deal with a difficult situation. Studies have shown that patients entering a hospital for diagnostic tests have elevated norepinephrine, epinephrine, cortisol, and growth hormone levels (242–245). Because these patients have little control over their situation, there is little effective coping behavior. Under these circumstances, in which limited control over the environment is possible, the stress hormones are maximized. Likewise, students during examination periods demonstrate a rise in cortisol, epinephrine, serum blood sugar, cholesterol, and blood pressure levels. Under exam stress, these same students exhibit a decline in white blood cells (242,243,245–249). This drop in white blood cells in part explains the high rate of physical illness under stressful situations. Tax accountants have been shown to have large increases in serum cholesterol (independent of diet) and a decrease in blood clotting time during tax season (250). Arousal, and as a consequence stress, will be high not only among individuals with little control over life circumstances, but also among individuals with a high demand for performance. Arousal that results from a lack of control will frequently manifest with anger or fear. Although high-demand situations are frequently accompanied by anxiety, they may result in extreme pleasure if the coping style is successful. However, this success in the end does not mean that the metabolic costs to the body are less.

Impact of Stress on CVD Risk Factors

In the Framingham Heart Study (251), hypertension was involved in over 80% of all cardiovascular deaths. In addition, hypertension was at least twice as strong a predictor of death as smoking or elevated blood cholesterol. Over 50 million Americans are currently hypertensive. In about 5%, a specific pathology such as a renal artery stenosis can be identified. In the remaining 95%, the blood pressure increase is not attributed to a specific pathology. Different mechanisms can contribute to the development of hypertension. Acute arousal leads to sympathetic stimulation and an increase in cardiac output. When arousal is maintained for long periods of time, the elevation in blood pressure remains even if the inciting stimulus is removed. At this stage, the hypertension is not sustained by increased cardiac output but by increased vascular resistance.

Stress may lead to hypertension through repeated blood pressure elevations and by increasing the amount of vasoconstricting hormones. Stress factors leading to hypertension include job strain, social environment, emotional stress, and white coat hypertension. Overall, studies conclude that, although stress does not directly cause hypertension, it can clearly affect its development. Stress leads to sympathetic nervous system activation with excessive amounts of cortisol, epinephrine, and aldosterone. The combination of increased cardiac output and vasoconstriction may transiently raise blood pressure. Feelings of frustration, exhaustion, and helplessness can activate the pituitary and adrenocortical hormones. Non-pharmacological treatments to manage stress such as meditation, acupuncture, biofeedback, and music therapy have been found to be effective in decreasing blood pressure and the development of hypertension (252).

Although not a substitute for pharmacological therapy, certain non-drug therapies offer support for individuals with hypertension. Steelman (253) studied the effect of tranquil music on blood pressure and anxiety in surgery patients. The experimental group listened to music during the intraoperative period. The control group received usual care. Music appeared to reduce blood pressure in the experimental group. Pender (254) studied the effect of progressive muscle relaxation (PMR) training in hypertensive patients. Those individuals who received PMR training reported less anxiety. Decreased anxiety correlated with decreased systolic blood pressure. Older African-Americans who were taught the transcendental meditation technique had a significant reduction in diastolic and systolic blood pressure (255).

Diabetes, like hypertension, remains an important risk factor for the development of CVD. Chronic arousal can contribute to diabetes in two ways. With arousal, there is an increase in catabolic hormones, most notably epinephrine, cortisol, growth hormone, and glucagon. These hormones antagonize the actions of insulin by mobilizing glucose, fatty acids, and protein breakdown. Furthermore, glucagon and norepinephrine act to suppress the secretion of insulin. The resulting hyperglycemia, hyperinsulinemia, and hyperlipidemia all accelerate pathology.

In addition to hypertension and diabetes mellitus, studies linking stress and cholesterol date back to the 1950s. These older studies suggest that stress associated with time pressure, repetitive assembly line work, and increased responsibility may raise serum cholesterol (250,256,257). Both cortisol and epinephrine have been linked in humans to serum cholesterol elevation. In many animal experiments, stress has accelerated atherosclerosis. Rabbits on a high-fat diet when stressed with electrical stimulation over 10 months have an increased number of atheromas in comparison with non-stressed controls. The administration of epinephrine to cholesterol-fed rabbits further intensifies lipid infiltration of the aortic intima. As mentioned previously, accountants show continuous monthly rises in cholesterol, despite maintaining a constant diet, which peaks at the end of the fiscal year (250).

Depression and the Development of CVD

A growing body of evidence suggests that depression may predispose to cardiovascular events (258). Individuals with mental stress during daily life have twice the risk of myocardial ischemia. In addition, those patients with post-MI depression have higher mortality rates than non-depressed controls. Depression is common after acute MI and is associated with an increased risk of mortality for at least 18 months. One reason for this higher morbidity and mortality within the first few months following an MI is that depressed patients are less likely to follow recommendations to reduce further cardiac events.

Ziegelstein et al. (259) found that patients who were identified with at least mild-to-moderate depression or major depression reported lower adherence to a low-fat diet, regular exercise, and stress management. Individuals with major depression and/or dysthymia reported taking their medication less often than prescribed. Those findings, in part, explain why depression in the hospital is related to long-term prognosis in patients recovering from an MI.

In addition, acute MI patients with unstable angina who were identified as depressed in the hospital were more likely to experience cardiac death or nonfatal MI than other patients (259). The impact of depression on 430 patients with unstable angina (41.4% depressed) remained after controlling for other prognostic factors such as left ventricular ejection fraction and number of diseased vessels (260).

In addition to depression, other research suggests that social support may influence prognosis following an acute MI. In a study of 887 post-MI patients, Frasure-Smith et al. (261) found that 32% had mild-to-moderate depression. After one year, follow-up interviews were conducted and demonstrated that elevated Beck depression scores were related to cardiac mortality. The relationship between depression and cardiac mortality decreased with increasing support. Furthermore, of those one-year survivors who were depressed at baseline, higher baseline social support was related to greater than expected improvement in depression symptoms.

The Enhancing Recovery in Coronary Heart Disease Patients Study (ENRICHD) was sponsored by the NHLBI. The study enrolled 2,481 patients at 73 hospitals within 28 days of an MI; participants had major or minor depression, low social support, or both. Patients were assigned to either a "treatment" or "usual medical care" group (262). Cognitive therapy was provided by the treatment group for six months. At the end of six months, patients in the treatment group scored significantly better on the Hamilton depression (57% reduction in depression versus 47% reduction in the usual medical care group) scale. Likewise, patients low in social support demonstrated a 27% improvement in this parameter versus 18% for the usual care group. However, despite the treatment groups' improvement in depression and social isolation, there was no improvement in heart disease survival.

Increased use of selective serotonin reuptake inhibitors (SSRIs) and their demonstrated safety in patients with CVD raises the question of whether early pharmaceutical treatment for depression in cardiac patients will improve clinical outcome (263–265). Yet despite this low-risk profile, very little research exists regarding the benefit of SSRIs in patients with CVD. The Sertraline Antidepressant Heart Randomized Trial (SADHART) has evaluated the efficacy and safety of sertraline therapy in patients with acute heart disease without evidence of statistically significant benefit (266). Until meaningful data are obtained, the use of antidepressants in cardiac patients requires a weighing of the risks versus potential benefit.

In addition to affecting lipids, enhancing weight loss and improving exercise tolerance, cardiac rehabilitation provides emotional support, reduces depression, improves quality of life scores, and decreases mortality by 25% (267–271). Such programs serve as the logical place to screen cardiac patients for psychosocial risk factors such as depression and anxiety. Once identified, appropriate intervention can be initiated.

In conclusion, although post-MI depression is a predictor of one-year cardiac mortality, high levels of social support appear to decrease the magnitude of depression. High levels of social support also predict improvements in depression symptoms over the first post-MI year in those individuals with baseline depression.

Summary of recommendations for mind/body relationship. Several complementary and alternative medicine techniques have been used as adjuncts to traditional therapies in the treatment of CVD as follows:

a. Coronary artery disease
   1. Stress reduction
   2. Meditation
   3. Group support

b. Arrhythmias
   1. Biofeedback
   2. Stress management
   3. Group support

c. Pre-surgery
   1. Guided imagery

d. Cholesterol
   1. Stress management
   2. Meditation

e. Congestive heart failure
   1. Biofeedback
   2. Group support

f. Hypertension
   1. Group support
   2. Biofeedback
   3. Meditation
   4. Pet acquisition (272–277)

Placebo

"Placebo," Latin for "I shall please," can be derived from a device, a drug, or complementary medicine modalities. A placebo is not necessarily a sham therapy but a potential response due to an interaction between the intent of the healer and the expectations of the patient. The response can be powerful, but the longevity of the response can vary by condition and type of placebo. Several reports in cardiology—BHAT (278), CHF-STAT trial (279), and the Coronary Drug Project (280)—have shown a remarkably strong effect regarding compliance with placebo. The reduction in mortality for those who take their placebo compared to those who are non-compliant is highly significant, but the mechanism (280) is unknown.

Shapiro (281) indicated that the physician was important in the dyadic dance of healing and proposed that perhaps doctors, independent of what they did, were actually potent placebos in their own right. He and others enumerated a number of specific variables that might endow some physicians with particular curative manna: enthusiasm for treatment, apparent warm feelings for the patient, confidence, and authority. Some physicians may be able to exhibit a placebo effect more intensely than others, but the mechanism for this and the extent of it are not understood.

The placebo effect has been described as a nonspecific psychological or psychophysiologic therapeutic effect, but this may not be correct and the response may be a crucial synergistic adjunct to any cardiovascular therapy. Placebos can elicit a real and substantial response, the extent of which is related to the type of the placebo, the condition being treated, and the response being elicited. No multivariate analysis has detected which specific patient characteristics are most associated with a profound placebo effect. The placebo response in major depression (282) ranges from 32% to 70% and can equal that of a drug intervention. After all, what occurs during psychotherapy is a form of placebo response. The importance of understanding the mechanisms responsible for the placebo response is crucial to understanding the basic nature of healing (283). Expectancy, beliefs, anxiety, hope, trust, and intent can alter outcomes regarding disease (284).

The placebo response may involve disease expression, specific neuroendocrine, neuronal and immune intermediary pathways, neuropeptides, enkephalins, endorphins, cholecystokinin, neurohormones (including glucocorticoids and prolactin), neurotransmitters (including 5-hydroxytryptamine, norepinephrine, dopamine), and other messengers such as nitric acid and prostaglandins. The power of expectancy of improvement was emphasized by controlled trials of arthroscopic surgery and of neurosurgery. Osteoarthritis of the knee responds as well to arthroscopic debridement, arthroscopic lavage, and placebo surgery. Similarly, sham neurosurgery improved Parkinson patients as well as cell implants and sham cardiovascular surgery improves patient chest pain as often as 90% of the time (285). It is, however, difficult to quantitate the benefit of either the placebo effect or sham procedure.

Hrobjartsson and Gotzsche (286) suggest there is little evidence that placebos in specific conditions, comparing no therapy to placebo therapy, had powerful clinical effects. Yet this is likely disease specific as many placebo-controlled studies showed enormous benefits of the placebo (282). Another form of the placebo response is relief to a patient when serious disease is excluded. Patients who have an evaluation ("tests") for atypical chest pain are less likely to be disabled than those who do not have such an evaluation (287).

IV. ACUPUNCTURE

Acupuncture has gained increasing acceptance by the lay public, partly as a result of increasing communication between the U.S. and China since the early 1970s (1,288). Texts on acupuncture date back to 206 BC, although the Yellow Emperor, Huang Di, the originator of traditional Chinese medicine lived in 2,697 BC (289). Acupuncture has been used for a wide variety of conditions, but it is most accepted for treatment of pain (290–293). Increasing evidence suggests that acupuncture may also be useful in treating patients with neurological disease, including disorders of the autonomic nervous system, hypertension, and other forms of CVD. The World Health Organization (WHO) has noted that acute infection and inflammation, dysfunction of autonomic nervous system, pain, and peripheral and central neurological diseases each represent conditions for which acupuncture may be indicated (291,292,294). The mechanism by which acupuncture is believed to benefit the subject is through its ability to modulate neural activity in several regions of the brain and thus reduce sympathetic outflow to the heart and vascular system (295).

There are four areas of CVD for which acupuncture eventually may be indicated. These include ischemic CVD, hypertension, heart failure, and arrhythmias. Studies from several groups, including Ballegaard (296) and Richter (297), have examined the role of acupuncture in treatment of patients with stable angina. Ballegaard, in an initial study, was unable to document a decrease in angina in humans as measured by a decrease in the rate of anginal attacks, consumption of nitroglycerin or exercise tolerance, comparing true acupuncture to sham acupuncture (296,298); the group concluded that true acupuncture cannot be distinguished from sham acupuncture in which needles were placed outside traditional meridians. Two other studies by the same group showed an acupuncture-related improvement in exercise capacity and rate-pressure product (299), particularly when acupuncture reduces sympathetic neural outflow (298). Separately, Richter (297) observed that acupuncture exerted a beneficial effect in patients with severe stable angina who had been aggressively treated with medical therapy. Manual acupuncture reduced the number

of anginal attacks per week, the severity of chest pain, electrocardiographic evidence of myocardial ischemia, and increased the workload required to provoke angina in patients with CAD and stable angina (297). The latter study used a tablet placebo control. These studies involved small numbers of patients, were unblinded, and did not use the most appropriate sham controls.

Prolonged peripheral vasodilation, measured by peripheral thermography, occurs following electroacupuncture (297). Acupuncture or its non-invasive surrogate, transcutaneous electrical nerve stimulation (TENS), appears to influence peripheral blood flow in patients with Raynaud's syndrome (300), skin flap survival in experimental preparations (301,302), and skin temperature in patients with polyneuropathy (303). The primary form of Raynaud's cold-induced vasoconstriction, assessed by Doppler flowmetry and clinical symptoms, is reduced by acupuncture compared to sham treatment (300). Secondary forms of Raynaud's appear to be less influenced by acupuncture. Survival of ischemic musculocutaneous skin flaps is increased in experimental preparations treated with either manual or electroacupuncture (301,302). Similarly, patients undergoing reconstructive surgery who are treated with TENS experience improved microvascular flow and reduced edema and capillary stasis relative to placebo TENS (304). Low-frequency TENS leads to a prolonged increase in skin temperature in patients with diabetic polyneuropathy (303). Most studies on the peripheral circulatory effects of acupuncture are small and were not blinded; confirmation of their observations is needed.

Several small trials suggest that hypertension may be improved by acupuncture (305–310). The magnitude of the effect of acupuncture on blood pressure in patients with hypertension is small but significant; reductions of 5 to 10 mm Hg have been noted. These and other small studies from outside the U.S. have led to funding of at least two ongoing clinical trials by the NCCAM to test the hypothesis that acupuncture can lower blood pressure in patients with hypertension.

Experimental studies indicate that acupuncture reduces demand-induced myocardial ischemia in felines (311), catecholamine- or stress-induced hypertension (312–315), or genetically associated hypertension (316). These studies also demonstrate that acupuncture limits myocardial ischemia by reducing myocardial oxygen demand rather than by increasing coronary blood flow in a feline model (311). Acupuncture also can inhibit ventricular extrasystoles induced by stimulating the hypothalamus (317), paraventricular nucleus (317) or following administration of $BaCl_2$ (314).

The rationale for using acupuncture to treat myocardial ischemia, hypertension, and arrhythmias stems from its ability to inhibit sympathetic outflow (316). Numerous experimental studies have shown that acupuncture, particularly low frequency (2 to 4 Hz) electroacupuncture, causes the release of opioids in a number of regions in the hypothalamus, midbrain, and medulla (290,318–323) that are concerned with processing information that ultimately influences sympathetic neural activity. Thus, by releasing endorphins, endomorphins, or enkephalins (324), which act as neuromodulators that likely reduce function of excitatory neurotransmitters, acupuncture appears to be able to inhibit sympathetic outflow and clinical events associated with heightened sympathetic activity. Other neurotransmitters that might be associated with the influence of acupuncture on sympathetic neural activity important in cardiovascular regulation include gamma-aminobutyric acid (GABA), serotonin or 5-hydroxydopamine (5-HT), acetylcholine, and nociceptin (131). High-frequency electroacupuncture (100 Hz) may influence the cardiovascular system through another opioid neurotransmitter/neuromodulator, dynorphin (325).

Acupuncture can be stimulated either manually by simply inserting a needle in an acupuncture point, then either leaving it in place or twisting and thrusting the needle or by stimulating the needles with a small amount of electrical current at low frequency (2 to 4 Hz) (312,314). Electroacupuncture appears to be the strongest form of acupuncture and can induce a long clinical response in rats lasting from 1 to 12 h (316). These responses have led to treatment regimens of 30 to 45 min of acupuncture administered two to three times per week for 2 to 4 weeks. Although there are no well-controlled studies in humans, there is a suggestion that one to four courses of 10 days' treatment with acupuncture lowers blood pressure (5 to 25 mm Hg) in some (e.g., borderline and essential hypertension) but not in all types of hypertension (307–310). Many practitioners use manual acupuncture at several acupoints including acupoints within the same spinal segment, called "segmental acupuncture," or a combination of segmental and distant acupoints (i.e., auricular acupuncture). In the treatment of pain, there are numerous variations of these techniques, including inserting needles at myofascial trigger points and at the specific site of pain (326). There are no data on the efficacy of different techniques of acupuncture with respect to cardiovascular treatment.

Specific acupuncture points, such as the *Neiguan* or *Zusanli* acupoints, overlying the median and deep peroneal nerves, respectively, have been used extensively for treatment of cardiovascular abnormalities (317), although the issue of point specificity for treating specific organ system ailments requires further research. The NIH has published a consensus statement indicating that a number of issues related to acupuncture concerning its efficacy, sham effects, adverse reaction, acupuncture points, training and credentialing, and mechanisms of action need further exploration (294).

The response to acupuncture has been suggested to be related to the placebo effect (293). Because placebo effects can occur in as many as 40% of patients and because acupuncture seems to be efficacious in only approximately 70% of patients, there appears to be a narrow window

between placebo and what might be a true response (i.e., 30% of patients) (327). Nevertheless, one mechanism of placebo appears to involve the endogenous opioid system (328). Most practitioners check for symptoms of tingling, local warmth, heaviness, or fullness, termed DeQi, to confirm proper placement of needles in acupoints. Such symptoms indicate stimulation of underlying neural pathways, but do not guarantee a true acupuncture versus a placebo response. Although experimental preparations circumvent this criticism, because the animals generally are anesthetized, clinical investigation in the future will need to include adequate sham controls to provide rigorous tests of the acupuncture hypothesis.

Worldwide, more than 40% of physicians recommend acupuncture to their patients and more than 15% of physicians want to add this modality to their therapeutic armamentarium (329). Although not required for licensed physicians, the practice of acupuncture by others, such as those trained in traditional Chinese medicine (i.e., acupuncturists), currently is regulated by more than 35 state boards in the U.S. Furthermore, the FDA regulates use of the disposable stainless steel acupuncture needles. Recently, a workshop held by the NHLBI and the NCCAM identified areas of needed research in complementary medicine in general and acupuncture specifically (330).

Areas of needed research in acupuncture include clinical efficacy, mechanisms of action, and side effects. Most authorities agree that the risk of an adverse event resulting from acupuncture is small, generally below 10% if performed by physicians. However, the risk of a serious event such as pneumothorax, the most common severe side effect, is significantly lower (2%), and although spinal cord lesions, hepatitis and HIV infections, endocarditis, arthritis, and osteomyelitis have been reported, they are rare. The risk of an adverse event for non-physician acupuncturists is higher (331), but again the risk of a serious event is low.

V. BIOENERGETICS (ENERGY MEDICINE)

Since ancient times, many cultures and religious disciplines have considered that an aura, a life force, a radiant energy field can emanate from, and surround, living things (332). This poorly understood vital energy (Hindu *prana*, Chinese *qi*, *chi*, and Japanese *ki*) associated with the soul, spirit, and mind, impinges on the potential boundaries of modern physics and the relationship of the mind to the physical world (333). *Bioenergetics* offers the possibility to harness a healing life force (334,335). The wide array of questionable energy-healing approaches opens the possibility of medical quackery that can put patients with serious underlying diseases at risk especially if standard, accepted, and effective therapies are overlooked.

Bioenergy, "life energy," is thought by some to influence mind/body, mind/mind (person to person) and mind/mind (person to infinite spirit) relationships (336) and is altered by conscious and unconscious efforts (336). Bioenergy is believed by some to affect psychological states and physiological processes of the nervous, endocrine, and immune systems (psychoneuroimmunology). It is likely that consciousness manifested as thought, emotion, memories, fears, and self-concept can create physical changes in the body, and this appears modulated by many circulating mediators such as tumor necrosis factor (TNF)-alpha, which may reduce or eliminate a reward response in animals and may be manifest by conditions such as MI. Blockers of TNF-alpha (etanercept) restore the reward response (337).

No sound scientific evidence demonstrates existence of bioenergy fields. Scientific or not, bioenergy concepts are deeply ingrained and has gained popularity. Out-of-hand dismissal of influence of bioenergetics by a physician may disrupt a relationship to a believing patient and cause the patient to turn elsewhere.

The mind can influence health, life, and death (338,339). Energy that facilitates connectedness, harmony, and health can be as simple as emotional release in the form of mirthful laughter or tears. Mirthful laughter can improve immune system functioning (340). This form of bioenergy can be harnessed to improve a patient's well-being and outcome.

Belief in the benefit of treatment can improve outcome even if the treatment is a placebo. Controlled studies showing benefit of bioenergy approaches over placebo raise the issue of a potential mechanism of effect with functional magnetic resonance imaging (MRI) that can show blood flow changes during brain mapping.

Many cardiovascular symptoms are not treated easily with present medical therapy. Functional complaints, such as chest pain, palpitations, dyspnea, fatigue, and weakness not associated with measurable physical abnormalities are poorly understood, and methods to eliminate consequences could greatly improve health (286). Reinterpretation of the symptoms and their severity by the patient (mental energy) may have an influence on outcome. The real benefit of these treatments might be as an adjunct to improve patient optimism and outcomes by their psychosocial effects (280).

A sense of peace, serenity, calm, power, or emotional connection can have potent influence on outcomes (286). Removal of stress (not yet well defined) by a technique utilizing bioenergy may modify severe disabling symptoms even if the therapy has no proven benefit. Such an approach can be advocated as long as it does not exclude standard therapy and does not cause harm.

Methods to Study Bioenergy

Although bioenergy may be immeasurable, patients—and therapists—will continue to use bioenergy approaches if convinced of their efficacy, no matter the resolve of a specific scientific, or medical community to discount benefits even if there is scientific demonstration of inefficacy. Adjusting bioenergy fields through acupuncture, therapeutic touch, *Qi Gong*, *Johrei*, *Reiki*, crystal therapy, and magnet therapy may improve health, but data are too preliminary to recommend

any therapy (341). If they do have an effect, both the extent of benefit and the mechanisms responsible are unknown.

Traditional Chinese medicine encompasses folk practices based on mysticism and bioenergy (342). A recent analysis of 2,938 clinical trials reported in Chinese medical journals shows these data to be inconclusive (343). Chinese trials were qualitative, short-term, small, poorly controlled, rarely blinded, and contained inadequate data.

Forms of Bioenergetics

The techniques share common features: focus on "bioenergy" by practitioners and "energy transfer" leads to beneficial effects.

Relaxation. Relaxation therapy in 192 men having two or more risk factors for CAD was associated with better outcomes compared to a control group (344). "Type A" persons tending to have a higher incidence of hypertension and death from CVD may benefit from a relaxation response (345–348). Progressive muscle relaxation techniques have been associated with improved cardiovascular outcomes, but data are still preliminary.

Yoga. Movements and positions in yoga and the breathing exercises can lower the blood pressure and alter breathing patterns (349). Among other improvements in physical fitness, yoga can increase absolute and relative maximal oxygen uptake by 7% and 6%, respectively, after eight weeks in a controlled setting (341). Yoga has been associated with improved heart rate variability and respiratory variables (350). There can be a decrease in sympathetic response (350,351) and changes in baroreflex sensitivity (352). Yoga may influence the progression and regression of atherosclerosis (353), and may beneficially alter the lipid profile (354), but the data are too preliminary to make a sound recommendation in favor of yoga.

Qi Gong. *Qi Gong* has increased dramatically. *Qi* means life-force energy and *Gong* is "practicing skill." Practitioners believe that vital energy circulates through "meridians," connecting all organs, and illness is an imbalance, or interruption, of *Qi*. *Qi Gong* is said to re-balance the energy (355).

Internal *Qi Gong* involving deep breathing, concentration, and relaxation is a self-discipline that trains body and mind to alter flow of "vital energy." In 76 post-MI patients, *Qi Gong* was associated with improvement in respiratory rate, heart rate, and respiratory sinus arrhythmia (356). In similar study, hospitalization was reduced in post-MI patients learning *Qi Gong* relaxation techniques (357). In hypertensive patients, *Qi Gong* was associated with an improvement in levels of prostoglandin (357).

"External *Qi Gong*" is performed by "masters" who claim to cure with energy from their fingertips. Control *Qi* is claimed to diagnose and cure various conditions (357). *Qi Gong* may influence and reduce respiratory rate, heart rate, blood pressure, and accentuate vagal tone demonstrated by changes in heart rate variability (358–360). However, th clinical significance and mechanisms are unclear (361).

Over 1,300 references on *Qi Gong* suggests benefit to treat hypertension, respiratory diseases, and cancer. For hypertension, lower stroke and mortality rates have been shown in preliminary studies (362). *Qi Gong* may benefit some patients with atherosclerotic obstruction of the lower extremities (363), and breathing approaches might influence symptoms in patients with mitral valve prolapse (364).

Reiki. *Reiki* is believed to use "healing energy" to enhance vitality, resiliency, and health for both practitioner and patient (365,366). There are over 500,000 practitioners. The technique's most profound effect is deep relaxation. It works, supposedly, only if the receiver can detect the subtle, personal, unconscious energy. A practitioner "attuned" to the energy places his hands onto or just above the patient's body at strategic points (chakras) to transfer energy. Channeling this energy is purported to have a positive effect, but scientifically demonstrable cardiovascular effects have not been shown (367).

Healing and therapeutic touch. Healing touch (HT) and therapeutic touch (TT) use the concept of energy fields (auras), energy centers (chakras), and energy tracts (medians) to empower healing similar to *Reiki*.

Healing touch, developed by Janet Mentgen, RN (368), is used extensively by nurses (68,000 participants in the U.S.) at all levels of health care, but it based on little supportive controlled data. Universal energy is believed to be channeled to work with human "energy fields" to restore harmony and balance. The technique utilizes the hands to clear, energize and balance the human energy fields, thus affecting physical, emotional, mental, and spiritual health.

Healing TT is a therapeutic intervention, an educational program, and an international organization that provides healing touch certification and formulates standards of practice (368).

In therapeutic touch, hands are used to direct healing energy. Healing supposedly results from transfer of "excess energy" from healer to patient. Therapeutic touch was conceived in the 1970s by Dolores Krieger (369). Therapeutic touch involves "centering" (align the healer to the patient's energy level), "assessment" (hands detect forces from the patient), "unruffling the field" (sweeping stagnant energy downward to prepare for energy transfer), and energy transfer (from practitioner to patient) (370).

Therapeutic touch was evaluated in a meta-analysis by Astin et al. (371). Of the 11 trials reviewed, 7 showed a positive treatment effect and at least one outcome. These included a 17% decrease in anxiety in cardiac care unit (CCU) patients, reduced need for postoperative pain medication, and improved wound healing.

Healing TT may reduce anxiety but no sound scientific evidence supports the postulated "energy transfer" benefits claimed. Benefits reported may simply be a placebo effect, literally a "laying on of hands" (372).

Distance healing. Similar to TT and distance (intercessory) prayer, "distance healing" is energy transfer that is said to occur over very long distances. Beutler et al. (373) showed

small but significant changes in diastolic blood pressure in a double-blind controlled study of distance healing. One study showed benefit of distance (blinded) prayer on autonomic tone based on skin conductance levels and "blood volume pulse" (373,374).

Applied kinesiology. This technique of kinesiology is performed by therapists using acupressure points and a muscle-testing method to diagnose nutritional and glandular "deficiencies," which are then "corrected" by manipulation or nutrition supplements. There is little substantiated supportive data.

Meditation. Meditation, not universally considered bioenergy therapy, can alter blood distribution in the brain observed by magnetic resonance imaging scans and can increase delta wave activity observed on the electroencephalogram. Rage behavior decreases. Transcendental meditation has been linked to reduction in cardiovascular mortality (375–382). It can lower blood pressure (383–385). Zen meditation has been associated with improved heart rate variability and slowing of respiratory rate (384). These data are preliminary and techniques cannot be recommended yet.

Vibrational medicine. Practitioners of vibrational medicine consider humans as dynamic energy systems ("body/mind/spirit" complexes). People are influenced by subtle emotional, spiritual, nutritional, and environmental energies that affect health (386). These concepts involve vibrational medicine: aromatherapy, chakra rebalancing, distance healing; flower essence therapy, homeopathy; Kirlian photography, moxibustion, orthomolecular medicine; past-life regression, radionics; and other unfounded approaches.

Magnetotherapy. "Magnetotherapy" is applied through the use of permanent or fluctuant magnetic fields, but there are no proven benefits for the CVD (387,388). Scherlag has been evaluating, in an animal model, low-level gauss fields to affect atrial arrhythmias in preliminary studies (389).

Homeopathy. Water is believed to retain the memory of and be energized by compounds that existed in it. Scanning of water by MRI suggests there might be some, but no data has demonstrated health benefits for CVD (390). A meta-analysis of homeopathic treatments in the *Lancet* of more than 80 studies indicated, compared to placebo, that homeopathic treatments might be effective (391,392). Although the results were significant as a whole, concerning any one-disease entity, no significant treatment could be discerned. The therapies were not standardized.

Caveats

Potential beneficial effects of these approaches may be in part due to an undefined psychological impact that might ultimately create a physiological effect. The approaches have not been tested for safety. There are no specific proven cardiovascular benefits from any of these therapies to treat disease.

Potential adverse influences may be the release of inhibitions causing anger, hostility, "negative" energy, or reduction of needed sympathetic tone. No bioenergy therapy has been shown to alter the natural course of CVD (392). These therapeutic approaches may appear to have benefit as an adjunct to standard medical therapies and for patients with severe functional, yet symptomatic, complaints, but actual benefits are difficult to measure. Bioenergy approaches should not be considered substitutes for standard medical care; they may offer false hope to patients and at an expensive price.

Practitioners and patients who use these techniques will likely continue to employ them even without a scientific foundation. Practitioner qualifications are difficult to measure (393).

"Benefits" may represent the natural course of a disease or the patient's or therapist's interpretation of the condition. Positive results may represent experimenter biases not obvious from the study design. Patients may undergo "energy healing" and be cured of a condition that they do not have or they may be misdiagnosed. A bioenergy practitioner might exaggerate or create an illusion of the benefit of therapy. Biases for, and against, bioenergy healing make it even more difficult to assess the quality of the data.

Ongoing studies including those funded by the NCCAM are evaluating energy healing approaches.

Recommendations

Conditions for which bioenergy therapies are not contraindicated (but not specifically recommended) include:

1. If a bioenergy treatment does not interfere with standard, accepted, and proven therapy.
2. If standard therapies do not provide optimal symptomatic improvement, or for a condition that is potentially functional or has functional overlay.

No bioenergy therapy should be considered a substitute for standard, accepted, and approved therapies. If any bioenergy approach is considered, one should choose a practitioner who has a good reputation, appears to have good results, and is willing to work with medical professionals.

V. SPIRITUALITY/INTENTIONALITY

Spirituality in Cardiovascular Applications

Anectdotally the will to live, a strong life force spirit or faith, a loving family or community, or the absence of these features has been considered related to outcomes in cardiovascular care. Synchrony between belief systems or other "connections" between patient and healer are also widely considered important on an intuitive basis.

Some indigenous master healers from various cultures and faiths assert that medicines and procedures constitute only about 20% of what heals and that 80% is mediated through the spirit (394,395). With remarkable uniformity across these healers, the "spirit" is considered an integral element of optimal diagnosis and therapy (396,397).

The ramifications of such claims, if even partly true, are

staggering. It is currently impossible to assess the accuracy of such claims based on available data. The ubiquitous presence of spiritual beliefs and practices present since ancient times mandates systematic examination (339,398–407).

Intuitively, the role of spirituality in modern cardiovascular care offers both the potential to better understand and support patients who face cardiac death and provide new questions for therapeutic interventions. Thousands of observational, instructional, anecdotal, theological, and philosophical treatises suggest the potential impact of the spirit in health, including passages from the Bible, the Koran, the Upanishads, the transcribed teachings of Buddha and other religious literature.

Compendia

A number of well-referenced overviews or comprehensive compendia of references have been compiled on scientific investigations into spiritual and religious practices correlated with cellular, physiologic, somatic and psychosomatic healing applications. These books and compendia can be found on the ACCF Web site as Appendix VI and include references using broad arrays of study designs with a heterogeneous nomenclature and definitions specific to the heart. Two consistent themes include epidemiologic observations that both personal and social spirituality have correlations with selected outcomes measures, and that spirituality, particularly prayer, may have efficacy in healing applications. Data quality, selection bias, interpretative bias, publication bias, and details of safety issues are not discernible from these compendia.

Review Articles and Meta-Analyses

Various structured reviews and meta-analyses of spiritual descriptors and therapies and their correlations with clinical outcomes (not specific to cardiology) have also emerged in the peer review literature and can be found on the ACCF web site as Appendix VII. This literature overall is well summarized in the Astin et al. (371) recent meta-analysis of clinical studies involving spirituality. The researchers acknowledge that available reports were so heterogeneous in structure, methods, population, and end points measured that their attempt to perform a classical meta-analysis had to be "abandoned." The present writing group's consensus overview of these reviews suggest:

1. The literature in this area is devoid of mechanistic insight and is heterogeneous as to the quality of study design.
2. There is no scientific evidence in the literature sufficiently definitive or compelling to provide a basis for specific recommendations on the use of spiritual intervention for healing purposes in a cardiology population.
3. There is a notable consistency across reports suggesting efficacy.
4. There are no obvious safety issues attendant to spiritual interventions.

Specific Reports of Spirituality and Cardiovascular Care

Epidemiologic evidence correlating individual spiritual practice, involvement within a spiritual community, and of communities characterized by their spiritual practices with improved cholesterol levels, more normative blood pressure, other risk factor modulations, incidence of clinically recognized coronary disease, incidence of MI, post-coronary artery bypass graft (CABG) survival, and improved survival overall provides an intriguing context for other observations of psychosocial descriptors—including personality type, hostility, depression, isolation, and cardiac outcomes (408–418). As with all epidemiologic data, however, it remains unclear whether or not there is actually a causal relationship between these spiritual features and the clinical outcomes.

Reports of palliation of subjectively perceived stress and/or pain levels in patients admitted to the CCU or undergoing cardiac catheterization constitute another area intriguing both for its consistency and for its apparent overlap with the use of imagery, relaxation, and other biofield and energy healing techniques in similar patients (419–421). Only one preliminary report, however, has actually correlated such palliative end points with clinical outcomes (394–397,422).

Four prospective, randomized, double-blinded clinical trials examining the influence of off-site prayer on clinical outcomes in cardiac patients have been reported (394,395). In three of the studies, CCU patients were assigned either to off-site intercessory prayer or no prayer in addition to standard care. In two of the CCU studies, a combined index of hospital course and complications severity was derived specifically for study purposes (397). Although findings were reported as significantly improved in each cohort treated with off-site prayer, clinical interpretation of these findings is difficult. In the third CCU study (396), no significant differences existed in clinical outcomes, although the study was powered to a higher treatment effect than may have been observed. The fourth study was a feasibility pilot examining an array of CAM practices in patients with acute coronary syndromes undergoing invasive catheterization and angioplasty (396). Using major adverse cardiac events (MACE) and blindly analyzed continuous electrocardiographic evidence of post-angioplasty ischemia, absolute reductions were observed in the prayer group relative to the standard therapy group; however, these difference did not reach statistical significance (423). Two additional prospective, multicenter clinical studies of double blind off-site prayer in patients undergoing CABG and percutaneous coronary intervention, respectively, have completed enrollment and will soon be reported (422).

Key Issues in Spirituality Applied to Cardiovascular Care

Support versus spiritual therapy. Careful consideration must be given to the important differences between rendering spiritual support for patients and families and the study of experimental, directed spiritual therapy.

Spiritual support constitutes the response of the health care system to the self-perceived spiritual needs of the patient and family. Access to a chapel, the presence of a chaplain, awareness of and sensitivity to spiritual and ethnic preferences—spiritual support services can broadly be seen as the health care system's readiness and sensitivity to needs identified by patient and family, particularly in the face of life-threatening illness. Spiritual support might be a component of therapy focused on recovery from illness, or it may be involved as tools for coping, for grief, or for transcendence of impending death. It is generally appropriate for spiritual support services to be assessed and advanced through a quality assurance/quality improvement (QA/QI) process. External agencies appropriate for overview of QA/QI include the Joint Commission for Hospital Accreditation.

Spiritual therapy implies a healing objective actively sought and documented through experimental intervention. Formal research protocols, Institutional Review Board processes, and informed consent from patients are appropriate. Specific considerations of methodology, mechanism, dose and dose response, and other aspects fundamental to work with any new therapeutic agent in cardiology patients are all applicable. Peer-review grant funding for spiritual therapy protocols is currently identifiable at the NCCAM and other agencies at the NIH. New standards and recommendations for study in this area have recently been published (424–429).

Spirituality and religion. "Religion," the "religious," and the "spiritual" are terms used synonymously to refer to that which connects the mortal being to the highest sense of meaning and order at a transpersonal level. In other usage, the term "religion" implies established ethnic and cultural groups, and in some cases evokes the concept of a divinity, whereas "spiritual" implies a more generic attribute.

Unique baseline spirituality patient descriptors. Epidemiologic evidence is compelling that baseline spirituality descriptors characterized by established questionnaires are associated with certain cardiac outcomes (417). In one report, the degree of the spirituality effect was equivalent to a history of cigarette smoking (430). Further study and especially prospective multivariate models will be important to better understand the predictive information content of baseline spirituality in conjunction with other classical cardiac predictors of outcome (e.g., age, ejection fraction, gender).

Methods and spiritual therapy. No discrete measurements report intensity or "dose" of spiritual therapies. Qualitative features include descriptions of the practice itself, the content of the prayer, meditation, intention or imagery used, the experience level of the practitioner, any notable ethnic affiliations, and/or the use of ancillary components such as music, soft abdominal breathing, humming or chanting, a prescribed body posture or the like. Quantitative features, such as the number of individuals praying, the duration of the prayers, and the proximity to the patient, are also of potential interest.

Mechanism of action and surrogate measures. "Divine intervention," "life force," "love," "joy," and "spirit" all share a common feature—the absence of any satisfactory mechanistic explanation as to how they operate in health or disease. Three explanations are widely discussed:

1. These forces are divine, and so cannot be comprehended, particularly within a deterministic model.
2. These forces cannot be measured because they do not exist.
3. These forces are self-evident, and we simply have not yet developed measurement tools.

In the absence of discrete measurements or appreciable mechanisms of action, and in the presence of spiritual practice imbued in the culture of patients, families, communities, and health care staff, a pure control group for spirituality trials is difficult, if not impossible, to develop. Thus, studies in this area can currently examine incremental, but not absolute, therapeutic effects.

Safety and efficacy end points in spiritual therapy studies. Selection of efficacy end points for study in this area must be consistent with the population studies. For patients with very advanced heart disease, where end of life issues may become ascendant over mortality per se, the influence of spiritual interventions on end of life measures would be a reasonable approach.

Conversely, if spiritual therapy shows a therapeutic effect it may be capable of causing harm. As with any new therapy whose mechanism is undefined, it is unreasonable to simply assume safety and study efficacy—addressing safety, with Data Safety Monitoring Boards, should be formally included in trials as a safety and efficacy study design.

Similarly, as research with potential safety issues attendant, clinical trials applying spiritual intervention to cardiology patients as an investigational therapy should do so with the informed consent of the patient.

Sensitivity, privacy, and ethics. Spiritual matters constitute one of the most private and personal areas for both patients and staff. Sensitivity to the broad array of belief systems and to the highly symbolic nature of certain terms, concepts, or icons is paramount to develop spiritual support systems and studies of spiritual therapy. Incorporation of spiritual assessments as part of standard nursing admission procedures or the acquisition of spirituality survey information in conjunction with research protocols must be conducted with strict attention to whether the patient finds the queries objectionable and to the confidentiality of the material and with informed consent.

Cultural preconceptions and bias regarding spirituality are substantial, with some issues that are primarily philo-

sophical, not subject to scientific study or resolution, and likely to be contentious when discussed broadly. Crucial issues include:

- How do we know when God answers prayer?
- Does one religion have more powerful prayer?
- How would a negative study of prayer be interpreted?
- Is death a negative end point?
- Is technology necessary in the setting of true faith?

It seems reasonable to examine spiritual therapy as an adjunct to modern technology, not as competition or a replacement for standard care. It is reasonable to assess the safety and efficacy of spiritual interventions with reasonable but rigorous science and clinical trial designs. It is reasonable to investigate physiologic signals that might provide either a marker of the presence of spiritual influence or even a key to mechanisms through which spiritual influence is mediated.

Extension of dialogue across the disciplines and constituencies concerned with spiritual support and spiritual therapy is timely and important.

Delivery Roles, Accreditation, and Certification Standards

Optimal spiritual support or therapy requires considerable re-thinking regarding the relative roles of the patient, the family, the community, the clergy, and hospital staff. As Don Carlos Peete stated in his 1955 book *The Psychosomatic Genesis of Coronary Artery Disease*: "I believe the most successful physician will instill into his patient hope, courage, and patience. He can do so only if he has these virtues himself. The discipline necessary to face the responsibilities that are ours as individuals and as a people can be attained only when we understand and use both the spiritual and physical laws in our daily lives" (311,323,324).

Summary and General Recommendations

Spiritual needs, influences, and therapeutic claims are ancient and ubiquitous. Spirituality issues are pertinent to patients with heart disease. Recommendations include:

1. Development of health care responsive to the spiritual needs of patients and families.
2. No practice guidelines for spiritually based therapy in cardiovascular care can be currently recommended.
3. Clinical research of spiritual interventions in cardiology settings is reasonable, should be conducted as safety and efficacy trials, and ethically must include the informed consent of patients.
4. The use of unique baseline descriptors of spirituality in clinical trials is suggested.
5. Development of a common nomenclature, use of standardized measures, and detailed methodological descriptions in clinical trials of spiritual interventions are recommended.

The cultivation of multidisciplinary forums on concepts of spirituality and healing, delivery roles, practice standards, and certification issues is suggested.

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APPENDIX I: RELATIONSHIPS WITH INDUSTRY

Writing committee members were asked to identify all relationships with industry that were relevant—or could be perceived as relevant—to this document. One member, Dr. Kenneth Pelletier, declared that he had past (not current) research grants with Medtronic and Merck. The other authors of this document declared that they had no relevant relationships with industry pertinent to this topic.

APPENDIX II: GLOSSARY

Acupressure. Acupressure is an ancient Asian healing art that uses the fingers to press key points on the surface of the skin. Practitioners believe this stimulates the body's immune system to self heal. When stimulated, these points may relieve muscular tension and promote the release of endorphins—neurochemicals that relieve pain. Acupressure uses the same points and meridians (patterns of energy flow) as acupuncture, but instead of needles it treats with gentle, firm pressure of fingers and hands.

Acupuncture. Acupuncture is a treatment based on an ancient Chinese medicine. Acupuncture places extremely thin, sharp needles (that are sometimes connected to a low-voltage power source) along a network of "lines of energy" or meridians on the body surface. Chinese medicine practitioners believe these meridians conduct energy throughout the body. However, recent (Western) evidence indicates that the needles stimulate sensory nerves underlying meridians to alter neurotransmitter release in regions of the central nervous system concerned with regulation of the autonomic nervous system and hence the heart and blood vessels. Acupuncture is believed by clinicians practicing traditional Chinese medicine (TCM) to balance the opposing forces of yin and yang, keep the normal flow of energy unblocked, and maintain or restore health to the body and mind (http://nccam.nih.gov/health/acupuncture/#glossary, accessed September 18, 2002). Eastern scientists have translated these TCM concepts into a neurophysiologic paradigm in which acupuncture, by evoking the release of inhibitory neurotransmitters (endorphins, enkephalins, and possibly endomorphins) in the hypothalamus, midbrain, and medulla, in turn, reduces activity of premotor neurons concerned with sympathetic outflow to the heart and vascular system (1).

AHA dietary guidelines. October 2000 revision of the AHA dietary guidelines to Americans (1).

Applied kinesiology. This chiropractic technique is performed by therapists, using acupressure points and a muscle-testing method. Practitioners believe they are able to diagnose nutritional and glandular "deficiencies" that are then "corrected" by manipulation or nutrition supplements.

Atkins diet. Developed by Dr. Robert Atkins, this diet limits carbohydrates to 20 g initially for rapid weight loss. This is done by eliminating high carbohydrate foods such as bread, potatoes, pasta, fruit, juices, and candy. Fats and proteins are the main source of fuel on this diet. Meat, eggs, butter, and most cheeses can be eaten without restriction.

Bioenergy (bioenergetics). Bioenergetics is a loosely collected series of healing "disciplines" that attempt to harness natural forces and powers to influence natural healing processes. Bioenergy fields are thought to be altered by conscious and unconscious efforts (330). Bioenergy medicine uses bioenergy (HT and TT, *Qi Gong*, *Johrei*, *Reiki*, crystal therapy, relaxation therapy, distance healing, applied kinesiology, and magnet therapy) to heal (431).

Biofeedback. Biofeedback (BF) techniques are treatment methods that use monitoring instruments of various degrees of sophistication. The BF techniques provide patients with physiologic information that allows them to reliably influence psychophysiological responses of two kinds: 1) responses not ordinarily under voluntary control, and 2) responses that ordinarily are easily regulated, but for which regulation has broken down. Technologies that are commonly used include electromyography (EMG BF), electroencephalography, thermometers (thermal BF), and galvanometry (electrodermal BF) (432).

Crystal therapy. Practitioners believe that crystals contain or possess energy fields that can be used to heal. Practitioners believe that each crystal is associated with different energy fields or emotions.

Distance healing. There is much overlap among TT, distance healing, and distance prayer. Spiritual healing practiced when the patient is not present is called distance healing and is similar to prayer. It can be practiced in groups or individually.

Guided imagery. A patient is asked to focus deliberately on a particular image in order to "relax, manage stress, or alleviate a specific symptom" (433). Key to this therapy is that the patient is in control of the image and can redirect it. The image does not have to be physiologically true, as in the case of a cancer patient imagining being free of cancer, or even real in the sense that the patient has or would ever experience what the image depicts. Imagery may be just simple visualization or a sensory perception such as a smell, a touch, or a sound (325,434,435). Although imagery uses the conscious mind, it may also be utilized to tap into the unconscious or less conscious mind.

Ho'oponopono. This Hawaiian approach alleges to find the divine within oneself to remove stress and release problems. It involves repentance and "transmutation" to provide spiritual freedom, love, peace, and wisdom (431).

Hydrotherapy. The concept behind this technique is that water is "energized" by compounds in extremely dilute amounts. Practitioners believe that water retains the memory of the compounds that existed in it. This may reflect dilute amounts of the retained original compound.

Hypnosis. Hypnotic techniques induce states of selective attentional focusing or diffusion combined with enhanced imagery. They are often used to induce relaxation and also may be a part of cognitive behavioral therapy. The techniques have both pre- and post-suggestion components. The pre-suggestion component involves attentional focusing through the use of imagery, distraction, or relaxation, and has features that are similar to other relaxation techniques. Subjects focus on relaxation and passively disregard intrusive thoughts. The suggestion phase is characterized by introduction of specific goals; for example, analgesia may be specifically suggested. The post-suggestion component involves continued use of the new behavior following termination of hypnosis (431).

Magnetotherapy. This therapy is applied through the use of permanent or fluctuant magnetic fields.

Meditation. Meditation is a self-directed practice for relaxing the body and calming the mind. Various meditation techniques are in common use; each has its own proponents. Meditation generally does not involve suggestion, autosuggestion, or trance (436,437).

Mediterranean diet. This is a diet high in fruits, vegetables, bread and other cereals, potatoes, beans, nuts, and seeds. Olive oil is an integral part of the diet and is an important source of monounsaturated fat. Dairy products, fish, and poultry are eaten in low to moderate amounts and little red meat is consumed. Up to four eggs are consumed weekly and wine is drunk with meals in low to moderate amounts.

Mental physics. This is purported to be a practical, holistic, futuristic science that manifests "hidden meaning" of the Bible and involves "astral travel;" aura reading chanting; meditation, pranayama ("deep scientific breathing exercises"); "pranic therapy" (a variant of channeling); reflexology; shiatsu; and individualization of diet according to "chemical type" (438).

Mind/body. Mainstream mind-body medicine, as defined by Chiarmonte (438a), is "based on the premise that mental or emotional processes (the mind) can affect physiologic function (the body)." Lazar (438b) elaborates on this point further, saying that mind-body medicine is an integrative discipline that examines the relationship between psychological states and psychological interventions and between physiology and pathophysiological processes. Conversely, most practitioners of CAM—which takes a different approach to mind/body medicine—hold that the mind's impact on the body is not unidirectional; rather, there is an integrated process in which both mind and body affect each other (439).

Music therapy. Music therapy is the prescribed use of music by a qualified person to effect positive changes in the

psychological, physical, cognitive, or social functioning of individuals with health or educational problems (440).

Nutrition. This concerns cardioprotective diets, including AHA Step I and Step II; Mediterranean; NCEP ATP III; DASH, low-fat and low-sugar diets. Also includes garlic, nuts, teas, and alcohol use.

Placebo. A placebo is defined as an inert or innocuous treatment that works not because of the therapy itself but because of its suggestive effect. It is considered a mind/body modality, but with some distinct differences. Placebo therapy depends on the power of a patient's belief that the therapy will be effective (431).

Pranic psychotherapy. Pranic psychotherapy includes removal and disintegration of "traumatic psychic energy," disintegration of "negative elementals" ("bad spirits"), and creation of a "positive thought entity."

Progressive muscle relaxation (PMR). Progressive muscle relaxation focuses on reducing muscle tone in major muscle groups. Each of 15 major muscle groups is tensed and then relaxed in sequence.

***Qi Gong*.** *Qi* is life force energy and *Gong* is "practicing skill." Practitioners of *Qi Gong* believe that vital energy circulates through "meridians," connecting all organs. Illness is attributed to an imbalance, or interruption, of *Qi*. *Qi Gong* is said to re-balance "yin" and "yang" (365).

Internal Qi Gong. Involves deep breathing, concentration, and relaxation. It is a self-discipline that trains body and mind to alter flow of "vital energy," for self-reliance and adjustment, to cure disease, and to strengthen and prolong life.

External Qi Gong. Affects things outside one's body. It is performed by "masters" who claim to cure with energy released from their fingertips.

Reiki. *Rei* is "universal," or "spiritual," and *Ki* is "life force energy." It is a form of laying on the hands (431).

Relaxation. Relaxation techniques are a group of behavioral therapeutic approaches that differ widely in their philosophical bases as well as in their methodologies and techniques. Their primary objective is the achievement of nondirected relaxation, rather than direct achievement of a specific therapeutic goal. They all share two basic components: 1) repetitive focus on a word, sound, prayer, phrase, body sensation, or muscular activity, and 2) adoption of a passive attitude toward intruding thoughts and a return to the focus. These techniques induce a common set of physiologic changes that result in decreased metabolic activity. Relaxation techniques may also be used in stress management (as self-regulatory techniques) and have been divided into deep and brief methods (441).

Reversal diet. The Ornish reversal diet consists of 10% fat and is combined with a program of smoking cessation, aerobic exercise, stress management training and psychological support.

Spirituality. Spirituality can be defined as a belief system focusing on intangible elements that impact vitality and meaning to life's events (431). In the absence of insight into the mechanism, the entire area of spirituality and cardiovascular health remains highly anecdotal, intuitive and speculative. As patients and families of loved ones who have heart disease face mortality in a very personal and immediate way, however, there is widespread interest in how cardiologists think about and approach spiritual issues in practice and in research.

Supplements. The Dietary Supplement Health and Education Act (DSHEA) of 1994 defined dietary supplements as a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following ingredients: vitamins, minerals, herbs, or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites. Whatever their form, DSHEA places dietary supplements in a special category under the general umbrella of "foods," not drugs, and requires that every supplement be labeled a dietary supplement (http://www.cfsan.fda.gov/~dms/ds-oview.html, accessed September 18, 2002). Other examples include antioxidants, plant sterols, soluble fiber, omega-3 fatty acids and soy; herbs, such as *Ginkgo biloba*, guggulipid, and HCSE; and other supplements, such as, L-arginine, L-carnitine, and CoQ10.

Therapeutic touch. Practitioners believe that their hands are used to direct healing energy. Healing supposedly results from transfer of "excess energy" from healer to patient.

Transcendental meditation. Transcendental meditation focuses on a "suitable" sound or thought (the mantra) without attempting to actually concentrate on the sound or thought.

Vibrational medicine. Considers humans as dynamic energy systems ("body/mind/spirit" complexes). The dynamic energy system, the life force, is influenced by subtle emotional, spiritual, nutritional, and environmental energies. Health and illness originate in "subtle energy systems."

Yoga. Developed in India, yoga is a psycho-physical discipline with roots dating back about 5,000 years. Today, most yoga practices in the West focus on the physical postures, termed "asanas," breathing exercises called "pranayama," and meditation (source: http://www.yogasite.com/yogafaq.html#What).

Zen meditation. This technique is a form of Buddhism originating in Asia; it teaches that desires are the primary cause of suffering. Meditative absorption in which all dualistic distinctions are eliminated (source: http://healing.about.com/cs/zen/index.htm?terms=zen+meditation) (236).

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