

Complementary and alternative medicine in cardiovascular disease: A review of biologically based approaches

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Background The use of complementary and alternative medical (CAM) practices in the United States is growing rapidly. In this manuscript, we review some of the most commonly used biologically based approaches, including herbs, supplements, and other pharmacological therapies, that are encountered in caring for patients with cardiovascular disease, focusing on potential effects, adverse effects, and treatment interactions.

Methods Between November 2002 and April 2003, we searched Medline and the National Center for Complementary and Alternative Medicine (NCCAM) web site and its various references and several complementary medicine text books. The key words used were: "cardiovascular diseases," "coronary disease," "heart failure, congestive," "complementary and alternative medicine," "complementary therapies," "drug interactions," and "plants, medicinal." A keyword search of each individual supplement identified was also performed. Additionally, we relied on expert opinion in the field.

Results Potentially serious adverse effects and interactions with conventional cardiovascular therapies exist for many herbs and supplements. There are currently scarce mechanistic data and very limited data on the effect of CAM therapies on clinical outcomes.

Conclusions Randomized clinical trials with adequate power to detect effects of CAM therapies on clinical outcomes and safety are needed. Until these data are available, clinicians must be aware of the increasing use of CAM approaches by their patients and the potential for interactions with conventional therapies and should focus on treatment with proven, evidence-based strategies. (*Am Heart J* 2004;147:401–11.)

Complementary and alternative medical (CAM) practices are those healthcare and medical practices that are not currently an integral part of conventional medicine and not routinely taught in western medical schools.¹ CAM therapies include, but are not limited to, meditation, yoga, relaxation/hypnosis, acupuncture, spiritual healing, chiropractic care, massage, and nutritional and naturopathic remedies.

Until a decade ago, no one realized how quickly the use of CAM practices was growing within the framework of the US health care system. A 1990 survey by Eisenberg et al showed that 34% of US adults used at least 1 unconventional therapy and estimated that \$13 billion was spent out-of-pocket for "alternative" thera-

pies every year.¹ A later survey showed that between 1990 and 1997, CAM therapy use increased 25%, and the numbers of Americans taking herbs nearly quadrupled.² Further, <30% of patients told their physicians about their use of CAM therapies, risking potentially dangerous interactions between supplements and conventional drugs.

According to a 1998 survey, the best predictor of patients seeking alternative practitioners was the alternative provider's congruence with their own philosophies on health and wellness. Dissatisfaction with conventional healthcare was not predictive of CAM therapy use. Patients who sought out CAM treatments generally were female, white, and had more education, more money, and more chronic illness than the general population.³

Because of the rapid growth of CAM practices, the National Center for Complementary and Alternative Medicine (NCCAM) was established by Congress in 1998 as 1 of the 27 institutes and centers of the National Institutes of Health. It has an annual budget of more than \$100 million, and its mission is to support rigorous research on CAM therapies, train researchers

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Table I. Overview of selected alternative medical systems and practices

Alternative medical systems	<p>Traditional Chinese medicine-Uses traditional methods of acupuncture, herbs, diet and nutrition, exercise stress reduction and lifestyle counseling, and massage to help restore and balance your Qi, or vital life energy.</p> <p>Ayurveda-A 5000 year-old system of mind-body medicine from India that uses herbs, nutrition, meditation, yoga and massage.</p> <p>Naturopathy-A system with a focus on prevention, believing the body has the power to heal itself and practitioners keep these powers strong and help them along when necessary. There are 3 accredited schools in the US and 1 in Canada.</p> <p>Homeopathy-Practitioners use very dilute preparations of natural substances to cure disease, so dilute that there is often no trace of the original substance in the solution, but the solvent has been postulated to contain some "memory." Homeopaths believe "like cures like."</p>
Mind-body interventions	<p>Meditation</p> <p>Stress reduction techniques</p> <p>Yoga</p> <p>Biofeedback</p> <p>Hypnosis and imagery</p>
Biologically-based treatments	<p>Herbs</p> <p>Vitamins</p> <p>Minerals/chelation therapies</p> <p>Other supplements</p>
Manipulative/body-based methods Energy therapies	<p>Chiropractic</p> <p>Osteopathy</p> <p>Light therapy</p> <p>Sound/music therapy</p> <p>Acupuncture</p> <p>Magnetic therapy</p> <p>Therapeutic touch</p> <p>Reike-A method that originated in Tibet, rediscovered in Japan. A healing technique were energy flows from the practitioners hands into the energy field of the client's body.</p>

in CAM practices, and disseminate information to the public and professionals on which CAM modalities work, which do not, and why. Thus far, most of the research by the NCCAM has focused on biologically based methods. However, they have also supported research on acupuncture, chiropractic, and mind-body interactions. For 2003, the NCCAM made it a priority to elucidate mechanisms of action and to conduct small, well-developed phase I and II clinical trials.⁴

Overview of CAM practices

Reviewing data for all types of CAM is a broad and growing topic. The list of practices that are considered to be CAM practices changes continually as practices

and therapies that are proven safe and effective become accepted as "mainstream" healthcare. Table I provides an overview of selected alternative medical systems and practices and a framework in which clinicians can reference CAM. The remainder of this review will focus on biologically based CAM therapies for cardiovascular disease. Although not a comprehensive review of all available biological treatments, we will address a select group on the basis of how commonly they are used and how much research and data are available. Additional literature assessing spirituality, mind-body approaches, and energy therapies (specifically acupuncture) for prevention and treatment of cardiovascular disease will not be addressed, nor will vitamin supplementation. Tables II and III provide overviews of the more commonly used dietary supplements for the treatment of both non-cardiovascular and cardiovascular disease, respectively, and their potential interactions with other more standard therapies.

Important drug/herb interactions with selected cardiovascular medications

Recognizing that nearly 25% to 50% of Americans use some form of alternative approach to healthcare (including herbal preparations), it is important to ask patients specifically about their use of CAM therapies and to be informed of potential herb/drug and herb/herb interactions. Although not an exhaustive list of interactions, this section focuses on potential consequences of interactions between commonly used herbs and cardiovascular drugs.

Warfarin and antiplatelet therapy

Many herbs interact with warfarin or alter platelet function such that the risk of bleeding is potentially increased in patients treated with warfarin or conventional antiplatelet therapy while using these herbal agents. In most cases, the potential for increased bleeding is hypothetical; however, there have been numerous case reports of increased bleeding tendency in patients taking herbal supplements with or without the concomitant use of warfarin. Because of what is known about the effects of these herbs on platelet function and markers of coagulation, their use should be avoided in patients requiring warfarin or other conventional antiplatelet therapy. Table II outlines these herbal agents, their CAM uses and the basis of their potential interactions.⁵⁻²³

Amiodarone

Amiodarone, used primarily for treatment of atrial fibrillation and life-threatening ventricular arrhythmias, has numerous potential adverse effects, including photosensitivity, hepatotoxicity, pulmonary fibrosis, and thyroid disorders. Its metabolism is complex, and mul-

Table II. Commonly used herbal agents for noncardiovascular conditions: Uses and potential mechanisms for interaction with cardiovascular drugs

Herbal Agent	CAM properties/uses	Effects on coagulation/bleeding
Feverfew	Prophylactic for migraine headaches	Inhibits platelet aggregation; inhibits release of serotonin from platelets and leukocytes
Garlic	Antispasmodic, antiseptic, promotes leukocytosis, hypocholesterolemic, vasoactive properties	Inhibits epinephrine-induced <i>in vitro</i> platelet aggregation, small study showing inhibition of <i>ex-vivo</i> platelet aggregation.
Ginger	Antiemetic, antispasmodic	Inhibits thromboxane synthetase; prolongs bleeding time
Ginkgo biloba	Treatment of Alzheimer's disease	Ginkgolide B component inhibits platelet activating factor with decreased arachidonate-independent platelet aggregation. 5 reports of clinical bleeding: 2 subdural hematomas; 1 each increased bleeding time, intracerebral hemorrhage, subarachnoid hemorrhage
Dashen	Chinese herb with various cardiac uses	Increased INR in patients on stable warfarin dose
Ginseng	Mood enhancer, improve vigor	Increased INR in patients on stable warfarin dose
St John's Wort (<i>Hypericum perforatum</i>)	Depression	Decreased INR in patients on stable warfarin dose

Table III. Common biologically-based complementary and alternative medicine therapies used in cardiovascular disease: Indications and potential interactions with standard pharmacotherapy

Biological agent	CAM properties/uses	Potential drug interactions
Vitamin E	Anti-oxidant; prevention of cardiovascular disease. Data unclear on efficacy.	Increased bleeding with antithrombotic and antiplatelet agents. May decrease efficacy of statins. ⁹⁷
CoEnzyme Q10	Anti-oxidant and free radical scavenger; used to treat heart failure, hypertension, and myopathies.	Decreased efficacy of chemotherapeutics and radiation. Procoagulant; lowers INR in patients on stable coumadin dose.
Hawthorn (<i>Crataegus</i> species)	Treatment of heart failure and arrhythmias.	Digoxin-like effects; potential interaction with digoxin.
L-Carnitine	Involved in cellular energy production, supplement in nutritional deficiency, possible role in heart failure and myocardial infarction.	Limited data on drug interactions.
Policosanol	Believed to inhibit cholesterol synthesis. Used in South America as hypocholesterolemic.	Limited data on drug interactions.
Red rice yeast	Typical HMG-CoA reductase inhibitor.	Drug interactions with macrolides, ketoconazole, protease inhibitors, verapamil, cyclosporine, and others.
Gugulipid	Lipid-lowering through blocking nuclear hormone receptor, farnesoid X.	Decrease bioavailability of diltiazem and propranolol.

multiple drug-drug interactions, including but not limited to some statins, warfarin, and digoxin, are well known. Therefore, extreme care should be taken to avoid herbal remedies that may further interact with amiodarone in this complex milieu.

Echinacea is used primarily for treating and preventing uncomplicated upper respiratory tract infections such as the common cold. Because hepatotoxic effects may be associated with persistent use, caution should be used when echinacea is taken in conjunction with other potentially hepatotoxic drugs such as amiodarone or other commonly used agents like statins, which may also, in rare cases, result in hepatotoxicity.²³

Kava-containing compounds, used to treat anxiety and insomnia, have been implicated in at least 11

cases of fulminant hepatic failure requiring transplantation in the United States and Europe since 1999.²⁴ This led to the US Food and Drug Administration (FDA) advisory against the use of kava in patients with underlying liver disease, and this herb should be avoided in patients taking potentially hepatotoxic drugs. Kava-containing compounds have already been removed from the market in several European countries.

Digoxin

Numerous herbs have been identified as containing digoxin-like substances, and therefore they may potentiate digoxin effects.^{23,25}

Kyushin, a Chinese medicine from Japan, (1 of the components of which is chan su, the dried venom of

the Chinese toad *Bufo bufo gargarizans cantor*) cross-reacts with digoxin assays and also purportedly has digoxin-like actions.^{26,27} Chinese silk vine (*Periploca sepium*), a toxic plant that contains cardiac glycosides, has occasionally been misidentified as Siberian ginseng (*Eleutherococcus senticosus*), which has led to interference with digoxin assays.^{28,29} Such assay interference could result in potentially serious consequences if dose adjustments were made on the basis of levels obtained in the setting of use of these agents.

St. John's wort (*Hypericum perforatum*) decreases serum levels of digoxin through induction of a p-glycoprotein drug transporter.³⁰ In a single-blind, placebo-controlled trial, after 10 days of taking St. John's wort, the amount of digoxin in the body was reduced >25%.³⁰ *Uzarae radix* (uzara root) in large doses has been found to have digoxin-like cardiac effects, so additive effects may be encountered.³¹

Potentially serious adverse effects of herbal therapies may also result from lack of standardization and regulation of preparation and packaging. In the case of digoxin reactions and interactions, it was found that various lots of plantain (used as an herbal laxative) were adulterated with potentially toxic woolly foxglove. This discovery resulted in withdrawal of certain products from the market, and an FDA advisory.^{32,33}

Cyclosporine

Cyclosporine, used for immunosuppression after orthotopic heart transplantation, is subject to many drug-drug interactions. The interaction with diltiazem, resulting in increased cyclosporine levels, has been used as cyclosporine-sparing, and for patients who have undergone heart transplantation and have hypertension, if diltiazem is used, cyclosporine doses must be reduced.

Although now shown in a randomized trial to be less effective than once touted, the use of St. John's wort as an herbal treatment for depression and mood disturbance continues.³⁴ Several reports have documented an unexpected interaction with cyclosporine, reducing cyclosporine levels and resulting in acute rejection.³⁵

In summary, the use of herbal remedies should be undertaken with extreme caution in patients concurrently receiving prescription medications for the management of a variety of cardiovascular disorders, because serious and potentially life-threatening treatment interactions may result.

Herbs and supplements with potential roles in the treatment of cardiovascular disease

Coenzyme Q10 (ubiquinone)

Coenzyme Q10 (CoQ10) is a vitamin-like, fat-soluble quinone found in high concentrations in the mitochon-

dria of the heart, liver, and kidney, where it is important for cellular mitochondrial respiration. CoQ10 acts in part as a redox link between flavoproteins and cytochromes, which are needed for oxidative phosphorylation and adenosine triphosphate (ATP) synthesis.³⁶ Thus, it is essential for energy production. It is also an antioxidant and free radical scavenger with membrane stabilizing properties. It is metabolized to ubiquinol, which prolongs the antioxidant effect of vitamin E.³⁶

CoQ10 has been used to treat congestive heart failure (CHF), angina, and hypertension, to prevent cardiotoxicity associated with doxorubicin, for immune stimulation in individuals with HIV/AIDS, and for treatment of muscular dystrophy. It is also used to prevent statin-induced myopathy and has FDA Orphan Drug status for mitochondrial cytopathies, including mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibers (MERRF), and Kearns-Sayre.³⁷ It is usually given orally in a dose from 50 mg twice a day to 100 mg 3 times a day. Reported adverse effects are limited to gastrointestinal distress.

Potential drug interactions with CoQ10 include additive blood pressure-lowering effects with antihypertensive agents and negative interaction between CoQ10 (or any antioxidant) and radiation therapy and chemotherapeutic agents (eg, alkylating agents) working through oxidative stress.^{37,38} CoQ10 is also reported to have vitamin K-like procoagulant effects, lowering international normalized ratios to subtherapeutic levels in patients who were previously stable when receiving warfarin.³⁹⁻⁴¹

CoQ10 in congestive heart failure. It is postulated that the depletion of CoQ10, demonstrated in endomyocardial biopsies of patients with CHF, may contribute to heart failure. The extent of myocardial CoQ10 deficiency correlates with the clinical severity of heart failure.⁴²⁻⁴⁵ CoQ10 has been commonly used in the treatment of CHF in Italy and Japan for many years, but supporting data are mixed. A meta-analysis of 8 randomized trials from 1984 to 1994 showed improvement in cardiac output (CO), stroke volume (SV), and left ventricular ejection fraction (LVEF), but was unable to address clinical end points.⁴⁶

In 1 of the earliest placebo-controlled trials, Morisco et al randomized 641 patients who were in New York Heart Association (NYHA) class III to IV to receive 2 mg/kg of CoQ10 daily or placebo.⁴⁵ There were no significant differences in medical therapy in the groups, but only half of all patients were treated with angiotensin-converting enzyme inhibitors (ACEI). There was statistically significant improvement in functional class after 3, 6, and 12 months in the treatment group, but no change in functional class in the control group. Decreased episodes of pulmonary edema and arrhythmias and a reduction in hospitalizations (20% in

the CoQ10 group vs 40% in the placebo group) also occurred with CoQ10 treatment.

In the Italian Muticenter Study on the Safety and Efficacy of Coenzyme Q10 as Adjunctive Therapy in Heart Failure, 2664 patients were treated in an open, non-comparative 3-month post-marketing observational study.⁴⁷ Improvement in clinical end points, including cyanosis, edema, rales, insomnia, and dizziness, were reported. No mention was made of interrater reliability on these measures, and no mortality or hospitalization rate data were provided.

In a double-blind, crossover designed Scandinavian trial, 79 patients with CHF were randomized to receive 100 mg/day of CoQ10 or placebo for 3 months.⁴⁸ Balanced randomization was used for ischemic versus non-ischemic etiology and treatment with or without ACEI. There was significant improvement in LVEF on the basis of multigated acquisition (MUGA) scans ($P = .025$), and slight but non-significant increase in maximal exercise capacity. Further, CoQ10 treatment resulted in significant decreases in scores for dyspnea ($P = .007$) and leg fatigue ($P = .04$). According to the quality of life questionnaire, the total score ($P = .016$), physical activity level score ($P = .048$), and life satisfaction score ($P = .016$) increased significantly during CoQ10 treatment.

Two recent studies investigated the effects of CoQ10 on a background of more contemporary treatment for CHF. Watson et al performed a randomized, double-blind, crossover trial of 30 patients with an LVEF $<35\%$ (mean, $26 \pm 6\%$), all of whom were given the maximum dose of ACEI and most of whom were given diuretics and digoxin.⁴⁹ Patients were randomized to receive 33 mg of CoQ10 three times a day or placebo for 12 weeks, followed by a 1-week washout period; then they were crossed over. Echocardiograms and right heart catheterizations were done at baseline and the end of each treatment period. A Minnesota "living with heart failure" questionnaire was completed twice during the study. The investigators found no improvement in LVEF, wedge pressure, cardiac index, or quality of life scores after 3 months of treatment. Doubling of plasma CoQ10 levels was demonstrated in the active treatment group, but replenishment of myocardial stores was not evaluated (ie, no biopsy). The study did not evaluate clinical outcomes.

A similar study performed at the University of Maryland enrolled 55 patients in a randomized, double-blind, placebo-controlled trial examining LVEF and peak O₂ consumption with exercise.⁵⁰ Similarly, there was no benefit on intermediate end points after 6 months of treatment. The study was underpowered to detect differences in clinically meaningful end points.

In summary, after reviewing the literature on CoQ10 use for adjuvant treatment of CHF, it is reasonable to conclude that it is safe. However, it is impossible to

draw conclusions about efficacy, with several fair-quality studies showing some benefit, 2 well-designed but underpowered trials showing no benefit on intermediate end points, and limited data from all studies on clinically meaningful end points. Until larger, randomized studies, powered for differences in clinically meaningful end points such as quality of life, mortality, and days hospitalized are completed, it is premature to recommend routine CoQ10 use in CHF management.

CoeQ10 for the prevention of statin-induced myopathy. Reductions in cardiovascular events and improved survival with lipid-lowering therapy are undisputed. 3-hydroxy, 3-methylglutaryl coenzyme-A (HMG-CoA) reductase inhibitors (statins) competitively inhibit the conversion of HMG-CoA to mevalonate, a precursor to CoQ10 synthesis. Several studies have shown that statins reduce plasma CoQ10 levels dose-dependently in patients with hyperlipidemia and that supplementation with CoQ10 has no effect on the lipid-lowering effect of statins.^{51,52} This is especially relevant in CHF, in which there is some evidence that CoQ10 supplementation leads to improvement in intermediate outcomes. To date, there have been no randomized trials of CoQ10 supplementation in patients treated with statins that look at either changes in outcomes for CHF or myopathy. Because of the antioxidant effects of its metabolite, ubiquinol, another potential benefit of CoQ10 supplementation could be decreased oxidation of low-density lipoprotein (LDL) cholesterol, leading to a reduction in this more atherogenic molecule.

CoQ10 for the treatment of angina and hypertension. One small study demonstrated a mild improvement in time to ST-segment depression and total exercise time in patients with known coronary artery disease (CAD) who were randomized to receive CoQ10 therapy,⁵³ and 3 small trials in hypertension showed a modest, but probably clinically insignificant, blood pressure reduction in patients receiving adjuvant CoQ10 therapy.^{38,54,55} There have been no studies of the effects on clinical outcomes in these groups, and the data are much too limited to recommend CoQ10 for routine treatment of angina or hypertension.

Policosanol

Policosanol is a naturally derived compound developed in Cuba and now used in >25 countries in South America and the Caribbean to lower LDL and total cholesterol levels. Policosanol is a combination of aliphatic alcohols derived most commonly from sugar cane wax by means of hydrolytic cleavage and subsequent purification. The major components are octacosanol (62.9%), also present in wheat germ oil and other vegetable oils, triacontanol (12.6%), and hexacosanol (6.2%).^{56,57} The hypothesized mechanism of action of policosanol involves inhibition of cholesterol

biosynthesis in a step between acetate and mevalonate and via an increase in LDL cholesterol receptor-dependent processing.⁵⁸ There is no evidence for direct inhibition of HMG-CoA reductase.⁵⁹

The bulk of research on policosanol has occurred in Cuba. A recent review by Gouni-Berthold et al highlighted this research, noting the efficacy of this compound, fewer adverse reactions than statins, and the attractiveness of a naturally-occurring compound to a public desiring alternatives to synthetically derived drugs.⁵⁶ Several studies, which investigated 5 to 10 mg/day of policosanol, suggest a lipid-lowering effect of approximately 15% for total cholesterol and 20% for LDL cholesterol that can be increased to 30% with doses ≥ 20 mg/day.⁵⁶ Lipid-lowering effects are similar to those with 10 mg/day of pravastatin, 20 mg/day of lovastatin, and 10 mg/day of simvastatin.⁶⁰⁻⁶³ Maximal effects occur after 6 to 8 weeks and are maintained in studies lasting >1 year.^{64,65} In addition the reduction of LDL and total cholesterol levels, investigators have demonstrated a significant increase in high-density lipoprotein (HDL) cholesterol levels in patients with dyslipidemia and type 2 diabetes mellitus.⁶⁶

In addition to its anticholesterolemic effects, policosanol has pronounced antiplatelet effects in both animal models and in human volunteers via a decrease in thromboxane B2 and an increase in prostacyclin levels.^{56,67-71} It has also been hypothesized to effect smooth muscle proliferation, prevent LDL cholesterol oxidation, and reduce development of atherosclerotic lesions.⁵⁶ Adverse effects are infrequent and include weight loss, polyuria, and headache.⁵⁶ Because most studies were done in 1 Cuban center on a very selected population, it is difficult to generalize these results to a worldwide population. Also, there have been no studies of the effects of this agent on clinically meaningful outcomes. Therefore, more studies are needed to confirm its place in alternative management of dyslipidemia.

Red rice yeast

Red rice yeast has been a food staple and folk remedy in the Far East for thousands of years. It was noted in the 1970s that a product of the yeast, Monacolin K (lovastatin), inhibited HMG-CoA reductase.⁷² The concentration of lovastatin in red rice yeast varies, but averages 0.4% by weight.

In the preliminary report of a multicenter study of 187 subjects presented by Rippe et al at the 39th Annual Conference on Cardiovascular Disease Epidemiology and Prevention in Orlando, Fla, in 1999, red rice yeast lowered total cholesterol levels 16.4%, LDL cholesterol levels 21.0%, triglyceride levels 24.5%, and the total cholesterol to HDL cholesterol ratio 17.7% and increased HDL cholesterol levels 14.6%. Although its reported adverse effects are few, including gastrointes-

tinal upset, headaches, and dizziness, red rice yeast must be considered to be a typical HMG-CoA reductase inhibitor, and caution should be exercised for potential adverse effects, including rhabdomyolysis. Similarly, drug interactions should be considered to be identical to those with lovastatin, which requires caution when combined with niacin, macrolides, cyclosporine, ketoconazole, and many other agents. Products range in their recommended dosage from 2.5 to 10 mg/day of lovastatin-equivalent.

Gugulipid(*Commiphora mukul*)

Guggul is derived from the mukul myrrh tree in India. It has played a role in traditional Indian medicine (Ayurveda) for thousands of years and is used in treating arthritis and digestive, skin, and menstrual problems. Today, guggul is used as a lipid-lowering agent believed to work by blocking a nuclear hormone receptor activated by bile acids, the farnesoid X receptor, in liver cells.⁷³ In a small randomized, double-blinded, placebo-controlled trial, 50 mg of gugulipid or placebo capsules twice-daily for 24 weeks were compared as adjuncts to a fruit- and vegetable-enriched low-fat diet in 61 patients with hypercholesterolemia.⁷⁴ Gugulipid decreased the total cholesterol level 11.7%, LDL cholesterol level 12.5%, triglyceride levels 12.0%, and the total cholesterol to HDL cholesterol ratio 11.1% from the post-diet levels. Levels were unchanged in the placebo group. The HDL cholesterol level was unchanged in both groups. Adverse effects included headache and mild gastrointestinal complaints. This trial was underpowered and much too short to detect differences in clinical outcomes.

For patients with hypercholesterolemia and established CAD or appropriate risk factors, statins are clearly superior treatment. However, in patients with mild hyperlipidemia who are advised to undergo lifestyle modifications to manage cholesterol, gugulipid may be an acceptable supplement to diet and exercise. However, 1 potential drug interaction must be considered; when guggul is used concomitantly with diltiazem or propranolol, there may be a reduction in the bioavailability of these drugs and therefore, decreased clinical efficacy.⁷⁵

L-carnitine

Carnitine is a quaternary amine, synthesized from methionine and lysine and found mainly in skeletal and heart muscle, where it plays a key role in energy production.³⁷ It transports free fatty acids, the preferred substrate for oxidative metabolism in the heart, into the mitochondria, preventing the build-up of toxic fatty acid esters during ischemic conditions.^{76,77}

L-carnitine is FDA-approved for replacement therapy in primary and secondary L-carnitine deficiency be-

cause of inborn errors of metabolism and in L-carnitine deficiency caused by hemodialysis.³⁷ It also has myriad off-label uses, including nutritional supplementation for patients who are anorexic, strict vegetarians, or vegans, treatment of valproate-induced hepatotoxicity, enhancement of athletic performance, improvement of fat use in preterm infants on total parenteral nutrition (TPN), and treatment of acute myocardial infarction (MI).^{37,78} Its main adverse effects are GI upset and seizures in high doses. It is supplied intravenously (50–100 mg/kg/day) or orally (2–6 g/day).³⁷

Carnitine and the myocardium. In ischemic myocardium, carnitine depletion occurs rapidly, leading to the accumulation of cardiotoxic fatty acid esters.^{76,77} In animal models, exogenous L-carnitine improves cardiac metabolism and left ventricular (LV) function during ischemia.⁷⁹ Studies show LV dilation after MI is a powerful predictor of functional deterioration, heart failure, and death, and the most important determinants of post-MI LV remodeling are infarct size, degree of residual stenosis in the infarct-related artery, and infarct zone viability.^{78,80–82} In addition to early reperfusion therapy and ACEI use, metabolic intervention with L-carnitine replacement may represent a therapeutic approach for preventing LV dilatation by improving mechanical function in viable myocytes surrounding the infarct zone.

The Carnitina Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM) trial was a 36-center, randomized, double-blind, placebo-controlled study that enrolled 472 patients <80 years old within 24 hours of sustaining an anterior MI.⁸² Among the exclusion criteria were previous MI, valvular or congenital heart disease, cardiomyopathy, absence of sinus rhythm, and left bundle branch block. Patients were assigned to receive placebo or carnitine (9 g/day intravenously for 5 days) then oral carnitine (2 to 3 g/day) or placebo for 12 months. Approximately 80% of the patients in both groups received thrombolytic therapy, two thirds within 3 hours of symptom onset. Only 8% of patients were treated with ACEI. Primary outcomes were LV systolic and diastolic volumes and LVEF. At 3, 6, and 12 months, there was a significant decrease in LV systolic and diastolic volumes, but no change in LVEF and no difference in clinical outcomes, including death.

In the Survival and Ventricular Enlargement (SAVE) trial, 2231 patients with acute MI and LVEF <40% without overt heart failure, were randomized to receive captopril (50 mg three times a day) or placebo and observed for 42 months. The all-cause mortality rate was 19% lower in the captopril group.⁸³ In an echocardiographic substudy, there was similar attenuation of LV dilation as in the CEDIM trial.⁸¹ It is unknown whether the combination of ACEIs, L-carnitine, and early reperfusion would provide even better out-

comes. The CEDIM-2 trial plans to enroll 4000 patients to answer that question.

In addition to the potential role of carnitine in acute ischemia, there is a large body of literature suggesting a role for carnitine in chronic cardiomyopathy, on the basis of the principles of metabolism and energy transport.⁸⁴ The role of carnitine in children with dilated cardiomyopathy is well defined, but evidence in adults is lacking.⁸⁵ Rizos studied 80 adults, aged 48 to 50 years, with non-ischemic cardiomyopathy, NYHA classes III to IV, and LVEF <35%. Patients were randomized to receive either L-carnitine (2 g/day) or placebo and observed for 3 years. The study was unblinded after 3 months of treatment. Results included non-significantly lower mortality rates with treatment (1 death vs 6 deaths in the placebo group) and improved hemodynamics and maintenance of sinus rhythm.⁸⁶ To date, this is the largest trial of carnitine in cardiomyopathy, with the longest follow-up.

A recent small, double-blind trial investigated the combination of carnitine, CoQ10, and taurine (a unique amino acid critical in intracellular calcium homeostasis) in a cocktail called MyoVive in patients with known CAD who were scheduled for elective bypass graft surgery.⁸⁷ Forty-one patients with an LVEF ≤40% were randomly assigned to receive the supplement or placebo. Radionuclide ventriculography was performed at randomization and before surgery. The mean period of supplement treatment was 29.7 ± 10.2 days, and the mean period for receiving placebo was 30.2 ± 9.6 days. Surgical myocardial biopsies, adjusted for protein content, revealed increased stores of carnitine, CoQ10, and taurine in biopsies from patients receiving MyoVive. Also noted was a decrease in LV end-diastolic volume (−7.5 ± 21.7 mL) in the supplement group and an increase (10.0 ± 19.8 mL) in LV end-diastolic volume in the placebo group ($P = .037$).⁸⁷

Hawthorn (crataegus)

For thousands of years, Chinese medicine has used the leaf and flower of the crataegus plant for treating CHF and other cardiovascular diseases, including arrhythmias.³⁷ Specialized leaf and flower extracts, LI132 and WS1442, have been studied. The constituents responsible for their pharmacological effects are flavonoids and procyanidins. These compounds have a standardized concentration of procyanidins (18%).³⁷ Adverse effects include nausea, GI upset, fatigue, sweating, palpitations, and agitation. There are potential additive effects with digoxin, coronary vasodilators (nitrates, adenosine, theophylline), and cardiac glycosides like oleander and Siberian ginseng.

Hawthorn and heart failure. Crataegus Special Extract WS1442 is widely used in Germany for treatment of mild CHF. It is thought to have a wider thera-

peutic window and less renal clearance and is preferred to digoxin. Experimental models show dose-dependent increased myofiber shortening and decreased ischemia-induced ventricular arrhythmias.^{88,89} Brixius et al and Münch et al showed a positive inotropic effect of WS1442 in human LV muscle preparations obtained from explanted failing hearts and a digitalis-like effect on Na⁺/K⁺-ATPase in human cardiac muscle tissue.^{90,91} Although the pharmacological action of WS1442 is unknown, several mechanisms have been suggested, including cAMP-independent positive inotropy, digoxin-like effect, peripheral and coronary vasodilation, protection against ischemia-induced ventricular arrhythmias, and antioxidative and anti-inflammatory properties.⁹²

Most crataegus studies in humans were of short duration and conducted in Germany. In a meta-analysis published in 1996, in NYHA class I-III CHF, crataegus extract yielded improvement in symptoms beyond placebo, with no increase in adverse events.⁹³ Recently, a randomized, multicenter, double-blind, placebo-controlled trial was undertaken to investigate the long-term effects of WS1442 (900 mg/day) on a background of contemporary medical therapy in patients with NYHA class II to III symptoms and a LVEF <35%.⁹² The primary outcome is time to first cardiac event (cardiac death, non-fatal MI, or hospitalization for CHF progression). Secondary outcomes include all-cause mortality rate, quality of life, NYHA class, LVEF by echocardiography, and hospitalization costs. The first patients were entered in October 1998, and >1600 patients have been randomized.

EDTA chelation therapy and CAD

The American College for Advancement in Medicine (ACAM), a professional association that supports chelation therapy, estimates that >800,000 visits for chelation therapy were made in the United States in 1997 alone. One theory suggests that EDTA chelation might work by directly removing calcium found in fatty plaques. Alternatively, the process of chelation may stimulate the release of hormones that in turn cause calcium removal from plaques or cause cholesterol level lowering. A third theory is that EDTA chelation therapy reduces the damaging effects of oxidative stress on blood vessel walls, reducing inflammation.⁴

To date, none of these theories has been tested in a large, randomized clinical outcomes trial, and adequate earlier research is lacking to verify the safety and effectiveness of EDTA chelation therapy. The bulk of evidence supporting EDTA chelation therapy is from case reports and case series. There are 12 published descriptive studies and 5 randomized, controlled clinical trials of EDTA chelation for atherosclerotic vascular disease showing no significant difference in direct or

indirect measurements of disease severity and subjective measures of improvement.⁹⁴ None of these studies reported rates of mortality, non-fatal events, or cerebrovascular events.

In a more recent randomized clinical trial, 84 patients with known CAD and predictable ST-segment depression on treadmill testing were randomized to receive EDTA chelation therapy (33 treatments in 3 months) or placebo.⁹⁵ Both groups had significant increases in exercise time to ischemia at the 27-week treadmill test, and there was improvement in quality of life scores in both groups, with no significant differences between active treatment and placebo. There were also no differences in the rates of death, revascularization, or other clinically significant end points, but the trial was underpowered to detect this. Because all randomized clinical trials have been underpowered, the NCCAM and the National Heart, Lung, and Blood Institute have launched the Trial to Assess Chelation Therapy (TACT). TACT is the first large-scale, multicenter study to address the safety and efficacy of EDTA chelation therapy for patients with CAD.⁹⁶ This placebo-controlled, double-blind trial will recruit 2372 participants aged ≥ 50 years with prior MI to test whether EDTA chelation therapy, high-dose vitamin therapy, or both are effective in secondary prevention. The primary end point is a composite of all-cause mortality, MI, stroke, hospitalization for angina, and revascularization. It will begin enrolling participants in 2003 and is expected to take 5 years to complete.

Conclusions

Many patients use CAM therapies for both prevention and treatment of a wide variety of disease states, including cardiovascular disease. There is a developing body of literature that suggests some approaches may be beneficial as adjuncts to conventional management of cardiovascular disease, but no evidence exists to support their role as primary treatment. There is scarce mechanistic data and very limited data on the effect of CAM therapies on meaningful clinical outcomes. More randomized clinical trials with adequate sample sizes to detect effects on clinical outcomes and safety are needed. Additionally, the potential is great for adverse effects and interactions with commonly prescribed medicines used in conventional management of cardiovascular disease. Clinicians must be aware of these potential interactions and, until further data are available, focus on treating patients in a safe, evidence-based manner.

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Arterial switch operation after mustard procedures in adult patients with transposition of the great arteries: Is it time to revise our strategy?

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Background After the Mustard or Senning procedure, adults with transposition of the great arteries may have right ventricular failure and require consideration of new therapies. A 2-stage arterial switch operation (ASO) may be performed as an alternative to heart transplantation. This procedure is relatively successful in children, but little is known about the 2-stage ASO in adults. We report our experience in adults undergoing pulmonary arterial banding as the first stage of a planned 2-stage arterial switch procedure after a failed Mustard operation.

Methods and results Three adult patients with systemic right ventricular failure late after Mustard procedures embarked, through pulmonary artery banding, on a course toward a 2-stage arterial switch at the Toronto General Hospital. Baseline clinical characteristics as well as preoperative hemodynamics were reviewed. Immediate perioperative and postoperative events, hemodynamic measurements, and clinical outcomes

were also recorded. Two patients were banded acutely such that their morphologic left ventricular to right ventricular (LV/RV) systolic pressure ratios were >0.65 after the initial banding procedure. The subpulmonary left ventricle failed in both cases. In contrast, the third patient had a more gradual approach to pulmonary artery banding (PAB), with an initial LV/RV pressure ratio of 0.5, which eventually led to a successful conversion to an arterial switch procedure.

Conclusions Our evidence suggests that in adult patients expected to undergo a 2-stage arterial switch procedure after a failed Mustard operation, acute PAB achieving near-systemic subpulmonary LV pressure leads rapidly to ventricular failure and failure of this treatment strategy. A more gradual approach to PAB may be required to achieve a successful outcome. (*Am Heart J* 2004;147:e8.)