Evidence Report/Technology Assessment
Number 83

Effect of Supplemental Antioxidants Vitamin C, Vitamin E, and Coenzyme Q10 for the Prevention and Treatment of Cardiovascular Disease

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
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Rockville, MD 20850
www.ahrq.gov

Contract No. 290-97-0001, Task Order No. 06

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AHRQ Publication No. 03-E043
July 2003

Suggested Citation:
Shekelle P, Morton S, Hardy M. Effect of Supplemental Antioxidants Vitamin C, Vitamin E, and Coenzyme Q10 for the Prevention and Treatment of Cardiovascular Disease. Evidence Report/Technology Assessment No. 83 (Prepared by Southern California–RAND Evidence-based Practice Center, under Contract No 290-97-0001). AHRQ Publication No. 03-E043. Rockville, MD: Agency for Healthcare Research and Quality. July 2003.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

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AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850.

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Structured Abstract

Objectives. The purpose of this study was to conduct a systematic review of the scientific literature to identify and assess the evidence for the efficacy of the antioxidant supplements vitamin C, vitamin E, and coenzyme Q10 for the prevention and treatment of cardiovascular disease or modification of known risk factors for cardiovascular disease. It was our intention to perform meta-analyses where possible. The results may be used to develop a research agenda as well as to assist clinicians in advising patients who desire to take antioxidants to modify their risk of cardiovascular disease.

Search Strategy. A comprehensive search was conducted for citations in English and other languages using 15 databases. We used the search terms antioxidant, vitamin E, vitamin C, coenzyme Q10, and all pharmacologic synonyms in combination with the MeSH term cardiovascular disease. We also identified appropriate literature by searching the bibliographies of review articles and asking our experts for articles.

Selection Criteria. The literature search was confined to controlled trials assessing supplements of the three antioxidants—vitamin E, vitamin C, and coenzyme Q10—and cardiovascular disease. Cardiovascular disease included coronary artery disease and its sequelae as well as stroke, heart failure, and peripheral vascular disease. Primary emphasis was given to studies reporting clinical outcomes such as mortality or myocardial infarction. Studies were also included if they affected risk factors for cardiovascular disease such as blood lipids or hypertension. Language of publication was not a barrier to inclusion.

Data Collection and Analysis. Information was collected about trial design and quality, number and characteristics of patients, details on the intervention, and time between intervention and outcome measurement. Two physicians independently reviewed each article, abstracted data, and resolved differences by consensus. Data were synthesized qualitatively or quantitatively as appropriate. For this report, pooled analysis was performed of the effects of vitamin E alone and in combination on death, myocardial infarction, and blood lipid levels.

Main Results. Our literature search process identified 156 articles that represented results from 159 reports on 144 unique trials (i.e., those reporting data not duplicated in another publication). Of the 159 reports, one-third were judged to be of high quality using the Jadad method.

Studies reporting on the outcomes of death, myocardial infarction, and/or blood lipid levels were selected for further analysis. For the interventions of vitamin E alone and in combination with other antioxidants, sufficient numbers of studies existed to perform pooled analysis.

Both the pooled analyses of smaller studies and the results of larger studies did not show, in general, any beneficial effect of vitamin E supplementation on cardiovascular outcomes. Some trials reported beneficial effects on only one outcome or in subgroups, but these results were either not confirmed or were contradicted by other studies.

We did not find evidence in the pooled analysis of smaller trials that vitamin E alone or in combination had a significant effect on levels of TC, LDL, or HDL. For the Heart Prevention Study, a small increase in LDL and HDL was reported.

We identified one meta-analysis of the effect of coenzyme Q10 that reported mostly beneficial effects on measures of cardiac function in patients with heart failure. Five placebo-controlled, randomized studies that measured clinically relevant outcomes, enrolled at least 60 patients, and had at least 6 months duration of treatment were identified and reported mixed results.

Four studies were identified that assessed the effect of vitamin C (mostly in combination with other antioxidants) on clinical outcomes in patients with or at high risk for cardiovascular disease using a placebo-controlled, randomized design, enrolling at least 60 patients, and having at least 6 months duration of treatment. The results were uniformly negative.

Conclusions. For the combinations and conditions studied, the pooled analysis of smaller studies does not show evidence of an effect of vitamin E alone or in combination with other agents on all-cause mortality, cardiovascular mortality, fatal or nonfatal MI, or blood lipid levels. Results from a number of large clinical trials not included in the pooled analysis were substantially in agreement with this conclusion. Large studies of vitamin C in combination with other antioxidants for the prevention of cardiovascular disease reported no favorable outcomes. There is no convincing evidence either supporting or refuting the value of coenzyme Q10 in cardiovascular disease.

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Summary

Overview

The purpose of this study was to conduct a systematic review of the scientific literature to identify and assess the evidence for the efficacy of three antioxidants, vitamin E, vitamin C, and coenzyme Q10, for the prevention and treatment of cardiovascular disease (CVD) or modification of known risk factors for CVD. A broad search found sufficient literature to perform a detailed review of the use of these antioxidants for CVD.

CVD, defined as coronary artery disease, hypertensive heart disease, congestive heart failure, peripheral vascular disease, and atherosclerosis, including cerebral artery disease and strokes, is the leading cause of death in the United States. Modification of the major risk factors for CVD (diabetes mellitus, hypertension, hypercholesterolemia, and smoking) has been associated with a decreased risk of CVD. Thus, identification of interventions that treat CVD or modify the underlying risk factors would be of great interest.

Observational data suggest that fruit and vegetable consumption lowered the risk of developing CVD. It has been postulated that the antioxidant component of fruits and vegetables accounted for the observed protection. Decreased risk of cardiovascular death has been associated with higher blood levels of vitamin C and coenzyme Q10. In addition, vitamin C, vitamin E, and coenzyme Q10 have demonstrated antioxidant effects, including beneficial effects on oxidation of low-density lipoprotein. There is evidence that these vitamins affect other risk factors for CVD such as hypertension. Vitamin E may also reduce coronary artery blockage by decreasing blood platelet aggregation. Thus, it was reasonable to expect that supplementation with these antioxidants would decrease the risk of developing CVD. Large numbers of people are taking antioxidants with the expectation that they will prevent disease.

Methodology

Search Strategy

A comprehensive search for citations in English and other languages was conducted using 15 databases. We used the search terms antioxidant, vitamin E, vitamin C, coenzyme Q10, and all pharmacologic synonyms in combination with the MeSH term cardiovascular disease. We also identified appropriate literature by searching the bibliographies of review articles and asking our experts for articles.

Selection Criteria

The literature search was confined to the three antioxidants—vitamin E, vitamin C, and coenzyme Q10—and cardiovascular disease. Reports were included in the synthesis of evidence, if they focused on one of the identified antioxidants, alone or in combination, for the selected disease state of CVD. CVD included coronary artery disease and its sequelae, as well as stroke, heart failure, and peripheral vascular disease. Studies were also included if they affected known risk factors for CVD such as blood lipids or hypertension. Language of publication was not a barrier to inclusion.

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Data Collection and Analysis

Information was collected about trial design and quality, number and characteristics of patients, details on the intervention, and time between intervention and outcome measurement. Two physicians independently reviewed each article, abstracted data, and resolved differences by consensus. After abstraction of data, all studies were considered for inclusion in the pooled analysis based on similarity of patients studied, interventions given, and outcomes measured. The only studies sufficiently similar for pooling were those on the effects of vitamin E alone and in combination regarding risk of death, myocardial infarction (MI), and blood lipid levels. We judged the studies on vitamin C and coenzyme Q10 to be insufficiently similar to justify pooling. Our synthesis of these studies is qualitative and restricted to placebo-controlled randomized trials that enrolled at least 60 patients, reported clinical outcomes, and were at least 6 months' duration of treatment.

Findings

Our literature search identified 1,339 articles that met our search criteria, of which we were able to find 1,127. Based on an independent review by two physicians, 528 were selected for screening. They included clinical trials, review articles, and reports that contained supplemental information. Of these, we identified 156 articles that represented results from 159 reports on 144 unique trials (i.e., those reporting data not duplicated in another publication). Of the 159 reports referred for further analysis, one-third was judged to be of high quality using the Jadad method.

Studies reporting on outcomes of death, MI, and/or blood lipid levels were selected for further analysis. For the interventions of vitamin E alone and in combination with other antioxidants, sufficient numbers of heterogeneous populations existed to perform pooled analysis.

The available evidence did not generally support the assertion that there was any positive benefit associated with the use of vitamin E either alone or in the combinations tested for the prevention of all-cause death or cardiovascular death. Neither was there any evidence of significant harm from the same interventions. An effect of vitamin E on overall mortality and on cardiovascular mortality reported in the GISSI trial was only observed in the "four way" analysis (that is, comparing each arm of the 2x2 factorial study separately), and not seen in the "two way" analysis (comparing all subjects who received vitamin E to all those who did not). The GISSI investigators themselves noted that the results in the "four way" analysis are probably due to chance, and concluded that vitamin E supplementation conferred no benefit. Reduction in all-cause mortality (9percent) reported in the Linxian study was primarily due to a decrease in cancer deaths, not cardiovascular deaths. Therefore, there is little evidence that vitamin E supplementation results in a reduction in cardiovascular mortality.

For the risk of MI, fatal and nonfatal, the evidence regarding results of supplementation with vitamin E alone or in combination is mixed. No pooled analysis yielded a beneficial or adverse effect for vitamin E supplementation, either alone or in combination. However, individual studies did report significant effects. The GISSI study reported a benefit on fatal MI but a nonsignificant adverse effect on nonfatal MI. Furthermore, the beneficial effects in GISSI were seen only in the "four way" analysis and not in the larger "two way" analysis. The Alpha-Tocopherol Beta Carotene (ATBC) trials reported just the opposite of the GISSI "four way" results: a significant adverse effect of vitamin E on fatal MI but a nearly significant beneficial effect of vitamin E on nonfatal MI. While there were distinct differences in the two trials (ATBC assessed 50 mg of vitamin E, while GISSI assessed 300 mg; but the baseline risk of both fatal and nonfatal MI was approximately equivalent in the two studies), such disparities in results cast doubt on the observed effects being due to a causal relationship, since consistency of effect and a dose response effect are two important constituents of causality.

Supplementation with vitamin E alone and in combinations in doses ranging from 100 IU to 1,200 IU did not demonstrate a statistically significant effect on serum lipids after at least 8 weeks and no more than 24 weeks of treatment. Two large primary prevention trials reported clinically insignificant (but statistically significant) changes in these outcomes. Thus, there is no evidence that vitamin E alone or in combination has a clinically and statistically significant favorable or unfavorable effect on lipids.

There have been few studies of the use of coenzyme Q10 that have enrolled at least 60 patients and completed at least 6 months' duration of treatment and measured clinical outcomes. A meta-analysis of the effect of coenzyme Q10 on indices of cardiac function concluded that its use was associated with a substantial improvement. This conclusion was not confirmed by two subsequent randomized trials. The studies reporting clinical outcomes yielded mixed results. Two studies reported distinctly favorable clinical outcomes for coenzyme Q10 treated patients. However, one study probably had a serious potential flaw in design and execution in that it is not reported to be placebo controlled or blinded with respect to outcome measurement. The second study is reported in insufficient detail to allow an adequate assessment of the enrolled population or the results. Four subsequent studies reported either no or clinically small improvements. Therefore, the value of coenzyme Q10 supplementation in patients with CVD is still an open question, with neither convincing evidence supporting nor refuting evidence of benefit or harm.

Four studies assessing vitamin C (mostly in combination with vitamin E) provide scant evidence that these combinations of antioxidant supplements have any cardiovascular health benefits. The only reported benefit was in the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) Study and that was in an intermediate outcome only, and then only in the subpopulation of male smokers. The Heart Protection Study, in particular, due to its size and follow-up provides good evidence that these antioxidant supplements in these doses are unlikely to have any substantial effects on coronary vascular disease outcomes.

Future Research

One outcome of this analysis is the discordant results between the observational data, which suggest that foods high in the selected antioxidants are beneficial, and the majority of the research presented here on supplemental antioxidants. These discordant results could occur for at least two reasons:

1. The tested antioxidant supplements do not contain the agents responsible for the benefit reported in observational studies.
2. The observational studies of food consumption are confounded by some other factor that is responsible for the effect. The recent failure of hormone replacement therapy to achieve in a randomized controlled trial (RCT) the cardiovascular benefit reported in observational studies has been attributed to confounding in the observational studies, demonstrating that no matter how well designed and how often replicated, confounding must always be considered a possibility.

Therefore, the thrust of new research into antioxidants and CVD should be randomized trials. These RCTs should consider the following:

- Use supplements that are standardized in terms of dose, source, and stereoisomers.
- Measure clinical outcomes (that include death, MI, hospitalization, quality of life, exercise tolerance, and so on) in addition to intermediate outcomes (levels of antioxidants, blood lipid levels, and so on).
- Be conducted over a sufficiently long period of time, e.g., years, to see an effect.
- Enroll heterogeneous populations so that the results may be extrapolated to the U.S. population. (Most existing studies have enrolled only or predominantly Caucasian participants.)

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Southern California–RAND Evidence-based Practice Center, under Contract No. 290-97-0001. It is expected to be available in June 2003. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 83, *Effect of Supplemental Antioxidants Vitamin C, Vitamin E, and Coenzyme Q10 for the Prevention and Treatment of Cardiovascular Disease*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

www.ahrq.gov
AHRQ Pub. No. 03-E042
June 2003

ISSN 1530-440X

Evidence Report

Chapter 1. Introduction

Purpose

The use of nonstandard therapies to prevent or treat disease, in addition to or instead of standard medical treatments, has come to be called complementary and alternative medicine (CAM). The use of CAM for chronic diseases has attracted growing interest. Proponents of CAM consider cardiovascular disease to be particularly well suited for prevention and/or treatment with one class of CAM therapies, that is, those with antioxidant activity, because the pathogenesis of atherosclerosis involves oxidative damage. Such antioxidant therapies include the use of dietary supplements that contain vitamin C, vitamin E, and coenzyme Q10, among others. The purpose of this study was to conduct a systematic review of the scientific literature to assess the evidence for the efficacy of supplements of these three antioxidants for the prevention and treatment of cardiovascular disease.

Specific Aims

The National Center for Complementary and Alternative Medicine (NCCAM) and the Agency for Healthcare Research and Quality (AHRQ) established the following specific aims for this study:

1. To identify controlled clinical trial reports on the efficacy of the antioxidant supplements vitamins C and E and coenzyme Q-10 for preventing and treating cardiovascular disease (CVD) or for modification of a risk factor for CVD,
2. To determine if sufficient evidence exists to recommend further study of these therapies, and
3. To suggest future research.

Cardiovascular Disease

Cardiovascular disease (CVD), defined as coronary artery disease, hypertensive heart disease, congestive heart failure, peripheral vascular disease, and atherosclerosis including cerebral artery disease and strokes, is the leading cause of death in the United States. In 1999, one in five Americans (n=61,800,000) had CVD and 958,775 died from it that year. This figure represented 40.1 percent of all deaths in the United States that year and was equal to the next seven leading causes of death. Cardiovascular death rates in the United States are almost twice the rate of death from cancer.[1] Globally, CVD accounts for an estimated 31 percent of the worldwide mortality and burden of disease from all noncommunicable diseases.[2] Further, rates of CVD are increasing in developed countries. The Heart Outcomes Prevention Evaluation (HOPE) study investigators predict a 29 percent increase in ischemic heart disease mortality and a 28 percent increase in the rates of mortality from cerebrovascular disease in developed countries from 1990 to 2020.[2] The rates of increase are expected to be three to four times higher in developing countries, as they increasingly adopt the sedentary Western lifestyle and its dietary habits.

Characterization by specific disease type demonstrates the significant contribution made by each of these conditions to the morbidity from CVD. In the United States, an estimated 1,100,000 people will develop new or recurrent myocardial infarctions in 2003 (approximately 650,000 will be new attacks and 450,000 recurrent cases). An estimated 400,000 cases of new stable angina and 150,000 cased of new unstable cases of angina occur each year. Of the 958,775 deaths from CVD in 1999, 55 percent were from coronary heart disease, 6 percent were from heart failure, 5 percent were attributed to hypertension, and 17 percent were from stroke. Stroke would be considered the third leading cause of death if considered separately from the rest of CVD.[1] The lifetime risk of developing heart failure was 20 percent as reported in the Framingham Heart Study, with a median survival of 1.7 years in men and 3.2 years in women after diagnosis.[3] Although less common, peripheral vascular disease (PVD), defined as atherosclerotic disease in the arms or legs, affects eight million adults in the United States and causes significant and often disabling pain and disability.[4] Thus, atherosclerotic cardiovascular disease, including stroke, represents a significant source of morbidity and cost for the American public.

Costs of Cardiovascular Disease

The economic cost of CVD in medical care expenditures, lost productivity, and premature mortality is substantial. CVD diagnoses are the most common of all hospital discharge diagnoses and increased 29 percent from 1977 to 1999. Medicare payments for expenses related to CVD hospital admissions in 1998 were $26.4 billion. Estimated total direct expenditures for heart disease in 2002 are expected to be $115 billion, with an estimated loss in productivity from all causes of CVD of $129.7 billion. Combining all expenses and losses for 2002, the American Heart Association has estimated the total cost of CVD in the United States at $329.2 billion.

Risk Factors for Cardiovascular Disease

The major common risk factors for CVD are diabetes mellitus, hypertension, hypercholesterolemia, and smoking.[5] In an evaluation of five large cohorts of young and middle aged men and women (n=72,144), mortality caused by stroke, myocardial infarction, and cancer was significantly reduced in the low-risk cohort, defined by low cholesterol, low blood pressure, and smaller body mass index (BMI).[6] For women in the Nurses Health Study, 82 percent of the cardiovascular mortality was attributed to the lack of adherence to a low-risk lifestyle that included minimizing BMI, exercising regularly, not smoking, and eating a high-fiber diet rich in fruits and vegetables.[7] Over 100,000,000 Americans are estimated to have a total cholesterol above 200mg/dl. Of these, approximately 41,000,000 are at particularly high risk for heart disease, with cholesterol over 240 mg/dl. A 10 percent decrease in total cholesterol is estimated to result in a 30 percent reduction in risk of coronary heart disease. Those with high low-density lipoprotein levels (LDL>130 mg/dl), now about 48 percent of the American population, are at especially high risk.[1] Persons with two or more risk factors are believed to have a 10 percent to 20 percent increase in risk for developing a significant cardiovascular event in the next ten years.[8]

Antioxidants and Cardiovascular Disease

Antioxidants

The Food and Nutrition Board has defined a dietary antioxidant as a substance in commonly consumed foods that significantly decreases the adverse effects of chemically reactive species, such as reactive oxygen and nitrogen species, on normal physiological functions in humans.[9] These reactive species, also called free radicals, possess one or more single unpaired electrons that make them highly disruptive to biological substances when they are allowed to accumulate. Although short lived, this diverse group of compounds is thought to induce oxidative stress, damaging key molecular constituents of cells, and participating in the genesis of chronic diseases such as coronary heart disease.[10] As part of a natural defense system, antioxidants can mitigate the activity of free radicals and other oxidative species that have been implicated in the development of atherogenesis.[11,12] The epidemiologic and observational literature has suggested a beneficial effect of antioxidant-rich foods, as well as specific antioxidants, on the risk of CVD and stroke.[13-19] Because oxidative functions also contribute positively to the health of the cell by their participation in energy metabolism, biosynthesis, detoxification, and cellular signaling, a balance is clearly required between the pro-oxidants and the antioxidant defense system to maintain health.[20]

A number of components in foods have been found to have antioxidant properties. These components include beta-carotene and the other carotenoids, vitamin C, vitamin E, and selenium. Dietary supplements are available that contain each of the putative antioxidants alone and in various combinations. For this report, the funding agencies—the Agency for Healthcare Research and Quality (AHRQ) and the National Center for Complementary and Alternative Medicine (NCCAM)—directed that we focus our analysis on the roles of supplements containing vitamin C, vitamin E and coenzyme Q10 as dietary antioxidants.

The Use of Antioxidants

The overall rate of dietary supplement use in the National Health and Nutrition Examination Survey (NHANES III), conducted between 1988 and 1994, was 40 percent for the general population, a prevalence and pattern of use that have been stable for the preceding 20 years. The prevalence of use is higher than average in women, older adults, white persons, and persons in a higher socioeconomic class or with a higher level of education.[21] In a more recent telephone survey of 2590 members of the general population, prevalence of use during the prior week was reported to be 26 percent for a multivitamin/mineral supplement, including antioxidants, 10 percent for vitamin E alone, and 9.1 percent for vitamin C alone.[22] The most common reason cited for antioxidant use in this study was maintenance of health, a belief frequently cited by users of all dietary supplements.[23]

As mentioned, the use of antioxidant supplements is common in several subgroups of the population. Almost 80 percent of the elderly subjects in one convenience sample reported regular use of at least one dietary supplement. Vitamin E was the most commonly used supplement, and the predominant reason for use was "to improve health."[24] In addition, 10 percent of a group of elderly Europeans reported taking vitamin C.[25] The Women Physicians' Health Study, a large survey of the rates and patterns of dietary supplement use by female

doctors, found that half of these women used a multivitamin-mineral supplement that typically included vitamins E and C and that those who were at risk for heart disease were higher users of antioxidants. However, the general health habits of women who were regular supplement users were also better than average: these habits include eating more fruits and vegetables, consuming less fat, and complying with preventative care recommendations.[26] Thus, it is important to consider that the associated health behaviors of supplement users may confound the effects of antioxidant use reported in observational studies.

Dietary Intervention and Risk of Cardiovascular Disease

Based on the results of a number of observational studies of dietary antioxidants, the American Heart Association has recommended, among other interventions, a diet that includes five to nine servings of fruits and vegetables per day as a means of lowering the risk of CVD.[27] Fruits and vegetables are considered a rich dietary source of a variety of antioxidants, including vitamins C and E. Results of a number of studies support the recommendation to increase consumption of fruits and vegetables.[28-34] In 1998, a meta-analysis of cohort studies showed that the risk of ischemic heart disease was approximately 15 percent lower among individuals in the 90th centile of fruit and vegetable intake than among those in the 10th centile.[35]

Antioxidants and Cardiovascular Risk

The strength of the dietary evidence regarding the benefits of antioxidants is challenged by the fact that the critical components in fruits and vegetables that confer benefit may not be the antioxidants alone.[14] For example, in the "Zutphen" study, a significant inverse correlation was observed between risk of stroke and intake of one specific category of dietary component, the flavonoids, but not vitamins C or E.[36] However, higher dietary levels of vitamin C and E have generally demonstrated protection against coronary artery disease (CAD in other studies). In a cohort of elderly Asian Indian subjects, an inverse relationship was observed between risk of CAD and plasma levels of vitamins C and E.[37] The adjusted odds ratio for CAD, comparing the lowest to the highest quartiles of vitamin levels, was 2.53 for vitamin E (95% CI: 1.11 to 5.31) and 2.21 for vitamin C (95% CI: 1.12 to 3.15). In a study of Finnish men and women, subjects who developed CVD ate more dairy foods and fewer fruits, vegetables, and foods high in vitamin E. For the three percent of participants in this study who used supplements, a trend towards decreased CVD was seen, but these results were not statistically significant,[38] This trend was also observed for vitamin C intake and was not attributable to other common major risk factors for CAD.[38] A review of the major epidemiological studies confirms the favorable association between high intake of antioxidant-rich foods (and high serum levels of vitamins C and E) with decreased risk of ischemic CVD and stroke.[39]

Studies of the effects of antioxidant vitamin status have even demonstrated a positive association between plasma vitamin C and E levels and the structural integrity of various organs. A British study of elderly men and women found an inverse correlation, in men only, between plasma vitamin C levels and decreases in intimal wall thickness (indicative of stenosis). For vitamin E, the male subjects with the lowest levels of this antioxidant were 2.5 times more likely to have significant carotid artery stenosis.[40] The Artherosclerosis Risk in Communities Study, a prospective cohort study designed to investigate the genesis of atherosclerosis, demonstrated a significant inverse relationship between vitamin C intake and wall thickness in both sexes, even

after adjusting for age and major risk factors.[41] In contrast to the previous study,[40] vitamin E intake was significantly correlated with wall thickness only in female patients, although a positive trend was observed for men.

In contrast to the effects of total dietary antioxidant consumption (both whole foods and supplements), observational studies of the effects of antioxidant supplementation alone have not consistently demonstrated a benefit for CVD or stroke.[18] Analysis of data from the Health Professionals Study showed no decrease in risk of stroke for men who used vitamin C or E supplements.[42] Moreover, a prospective cohort study of almost 35,000 postmenopausal women showed a decrease in stroke and cardiovascular death risk with increased dietary vitamin E but not with use of supplemental vitamin E or general antioxidants.[43] In the same large study, intake of supplemental vitamin C was also not associated with a decreased risk of cardiovascular death.[44] In contrast, in another study, both male and female subjects taking vitamin E supplements showed a decrease in carotid artery intimal thickness and were significantly less likely to have stenosis.[40] Thus, the observational data on the effect of supplemental antioxidants are mixed.

Vitamin C and Cardiovascular Disease

Vitamin C, a potent, water-soluble antioxidant, has been known as an essential micronutrient since the late 1700s, when the British Navy supplemented the diet of their sailors with citrus fruits to prevent scurvy. Also known as ascorbic acid, vitamin C is a six-carbon derivative of the sugar hexose, but it cannot be synthesized by primates (see Figure X).[45] Good dietary sources of vitamin C include fruits—especially currants, citrus, and rose hips—and many vegetables. Because of its asymmetrical ring structure, ascorbic acid may exist in four stereoisomers, but L-ascorbic acid is the biologically active form.[46] It represents the primary antioxidant defense in blood,[47] is able to react with virtually all oxygen species, and can terminate free radical chain reactions.[48] Vitamin C also has crucial interactions with a number of other antioxidants. Glutathione is important in recycling oxidized vitamin C, and vitamin C itself is crucial to the regeneration of lipid-bound vitamin E.[47-49]

An association between risk of death from cardiovascular disease and vitamin C intake was reported as early as 1950.[18] Persons at risk for low serum or plasma levels of vitamin C would include smokers, the elderly, and those who are poorly nourished or suffer from chronic disease.[50] Low levels of vitamin C were associated with higher rates of death from CVD or stroke in the Basel study.[51] Conversely, high serum levels of vitamin C appear protective and have been associated with decreased coronary mortality.[52] Data from the First National Health and Nutrition Examination Survey (NHANES I) showed an inverse relationship between all-cause mortality and vitamin C intake, even after adjusting for age, sex, and potentially confounding variables.[53] The inverse relationship between risk for all causes of death and intake of vitamin C was strong in men and weaker for women.[53] The World Health Organization's MONICA study also showed an inverse relationship between plasma vitamin C levels and mortality from coronary artery disease.[54]

Vitamin C is also thought to modify incidence of and risk factors for CVD. Higher plasma levels of vitamin C have been associated with reduced risk of stroke or coronary heart disease and with a lesser degree of stenosis in carotid arteries.[40] In a review of five population studies,

Trout[46] reported that vitamin C supplementation decreased total cholesterol and increased high-density lipoprotein (HDL), mainly in patients with low pretreatment levels of vitamin C. He also noted an inverse relationship between blood pressure and vitamin C. In another study, individuals who received supplements of vitamin E, vitamin C, and beta-carotene displayed inhibited lipid oxidation (in *ex vivo* tissue samples).[55] Other studies have found a decrease in endothelial dysfunction and in monocyte chemotactive processes with vitamin C supplementation.[56]

Vitamin E and Cardiovascular Disease

Vitamin E, the principal lipid-soluble antioxidant, was first discovered in 1936.[57] Vitamin E includes 8 naturally occurring forms, which can be divided into two families of compounds, the tocopherols and the tocotrienols (collectively known as tocols) (see Figure Y). The four tocopherols consist of a six-chromanol ring or head with a phytyl side chain. Three chyral centers exist in the tail at the 2, 4, and 8 positions; thus, a number of stereoisomers are possible. The tocopherols are designated alpha, beta, gamma, and delta, depending on the methyl substitutions in the chromanol ring. The tocotrienols differ from the tocopherols by the presence of three double bonds in the phytyl chain of the former. Thus, by virtue of a chyral center and the presence of the double bonds, tocotrienol can exist in eight different isomers. The tocotrienols are also designated as alpha, beta, gamma, or delta, based on the methyl substitutions in the head ring.[45]Of the 8 naturally occuring forms of vitamin E, only alpha-tocopherol is carried in human blood and is considered to be the active form.

Vitamin E is an essential micronutrient, that is, it must be obtained from the diet. Dietary vitamin E is absorbed in the small intestine, a process that depends on an intact ability to micellize fat and transport it across intestinal cell walls [where it is packaged into chilomicrons for transport]. Thus, severe pancreatic or biliary dysfunction or fat malabsorption may affect vitamin E absorption.[57] For optimal absorption, it is recommended that vitamin E supplements be taken with a meal.[58] Once in the blood stream, vitamin E is bound to plasma carrier proteins, transported to the liver;incorporated into lipoproteins, especially very low-density lipoproteins (VLDL); and secreted into the bloodstream.

Data from NHANES II showed that dietary intake of vitamin E was generally below recommended levels for both men and women.[59] Significant food sources for vitamin E in this survey included foods fortified with the vitamin, salad and cooking oils, peanuts and tree nuts, mayonnaise and other oil-based dressings, and some vegetables. The largest percentage of dietary vitamin E was derived from fats and oils. Acute deficiencies of vitamin E have been generally attributed to severe malnutrition or severe fat malabsorption. Some congenital deficiency syndromes exist as well, but they are rare. Vitamin E deficiency patterns are species specific, but in humans, they primarily involve hematologic and neurologic sequelae.[57]

A significant body of literature exists that correlates dietary vitamin E levels with cardiovascular disease incidence and mortality.[60-65] A protective effect of vitamin E has been reported in 16 European study populations, in which a strong inverse correlation was observed between vitamin E levels and risk of CVD mortality.[66]

The cardioprotective effects of vitamin E are attributed to its antioxidant properties. Specifically, vitamin E is able to extinguish single oxygen species as well as to terminate free-radical chain reactions.[67] Alpha-tocopherol acts as an antioxidant either by donating a hydrogen radical to remove the free lipid radical, reacting with it to form nonradical products, or simply trapping the lipid radical.[68] It is thought to exert its primary protective effects via the protection of LDL from oxidation. This effect has been demonstrated in laboratory animals *in vivo*,[69] in isolated tissues *ex vivo*, and in human populations.[60] For example, in a population-based study, resistance to LDL oxidation was lower in Lithuanian and Swedish men with the higher levels of alpha tocopherol.[70] In a case-control study of 25,000 blood donors, higher levels of alpha-tocopherol were associated with lower risk of developing a myocardial infarction but only in those patients with high cholesterol.[71]

As noted above, antioxidant vitamins have been shown to interfere with the oxidation of LDL. Of the antioxidant vitamins, vitamin E may be the most potent inhibitor of lipid oxidation because it is fat-soluble and constitutes part of the LDL molecule. Oxidation of LDL particles initiates a plaque-forming cascade, which involves the ingestion of oxidized LDL by macrophages, thereby creating foam cells. These foam cells secrete chemotactic molecules that attract more white cells, which damage local endothelium, increase inflammatory cytokines, and promote procoagulant activity.[60] Vitamin E supplementation has been shown to decrease the oxidation of LDL, measured in prolongation of lag-time before LDL oxidation, often experimentally induced by heavy metals such as copper.[72] This protective activity of vitamin E that occurs in the LDL molecule depends on vitamin C to recycle oxidized vitamin E.[47]

Vitamin E may affect the pathogenesis of atherosclerotic vascular disease beyond its direct effects on lipids. The majority of morbidity and mortality from CVD occurs as a result of thrombosis at the site of an unstable atheromatous plaque in an atherosclerotic artery. Vitamin E could affect CVD morbidity and mortality by reducing platelet adhesion, inhibiting vitamin-K-dependent clotting factors, or stimulating nitric-oxide formation by the endothelial cell.[60] Effects on platelet aggregation and adhesion that may affect clot formation have been demonstrated.[73] Furthermore, the oxidized LDL interferes with the normal production of nitric oxide by the endothelium. Nitric oxide is an essential vasodilator and plays an important role in the inhibition of platelet aggregation and smooth-muscle-cell proliferation.[56]

Coenzyme Q10 and Cardiovascular Disease

Coenzyme Q10, a naturally occurring antioxidant, is so widely distributed throughout the human body that it is also known as ubiquinone. Its chemical name is 2,3 dimethoxy,5-methyl-6-polyisoprene parabenzoquinone.[74] It contains 10 isoprene units of five carbons each (see Figure Z). Coenzyme Q10 is a lipid-soluble provitamin that is structurally similar to vitamin K. It is incorporated into the walls of the mitochondria and functions in electron transport and the production of the high-energy compound adenosine triphosphate (ATP). Concentrations are highest in tissues with high-energy demands, such as heart muscle, liver, and kidney tissues.

Although it is present in a wide variety of foods, coenzyme Q10 is mainly supplied by biosynthesis, a process that involves the enzyme HMG-CoA reductase, which is also responsible for cholesterol synthesis. HMG-CoA reductase inhibitors, a class of lipid-lowering drugs referred to as statins, have been shown to decrease levels of coenzyme Q10.[75-77] Levels of coenzyme Q10

can be normalized with oral supplements taken concurrently with the statin drugs, although the clinical significance of this normalization has not been determined.[78,79]

Coenzyme Q10 is believed to exert its effects via three main mechanisms. First, it participates in oxidative phosphorylation as a coenzyme for three critical mitochondrial enzyme systems, complexes I, II, and III. To a lesser degree, free coenzyme Q10 in the cytosol may also contribute to electron transfer outside of the mitochondria as well. By increasing ATP production, it is thought to improve energy function in tissues with high oxidative demands. Second, coenzyme Q10 has significant antioxidant activity. It exists in the cell in both oxidized and reduced forms and is one of the few substances for which there are enzymes whose sole function is to restore their reduced state. Coenzyme Q10 also serves to restore oxidized alpha-tocopherol and thus is important for the function of this important antioxidant as well. Finally, due to its lipid solubility, it is present in the cell membrane phospholipid layer and may influence membrane stability as well.

A number of diseases have been associated with coenzyme Q10 deficiency. These include diabetes mellitus, periodontal disease, muscular dystrophy, and a variety of cardiac conditions such as mitral valve prolapse, angina, coronary artery disease, congestive heart failure, hypertension, cardiomyopathy, and injury following revascularization procedures.[80] Coenzyme Q10 levels are also reportedly low following cardiac surgery and in patients with heart failure (HF) and myocardial infarction (MI). The decrease in coenzyme Q10 levels has been demonstrated to correlate positively with the severity of HF.[81,82] Animal models have demonstrated improved cardiac function and protection from reperfusion injury with coenzyme Q10 supplementation and increased tissue and blood levels of this antioxidant.[83]

In its reduced form, coenzyme Q10 is present in the LDL particle and is believed to act in conjunction with alpha-tocopherol to prevent LDL oxidation, an initiating event in intimal injury and atherosclerosis.[84] In patients with ischemic heart disease, low coenzyme Q10 levels have been correlated with higher levels of total cholesterol, triglyceride (TG) and LDL, known risk factors for coronary artery disease.[85] A protective benefit of coenzyme Q10 was suggested by the results of an observational study of 94 consecutive hospital patients with a variety of medical conditions, including malignancies and HF. Patients who died within six months of hospitalization had lower coenzyme Q10 levels than those who survived.[86]

A meta-analysis of the efficacy of coenzyme Q10 supplementation for the treatment of HF was conducted by Soja and Mortensen[87] in 1997. It suggested significant positive effects on hemodynamic measures such as ejection fraction, stroke volume, cardiac output, and end diastolic volume index.

Safety of Antioxidant Supplements

In general, supplement forms of the three antioxidants, vitamin C, vitamin E, and coenzyme Q10, are believed to be safe, with low toxicity reported and few significant drug interactions.[45,88] Animal studies of oral vitamin E have not revealed significant toxicity, carcinogenicity, or teratogenicity.[89]

For vitamin E, few adverse events have been reported in clinical trials for doses up to 1000 IU (about 660 mg).[90] The tolerable upper intake level is set at 1000 mg.[9] Because of vitamin E's effects on platelets, interactions with anticoagulants and other platelet drugs are of potential concern. At doses greater than 400 IU, reports of a potential interaction with warfarin have been described.[91] In the Alpha Tocopherol Beta Carotene (Cancer Prevention) study (ATBC, discussed in more detail later), alpha tocopherol supplementation was associated with a 50 percent increase in the risk of subarachnoid hemorrhage (p=0.07) and a 181 percent increase in the risk of fatal subarachnoid hemorrhage (p=0.01).[92] A greater number of adenomas were reported from the ATBC study in the subjects taking alpha tocopherol. (relative risk=1.66) However, this finding is postulated to be due to the increased rate of rectal bleeding in this intervention group leading to greater frequencies of colonoscopy rather than actual promotion of polyp formation.[93] The MRC/BHF study in 20,536 patients concluded that the combination of 600 mg (about 900 IU) of vitamin E and 250 mg of vitamin C taken daily for up to 5 years was safe.[94]

For vitamin C, minor episodes of gastric distress have been reported for daily doses greater than several grams.[95,96] This lack of toxicity seems to be sustained over even long periods of use. Although not a toxic effect, vitamin C can interfere with common lab tests for glucose, uric acid, creatine, and fecal occult blood.[97]

Coenzyme Q10 has been described to decrease the effectiveness of warfarin in a case report and may, through effects on glucose in type II diabetics, exaggerate the hypoglycemic effects of diabetic medications.[95] Mild gastrointestinal intolerance has been reported at higher doses (700 mg or more daily), and a number of drugs such as statins and beta-blockers decrease the levels and/or effectiveness of coenzyme Q10.

Chapter 2. Methodology

We synthesized evidence from the scientific literature on the effectiveness of vitamin C, vitamin E, and coenzyme Q10 for the prevention and treatment of cardiovascular disease using the evidence review and synthesis methods of the Southern California Evidence-based Practice Center (SCEPC). Established by the Agency for Healthcare Research and Quality (AHRQ), the center conducts systematic reviews and technology assessments of all aspects of health care; performs research on improving the methods of synthesizing the scientific evidence, developing evidence reports and conducting technology assessments; and provides technical assistance to other organizations in their efforts to translate evidence reports and technology assessments into guidelines, performance measures, and other quality-improvement tools.

Project staff collaborated with the National Institutes of Health's National Center for Complementary and Alternative Medicine (NCCAM), the Task Order Officer at AHRQ, and technical experts representing disciplines related to the intervention topic, conditions studied, and methods used.

Scope of Work

The literature review process included:

Establishing criteria for inclusion of articles in review,
Identifying sources of evidence in the scientific literature,
Identifying potential evidence with attention to controlled clinical trials using antioxidants,
Evaluating potential evidence for methodological quality and relevance,
Extracting data from studies meeting methodological and clinical criteria,
Synthesizing the results,
Performing further statistical analysis on selected studies,
Performing pooled analysis where appropriate,
Submitting the results to technical experts for peer review,
Incorporating reviewers' comments into a final report for submission to AHRQ.

Objectives

Based on a discussion with the Task Order Officer for AHRQ, the Director of NCCAM, Co-Directors of SCEPC, and project staff, we were directed to study the effect of supplements of the antioxidants vitamin C, vitamin E, and coenzyme Q10 for the treatment and prevention of cardiovascular disease. While many other antioxidants, such as beta carotene or selenium, would be of interest to study, the scope of this report is limited to the three interventions chosen by the funding agency.

Literature Search Design

Technical Expert Panel

The SCEPC is advised on CAM topics by a group of technical experts regarding the search and inclusion criteria and appropriate analyses. The technical experts represent diverse disciplines including acupuncture, Ayurvedic medicine, chiropractic, dentistry, general internal medicine, gastroenterology, rheumatology, integrative medicine (the practice of combining alternative and conventional medicine), neurophysiology, pharmacology, psychiatry, psychoneuroimmunology, psychology, sociology, botanical medicine, and traditional Chinese medicine. The technical experts assisted the project in several ways: they identified potential topics for review, appropriate sources of relevant literature, and technical experts for peer review; assessed our search strategies; and addressed specific questions in their areas of expertise. Appendix A lists members of the technical expert panel along with their affiliations.

Identification of Literature Sources

Potential evidence for the report came from three areas: on-line library databases, the reference lists of all relevant articles, and other sources such as experts and the personal libraries of project staff and their associates. The reference librarian at RAND identified traditional biomedical databases as well as databases that focus on the condition of interest and alternative and complementary medicine (Table 1).

We conducted four searches specifically on the interventions of interest. The full search strategies are displayed in Appendix B. Limiting the output to human studies, we searched using the terms coenzyme Q10, vitamin E, and vitamin C, and their many pharmacological synonyms (Table 2) and the condition of interest (cardiovascular disease). These searches yielded a total of 8173 titles, some of which were duplicates, because the same article may be found by different searches.

Two reviewers (a physician and a Ph.D.) independently evaluated de-duplicated lists of titles that the on-line database searches generated, as well as additional titles from other sources such as the personal libraries of our experts and reference mining. The reviewers read the lists of titles and ordered articles that

focused on the supplements vitamin C, vitamin E, or coenzyme Q10 for treatment or prevention of cardiovascular disease
were controlled trials in humans
presented a meta-analysis or systematic review of the interventions and condition
presented historical or descriptive background information about antioxidants and their use.

Articles that either reviewer classified as meeting these criteria were ordered. Articles were accepted for further analysis if a determination could not definitively be made from the title.

Language was not considered a barrier to inclusion.

At this stage, reviewers screened 528 articles with a one-page data collection instrument. Appendix C contains a copy of this screening instrument.

Using Microsoft Access database software, we tracked requests for articles. We used Pro-Cite as a link to read the citations into the Access database and to manage our reference list. We also used the database to produce and store our data collection instruments. Table 3 summarizes the search strategy shown in Appendix B. The details of the screening process are discussed in the next section.

Evaluation of Evidence

Two physicians, each trained in the critical analysis of scientific literature, independently reviewed each article, abstracted data, and resolved disagreement by consensus. From the 528 articles accepted after the initial title screening, the reviewers accepted 156 for further study, based on the data collected using the screening form. These articles were included in the synthesis of evidence because they

assessed the effect of the supplements vitamin C, vitamin E, or coenzyme Q10, for the prevention or treatment of cardiovascular disease
presented research on human subjects
reported the results of a clinical trial
reported on outcomes of interest.

Outcomes of interest were defined as clinical outcomes—for example, death or myocardial infarction—or as intermediate outcomes that were closely associated with a clinical outcome, such as lipid levels for myocardial infarction. The 156 articles presented data on 159 studies. The 159 studies presented the results of 144 trials. To be clear about our terminology: A "trial" refers to a controlled clinical trial; a "study" refers to a presentation of a specific portion of a trial's results, e.g., focused on particular outcomes or at a particular followup time; and an "article" refers to a published document. An article may contain more than one study if it contains results from more than one trial. Some trials, especially large ones, have many associated studies and articles. Trial is the unit of analysis for synthesis.

Extraction of Data

Detailed information from each of the 159 studies was collected on a specialized data collection instrument (the Quality Review Form) designed for this purpose. This Quality Review Form (Appendix D) was developed in consultation with our technical experts. We included questions about the trial design; the quality of the trial; the number and characteristics of the patients; patient recruitment information; details on the intervention, such as the dose, route of administration, frequency, and duration; the types of outcome measures; and the time between intervention and outcome measurement. Two trained reviewers, working independently, extracted data in duplicate and resolved disagreements by consensus. A senior physician researcher on the project staff resolved any disagreements not resolved by consensus.

A note about equivalence of units for data extraction: dosages of vitamin E, often given as alpha-tocopherol, are reported in either milligrams or international units (IU). To interconvert these units, consider 1 milligram of alpha-tocopherol approximately equal to 1.5 IU of vitamin E.

To evaluate the quality of the design and execution of trials, we collected information on the study design, appropriateness of randomization, blinding, description of withdrawals and dropouts, and concealment of allocation.[98,99] A score for quality was calculated for each trial using a system developed by Jadad.[98] We note that if a trial was presented in more than one study, its quality score was equal to the maximum score calculated across its associated studies. While other elements of the design and execution of controlled trials have been proposed as quality measures, empirical evidence supporting their use as generic quality measures is lacking.

The Jadad score rates studies on a 0 to 5 scale. A score is based on the answer to three questions: Was the study described as randomized? Was the study described as double blind? Was there a description of withdrawals and dropouts? One point is awarded for each "yes" answer, and no points are given for a "no" answer. An additional point is given if the randomization method described was appropriate. A point is deducted if the method is described but is not appropriate. A point is awarded if the method of blinding is appropriate and described, and one point is deducted if the blinding method is described, but inappropriate. Empirical evidence has shown that studies scoring 2 or less report exaggerated results compared with studies scoring 3 or more.[100] Thus, studies with a Jadad score of 3 or more are referred to as "high quality," and studies scoring 2 or less are referred to as "poor quality."

The flow of articles from the point at which they entered our database, through the article ordering, screening, quality review, and statistical analysis stages is displayed in Figure 4. All articles that went on for abstraction were examined for inclusion in the data synthesis.

Data Synthesis

Our synthesis of the evidence is both qualitative and quantitative. For those studies that assessed interventions, populations, and outcomes sufficiently clinically similar to justify pooling, we performed meta-analysis. For other studies, our synthesis is qualitative and narrative. Only vitamin E had a sufficient number of clinically similar studies to support meta-analysis, and then only for three outcomes: two clinical outcomes, death and myocardial infarction; and one intermediate outcome, lipid levels. For vitamin C and Coenzyme Q10, among the numerous studies identified, within the resources available for their project we focused our narrative review on the randomized controlled trials that reported clinical outcomes, enrolled the largest number of subjects, and had the longest duration of follow up. Tables 4 and 5 display the type and number of studies reporting outcomes in the included studies of vitamin C and coenzyme Q10. Based on these data, we selected studies that reported the outcomes death, myocardial infarction, stroke, angina, severity of heart failure, hospitalizations, exercise tolerance, quality of life, restenosis rate, cardiac output and left ventricular ejection fraction. From these studies, we selected studies that enrolled at least 60 patients in total and had at least 6 months duration of treatment or followup. These studies were then synthesized qualitatively and reported in narrative form.

Selection of Trials for Meta-Analysis

The most commonly reported clinically relevant cardiovascular outcomes—death, myocardial infarctions (MI) and lipid levels—were selected for meta-analysis. TC, LDL, and HDL were accepted as lipid measures. All-cause mortality and cardiovascular deaths were extracted for the death outcomes. For MI, both fatal and nonfatal events were collected. For a trial to be included in our analysis, its associated study, or in some case studies, had to contain sufficient statistical information for the calculation of an effect size or risk ratio as appropriate for the relevant outcome, and the studies could not contain duplicate data. By duplicate data, we mean that some studies reported the same outcome data from a trial. In these cases, to avoid double counting of data, we included the data for that trial from the most recent study.

We attempted to group studies assessing clinically similar subjects. We defined a study as assessing primary prevention if it enrolled subjects from the general population. We defined a study as assessing secondary prevention if it enrolled subjects selected because they already had CVD, or if they were selected because they were at high risk of CVD. We defined a study as a treatment trial if it did not assess a clinical outcome such as death or myocardial infarction but did report a biochemical or physiologic outcome.

Several trials contained multiple intervention arms (treatment groups). Vitamin E and vitamin E in combination with other agents were the most commonly reported intervention arms. We therefore limited our analyses to the comparisons of these arms with a placebo arm, conducting separate meta-analyses for each intervention-versus-placebo subgroup of trials. Some trials reported multiple arms of the same treatment that varied by dose. While we had originally hoped to stratify our analysis by dose, we were unable to do so because we did not have enough data. Therefore, for trials with multiple arms of the same intervention, the most clinically relevant dose was selected for inclusion in the meta-analysis. Finally, all trials that were included in the meta-analysis were secondary prevention trials. For each outcome, there were only one or two primary prevention trials, which were considered too clinically different to pool with the secondary trials, and were too few in number to pool separately.

Based on clinical knowledge, clinically relevant and comparable followup times were determined for each outcome. For lipid levels, all trials were included that reported sufficient statistics and outcomes with followup times of at least six weeks. Trials with followup times of at least one year were included for our analyses for death and MI.

After determining which trials could contribute to the analyses, we extracted data into the spreadsheet program Microsoft Excel[101] and statistical and meta-analytic studies using the statistical package Stata.[102]

Risk Ratio Estimation

The data for death and MI were dichotomous. We used a risk ratio to summarize each individual comparison (intervention versus placebo) for each trial. We estimated the log risk ratio, the standard error of the log risk ratio, and the 95% confidence interval for each comparison. We conducted the analysis on the log scale to stabilize the variance. The log risk ratio and its confidence interval were then back-transformed to the risk ratio scale for interpretability. As an example of how to interpret a risk ratio, consider the outcome of all-cause

mortality when comparing vitamin E versus placebo. A risk ratio smaller than 1 indicates that a lower risk of death is associated with vitamin E as compared to placebo.

Effect Size Estimation

Continuous data were collected for the lipid analysis. Trials needed to report the number of people in each arm, the followup mean, and standard deviation of the lipid level. Several trials did not report a standard deviation. For these trials, we imputed a standard deviation equal to the average standard deviation across trials that did report these data.

An unbiased estimate of Hedges' g effect size and its standard deviation were calculated for each comparison of interest.[103] A negative effect size indicates that the intervention is associated with a decrease in the outcome at followup as compared with placebo.

Meta-Analysis

Trials that were considered clinically homogeneous were pooled for meta-analysis. We performed meta-analysis for any subgroup of three or more trials that had similar designs and comparison groups. For fatal and nonfatal MI, the trials were pooled separately for vitamin E versus placebo and vitamin E combination versus placebo. The trials reporting on death were pooled for meta-analysis for (1) vitamin E versus placebo for both all cause mortality and CVD, and (2) vitamin E combination versus placebo only for CVD. Only two trials contributed to the vitamin E combination-versus-placebo analysis for all-death mortality, so they were not pooled meta-analytically. Only the individual trial results are presented. Two lipid trials had sample sizes that were far larger than the remaining trials, therefore, these two studies were excluded from pooling and were reported separately. To include them in the pooled analysis would render the smaller studies statistically meaningless. Thus, we were able to compare and contrast the results from the large trials with the pooled analysis of the smaller trials.

For each outcome and comparison arm of interest that qualified for meta-analysis, we estimated the DerSimonian and Laird random-effects pooled log risk ratio or effect size.[104] We also calculated the chi-squared test for heterogeneity p-value.[103] We back-transformed the pooled log risk ratio to the risk ratio scale for interpretability. For each pooled result, we present its 95% confidence interval and associated forest plot. In this plot, each individual trial estimate is shown with its confidence interval as a box whose area is inversely proportional to the estimated trial variance. The pooled estimate and its confidence interval are shown as a diamond at the bottom of the plot with a dotted vertical line indicating the pooled estimate. A vertical solid line either at 1 for the risk ratio or at 0 for the effect size indicates no treatment effect.

Sensitivity Analysis

After conducting our analyses, we performed some post hoc sensitivity analyses motivated by the observed heterogeneity among the trials and suggestions received during peer review. These post hoc sensitivity analyses included removing any trials that appeared to have extreme estimates.

Publication Bias

For each subgroup of trials for which we conducted a meta-analysis, we assessed the possibility of publication bias by evaluating a funnel plot of the log risk ratios or effect sizes graphically for asymmetry resulting from the non-publication of small, negative trials. Because graphical evaluation can be subjective, we also conducted an adjusted rank-correlation test and a regression asymmetry test as formal statistical tests for publication bias.[105]

Peer Review

A draft version of this report was sent for review to a select group of experts in cardiology, clinical trials, antioxidants, pharmacology and nutrition. The names of peer reviewers are listed in Appendix A. Peer review comments received were entered into a database, and comments about similar sections of the report were collated. To each comment or group of related comments, we prepared a response detailing how we changed the report, or why we did not feel a change was justified. The complete list of peer reviewed comments, and our responses, are included in Appendix E.[106] Service as a peer reviewer does not imply agreement or endorsement of the findings of this report.

Chapter 3. Results

Description of the Evidence

Our literature search process identified 156 articles that represented results from 159 studies on 144 unique trials. A number of articles reported on different aspects of several large clinical trials. Ten of these articles were from the Alpha-Tocopherol Beta Carotene trial (ATBC), three were from the Multiple Antioxidant Supplementation Intervention trial (MASI), two were from the Cambridge Heart Antioxidant Study (CHAOS), and two from the Antioxidant Supplementation in the Atherosclerosis Prevention trial (ASAP).

Of the 144 trials referred for further analysis, six had a Jadad score of "5", 18 had a Jadad score of "4", 27 had a Jadad score of "3", 50 had a Jadad score of "2", 27 had a Jadad score of "1", and 16 had a Jadad score of "0". Thus, for this group of studies, more than a third (35 percent) would be considered to be of high quality using the Jadad scale.

Four outcomes of clinical importance were identified for consideration for pooled analysis. Death, fatal myocardial infarction (MI), nonfatal MI, and the effects on blood lipids were chosen. Sixty-nine trials did not involve these outcomes and therefore were not analyzed further. Thirty-two studies were identified that reported on death and 19 that reported on MI. Fifty-eight studies were identified that concerned the effects of vitamins C or E or coenzyme Q10 on CVD outcomes. Individual studies may have contributed to more than one analysis. Table 6 lists the 58 studies, the "name" of the trials (if applicable), our designation as primary or secondary prevention or treatment, the outcomes assessed, the duration of the trial and the interventions.

Details of the "Named" Clinical Trials Included in Analysis

A number of large named clinical trials are included in various pooled analyses. For the sake of efficiency their clinical designs will be discussed here and not in the individual sections.

Primary Prevention Trials

ATBC

A primary prevention trial designed to assess cancer prevention, the Alpha Tocopherol Beta Carotene (ATBC) trial, randomized 29,133 male smokers from Finland to receive one of four possible regimens: placebo, d-, l-alpha-tocopherol acetate (AT) alone (50 mg/day), beta-carotene (BC) alone (20 mg/day), or both vitamins. CVD endpoints were analyzed as secondary endpoints for this trial. Patients were followed for a minimum of five years and a maximum of eight years.[107] In addition, two articles focused on a subpopulation of the ATBC trial who had preexisting cardiovascular disease.[108,109] The median time for followup was 510 days, this is the value used in this analysis.

Linxian

The Linxian Nutrition Intervention trial (Linxian), also a primary prevention trial, enrolled approximately 30,000 apparently healthy but vitamin deficient members of the general population in an area of southwestern China that had a very high incidence of carcinoma of the

esophagus and stomach. This trial was designed to assess risk of developing esophageal and gastric cancer, so the analysis of CVD endpoints represented a secondary outcome analysis. In addition, the baseline clinical examination of COD and the measurement of outcomes for these parameters were not as rigorous for these secondary outcomes. These patients (the general population group) were randomized to receive one of five treatments singly and in combination for 5.2 years. They were given either placebo or formula A (retinol (5000 IU) and zinc oxide (22.5 mg)), formula B (riboflavin (3.2 mg) and niacin (40 mg)), formula C (ascorbic acid (120 mg) and molybdenum (30 µg)), or formula D (selenium (50 µg) and beta-carotene (15 mg) and alpha-tocopherol (30 mg)). Each of these formulas was given alone and in combination with the other formulas. All four formulas were given together and a placebo group was included.[110]

PPP

The primary prevention trial (PPP) involved 4495 subjects in a 2x2 factorial design testing the effects of low dose aspirin (110 mg/day) and vitamin E (synthetic alpha-tocopherol, 500 mg/day) in patients with risk factors for cardiovascular disease. Followup in this study was stopped after 3.6 years because of the proven benefit of aspirin supplementation in atherosclerosis (ASA) for cardiac patients.[111]

Trials of patients with risk factors for cardiovascular disease

A number of trials reported on the use of antioxidants to decrease the risk of cardiovascular disease in patients with risk factors for cardiovascular disease.

HOPE

The Heart Outcomes Prevention Evaluation Study (HOPE)[112] enrolled 2545 men and 6996 women more than 55 years old who were judged at increased risk for CVD due to the presence of certain risk factors in a 2x2 factorial trial for 4.5 years. The interventions tested were vitamin E 400 IU from natural sources, ramipril (an angiotensin converting enzyme inhibitor), both, or neither.

MASI

The MASI trial enrolled 60 healthy male smokers in a single blind placebo controlled trial to evaluate the effect of vitamin E on lipid oxidation. Volunteers were given either a placebo, 200 mg of RRR-alpha-tocopherol acetate daily or 200 mg RRR–alpha-tocopherol acetate plus 500 mg ascorbic acid daily for 2 months. Lipid oxidation, lipid levels and vitamin serum concentration were measured.[113]

Secondary Prevention Trials

A number of studies tested the effects of antioxidants in preventing further disease in patients with pre-existing cardiovascular disease.

ASAP

The Antioxidant Supplementation in Atherosclerosis Prevention Study (ASAP) tested in a randomized placebo-controlled trial the effect of vitamin C (250 mg) and vitamin E (91 mg

d-alpha-tocopherol) in progression of carotid atherosclerosis.[114] The subjects (n=520) all had elevated lipid levels and included both smokers and nonsmokers. Serum lipids were measured as secondary outcomes.

MRC/BHF

The MRC/BHF trial enrolled 20,536 British adults with preexisting coronary artery disease, peripheral vascular disease, or diabetes in a five-year trial evaluating the effects of a combination of vitamin E (600 mg of synthetic vitamin E), beta carotene (20 mg), and vitamin C (250 mg) versus placebo on the primary outcomes of MI, stroke, and death from cardiovascular causes.[94]

GISSI

In the GISSI-Prevenzione trial, investigators enrolled 11,324 subjects surviving recent MI into four groups: vitamin E (300 mg/day as synthetic alpha-tocopherol), n-3 polyunsaturated fatty acids (PUFA) (1 gm/day), both or placebo for 3.5 years—and evaluated the risk of developing death, nonfatal MI, or nonfatal stroke as primary outcomes.[115]

CHAOS

Stephens et al. report on results from the Cambridge Heart Antioxidant Study (CHAOS) in which 2002 subjects with angiographically proven coronary artery disease were randomized to receive either vitamin E (400 or 800 IU/day of alpha-tocopherol) or placebo and were followed for a median of 510 days.[116]

HATS

The HDL-Atherosclerosis Treatment Study (HATS) enrolled 160 subjects with preexisting cardiovascular disease and tested them with the following combinations simvastatin (10 to 20 mg/day) plus niacin (500-1000 mg/day slow release); antioxidants including vitamin E alone (800 IU of d-alpha-tocopherol); simvastatin, niacin, and vitamin or placebo.[117] The primary endpoint for this study was the change in angiogram over the course of the trial, but secondary endpoints included death and nonfatal MI. Treatment was continued for three years.

MVP

The Multi-vitamins and Probucol Study (MVP) enrolled 317 patients scheduled for percutaneous angioplasty and having preexisting coronary artery disease in a six-month study of a combination of vitamin E (700 IU as d-, l-alpha-tocopherol), vitamin C (500 mg), and beta-carotene (30,000 IU), with and without probucol versus placebo.[118]

SPACE

The Secondary Prevention with Antioxidants of Cardiovascular Disease in End-stage Renal Disease (SPACE) trial[119] enrolled 196 subjects receiving hemodialysis and with known cardiovascular disease who were randomized to receive vitamin E (800 IU/day as natural alpha-tocopherol) or placebo. They were followed for a median of 519 days and the CVD outcomes were the primary outcomes in this trial.

Vitamin E Trials That Report Death as an Outcome

Trial Inclusion

Thirty-two studies corresponding to 20 trials reported on death as an outcome and were therefore considered for pooled analysis. Twenty-three studies corresponding to 12 trials were considered ineligible for pooled analysis for a variety of reasons. We decided not to pool the primary prevention trials with the secondary prevention trials. The primary prevention trials enrolled members of the general population, not individuals with known preexisting CVD or multiple risk factors for CVD. Thus, the death rates from these trials was expected to be lower because the patients did not have significant preexisting disease. Therefore, due to the clinical differences and the differences in expected death rates, the four primary prevention trials (ATBC, PPP, ASAP, Linxian) presented in five studies[92,110,111,114] were not pooled with the secondary prevention trials. We considered pooling primary prevention trials. We judged these four trials to be too heterogeneous in terms of interventions to support statistical pooling and the studies are reported narratively.

The remaining trials used vitamin E as an intervention, but four had inadequate followup time (i.e. less than 6 months) to allow for a meaningful consideration of mortality outcomes.[118,120-122] Six trials did not have sufficient statistics to permit analysis.[123-128] Finally, three studies[108-109,130] reported trial data already included in analysis from other studies,[108,108,116] respectively.

Thus, eight secondary prevention trials that considered the effect of intervention with vitamin E on risk of cardiovascular death,[94,108,112,115-117,119,131] were eligible for pooled analysis.[94,108,112,115-117,131]

Of the trials included in this pooled analysis, all had more than six months followup. The followup of the trials ranged from two[116,119] to seven years.[131] All of the trials were secondary prevention trials that tested the effect of treatment with vitamin E alone or in combination with other antioxidants on the outcome of death. The trials used vitamin E alone or in combination with other antioxidants, typically vitamin C or beta carotene, as interventions. Four of the trials tested a low dose of vitamin E (i.e., less than or equal to 400 IU),[108,112,115,131] and the remaining four trials tested a high dose of vitamin E (greater than 400 IU).[94,116,119,132] For details of these trials, please see the Evidence Table.

Death was reported in two ways in these studies, either as all-cause mortality or as cardiovascular death. We pooled these two outcomes separately. Results from the pooled analysis will be discussed based on outcome and intervention in the following sections. Risk ratios (RR) were calculated for each outcome and intervention with a favorable result was indicated by a RR of less than 1.

Meta-Analysis of Vitamin E Alone vs. Placebo: All-Cause Mortality

Four studies from large named clinical trials reported on all-cause mortality using vitamin E alone as an intervention: the SPACE trial,[119] the HOPE trial,[112] the GISSI trial,[115] and the CHAOS trial.[116] A fifth smaller trial by deGaetano et al. is also included in this meta-analysis.[131]

Pooled RRs of these five studies were calculated for the outcome of all-cause mortality. The results are displayed in Table 7 and the forest plot is presented in Figure 5. The random-effects pooled estimate was 0.96 (95% CI: 0.84, 1.10). The chi-squared test did not demonstrate significant heterogeneity (p=0.22). A sensitivity analysis dropping SPACE and the study by Haeger did not change our results.

Neither formal test demonstrated evidence of publication bias (Table 8). The visual inspection of the funnel plot does not show an obvious bias although we acknowledge that the small number of trials makes assessment difficult. The funnel plot for this analysis is displayed in Figure 6.

Risk ratios were also calculated for three additional trials that were not included in the pooled analysis. Results from these trials are displayed at the bottom of Table 7. A small secondary prevention study by Gillian[120] was not included in the pooled analysis because of insufficient followup time (six months). This trial reported a RR for all-cause mortality of 0.85 (95% CI: 0.13, 5.52). The remaining two studies were primary prevention trials, and were therefore not included in the pooled analysis of the secondary prevention trials. Salonen, reporting results from the ASAP trial,[114] showed a RR of 3.00 (95% CI: 0.32, 28.47). Finally, from the PPP trial,[111] a RR of 1.07 (95% CI: 0.78, 1.49) was calculated. Thus, the results of the three trials not pooled agree with the pooled analysis that there is no significant effect of vitamin E alone on all-cause mortality, either in primary or secondary prevention trials.

Meta-Analysis of Vitamin E in Combination vs. Placebo: All-Cause Mortality

Five trials were considered in this pooled analysis. Two trials were primary prevention trials, and we judged them not appropriate to pool with secondary prevention trials.[110,114] Of the secondary prevention trials, one [118] had a followup time of six months and we judged this insufficient for pooling. This left only two trials,[94,94,115] an insufficient number for pooling. The calculated risk ratios are summarized in Table 9.

The Linxian study[110] and the GISSI study[115] both reported statistically significant benefits. The effect on all cause mortality in the GISSI trial was almost certainly a result of the agent combined with vitamin E, omega-3 polyunsaturated fatty acids with the latter providing all of the benefit. In an analysis of the effect of individual component in this 2x2 factorial trial, omega-3 polyunsaturated fatty acid supplementation resulted in a benefit in terms of all cause mortality (RR = 0.80, 95%CI: 0.67, 0.94) while vitamin E supplementation did not (RR = 0.86, 95% CI: 0.72, 1.02). Therefore, the beneficial effect reported for the combination of these two agents is almost certainly due to the omega-3 polyunsaturated fatty acids alone.

The results from the Linxian trial report a statistically significant 9% reduction in all cause mortality for subjects who received beta-carotene, selenium and vitamin E.[110]

Meta-Analysis of Vitamin E Alone vs. Placebo: Cardiovascular Deaths

Seven studies corresponding to five trials were considered for this pooled analysis. Three studies from the ATBC trial reported on the same dataset at two different time intervals.[107-109]

Only the study with the longer followup period[108] was considered for pooling to avoid double counting these data. This left five trials for the pooled analysis.[108,112,115,116,119]

Risk ratios were calculated for these trials. The results are summarized in Table 10 and the forest plot is shown in Figure 7. The random-effects pooled estimate for all studies was a RR = 0.97 (95% CI: 0.80,1.90). The chi-squared test did not demonstrate significant heterogeneity with a p-value of 0.09. A sensitivity analysis dropping SPACE did not change the results. The GISSI study reported a significant benefit on mortality (RR = 0.80), while three of the other four studies actually reported non-significant increases in mortality in the treated group.

Neither formal test demonstrated evidence of publication bias (Table 8). Although the number of studies was small, the visual inspection of the funnel plot does not demonstrate an obvious bias, although we acknowledge that the small number of studies makes assessment difficult. The funnel plot for this analysis is displayed in Figure 8.

Meta-Analysis of Vitamin E in Combination vs. Placebo: Cardiovascular Death

Four trials were included in this analysis. A small secondary prevention trial, the HATS trial, was pooled[117] along with three large secondary prevention trials: the ATBC trial[108] (CVD subpopulation); the GISSI trial;[115] and the MRC/BHF trial.[94]

Risk ratios were calculated for these trials; and the results are summarized in Table 11 and the forest plot is shown in Figure 9. The random-effects pooled estimate of the four studies was a RR of 1.03 (95% CI: 0.81,1.32). The chi-squared test did demonstrate significant heterogeneity (p=0.02). A sensitivity analysis dropping SPACE did not change the results. As with vitamin E alone, the GISSI trial reported a statistically significant benefit, while two of the other three trials reported increases in the numbers of events in the vitamin E treated group.

There was no evidence of publication bias. The funnel plot for this analysis is shown in Figure 10.

Risk ratios were also calculated for two trials not included in the pooled analysis. Two studies of the ATBC trial were available—the primary prevention ATBC study[107] and the subgroup analysis of CVD patients in the ATBC study at the shorter follow-up time.[109] The unadjusted risk ratio for the full sample ATBC study at 5.5 years for this intervention was not significant at 1.14 (95% CI: 0.75, 1.73) as opposed to the significant increase seen at 5.3 years of followup. Finally, a small secondary prevention trial of Indian men following acute myocardial infarction was excluded because of insufficient follow up.[122] This risk ratio is displayed at the bottom of Table 7. These results agree with the pooled analysis and do not demonstrate any evidence of a significant effect from treatment with vitamin E in the combinations tested associated with the risk of CVD death.

Summary of the Results of Vitamin E Alone and in Combination on Risk of Death

For the four preceding analyses, the results did not generally support the assertion that there was any positive benefit associated with the use of vitamin E either alone or in the combinations tested for the prevention of all-cause death or cardiovascular death. Neither was there any evidence of significant harm from the same interventions. The effects on overall mortality and on cardiovascular mortality reported in the GISSI trial were only observed in the "four way" analysis (that is, comparing each arm of the 2x2 factorial study separately), and not seen in the "two way" analysis (comparing all subjects who received vitamin E to all those who did not). The GISSI investigators themselves attributed the results in the "four way" analysis to be probably due to chance, and concluded that vitamin E supplementation conferred no benefit. Reduction in all cause mortality reported in the Linxian study was primarily due to a decrease in cancer deaths, not cardiovascular deaths. Therefore, there is little evidence that vitamin E supplementation results in a reduction in cardiovascular mortality.

While this report was being peer reviewed in draft form, a new RCT was reported that assessed the effect of vitamin E, vitamin C and estrogen in 423 post-menopausal women with pre-existing CVD. No benefit was reported for patients treated with vitamins E and C. A potential for increased mortality was reported in the antioxidant treated group.[133]

Vitamin E Trials That Report on Myocardial Infarction as an Outcome

Trial Inclusion

Nineteen studies corresponding to 11 trials were considered for inclusion in this analysis. Two studies were found to have insufficient statistics for analysis and were thus removed from the analysis.[134,135] We judged the two reports of primary prevention trials not clinically appropriate to pool with secondary prevention studies because of the differences in the populations studied.[107,111] We judged 2 years of followup to be the minimal appropriate time for an adequate assessment of this intervention and this outcome. Therefore, four studies were eliminated for insufficient followup time.[118,121,122,136,137] Four studies[107-109,130] were excluded because they reported data that were already included in our analysis from another ATBC trial study.[108] Two studies[121,130] were excluded because they presented data that were included in our analysis from another CHAOS trial study.[116] Therefore, seven trials were included in the pooled analysis.[94,108,112,115-117,119] All of the trials were secondary prevention trials, therefore the populations tested all had a previous history of or significant risk factors for CVD.

For treatment, either vitamin E alone or in combination with other antioxidants was used. Three of the trials tested a low dose of vitamin E (i.e., less than or equal to 400 IU)[108,112,115] and the remaining four trials tested a high dose of vitamin E (greater than 400 IU).[94,116,119,132] For details of these trials, please see the Evidence Table.

MI was reported two ways in these trials, either as fatal or as nonfatal MI. We pooled these two outcomes separately.

Meta-Analysis of Vitamin E Alone vs. Placebo: Fatal Myocardial Infarction

Five trials, four of which were secondary prevention trials, were included in the pooled analysis: the SPACE trial,[119] the HOPE trial,[112] the report of the ATBC subpopulation with preexisting CVD,[108] the GISSI trial,[115] and the CHAOS trial.[116] Risk ratios were calculated for these studies; and the results are summarized in Table 12 and the forest plots are shown in Figure 11.

The random-effects pooled estimate of the RR was 0.97 (95% CI: 0.74,1.27). The chi-squared test did demonstrate significant heterogeneity (p=0.03). A sensitivity analysis dropping SPACE did not change the results. No evidence of publication bias was demonstrated. The funnel plot for this analysis is shown in Figure 12. As with the analyses of vitamin E and mortality, the GISSI study differed from the others in that it alone reported a statistically significant result (RR = 0.75, 95% CI: 0.55, 0.96). This statistically significant benefit was only seen in the "four way" analysis; in the "two way" analysis the effect was not significant. Three of the remaining four trials reported nonsignificant results with the point estimates actually reflecting increased fatal myocardial infarction in the vitamin E treated group.

Risk ratios were calculated for additional trials that were not included in the pooled analysis. The PPP trial[111] RR is displayed in the table with the pooled studies (Table 12). Two were reports of outcomes from the ATBC study. The first ATBC study,[107] reported on the results of the primary intervention portion of this trial. This report and the report of the PPP trial,[111] another primary prevention study, were not appropriate to combine with secondary prevention studies and thus were excluded from the pooled analysis. The second ATBC study[109] reported on a subset of the original population with previous CVD. This was the same population and intervention as the first study,[108] but was reported at an earlier followup point. The results at the earlier time point were similar to those seen at the later time point. In order to avoid double-counting of the data, the longer of the two studies was included in the pooled analysis. None of these primary prevention studies reported a statistically significant benefit for vitamin E on fatal myocardial infarction.

Meta-Analysis of Vitamin E in Combination vs. Placebo: Fatal Myocardial Infarction

Four trials were included in this pooled analysis. A prevention trial, HATS,[117] and the longer version of the ATBC trial, which focused on the patients with prior CVD,[108] the GISSI trial,[115] and the MRC/BHF trial,[94] were included. Risk ratios were calculated for these studies; and the results are summarized in Table 13 and the forest plot is shown in Figure 13.

The random-effects pooled estimate of the four studies was 1.02 (95% CI: 0.77, 1.37). This result was not significant, but the chi-squared test did demonstrate significant heterogeneity (p=0.01). No sensitivity analysis was performed. No evidence of publication bias was demonstrated. The funnel plot for this analysis is shown in Figure 14.

As in previous analyses, the GISSI study was the only individual study to report a benefit of vitamin E supplementation (RR = 0.75, 95% CI: 0.59, 0.96). As in the previous case, in the "two

way" analysis of the GISSI data the effect on fatal myocardial infarction was not statistically significant. In contradiction to previous analyses, one trial, the ATBC study of subjects with prior CVD, reported a statistically significant adverse effect of vitamin E supplementation (RR = 1.51; 95%CI: 1.04, 2.20). The GISSI trial used a higher dose of vitamin E, but even so it would be exceedingly rare for an effect to be real and in the opposite direction solely due to differences in dose. The ATBC adverse effect was not seen at an earlier followup time (RR = 1.14, 95% CI: 0.75, 1.73) and it is possible that the adverse ATBC result, as well as the GISSI result, was due to chance.

A RR was calculated for an additional trial by Singh et al. which was not included in the pooled analysis but whose results are shown in the pooled table.[122] These results agreed with the pooled analysis and did not demonstrate any significant effect of treatment with vitamin E in the combinations tested for the risk of fatal MI. The primary prevention sample of the ATBC trial[107] reported no effect on fatal myocardial infarction.

Meta-Analysis Vitamin E Alone vs. Placebo: Nonfatal Myocardial Infarction

The same five trials included in a prior pooled analysis of fatal MI report on the outcome of nonfatal MI. These trials are the SPACE trial,[119] the HOPE trial,[112] the report of the ATBC trial[108] that focused on patients with prior CVD, the GISSI trial,[115] and the CHAOS trial.[116] Risk ratios were calculated for these studies; the results are summarized in Table 14 and the forest plot is shown in Figure 15.

The random-effects pooled estimate was 0.72 (95% CI: 0.51,1.02), The chi-squared test did demonstrate significant heterogeneity (p=0.01). A sensitivity analysis dropping SPACE did not change the results.

There was no evidence of publication bias. The funnel plot for this analysis is shown in Figure 16.

In contrast to prior analyses, in this analysis the GISSI trial did not report a statistically significant effect favoring vitamin E. In fact, the point estimate of effect for nonfatal MI was in the opposite direction (RR = 1.04, 95%CI: 0.80, 1.34). Surprisingly, in this analysis the ATBC trial, which reported a statistically significant adverse effect of vitamin E on fatal myocardial infarctions, reports for nonfatal myocardial infarctions, a beneficial effect that just fails to reach conventional levels of statistical significance (RR = 0.68, 95% CI: 0.46, 1.01). Either these disparate results within and across trials are due to chance, or the mechanism of action of vitamin E with respect to myocardial infarctions is very complicated.

Risk ratios were calculated for two additional studies which were not included in the pooled analysis. The ATBC study, reported on the results of the primary intervention portion of this trial.[107] The risk ratio at 6.1 years was 1.04 (95% CI:0.89, 1.22). This report and the report of the PPP trial,[111] another primary prevention trial (whose results are displayed in Table 14), were excluded from pooling with the secondary prevention trials for clinical reasons. These RRs agree with the pooled analysis in that no significant of treatment with vitamin E alone for reducing the risk of non-fatal MI was demonstrated.

Meta-Analysis of Vitamin E in Combination vs. Placebo: Nonfatal Myocardial Infarction

Four trials were included in this pooled analysis. They were the same four studies included in the prior analysis of fatal MI: the HATS trial,[117] the longer version of the ATBC trial of subjects with prior CVD,[108] the GISSI trial,[115] and the MRC/BHF trial.[94] Risk ratios were calculated for these trials; the results are summarized in Table 15 and the forest plot is shown in Figure 17.

The random-effects pooled estimate was 0.99 (95% CI: 0.89, 1.10). The chi-squared test did not demonstrate significant heterogeneity (p=0.60). There was no evidence of publication bias. The funnel plot for this analysis is shown in Figure 18. In this analysis, no individual study reported a statistically significant beneficial or adverse effect of vitamin E and myocardial infarction.

Two secondary prevention trials with insufficient length of treatment (28 days) were excluded from the pooled analysis. Their results are displayed at the bottom of Table 15. The first, the Indian Infarct survival trial, was a secondary prevention trial of recurrent MI following acute MI.[122] The final study by Sisto and colleagues[136] evaluated the effect of a combination which included vitamin E on the result of recurring infarction following percutaneous transluminal angioplasty (PTCA). The RRs of the unpooled studies agree with the pooled analysis that no significant effect of treatment with vitamin E in the combinations tested could be demonstrated for the risk of having a nonfatal MI. In addition, the full ATBC primary prevention sample reported a RR = 0.99 (95% CI: 0.84, 1.16).[107]

Summary of the Results of Vitamin E Alone and in Combination on Risk of Myocardial Infarction

For the risk of MI, fatal and nonfatal, the results of treatment with vitamin E alone or in combination are mixed. No pooled analysis yielded a beneficial or adverse effect for vitamin E supplementation, either alone or in combination. However, individual studies did report significant effects. The GISSI study reported a benefit on fatal myocardial infarction but a nonsignificant adverse effect on nonfatal myocardial infarction. Furthermore, the beneficial effects in GISSI were only seen in the “four way” analysis, and not in the larger “two way” analysis. The ATBC trials reported just the opposite of the GISSI “four way” results: a significant adverse effect of vitamin E on fatal myocardial infarction but a nearly significant beneficial effect of vitamin E on nonfatal myocardial infarction. While there were distinct differences in the two trials (ATBC assessed 50 mg of vitamin E while GISSI assessed 300 mg; but the baseline risk of both fatal and nonfatal MI was approximately equivalent in the two studies), such disparities in results cast doubt on the observed effects being due to a causal relationship, since consistency of effect and a dose response effect are two important constituents of causality.

Vitamin E Trials That Reported on Lipids as an Outcome

Trial Inclusion

Fifty-eight studies corresponding to 56 trials were identified that examined the effects of the these antioxidants on the intermediate outcome of blood lipids. Intermediate outcomes that have direct evidence of a relation to CVD clinical outcomes, namely total cholesterol, LDL cholesterol and HDL cholesterol, were chosen for continued analysis. Other intermediate outcomes, such as lipid or LDL oxidation, were not chosen for analysis since they lack direct evidence of a relation to clinical CVD outcomes such as mortality. Therefore, four trials that reported on the indirect outcome of lipid oxidation only were not included in pooling.[138-141] For one trial,[142] none of the chosen lipid outcomes was identified.

A number of interventions did not have sufficient numbers of trials to permit pooled analysis. One trial reported on a closely related compound to tocopherol, tocotrienol;[143] three trials used vitamin C as an intervention;[144-146] one trial combined methionine with vitamins C and E;[147] one trial tested the effect of a statin drug with and without coenzyme Q10;[78] and four trials used coenzyme Q10 as an intervention.[128] The vitamin C and coenzyme Q10 trials will be discussed later. [148-150]

Two trials, the GISSI[115] and the MRC/BHF trial[94] were excluded from pooled analysis because their sample sizes were more than an order of magnitude larger than the rest of the trials and would have rendered the results of any smaller studies statistically meaningless in pooled analysis. Instead, we compared the results of these large trials with the pooled results of the smaller trials. Another study[151] was excluded because it was a pharmacokinetics study of coenzyme Q10.

Of the remaining trials, all using vitamin E alone or in combination, six additional trials were eliminated for reasons having to do with their experimental design. One trial did not have a true concurrent control group; rather, each person served as his or her own control.[152] Another trial reported on the results of a crossover trial, but the results of the first crossover were not reported separately for the lipid outcome.[153] Finally, five trials did not have a true placebo group and thus were eliminated.[134,154-157] All these trials assessed vitamin E versus placebo.

We judged that the minimum treatment time for a reasonable trial of an antioxidant on blood lipids was eight weeks. All trials with a shorter treatment time were therefore eliminated. Five trials were excluded from pooled analysis on this basis.[117,158-161] Finally, six trials did not have sufficient statistics to permit pooling.[5,162-166] Thus, 21 trials were available to pool for analysis of the outcomes of TC, LDL, and HDL.[55,113,151,167-184]

Trials Using Vitamin E Alone vs. Placebo: Lipid Analysis

Sixteen trials reported on the effect of vitamin E alone versus placebo on TC, LDL, and HDL.[113,115,151,167-174,177,178,180,182,184] For details of these studies, please see the Evidence Table. All trials had at least eight weeks duration of treatment and the maximum was 24 weeks of treatment. One study[182] reported two eligible followup times, eight and sixteen weeks. The longer time was used for this analysis. One trial[173] tested multiple doses of vitamin E. The results

of largest dose for the pooled analysis were used. Dosages of vitamin E in the pooled trials ranged from a low of 100 IU to a maximum of 1200 IU. The majority of the trials used higher doses of vitamin E (greater than 400 IU); however, six of the trials did use doses of vitamin E less than or equal to 400 IU.

For five of the trials, the patients had significant prior CVD; in two trials, preexisting diabetes. The remaining eight trials evaluated populations without known CVD. The GISSI trial[115] and the MRC/BHF trial, primary prevention trials in healthy populations, were not included in the pooled analysis because their sizes were more than an order of magnitude greater than the next-largest trial. We compare and contrast the results of the very large trials with the pooled results from smaller trials.

Meta-Analysis of Vitamin E Alone vs. Placebo: Total Cholesterol

The results of the pooled analysis for the outcome of TC of the fifteen appropriate trials are summarized in Table 16. The random-effects effect size is not significant with a value of -0.07 (95% CI: -0.31, 0.18). A negative value in this analysis demonstrates a favorable effect of treatment by lowering the TC. The forest plot of these values is shown in Figure 19. The chi-squared test for heterogeneity demonstrated a significant degree of heterogeneity (p=0.01).

A sensitivity analysis removing the the trial by Paolisso[180] did not materially change the outcome of the analysis [random effects size = 0.01 (95% CI: -0.15, 0.18)] but did decrease the heterogeneity as demonstrated by the chi-square test (p=0.96).

No evidence of publication bias was found. The funnel plot for this analysis is shown in Figure 20.

Although the GISSI trial[115] was not included in the pooled analysis, its outcome was similar to the pooled results from the smaller studies. The effect size for TC was reported as -0.01 (95% CI: -0.07, 0.04).

Meta-Analysis of Vitamin E Alone vs. Placebo: Low-Density Lipoprotein

The results of the pooled analysis of the 14 appropriate studies for the outcome of LDL, are summarized in Table 17. The pooled random-effects effect size is not significant with a value of -0.07 (95% CI: -0.24, 0.10). A negative value in this analysis demonstrates a favorable effect of treatment by lowering the LDL. The forest plot of these values is shown in Figure 21. The chi-squared test for heterogeneity did not demonstrate a significant degree of heterogeneity (p= 0.41).

As in the prior analysis, a similar sensitivity analysis was performed for this analysis by removing the Paolisso trial.[180] Again, the results are not materially different from the prior analysis. The random-effects pooled effect size is -0.03 (95% CI: -0.20, 0.14). This was the only analysis to have a sufficient number of studies of vitamin E at different dose levels to support an attempt at stratifying by dose. No dose effect was discernable.

No evidence of publication bias was found. The funnel plot for this analysis is shown in Figure 22.

The outcome of the GISSI trial is similar to the pooled results from the smaller studies for this result. The effect size for LDL is -0.02 (95% CI; -0.8 to 0.03).

Meta-Analysis of Vitamin E Alone vs. Placebo: High-Density Lipoprotein

The results of the pooled analysis for the outcome of HDL of the 15 appropriate trials are summarized in Table 18. The pooled random-effects effect size is not significant with a value of 0.01 (95% CI: -0.21, 0.22). A positive value in this analysis demonstrates a favorable effect of treatment by raising the HDL. The forest plot of these values is shown in Figure 23. The chi-squared test for heterogeneity approaches a significant degree of heterogeneity (p=0.07). A sensitivity analysis dropping the study by Paolisso did not materially change the results. Attempts to stratify the analysis by vitamin E dose level were not helpful.

No evidence of publication bias was found. The funnel plot for this analysis is shown in Figure 24.

The outcome of the GISSI trial is similar to the pooled results from the smaller studies for this result. The effect size for HDL was reported as -0.03 (95% CI: -0.09, 0.02).

Meta-Regression Analysis of Vitamin E Treatment Over Time

A meta-regression was performed to determine if the effect of treatment with vitamin E alone was different over time. Half of the trials (n=8) reported results at 8 weeks, a fourth (n=4) reported results at 3 months, three reported results at 4 months and one reported results at 6 months. For the outcome of TC, there was no significant difference in treatment demonstrated for the intervals of 2 months, 3 months or 4 months versus 6 months. For the outcome of LDL or HDL there was no significant difference in treatment demonstrated for the intervals of 2 months, 3 months or 4 months versus 6 months. Thus, the effect of treatment with vitamin E alone did not appear to significantly differ over the time intervals tested in the eligible clinical trials.

Trials Using Vitamin E in Combination vs. Placebo

Seven trials reported on the results of treatment with vitamin E in combination with other antioxidants or medications and were eligible for pooled analysis.[55,151,175,176,179,181,183] Only a single study[151] was included in both the vitamin E alone and vitamin E in combination analysis. For details of these trials, please see the Evidence Table.

Two trials[55,55,183] reported results at two times. One trial[183] reported duration of treatment results at 12 and 24 weeks. The shorter duration of treatment time from this trial was used because it was more similar to the duration of treatment times in the other pooled studies. Another trial[55] reported results at 6 and 12 weeks. The longer duration of treatment was included in this analysis. This trial[55] also used two levels of vitamin E (400 IU and 800 IU) in combination with vitamin C and beta-carotene. The higher dose was included in this analysis.

Four trials used a low dose of vitamin E (less than or equal to 400 IU)[176,179,181,183] and three used high doses of vitamin E (greater than 400 IU).[55,151,175]

For four of the trials, the populations studied had either elevated lipids or preexisting CVD.[55,151,176,183] Three of the trials featured healthy populations.[175,179,181] Although the MRC/BHF trial[94] and the GISSI trial,[115] tested appropriate interventions, they were not included in this pooled analysis because the size of the study populations were several orders of magnitude greater than the remainder of the studies. In this analysis we compare and contrast the results of the very large trials with the pooled results of smaller trials.

Meta-Analysis of Vitamin E in Combination vs. Placebo: Total Cholesterol

All of the eligible trials reported this outcome. The results of the pooled analysis for the outcome of TC of the seven appropriate trials are summarized in Table 19. The pooled random-effects effect size is not significant with a value of 0.24 (95% CI: -0.10, 0.59). A positive value in this analysis demonstrates an unfavorable effect of treatment by raising the TC. The forest plot of these values is shown in Figure 25. The chi-squared test for heterogeneity did not demonstrate a significant degree of hetereogeneity (p=0.18). No sensitivity analyses were performed.

No evidence of publication bias was found. The funnel plot for this analysis is shown in Figure 26.

Effect sizes from the two large trials, which were not included in the pooled analysis, were also calculated. Results from the GISSI trial[115] and the MRC/BHF trial[94] showed a small unfavorable effect of treatment with effect sizes of 0.07 (95% CI: 0.02, 0.13) and 0.09 (95% CI: 0.06, 0.11) respectively.

Meta-Analysis of Vitamin E in Combination vs. Placebo: Low-Density Lipoprotein

Only five of the eligible trials reported this outcome.[55,151,175,176,183] The results of the pooled analysis for the outcome of LDL is summarized in Table 20. The pooled random-effects effect size is not significant with a value of 0.21 (95% CI: -0.35, 0.77). A positive value in this analysis demonstrates an unfavorable effect of treatment by raising the LDL. The forest plot of these values is shown in Figure 27. The chi-squared test for heterogeneity did demonstrate a significant degree of heterogeneity (p=0.04). A visual inspection of the forest plot shows variability in the outcomes of the studies, but no obvious outlier study was identified. Heterogeneity is likely the result of clinical differences in the studies. No sensitivity analyses were performed.

No evidence of publication bias was found. The funnel plot for this analysis is shown in Figure 28.

Effect sizes from the two large trials, which were not included in the pooled analysis, were also calculated. Results from the GISSI trial[115] and the MRC/BHF trial[94] showed a small

unfavorable effect of treatment with effect sizes of 0.13 (0.07, 0.18) and 0.06 (0.03, 0.08) respectively.

Meta-Analysis of Vitamin E in Combination vs. Placebo: High-Density Lipoprotein

Only five of the eligible trials reported this outcome.[55,151,175,176,183] The results of the pooled analysis of the five appropriate trials for the outcome of HDL are summarized in Table 21. The pooled random-effects effect size is not significant with a value of -0.06 (95% CI: -0.40, 0.27). A negative value in this analysis demonstrates an unfavorable effect of treatment by lowering the HDL. The forest plot of these values is shown in Figure 29. The chi-squared test for heterogeneity did not demonstrate a significant degree of heterogeneity (p=0.76). No sensitivity analyses were performed.

No evidence of publication bias was found. The funnel plot for this analysis is shown in Figure 30.

Effect sizes were calculated for the large trials not included in the pooled analysis, the GISSI and the MRC/BHF trials.[94,115] The results for the GISSI trial were similar to the pooled results and showed no significant effect of vitamin E in the combinations tested on HDL. The MRC/BHF trial showed a small but statistically significant favorable effect on HDL with an effect size of 0.06 (95% CI: 0.03, 0.09). This small value is not likely to be of clinical significance.

Meta-Regression Analysis of Treatment with Vitamin E in Combination over Time

A meta-regression was performed to determine if the effect of treatment with vitamin E in combination with other vitamins or medication on lipids was different over time. Three-quarters of the trials (n=6) reported results at 2 months, a fourth (n=2) reported results at 3 months. None reported results at either 4 or 6 months. For the outcomes of TC, LDL, and HDL there was no significant difference in treatment demonstrated for the interval of 2 months compared with 3 months. Thus, the effect of treatment with vitamin E in combination with other antioxidants or medications did not appear to differ significantly over the time intervals tested in the eligible clinical trials.

Summary of the Results of Vitamin E Alone and in Combination on Serum Lipids

For the outcomes of TC, LDL and HDL in the populations studied, interventions with vitamin E alone and in combinations in doses ranging from 100 IU to 1200 IU did not demonstrate a statistically significant effect on serum lipids after at least 8 weeks and no more than 24 weeks of treatment. The two large primary prevention trials reported clinically insignificant (but statistically significant) changes in these outcomes. Thus, there is no evidence that vitamin E alone or in combination has a clinically and statistically significant favorable or unfavorable effect on lipids.

Trials that Report on the Effect of Coenzyme Q10 Supplementation on Cardiovascular Disease Outcomes.

We identified one meta-analysis and 54 studies that met our initial screening criteria. These studies assessed the effect of supplemental coenzyme Q10 on a wide variety of cardiovascular conditions, including heart failure, the effect on lipids, use during cardiovascular surgery, hypertension, mitral valve prolapse, ischemic cardiomyopathy, and chronic stable angina. The 7 studies assessing the effect of coenzyme Q10 use during cardiac surgery were judged not directly relevant to this evidence report about the use of supplements to prevent or treat cardiovascular disease, and were not reviewed further.[185-191] As previously noted, we judged the coenzyme Q10 trials to be insufficient clinically similar in terms of the conditions studied and outcomes measured to justify statistical pooling with meta-analysis. Our review of these trials is, therefore, narrative. Many of the 54 studies enrolled only small numbers of patients or reported only outcomes such as blood levels of antioxidants, markers of myocardial injury, and oxidative status, that are of uncertain relationship to patient clinical outcomes such as death, myocardial infarction, and hospitalization. We concentrated our narrative review, therefore, on only the larger studies that assessed patient clinical outcomes. We identified five studies that used a placebo-controlled randomized design, assessed the effect of coenzyme Q10 on clinical outcomes, included at least 60 patients (or the equivalent of about 30 patients in both acute treatment and placebo group), and had at least six months of follow-up.

The meta-analysis assessed the use of coenzyme Q10 for the treatment of patients with heart failure. This study, [87] published in 1997, included randomized controlled trials published between 1984 and 1994, of which the authors identified 14 studies and 8 of which met their inclusion criteria. The studies had sample sizes from six to 180, with all but two studies having less than 25 subjects studied. Heart failure from a variety of causes was included and the authors' principle objective was to assess the effect of coenzyme Q10 on measures of cardiac performance. The authors report that all measures of cardiac performance assessed had improved when treated with coenzyme Q10. These findings were statistically significant for ejection fraction, which had an effect size of 1.37; stroke volume, with an effect size of 0.71; cardiac output, with an effect size of 0.61; cardiac index with an effect size of 1.15; and end diastolic volume index, with an effect size of 1.23. The authors concluded that coenzyme Q10 led to a statistically significant improvement in these indices and called for additional randomized double-blind studies to confirm and extend these results.

The first study assessed the effect of coenzyme Q10 on 806 patients with heart failure or ischemic heart disease treated with 50 milligrams twice a day of coenzyme Q10 added to cardiovascular standard therapy. The period of treatment lasted for 24 weeks. No other information is available about participants other than 541 had "heart failure" and 265 had "ischemic heart disease" and that at baseline, there was no significant difference between the two groups concerning sex, age, weight, height, blood pressure, heart rate, hypertension, cholesterol level, diabetes, smoking, and several other clinical variables. Follow-up data were available for 96% of patients. One death occurred in both groups. For heart failure patients, in both groups, the proportion of patients with more severe classes of heart failure decreased over time (baseline proportion of patients in New York Heart Association class III of about 40% in both groups, reducing to a proportion of 18.7% at six months in the conventional therapy only group, and

10.6% in the coenzyme Q10 supplement treated group). The authors also report that patients in the control group required more or increased doses of cardiovascular medications, compared to the coenzyme Q10 supplemented groups. For patients with ischemic heart disease, similar results were reported, with a decrease in class III angina from 32% to 3% at six months in the coenzyme Q10 supplemented group, compared to an initial value of 22%, reducing to 9% in the control group. Likewise, the control group required more or increased doses of cardiovascular drugs. The authors did not report any significant change in blood lipids between groups, and noted that "tolerability was good" and that any side effects were "very few and without clinical importance". No additional information about side effects is available. It is not clear whether patients in this latter group received placebo to mask the therapy, nor is it clear whether the participating cardiologists were blinded to treatment type.[128]

The second study assessed the effect of coenzyme Q10 supplementation on patients with heart failure, and was described as a multi-center, randomized, double blind, placebo controlled, parallel group trial. Patients needed to be New York Heart Association class III or IV at baseline, and were excluded if they had a myocardial infarction within the prior three months or thought to be likely to require a revascularization procedure. Patients were randomized to receive coenzyme Q10 (2 milligrams per kilogram) per day or placebo and the duration of treatment was 12 months. A total of 641 patients were enrolled, of which 88% completed the one-year study. The mean age of patients was about 66 years and men and women were equally represented. The authors report that there were no statistically significant differences between the clinical characteristics of the two patient groups at baseline. In terms of the results, the authors report that there were 16 deaths in the coenzyme Q10 group and 21 deaths in the placebo group, a difference that was not statistically significant. In the text, but without supporting data, the authors note that "in the coenzyme Q10 group, there was a progressive reduction in the [functional] class, indicating an improvement in functional status, which was statistically significant after three, six and at twelve months. No significant change in functional class was observed in the placebo group." The authors also note that there was an approximate 50% decrease in the incidence of acute pulmonary edema, cardiac asthma, and "arrhythmia appearance" in the coenzyme Q10 treated group compared with placebo, and that this difference was statistically significant[192]

The third study assessed the effect of either placebo or a combination of antioxidants in patients who were within six hours of an acute myocardial infarction. Members of the intervention group received 500 micrograms of selenium, followed by a daily dosage of 100 milligrams of coenzyme Q10 and a 100 micrograms of selenium, for a period of one year. There were 32 subjects in the antioxidant group and 29 in the placebo group, males were more than 75% of the sample and the average age of subjects was approximately 62. About 10% of patients had received fibrinolytic therapy and no more than one quarter of patients were on either aspirin, beta-blockers or nitrates. The authors report a variety of changes in echocardiographic findings during the early post-infarction period. In the antioxidant group compared to the placebo group, they report that at one-year follow-up, six patients in the placebo group had died from reinfarction, while one patient in the antioxidant group had died following a pulmonary embolism.[135]

The fourth study assessed the effect of oral coenzyme Q10 in 30 patients with heart failure in a randomized double-blind crossover trial with three months of follow-up. The patients averaged

55 years of age and 87% were male. They had had heart failure of approximately 41 months duration and three quarters of patients had dilated cardiomyopathy. All of them were on maximum-tolerated doses of angiotensin-converting enzyme inhibitor therapy. Most were also taking digoxin, furosemide, and hydralazine or nitrates. The dose of coenzyme Q10 given was 300 mg/day. Plasma levels of coenzyme Q10 increased markedly during therapy with coenzyme Q10. There was no difference between placebo and coenzyme Q10 on a variety of hemodynamic variables assessed by echocardiography. In addition, there was no difference in well being or functional capacity between treatment with coenzyme Q10 or placebo.[193]

The fifth study assessed the effect of coenzyme Q10 as an adjunct to the treatment of chronic heart failure in 79 patients in a double blind, randomized crossover trial. Patients were 61 years of age on average and 69 of the 79 patients enrolled were male. They had had heart failure of approximately four years duration and just over half had a nonischemic etiology of heart failure. Most patients were on ACE inhibitors, diuretics and digitalis, and the ejection fraction averaged 20%. During the six-month period of study, seven patients died, four during placebo therapy, and three during the coenzyme Q10 period of therapy. Three patients were withdrawn for a variety of reasons. The primary endpoint of the study was ejection fraction. There was a slight increase in ejection fraction during the coenzyme Q10 period that was only statistically significant during volume load (leg lift). Symptom limited maximal exercise tolerance and quality of life also increased slightly, which was statistically significant. The authors conclude that coenzyme Q10 had a significant, but minor adjuvant effect on exercise capacity and symptoms measured as quality of life.[123]

One additional study, that did not meet our inclusion criteria because it enrolled only 55 (instead of a minimum of 60) subjects, is discussed briefly here in response to a specific request from a peer reviewer. This study[124] enrolled 55 patients with New York Heart Association class III or IV symptoms of heart failure and a left ventricular ejection fraction of 40% or less and randomized them to receive 200 mg of coenzyme Q10 or matched placebo in a double-blind trial of 6 months duration. Forty-six patients completed the study. Two patients in the coenzyme Q10 group and one patient in the placebo group died. Compared to baseline values, after six months of therapy there was no improvement in measures of cardiac function, aerobic capacity, exercise duration, or symptoms, despite a 100% increase in serum coenzyme Q10 levels in the blood of subjects taking active treatment.

Summary of the Results Of Coenzyme Q10 Supplementation on Cardiovascular Disease Outcomes

In summary, there have been few studies of the use coenzyme Q10 that have enrolled at least 60 patients and completed at least six months duration of treatment and measured clinical outcomes. A meta-analysis of the effect of coenzyme Q10 on indices of cardiac function concluded that its use was associated with a substantial improvement. This conclusion was not confirmed by two subsequent randomized trials. The studies reporting clinical outcomes yielded mixed results. Two studies reported distinctly favorable clinical outcomes for coenzyme Q10 treated patients. However, one study probably had a serious potential flaw in design and execution in that it is not reported to be placebo controlled or blinded with respect to outcome measurement. The second study is reported in insufficient detail to allow an adequate assessment of the enrolled population or the results. Four subsequent studies reported either no

or clinically small improvements. Therefore, the value of coenzyme Q10 supplementation in patients with cardiovascular disease is still an open question, with neither convincing evidence supporting nor refuting evidence of benefit or harm.

Trials that Report on the Effect of Vitamin C Supplementation on Cardiovascular Disease Outcomes.

As we previously noted, we judged the vitamin C trials to be insufficiently clinically similar in terms of enrolled populations and interventions to justify statistical pooling with meta-analysis. Our review of these trials is therefore narrative. Thirty-seven studies met our initial screening criteria, but many of these enrolled only small numbers of patients or reported only outcomes such as blood levels of antioxidants, oxidative status, and blood vessel reactivity, that are of uncertain relationship to patient clinical outcomes such as death, myocardial infarction, and hospitalization. We concentrated our narrative review, therefore, on only the larger studies that assessed patient clinical outcomes.

We identified four studies that used a placebo-controlled randomized design, assessed the effect of vitamin C on clinical outcomes, included at least 60 patients, and had at least six months of follow-up. The first study,[118] was designated the Multi-Vitamins and Probucol (MVP) Study and assessed the hypothesis that the antioxidant Probucol, a combination of the antioxidants vitamins E and C and beta-carotene, or the combination of both, would reduce the rate and severity of restenosis as assessed by quantitative coronary angiography, within the first six months after angioplasty. The study was double blind and enrolled patients who had been referred for elective coronary angioplasty. Patients received either Probucol or the multi-vitamin complex, which contained 15,000 IU of beta-carotene, 250 milligrams of vitamin C and 350 IU of vitamin E or matched placebo. Patients then received balloon angioplasty according to standard techniques. They also received standard medical coronary interventions including aspirin therapy. Patients had repeat coronary angiography five to seven months after the angioplasty. The primary end point was the extent of restenosis, defined as the reduction in the minimal luminal diameter from the angiogram obtained 15 minutes after the angioplasty, compared to that obtained at follow-up. A total of 317 patients were enrolled. Their average age was between 57 and 60 years of age. Approximately three quarters of the patients were men, 10% had diabetes, about 40% had hypertension, 43% had prior myocardial infarction, and the majority had single or two-vessel disease. There was one death in the placebo treated group and no deaths in the multi-vitamin group, one myocardial infarction in the multi-vitamin group, and none in the placebo group. Five patients underwent CABG in the multi-vitamin group, compared with two in the placebo group, and 19 and 21 patients underwent repeated percutaneous transluminal coronary angioplasty in the multi-vitamin and placebo group, respectively. None of these differences was statistically significant. There was no difference in coronary restenosis comparing the multi-vitamin group to the placebo group. This was in contrast to the Probucol group, which had a marked reduction in the degree of coronary restenosis compared to placebo. Regarding adverse events, more than four times as many patients in the multi-vitamin group reported diarrhea than in the placebo group (7.8% versus 1.6%) and yellow skin pigmentation was observed in 56% of all patients taking multi-vitamins.

The second study also assessed the effects of vitamins E and C, this time on the three-year progression of carotid atherosclerosis. This study,[107] called the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) Study, was a double-blind two-by-two factorial design randomized trial in which subjects were to receive either 91 milligrams of vitamin E twice a day, 250 milligrams of vitamin C twice a day, a combination of these, or placebo. Five hundred and twenty subjects were enrolled and dropouts over the three years were between 10 and 20% in each group. The primary outcome was ultrasound determination of the degree of carotid stenosis. The average age of participants was about 60 years of age, and about 30% of subjects were taking at least one cardiovascular medication. Deaths were few in all groups. One person died in the placebo group, three in the vitamin E group, one in the vitamin C group, and one in the combined vitamin group. There was no significant change in the degree of progression of carotid stenosis in the groups taking either vitamin E or vitamin C alone, but there was a statistically significant halving of the rate of progression in the patients randomized to receive both vitamins. However, this effect was observed only in men, and was most pronounced in smoking men, compared to non-smoking men.

The third study was the HDL-Atherosclerosis Treatment Study (HATS), which enrolled 160 men and women with clinical coronary disease that was defined as previous myocardial infarction, coronary interventions, or confirmed angina. These patients had at least three stenoses of at least 30% of the luminal diameter or one stenosis of at least 50%, low levels of HDL cholesterol and high levels of LDL cholesterol. The participants were then randomized to receive either simvastatin plus niacin or a combination of antioxidant vitamins that included a total daily dose of 800 IU of vitamin E (as d-alpha-tocopherol), 1,000 milligrams of vitamin C, 25 milligrams of natural beta-carotene, and 100 micrograms of selenium, both, or placebo in a 2 X 2 factorial design. All patients also received counseling about weight loss and diet and were encouraged to enter a free, supervised rehabilitation program involving three hours per week of exercise for four months. The duration of treatment was three years. The average age of enrolled patients was 53 years, 13% of subjects were female, 49% had hypertension, 46% were former smokers and 24% were current smokers, 55% had previously had a myocardial infarction, 49% had previously undergone angioplasty, and 16% had diagnosed diabetes. Ninety-one percent of patients completed the angiographic protocol. Two patients died. The effect of antioxidants on blood lipids was null or adverse, with the only statistically significant effect being a 15% lowering of HDL2, the component considered to be most protective. Plasma vitamin concentrations increased significantly in the patients who received active vitamin therapy, and measures of resistance of LDL to oxidation also increased by 35%. The group receiving simvastatin and niacin, but not the group receiving antioxidants, showed significantly lower increases in percent stenosis in proximal arteries at three years. In the placebo therapy group, the mean percent stenosis increased 3.9%, while in the antioxidant therapy group, this value was 1.8%. The percent stenosis decreased in the simvastatin-niacin group, but increased in the group receiving simvastatin-niacin plus antioxidants, raising the possibility of an adverse effect of these antioxidants on simvastatin and niacin therapy.[117]

The fourth and most recent study was the MRC/BHF Heart Protection Study, which assessed antioxidant vitamin supplementation in a randomized placebo controlled trial of 20,536 subjects. Persons were enrolled if they were considered at substantial five-year risk of death from coronary heart disease because of a past medical history of coronary heart disease, other occlusive arterial disease, diabetes mellitus, or treated hypertension alone. Patients were

randomized to receive daily either a combination of antioxidant vitamins including 600 milligrams of synthetic vitamin E, 250 milligrams of vitamin C, and 20 milligrams of beta-carotene or matching placebo. Patients were followed-up for an average of five years with more than 99% of patients completing follow-up. All-cause mortality was slightly increased in the group randomized to receive multi-vitamins, with a death rate ratio of 1.04 (95% confidence intervals 0.97 to 1.12). There were no statistically significant differences between groups in any of the major outcomes, including coronary events, stroke and revascularization. Numerous subgroup analyses and analyses on secondary outcomes failed to demonstrate any sub-population or outcome for which five years of daily supplementation with these multi-vitamins produced either benefit or harm.[94]

Summary of the Results of Vitamin C Supplementation on Cardiovascular Disease Outcomes

In summary, these four studies assessing vitamin C (mostly in combination with vitamin E) provide scant evidence that these combinations of antioxidant supplements have any cardiovascular health benefits. The only reported benefit was in the ASAP Study and that was in an intermediate outcome only, and then only in the sub-population of male smokers. The Heart Protection Study, in particular, due to its size and follow-up provides good evidence that these antioxidant supplements in these doses are unlikely to have any substantial effects on coronary vascular disease outcomes.

Chapter 4. Limitations

Literature

Our search procedures for randomized controlled trials were extensive and included canvassing experts regarding studies we may have missed. In addition, we observed little to no evidence of publication bias via visual inspection or formal testing for the vitamin E studies. However, we acknowledge that publication bias may still exist despite our best efforts to conduct a comprehensive search and the lack of statistical evidence of the existence of bias. Publication bias may occur for a variety of reasons, including investigators' loss of interest in the study if "negative" results are found or if results are obtained that are contrary to the interest of the sponsor or investigator.

Quality of Trials

An important limitation common to many systematic reviews, whether or not a formal meta-analysis is conducted, is the quality of the original studies. Only a third of our trials scored a three or greater using the Jadad method to assess quality. It has been suggested in the literature that there is a possibility of bias in trials that score lower than this. Other elements of the design and execution of studies have been proposed as measures of quality. For example, the Linxian trial was not designed to assess CVD outcomes as its primary purpose, hence the baseline data on CVD was not as complete as some of the other studies. However, recent attempts to define elements of study design and execution that are related to bias have shown that in many cases, such efforts are not reproducible and do not distinguish studies based on their results.

Appropriateness of the Intervention and Population

A proposed explanation for the lack of effect reported in many of the reviewed studies is that the antioxidant was not administered in a sufficient dose or combined with other agents essential for its success, or given for a long enough period of time, or not given to a population sufficiently likely to benefit. One of the explanations given for the GISSI fatal myocardial infarction results is that the vitamin E may have been better absorbed due to the higher fat content of Italian breakfasts. Many of the vitamin C trials have been criticized as administering too low a dose of vitamin C. Both the GISSI study and the HOPE study were stopped early due to evidence of benefit of other intervention arms. It has been suggested that if these studies were allowed to continue longer a benefit of antioxidants would have become more apparent. Some experts have called for new ways to identify populations most likely to benefit, such as selection participants based on some measure of oxidative stress or low levels of antioxidants. The results reported here cannot necessarily be extrapolated to populations and interventions other than those included in the original studies. Whether higher doses or different formulations of antioxidants or using them for a longer duration will prove more effective is unknown. The findings we report here make it less likely, in our view, that a particular population and antioxidant intervention will be found that proves to be markedly beneficial.

Heterogeneity

Heterogeneity existed in the trial design, populations, size, interventions, and outcomes. This affected our ability to pool studies. We made clinical judgments about pooling studies and describe these explicitly. Many reviewers suggested different combinations of studies to pool, or to avoid pooling altogether. We tested other combinations of studies in sensitivity analyses; no difference in results were seen. Furthermore, almost without exception individual studies also failed to demonstrate a benefit of antioxidant supplementation. Therefore, while there was heterogeneity among studies, we do not think our choices for pooling studies introduced significant bias in either direction.

In addition, a large number of trials reported on the effects of vitamin E in various combinations. To the extent that other agents in the formulas had stronger or contradictory effects to the antioxidant of interest, a potential confounder that we cannot control could have been introduced into the analysis, given the available data.

Chapter 5. Conclusions

The available scientific studies offer little evidence that supplementation with vitamin C, vitamin E, or coenzyme Q10 has any benefit on cardiovascular disease prevention or treatment. Indeed, for vitamin E and vitamin C there is good evidence that supplementation at the doses tested provides no benefit, in that large placebo controlled, randomized studies have reported no benefit in terms of all cause mortality, cardiovascular mortality, myocardial infarction, or blood lipids (e.g., the MRC/BHF trial, GISSI, HOPE, PPP, ATBC). Isolated examples of possible benefit for vitamin E or vitamin C supplementation reported for specific outcomes in certain trials failed to be supported by other outcomes in the same trials (for example, the statistically significant beneficial effect of vitamin E supplementation on incidence of nonfatal myocardial infarction observed in the CHAOS trial must be balanced against the nonsignificant increase in fatal myocardial infarction with vitamin E in the same trial) or be confirmed in other trials. This lack of consistency in the evidence casts doubt on any of the reported associations being causal.

There is good evidence that vitamin E supplementation has no clinically important effect on lipid levels.

Regarding coenzyme Q10, the available evidence is much less, in terms of large randomized trials, than for vitamins C or E. Therefore, our conclusions are less definitive. The reported results have been mixed, with a meta-analysis and some individual studies reporting improvements in measures of cardiac function, but other studies reporting no such benefit. The more recent randomized trials report smaller benefits, if any, than older trials. The most that can be concluded at this point is that there is no conclusive evidence either supporting or refuting an effect of coenzyme Q10 on cardiovascular disease.

Chapter 6. Future Research

One outcome of this analysis is the discordant results between the observational data, which suggest that foods high in the selected antioxidants are beneficial, and the majority of the research presented here on supplemental antioxidants. These discordant results could occur for at least two reasons.

The tested antioxidant supplements do not contain the agents responsible for the benefit reported in observational studies.

The observational studies of food consumption are confounded by some other factor that is responsible for the effect. The recent failure of hormone replacement therapy to achieve in an RCT the cardiovascular benefit reported in observational studies has been attributed to confounding in the observational studies, demonstrating that no matter how well designed and how often replicated, confounding must always be considered a possibility.

Therefore, it would seem to us that the thrust of new research into antioxidants and CVD should be randomized trials. These RCTs should consider the following:

Use supplements that are standardized in terms of dose, source and stereoisomers;

Measure clinical outcomes (that include death, MI, hospitalization, quality of life, exercise tolerance, etc.) in addition to intermediate outcomes (levels of antioxidants, blood lipid levels, etc.);

Be conducted over a sufficiently long period of time to see an effect (on the order of years);

Enroll heterogeneous populations so that the results may be extrapolated to the US population (most existing studies have enrolled only or predominantly Caucasian participants).

Such studies may also want to consider:

Testing interventions that have constituents that more closely mimic the chemical constituents of the foods reported to have protective benefits.

Assessing whether any agreement can be reached among exports in the field regarding dose and formulation so that in the event no benefit is observed in the trial the study will not be subject to post hoc criticism that inadequate doses and/or formulations were tested.

Assessing whether patients should be selected for the trial on some basis other than presence of CVD or risk factors for CVD. For example, it has been proposed that antioxidants may be most beneficial in subjects with low levels of antioxidants and/or have high oxidative stress.

No doubt such RCTs will be expensive to conduct and take years to produce their results. However, the pay off for successful completion of such a trial is usually a definitive answer to a clinical question (for example, the MRC/BHF study, the HOPE study, the HERS trial,[194] and the ALLHAT[195] study).

With regard to what antioxidant supplements study, the results reported here leave us less than enthusiastic about vitamin E or vitamin C as individual agents having any substantial clinical benefit. There have been several trials of coenzyme Q10 that report favorable clinical

outcomes other than death, but methods or reporting problems preclude us drawing conclusions. Of note, coenzyme Q10 is the only one of the three supplements we assessed not to have been subjected to a major RCT enrolling thousands of patients. Consideration must also be given to ongoing trials of antioxidants, in order to avoid repetition. Identifying all of these and their expected completion dates was beyond the scope of this study, but must be known to experts in the field, such as those who would be assembled by NCCAM to make recommendations about a research agenda.

Lastly, independent of the above, something in the observational studies was associated with substantial cardiovascular benefit, and a careful study of the behaviors of individuals who consume fruits and vegetables containing antioxidants may also be worthwhile."

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1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Anderson 1974a Study 1	Named trial:	Other	1	Placebo Placebo for 9 Weeks	N entered: N analyzed:	24 18	Excluded from statistical analysis because no outcomes of interest were reported. No significant effect of vitamin E on angina symptoms.
	Design:	RCT	2	Vitamin E 3200 IU orally for 9 Weeks	N entered: N analyzed:	24 15	
	Jadad:	5					
	Population:	Unspecified					
	Condition:	Angina					
Anderson 1974a Study 2	Named trial:	Other	1	Placebo Placebo for 9 Weeks	N entered: N analyzed:	10 4	Excluded from statistical analysis because no outcomes of interest were reported. No significant effect of vitamin E on angina symptoms.
	Design:	RCT	2	Vitamin E Dose N/A orally for 9 weeks	N entered: N analyzed:	10 6	
	Jadad:	5					
	Population:	Unspecified					
	Condition:	Angina					
Anderson 1974b	Named trial:	Other	1	Placebo Placebo for 9 Weeks	N entered: N analyzed:	18 N/A	Excluded from statistical analysis because no outcomes of interest were reported. No significant effect of vitamin E on angina symptoms.
	Design:	RCT	2	Vitamin E 3200 IU orally for 9 Weeks	N entered: N analyzed:	18 N/A	
	Jadad:	5					
	Population:	Unspecified					
	Condition:	CAD, angina					

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
Anderson 1999	Named trial: Other Design: CCT Jadad: 0 Population: Unspecified Condition: CAD	1	Placebo Placebo for 8 Weeks	N entered: 20 N analyzed: 16	Excluded from meta-analysis of lipids due to study design. Antioxidant combination group showed significant reduction in LDL oxidation as compared to placebo.
		2	Vitamin C 1000 mg orally for 12 Weeks Vitamin E 800 IU orally for 12 Weeks Beta-carotene 24 mg orally for 12 Weeks	N entered: 20 N analyzed: 18	
Boaz 2000	Named trial: SPACE Design: RCT Jadad: 4 Population: Unspecified Condition: CAD, CVA/TIA, PVD, angina	1	Placebo Placebo for 26 Months	N entered: 99 N analyzed: 99	Included in meta-analysis of death and MI.
		2	Vitamin E 800 IU orally for 26 Months	N entered: 97 N analyzed: 97	
Brown 1994	Named trial: Other Design: CCT Jadad: 2 Population: Unspecified Condition:CAD, LDL oxidation	1	Placebo Placebo for 10 Weeks	N entered: N/A N analyzed: N/A	Included in meta-analysis of lipids.
		2	Vitamin E 280 mg orally for 10 Weeks	N entered: N/A N analyzed: N/A	

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
Brown 2001	Named trial: HATS Design: RCT Jadad: 4 Population: Unspecified Condition: CAD, CVA/TIA, angina	1	Placebo Placebo for 3 Years	N entered: N/A N analyzed: 34	Included in meta-analysis of death and MI. Excluded from meta-analysis of lipids due to insufficient followup time.
		2	Niacin Dose N/A orally for 3 years Statin drug Dose N/A orally for 3 years	N entered: N/A N analyzed: 33	
		3	Vitamin E 800 IU orally for 3 Years Vitamin C 1000 mg orally for 3 Years Beta-carotene 25 mg orally for 3 Years Selenium 100 µg orally for 3 Years	N entered: N/A N analyzed: 39	
		4	Selenium 100 µg orally for 3 Years Beta-carotene 25 mg orally for 3 Years Vitamin E 800 IU orally for 3 Years Vitamin C 1000 mg orally for 3 Years Niacin Dose N/A orally for 3 years Statin drug Dose N/A orally for 3 years	N entered: N/A N analyzed: 40	

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
Chamiec 1996	Named trial: Other Design: RCT Jadad: 2 Population: Unspecified Condition: CAD	1	Control or Usual care No dosage data reported	N entered: N/A N analyzed: 28	Excluded from statistical analysis because no outcomes of interest were reported. Significant decrease in measures of myocardial free radical injury among group treated with vitamins E and C.
		2	Vitamin C 600 mg orally for 14 Days Vitamin E 600 mg orally for 14 Days	N entered: N/A N analyzed: 33	
Chello 1994	Named trial: Other Design: RCT Jadad: 2 Population: Unspecified Condition: CAD	1	Control or Usual care No dosage data reported	N entered: 20 N analyzed: 20	Excluded from statistical analysis because no outcomes of interest were reported. Significant decrease in rate of arrhythmias and improvement in some measures of hemodynamics in Co-Q10 group following bypass surgery.
		2	Co-Q10 150 mg orally for 7 Days	N entered: 20 N analyzed: 20	
Chello 1996	Named trial: Other Design: RCT Jadad: 3 Population: Unspecified Condition:Reperfusion injury	1	Placebo Placebo for 7 Days	N entered: 15 N analyzed: 15	Excluded from statistical analysis because no outcomes of interest were reported. Statistically significant decrease in muscle reperfusion injury measures after cross-clamping of abdominal aortae intraoperatively in subjects pre-treated with Co-Q10.
		2	Co-Q10 150 mg orally for 7 Days	N entered: 15 N analyzed: 15	

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Chen 1994	Named trial:	Other	1	Placebo Placebo for 6 Days	N entered: N analyzed:	11 11	Excluded from statistical analysis because no outcomes of interest were reported. Significant improvement in some, but not all, measures of hemodynamics in Co-Q10 group following cardiovascular surgery.
	Design:	RCT	2	Co-Q10 150-200 mg orally for 6 Days	N entered: N analyzed:	11 11	
	Jadad:	2					
	Population:	Unspecified					
	Condition:	CAD					
de Lorgeril 1994	Named trial:	Other	1	Control or Usual care Control or Usual care for 2 Months	N entered: N analyzed:	10 10	Included in meta-analysis of lipids.
	Design:	RCT	2	Vitamin E 500 IU orally for 2 Months	N entered: N analyzed:	10 10	
	Jadad:	1					
	Population:	Unspecified					
	Condition:	CAD					
De Waart 1997	Named trial:	Other	1	Placebo Placebo for 3 Months	N entered: N analyzed:	41 41	Included in meta-analysis of lipids.
	Design:	RCT	2	Vitamin E 100 IU orally for 3 Months	N entered: N analyzed:	42 41	
	Jadad:	3					
	Population:	Elderly (over 65)					
	Condition:	CAD					

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
DeMaio 1992	Named trial: Other Design: RCT Jadad: 2 Population: Unspecified Condition: CAD, reperfusion injury	1	Placebo Placebo for 4 Months	N entered: N/A N analyzed: 48	Included in meta-analysis of lipids.
		2	Vitamin E 1200 IU orally for 4 Months	N entered: N/A N analyzed: 52	
Di Somma 1991	Named trial: Other Design: RCT Jadad: 2 Population: Unspecified Condition: CAD, CHF	1	Control or Usual care No dosage data reported	N entered: 318 N analyzed: 306	Excluded from meta-analysis of death due to insufficient statistics. Excluded from meta-analysis of lipids as not relevant intervention. Significant improvement in heart failure and angina was found from Co-Q10.
		2	Co-Q10 100 mg orally for 24 Weeks	N entered: 488 N analyzed: 466	
Dieber-Rotheneder 1991	Named trial: Other Design: CCT Jadad: 0 Population: Unspecified Condition: CAD, LDL oxidation	1	Placebo Placebo for 21 Days	N entered: 4 N analyzed: 4	Excluded from meta-analysis of lipids due to insufficient statistics. Vitamin E group showed significant reduction in LDL oxidation as compared to placebo.
		2	Vitamin E 150 IU orally for 21 Days	N entered: 2 N analyzed: 2	
		3	Vitamin E 225 IU orally for 21 Days	N entered: 2 N analyzed: 2	
		4	Vitamin E 800 IU orally for 21 Days	N entered: 2 N analyzed: 2	
		5	Vitamin E 1200 IU orally for 21 Days	N entered: 2 N analyzed: 2	

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Digiesi 1990	Named trial:	Other	1	Placebo Placebo for 10 Weeks	N entered: N analyzed:	18 18	Excluded from statistical analysis because no outcomes of interest were reported. Statistically significant decrease in blood pressure in Co-Q10 group.
	Design:	RCT	2	Co-Q10 100 mg orally for 10 Weeks	N entered: N analyzed:	18 18	
	Jadad:	1					
	Population:	Unspecified					
	Condition:	HTN					
Duffy 1999	Named trial:	Other	1	Placebo Placebo for 1 Day Placebo Placebo for 30 Days	N entered: N analyzed:	23 20	Excluded from statistical analysis because no outcomes of interest were reported. Significant decrease in systolic blood pressure in vitamin C group.
	Design:	RCT					
	Jadad:	3	2	Vitamin C 2 gm orally for 1 Day Vitamin C 500 mg orally for 30 Days	N entered: N analyzed:	22 19	
	Population:	Unspecified					
	Condition:	CAD, HTN					
Duffy 2001	Named trial:	Other	1	Placebo Placebo for 1 Day Placebo Placebo for 1 Month	N entered: N analyzed:	20 20	Excluded from statistical analysis because no outcomes of interest were reported. Chronic vitamin C therapy group exhibited significantly lowered systolic and mean blood pressure.
	Design:	RCT					
	Jadad:	2	2	Vitamin C 2 gm orally for 1 Day Vitamin C 500 mg orally for 1 Month	N entered: N analyzed:	19 19	
	Population:	Unspecified					
	Condition:	HTN					

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Duthie 1991	Named trial:	Other	1	Placebo Placebo for 14 Days	N entered: N analyzed:	10 10	Excluded from meta-analysis of lipids due to insufficient statistics. Vitamin E group showed no significant difference in total cholesterol among male smokers.
	Design:	CCT	2	Vitamin E 1000 mg orally for 14 Days	N entered: N analyzed:	10 10	
	Jadad:	0					
	Population:	Unspecified					
	Condition:	N/A					
Fuller 1996a	Named trial:	Other	1	Placebo Placebo for 4 Weeks	N entered: N analyzed:	9 9	Excluded from statistical analysis because no outcomes of interest were reported. Significant reduction in LDL oxidation among vitamin C group.
	Design:	RCT	2	Vitamin C 1000 mg orally for 4 Weeks	N entered: N analyzed:	10 10	
	Jadad:	1					
	Population:	Smokers					
	Condition:	CAD					
Fuller 1996b	Named trial:	Other	1	Placebo Placebo for 8 Weeks	N entered: N analyzed:	13 13	Included in meta-analysis of lipids.
	Design:	RCT	2	Vitamin E 1200 IU orally for 8 Weeks	N entered: N analyzed:	15 15	
	Jadad:	1					
	Population:	Unspecified					
	Condition:CAD, LDL oxidation						
Galley 1997	Named trial:	Other	1	Placebo Placebo for 8 Weeks	N entered: N analyzed:	40 38	Excluded from statistical analysis because no outcomes of interest were reported. Significantly reduced blood pressure levels among those in group receiving high-dose combinations of antioxidants including vitamins C and E.
	Design:	RCT	2	Vitamin C 500 mg orally for 8 Weeks Vitamin E 600 mg orally for 8 Weeks	N entered: N analyzed:	40 38	
	Jadad:	5					

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
	Population:	Unspecified		Beta-carotene 30 mg orally for 8 Weeks			
	Condition:	HTN		Multi-vitamin Multi-vitamin orally for 8 Weeks			
Gatto 1996	Named trial:	Other	1	Placebo Placebo for 4 Weeks	N entered: N analyzed:	10 10	Excluded from meta-analysis of lipids as not relevant intervention. Vitamin C group showed significant improvements in lipid profiles after 4 weeks of therapy.
	Design:	RCT	2	Vitamin C 1000 mg orally for 4 Weeks	N entered: N analyzed:	10 10	
	Jadad:	2					
	Population:	Female					
	Condition:	CAD					
Ghatak 1996	Named trial:	Other	1	Placebo Placebo for 4 Weeks	N entered: N analyzed:	7 7	Excluded from statistical analysis because no outcomes of interest were reported. Significant reduction in measures of antioxidant stress among vitamin E group.
	Design:	RCT	2	Vitamin E 400 mg orally for 4 Weeks	N entered: N analyzed:	5 5	
	Jadad:	1					
	Population:	Unspecified					
	Condition:	CHF					
Gillilan 1977	Named trial:	Other	1	Placebo Placebo for 6 Months	N entered: N analyzed:	52 48	Excluded from meta-analysis of death due to insufficient followup time. No change in exercise capacity, angina or cardiac function were found with the use of vitamin E.
	Design:	RCT	2	Vitamin E 1600 IU orally for 6 Months	N entered: N analyzed:	52 48	
	Jadad:	3					
	Population:	Unspecified					
	Condition:	CAD					

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
GISSI 1999	Named trial: GISSI/GIZZI Design: RCT Jadad: 3 Population: Unspecified Condition: CAD, CVA/TIA	1	Placebo Placebo for 3.5 Years	N entered: 2828 N analyzed: 2809	Included in meta-analysis of death and MI. Excluded from meta-analysis of lipids due to heterogeneous sample-size.
		2	n3 PUFA 1 gm orally for 3.5 Years	N entered: 2836 N analyzed: 2065	
		3	Vitamin E 300 mg orally for 3.5 Years	N entered: 2830 N analyzed: 2128	
		4	Vitamin E 300 mg orally for 3.5 Years n3 PUFA 1 gm orally for 3.5 Years	N entered: 2830 N analyzed: 1170	
Guetta 1995	Named trial: Other Design: RCT Jadad: 1 Population: Female Condition: CAD	1	17 beta estradiol 0.1 mg 3 for 3 Weeks	N entered: 9 N analyzed: 9	Excluded from meta-analysis of lipids due to no placebo arm. Both vitamin E and hormonal therapy groups showed significant reductions in LDL oxidation.
		2	Vitamin E 800 IU orally for 6 Weeks	N entered: 10 N analyzed: 10	
		3	Vitamin E 800 IU orally for 6 Weeks 17 beta estradiol 0.1 mg 3 for 3 Weeks	N entered: 19 N analyzed: 19	
Haeger 1968	Named trial: Other Design: CCT Jadad: 0 Population: Unspecified Condition: PVD	1	Vasodilators Dose N/A orally for 7 years	N entered: 37 N analyzed: N/A	Included in meta-analysis of death.
		2	Coumadin Dose N/A orally for 7 years	N entered: 44 N analyzed: N/A	
		3	Multi-vitamin Multi-vitamin orally for 7 Years	N entered: 42 N analyzed: N/A	
		4	Vitamin E 300 mg orally for 7 Years	N entered: 104 N analyzed: N/A	

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1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
Haeger 1973	Named trial: Other Design: CCT Jadad: 0 Population: Unspecified Condition: PVD	1	Control or Usual care No dosage data reported	N entered: N/A N analyzed: 14	Excluded from statistical analysis because no outcomes of interest were reported. Significant improvement in walking distance with vitamin E among subjects with intermittent claudication.
		2	Vitamin E 300 mg orally for 5 Years	N entered: N/A N analyzed: 33	
Haeger 1974	Named trial: Other Design: CCT Jadad: 0 Population: Unspecified Condition: CAD, PVD	1	Control or Usual care No dosage data reported	N entered: N/A N analyzed: N/A	Excluded from statistical analysis because no outcomes of interest were reported. Significant improvement in claudication symptoms among vitamin E group.
		2	Vitamin E 300 mg orally for 3.5 Years	N entered: N/A N analyzed: N/A	
Hamabe 2001	Named trial: Other Design: RCT Jadad: 1 Population: Unspecified Condition: CAD, angina	1	Placebo Placebo for 0.33 Hours	N entered: 17 N analyzed: 17	Excluded from statistical analysis because no outcomes of interest were reported. No effect of vitamin C on blood pressure.
		2	Vitamin C 1000 mg intravenously for 0.33 Hours	N entered: 17 N analyzed: 17	
Harats 1990	Named trial: Other Design: CCT Jadad: 0	1	Control or Usual care Control or Usual care for 4 Weeks	N entered: 3 N analyzed: 3	Excluded from meta-analysis of lipids due to insufficient statistics. Both vitamin E and hormonal therapy groups showed significant reductions in LDL oxidation.
		2	Vitamin C 1.5 gm orally for 4 Weeks	N entered: 3 N analyzed: 3	

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
			3	Vitamin E	N entered:	4	
	Population:	Smokers		600 mg orally for 4 Weeks	N analyzed:	4	
	Condition:	CAD					
Herbaczynska-Cedro 1995	Named trial:	Other	1	Control or Usual care Control or Usual care for 14 Days	N entered: N analyzed:	22 22	Excluded from statistical analysis because no outcomes of interest were reported. Vitamin C and E group showed significantly lower measures of lipid oxidation and free radical production.
	Design:	RCT	2	Vitamin C 600 mg orally for 14 Days Vitamin E 600 mg orally for 14 Days	N entered: N analyzed:	23 23	
	Jadad:	1					
	Population:	Unspecified					
	Condition:	CAD					
Hiasa 1984	Named trial:	Other	1	Placebo Placebo for 7 Days	N entered: N analyzed:	6 6	Excluded from statistical analysis because no outcomes of interest were reported. Improvement in exercise tolerance with Co-Q10 among subjects with stable angina.
	Design:	CCT	2	Co-Q10 1.5 mg/kg intravenously for 7 Days	N entered: N analyzed:	12 12	
	Jadad:	2					
	Population:	Unspecified					
	Condition:	CAD, angina					
Hoffman 1999	Named trial:	Other	1	Placebo Placebo for 6 Months	N entered: N analyzed:	12 11	Included in meta-analysis of lipids.
	Design:	RCT	2	Vitamin E 400 mg orally for 6 Months	N entered: N analyzed:	27 22	
	Jadad:	2					
	Population:	Unspecified					
	Condition:	CAD, LDL oxidation					

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size	Summary of Results
Hofman-Bang 1992	Named trial:	Other	1	Placebo Placebo for 3 Months	N entered: 7 N analyzed: N/A	Excluded from statistical analysis because no outcomes of interest were reported. Co-Q10 group showed significant improvements in some, not all, measures of exercise hemodynamics with no change in hemodynamics at rest among heart failure subjects.
	Design:	RCT	2	Co-Q10 100 mg orally for 3 Months	N entered: 11 N analyzed: N/A	
	Jadad:	2				
	Population:	Unspecified				
	Condition:	CHF				
Hofman-Bang 1995	Named trial:	Other	1	Placebo Placebo for 3 Months	N entered: 79 N analyzed: 69	Excluded from meta-analysis of death due to insufficient statistics. Significant improvements in some, but not all, measures of hemodynamics and significant improvements in quality of life in the Co-Q10 group among subjects with heart failure.
	Design:	RCT	2	Co-Q10 100 mg orally for 3 Months	N entered: 79 N analyzed: 69	
	Jadad:	3				
	Population:	Unspecified				
	Condition:	CHF				
(HPSCG, Heart Protection Study Collaborative Group, 2002)	Named trial:	MRC/BHF	1	Placebo Placebo for 5 Years	N entered: 10267 N analyzed: 10228	Included in meta-analysis of death and MI. Excluded from meta-analysis of lipids due to heterogeneous sample-size.
	Design:	RCT	2	Vitamin E 600 mg orally for 5 Years Vitamin C 250 mg orally for 5 Years Beta-carotene 020 mg orally for 5 Years	N entered: 10269 N analyzed: 10241	
	Jadad:	5				
	Population:	Unspecified				
	Condition:	CAD				

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
Iarussi 1994	Named trial: Other Design: RCT Jadad: 2 Population: Children (under 18) Condition: Cardiotoxicity	1	Control or Usual care No dosage data reported	N entered: 10 N analyzed: 10	Excluded from statistical analysis because no outcomes of interest were reported. Statistically significant reduction in cardiotoxicity from anthracycline hemotherapy among Co-Q10 group.
		2	Co-Q10 200 mg orally duration N/A	N entered: 10 N analyzed: 10	
Iino 1977	Named trial: Other Design: CCT Jadad: 2 Population: Unspecified Condition: CVA/TIA, HTN	1	Placebo Placebo for 4 Weeks	N entered: 48 N analyzed: 45	Excluded from meta-analysis of lipids as not relevant outcome. Symptoms of cerebrovascular disease and hypertension were decreased in vitamin E group as compared to placebo.
		2	Vitamin E 600 mg orally for 4 Weeks	N entered: 46 N analyzed: 44	
Inagaki 1978	Named trial: Other Design: CCT Jadad: 2 Population: Unspecified Condition: CAD, CVA/TIA, PVD, HTN	1	Placebo Placebo for 5 Weeks	N entered: 37 N analyzed: 37	Excluded from statistical analysis because no outcomes of interest were reported. Significant effect of vitamin E on several measures of cardiac symptoms and function including hypertension.
		2	Vitamin E 600 mg orally for 5 Weeks	N entered: 40 N analyzed: 38	

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Inal 1997	Named trial:	Other	1	17 beta estradiol 0.05 gm 3 for 6 Months	N entered: N analyzed:	22 22	Excluded from meta-analysis of lipids due to no placebo arm. All groups showed significant reductions in lipid levels.
	Design:	RCT	2	17 beta estradiol 0.05 gm 3 for 6 Months Progesterone 10 mg orally for 10 Days	N entered: N analyzed:	22 22	
	Jadad:	1					
	Population:	Female	3	Vitamin E 600 mg orally for 6 Months 17 beta estradiol 0.05 gm 3 for 6 Months Progesterone 10 mg orally for 10 Days	N entered: N analyzed:	22 22	
	Condition:	CAD					
Jain 1996	Named trial:	Other	1	Placebo Placebo for 3 Months	N entered: N analyzed:	N/A 16	Included in meta-analysis of lipids.
	Design:	CCT	2	Vitamin E 100 IU orally for 3 Months	N entered: N analyzed:	N/A 13	
	Jadad:	2					
	Population:	Unspecified					
	Condition:	CAD					
Jialal 1992	Named trial:	Other	1	Placebo Placebo for 12 Weeks	N entered: N analyzed:	12 12	Included in meta-analysis of lipids.
	Design:	RCT	2	Vitamin E 800 IU orally for 12 Weeks	N entered: N analyzed:	12 12	
	Jadad:	1					
	Population:	Unspecified					
	Condition:	CAD					

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
Jialal 1993	Named trial: Other Design: RCT Jadad: 1 Population: Unspecified Condition: CAD	1	Placebo Placebo for 12 Weeks	N entered: 12 N analyzed: 12	Included in meta-analysis of lipids.
		2	Vitamin E 800 IU orally for 12 Weeks Vitamin C 1 gm orally for 12 Weeks Beta-carotene 30 mg orally for 12 Weeks	N entered: 12 N analyzed: 12	
Jialal 1995	Named trial: Other Design: RCT Jadad: 1 Population: Unspecified Condition:CAD, LDL oxidation	1	Placebo Placebo for 8 Weeks	N entered: 8 N analyzed: 8	Included in meta-analysis of lipids.
		2	Vitamin E 60 IU orally for 8 Weeks	N entered: 8 N analyzed: 8	
		3	Vitamin E 200 IU orally for 8 Weeks	N entered: 8 N analyzed: 8	
		4	Vitamin E 400 IU orally for 8 Weeks	N entered: 8 N analyzed: 8	
		5	Vitamin E 800 IU orally for 8 Weeks	N entered: 8 N analyzed: 8	
		6	Vitamin E 1200 IU orally for 8 Weeks	N entered: 8 N analyzed: 8	
Judy 1986a	Named trial: Other Design: CCT Jadad: 0 Population: Unspecified Condition: CHF	1	Control or Usual care Control or Usual care for 3 Years	N entered: 55 N analyzed: N/A	Excluded from meta-analysis of death as not relevant intervention. Co-Q10 significantly improved measures of cardiac function and survival among heart failure subjects.
		2	Co-Q10 100 mg orally for 3 Years	N entered: 55 N analyzed: N/A	

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
Judy 1986b	Named trial: Other Design: RCT Jadad: 4 Population: Unspecified Condition: CHF	1	Placebo Placebo for 90 Days	N entered: 14 N analyzed: 10	Excluded from meta-analysis of death as not relevant intervention. Co-Q10 significantly improved measures of cardiac function among heart failure subjects.
		2	Co-Q10 100 mg orally for 90 Days	N entered: 14 N analyzed: 10	
Judy 1991	Named trial: Other Design: CCT Jadad: 0 Population: Unspecified Condition: CHF	1	Control or Usual care Control or Usual care for 8 Years	N entered: 90 N analyzed: N/A	Excluded from meta-analysis of death as not relevant intervention. Co-Q10 significantly improved measures of cardiac function and survival among heart failure subjects.
		2	Co-Q10 100 mg orally for 8 Years	N entered: 90 N analyzed: N/A	
Judy 1993	Named trial: Other Design: RCT Jadad: 2 Population: Unspecified Condition: CAD, reperfusion injury	1	Placebo Placebo for 44 Days	N entered: 10 N analyzed: 10	Excluded from statistical analysis because no outcomes of interest were reported. Significant improvement in some, but not all, hemodynamic measures among Co-Q10 group following cardiovascular surgery.
		2	Co-Q10 100 mg orally for 44 Days	N entered: 10 N analyzed: 10	

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
Kaikkonen 1997	Named trial: MASIT Design: RCT Jadad: 3 Population: Smokers Condition: CAD	1	Placebo Placebo for 2 Months	N entered: 20 N analyzed: N/A	Excluded from statistical analysis because no outcomes of interest were reported. No significant impact of Co-Q10 on LDL oxidation.
		2	Co-Q10 90 mg orally for 2 Months	N entered: 20 N analyzed: N/A	
		3	Co-Q10 90 mg orally for 2 Months	N entered: 20 N analyzed: N/A	
Kaikkonen 1998	Named trial: Other Design: RCT Jadad: 3 Population: Unspecified Condition:CAD, LDL oxidation	1	Placebo Placebo for 3 Weeks	N entered: 19 N analyzed: 18	Excluded from meta-analysis of lipids as not relevant outcome. The combination of Co-Q10 and vitamin E significantly decreased LDL oxidation at rest, but had no effect on lipid oxidation after vigorous exercise.
		2	Co-Q10 90 mg orally for 3 Weeks Vitamin E 13.5 mg orally for 3 Weeks	N entered: 18 N analyzed: 18	
Kaikkonen 2000 Study 1	Named trial: Other Design: RCT Jadad: 2 Population: Unspecified Condition: CAD	1	Placebo Placebo for 3 Months	N entered: 10 N analyzed: 10	Included in meta-analysis of lipids.
		2	Vitamin E 700 mg orally for 3 Months Co-Q10 200 mg orally for 3 Months	N entered: 10 N analyzed: 10	
		3	Co-Q10 200 mg orally for 3 Months	N entered: 10 N analyzed: 10	
		4	Vitamin E 700 mg orally for 3 Months	N entered: 10 N analyzed: 10	

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Kaikkonen 2000 Study 2	Named trial:	Other	1	Placebo Placebo for 7 Days	N entered: N analyzed:	10 10	Excluded from meta-analysis of lipids as not relevant intervention. There was no significant change in lipid levels among any of the treatment groups.
	Design:	RCT	2	Co-Q10 90 mg orally for 7 Days	N entered: N analyzed:	10 10	
	Jadad:	1					
	Population:	Unspecified					
	Condition:	CAD					
Kamikawa 1985	Named trial:	Other	1	Placebo Placebo for 4 Weeks	N entered: N analyzed:	12 12	Excluded from statistical analysis because no outcomes of interest were reported. Statistically significant increased exercise tolerance found among subjects in Co-Q10 group.
	Design:	RCT	2	Co-Q10 150 mg orally for 4 Weeks	N entered: N analyzed:	12 12	
	Jadad:	2					
	Population:	Unspecified					
	Condition:	CAD, angina					

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Keith 2000	Named trial:	Other	1	Placebo Placebo for 12 Weeks	N entered: N analyzed:	N/A N/A	Excluded from statistical analysis because no outcomes of interest were reported. No effect of vitamin E on quality of life or measures of oxidative stress among subjects with heart failure.
	Design:	RCT	2	Vitamin E 1000 IU orally for 12 Weeks	N entered: N analyzed:	N/A N/A	
	Jadad:	1					
	Population:	Unspecified					
	Condition:	CHF					
Keith 2001	Named trial:	Other	1	Placebo Placebo for 12 Weeks	N entered: N analyzed:	30 30	Excluded from statistical analysis because no outcomes of interest were reported. No statistically significant effects of vitamin E on cardiac function and quality of life among heart failure subjects.
	Design:	RCT	2	Vitamin E 500 IU orally for 12 Weeks	N entered: N analyzed:	26 26	
	Jadad:	4					
	Population:	Unspecified					
	Condition:	CHF					
Khatta 2000	Named trial:	Other	1	Placebo Placebo for 6 Months	N entered: N analyzed:	27 23	Excluded from meta-analysis of death due to insufficient statistics. No improvement with Co-Q10 over standard treatment in subjects with heart failure.
	Design:	RCT	2	Co-Q10 200 mg orally for 6 Months	N entered: N analyzed:	28 23	
	Jadad:	4					
	Population:	Unspecified					
	Condition:	CHF					

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Kuklinski 1994	Named trial:	Other	1	Placebo Placebo for 1 Year	N entered: N analyzed:	29 29	Excluded from meta-analysis of death as not relevant intervention. Excluded from meta-analysis of MI due to insufficient statistics. Antioxidant group showed no significant difference in post-MI complications, and fewer deaths at long term followup.
	Design:	RCT	2	Co-Q10 100 mg orally for 1 Year Selenium 100 µg orally for 1 Year	N entered: N analyzed:	32 32	
	Jadad:	2					
	Population:	Unspecified					
	Condition:	CAD					
Langsjoen 1985a	Named trial:	Other	1	Placebo Placebo for 12 Weeks	N entered: N analyzed:	N/A 19	Excluded from statistical analysis because no outcomes of interest were reported. Statistically significant improvement in hemodynamics with Co-Q10 among heart failure subjects.
	Design:	RCT	2	Co-Q10 99 mg orally for 12 Weeks	N entered: N analyzed:	N/A 19	
	Jadad:	3					
	Population:	Unspecified					
	Condition:	CHF					
Langsjoen 1985b	Named trial:	Other	1	Placebo Placebo for 12 Weeks	N entered: N analyzed:	19 19	Excluded from statistical analysis because no outcomes of interest were reported. Statistically significant improvement in cardiac function with Co-Q10 among heart failure subjects.
	Design:	RCT	2	Co-Q10 100 mg orally for 12 Weeks	N entered: N analyzed:	19 19	
	Jadad:	2					
	Population:	Unspecified					
	Condition:	CHF					
Lankin 2000	Named trial:	Other	1	Statin drug 40 mg orally for 6 Months Placebo Placebo for 6 Months	N entered: N analyzed:	N/A N/A	Excluded from meta-analysis of lipids as not relevant intervention. Co-Q10 prevented statin-induced increase in LDL oxidation as compared to placebo.
	Design:	RCT	2	Statin drug 40 mg orally for 6 Months	N entered: N analyzed:	N/A N/A	
	Jadad:	2					

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1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size	Summary of Results
	Population:	Unspecified		Co-Q10 60 mg orally for 6 Months		
	Condition:	CAD				
Leppala 2000a	Named trial:	ATBC	1	Placebo Placebo for 6 Years	N entered: 7153 N analyzed: 6901	Excluded from meta-analysis of death as primary prevention study. ATBC study for vitamin E had small significant increase in fatal hemorrhagic stroke risk, non-significant reduction in stroke risk, no effect on incidence or mortality from total strokes.
	Design:	RCT	2	Vitamin E 50 mg orally for 6 Years	N entered: 7120 N analyzed: 6869	
	Jadad:	3	3	Beta-carotene 20 mg orally for 6 Years	N entered: 7128 N analyzed: 6832	
	Population:	Smokers	4	Vitamin E 50 mg orally for 6 Years Beta-carotene 20 mg orally for 6 Years	N entered: 7118 N analyzed: 6860	
	Condition:	CVA/TIA				
Leppala 2000b	Named trial:	ATBC	1	Placebo Placebo for 6 Years	N entered: 7153 N analyzed: N/A	Excluded from meta-analysis of death due to insufficient statistics. The ATBC study for vitamin E showed a small but significant increase in risk of hemorrhagic stroke, a significant reduction in risk of stroke among hypertensive men.
	Design:	RCT	2	Beta-carotene 20 mg orally for 6 Years	N entered: 7128 N analyzed: N/A	
	Jadad:	3	3	Vitamin E 50 mg orally for 6 Years	N entered: 7120 N analyzed: N/A	
	Population:	Smokers	4	Vitamin E 50 mg orally for 6 Years Beta-carotene 20 mg orally for 6 Years	N entered: 7118 N analyzed: N/A	
	Condition:	CVA/TIA				
Mark 1998	Named trial:	Linxian	1	Placebo Placebo for 5.25 Years	N entered: N/A N analyzed: N/A	Excluded from meta-analysis of death as primary prevention study. Reductions in total mortality was found among the group receiving vitamin E in combination with other antioxidants. No improvement was found in blood pressure.
	Design:	RCT	2	Niacin 40 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years	N entered: N/A N analyzed: N/A	
	Jadad:	1				
	Population:	Unspecified				

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size		Summary of Results
	Condition: CVA/TIA, HTN	3	Vitamin C 120 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years	N entered: N analyzed:	N/A N/A	
		4	Vitamin C 120 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years	N entered: N analyzed:	N/A N/A	
		5	Vitamin E 30 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years	N entered: N analyzed:	N/A N/A	
		6	Vitamin C 120 mg orally for 5.25 Years Vitamin E 30 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years	N entered: N analyzed:	N/A N/A	
		7	Vitamin C 120 mg orally for 5.25 Years Vitamin E 30 mg orally for 5.25 Years Multi-vitamin Multi-vitamin orally for 5.25 Years	N entered: N analyzed:	N/A N/A	
		8	Vitamin E 30 mg orally for 5.25 Years	N entered: N analyzed:	N/A N/A	

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
			Multi-vitamin Multi-vitamin orally for 5.25 Years		
Mazzola 1987	Named trial: Other Design: RCT Jadad: 2 Population: Unspecified Condition: CHF, angina	1	Placebo Placebo for 4 Weeks	N entered: 20 N analyzed: 20	Excluded from statistical analysis because no outcomes of interest were reported. Significant reduction of anginal symptoms and heart failure scores and improved effort tolerance among Co-Q10 group.
		2	Co-Q10 60 mg orally for 4 Weeks	N entered: 20 N analyzed: 20	
McDowell 1994	Named trial: Other Design: RCT Jadad: 2 Population: Unspecified Condition: CAD, LDL oxidation	1	Placebo Placebo for 8 Weeks Statin drug 20 mg orally for 8 Weeks	N entered: 8 N analyzed: 8	Included in meta-analysis of lipids.
		2	Probucol 1000 mg orally for 8 Weeks Statin drug 20 mg orally for 8 Weeks	N entered: 8 N analyzed: 8	
		3	Vitamin E 400 IU orally for 8 Weeks Statin drug 20 mg orally for 8 Weeks	N entered: 8 N analyzed: 8	
McGavin 2001	Named trial: Other Design: RCT Jadad: 3 Population: Unspecified Condition: CAD	1	Placebo Placebo for 8 Weeks	N entered: 40 N analyzed: 35	Included in meta-analysis of lipids.
		2	Vitamin E 28 IU orally for 8 Weeks	N entered: 40 N analyzed: 37	
		3	Vitamin E 200 IU orally for 8 Weeks	N entered: 10 N analyzed: 10	

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
Meagher 2001	Named trial: Other Design: RCT Jadad: 3 Population: Unspecified Condition: CAD	1	Placebo Placebo for 8 Weeks	N entered: 5 N analyzed: 5	Excluded from statistical analysis because no outcomes of interest were reported. No effect of vitamin E on lipid peroxidation.
		2	Vitamin E 200 IU orally for 8 Weeks	N entered: 5 N analyzed: 5	
		3	Vitamin E 400 IU orally for 8 Weeks	N entered: 5 N analyzed: 5	
		4	Vitamin E 800 IU orally for 8 Weeks	N entered: 5 N analyzed: 5	
		5	Vitamin E 1200 IU orally for 8 Weeks	N entered: 5 N analyzed: 5	
		6	Vitamin E 2000 IU orally for 8 Weeks	N entered: 5 N analyzed: 5	
Mensink 1999	Named trial: Other Design: RCT Jadad: 2 Population: Unspecified Condition:CAD, LDL oxidation	1	Vitamin E 80 mg orally for 6 Weeks Palm olein 960 mg orally for 6 Weeks Tocotrienols in general 160 mg orally for 6 Weeks	N entered: 20 N analyzed: 20	Excluded from meta-analysis of lipids due to no placebo arm. No effect of vitamin E concentrate versus low-dose vitamin E on serum lipids among men with hyperlipidemia.
		2	Vitamin E 80 mg orally for 6 Weeks Palm olein 1120 mg orally for 6 Weeks	N entered: 20 N analyzed: 20	
Meraji 1997	Named trial: Other Design: RCT Jadad: 2 Population: Unspecified Condition: CAD	1	Beta-carotene 30 mg orally for 10 Weeks Placebo Placebo for 10 Weeks	N entered: 10 N analyzed: 7	Excluded from meta-analysis of lipids due to insufficient statistics. Vitamin E group showed significantly higher reduction in lipid oxidation than the other groups.
		2	Beta-carotene 30 mg orally for 10 Weeks Vitamin E 400 IU orally for 10 Weeks	N entered: 11 N analyzed: 9	

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1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
Morisco 1993	Named trial: Other Design: RCT Jadad: 4 Population: Unspecified Condition: CHF	1	Placebo Placebo for 52 Weeks	N entered: 322 N analyzed: 281	Excluded from meta-analysis of death as not relevant intervention. CO-Q10 group had significantly fewer episodes of pulmonary edema and hospitalizations over the placebo group among heart failure subjects
		2	Co-Q10 2 mg/kg orally for 52 Weeks	N entered: 319 N analyzed: 282	
Morisco 1994	Named trial: Other Design: RCT Jadad: 2 Population: Unspecified Condition: CHF	1	Placebo Placebo for 4 Weeks	N entered: 6 N analyzed: 6	Excluded from statistical analysis because no outcomes of interest were reported. Statistically significant improvement in hemodynamics at exercise in Co-Q10 group.
		2	Co-Q10 150 mg orally for 4 Weeks	N entered: 6 N analyzed: 6	
Mosca 1996	Named trial: Other Design: RCT Jadad: 1 Population: Unspecified Condition:CAD, LDL oxidation	1	Placebo Placebo for 12 Weeks	N entered: 15 N analyzed: N/A	Excluded from statistical analysis because no outcomes of interest were reported. Antioxidant combination including vitamins C and E was associated with decreased LDL oxidation.
		2	Vitamin E 400 IU orally for 12 Weeks Vitamin C 500 mg orally for 12 Weeks Beta-carotene 12 mg orally for 12 Weeks	N entered: 15 N analyzed: N/A	
		3	Vitamin E 800 IU orally for 12 Weeks Vitamin C 1000 mg orally for 12 Weeks Beta-carotene 24 mg orally for 12 Weeks	N entered: 15 N analyzed: N/A	

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Mosca 1997	Named trial:	Other	1	Placebo Placebo for 12 Weeks	N entered: N analyzed:	15 14	Included in meta-analysis of lipids.
	Design:	RCT	2	Vitamin E 400 IU orally for 12 Weeks Vitamin C 500 mg orally for 12 Weeks Beta-carotene 12 mg orally for 12 Weeks	N entered: N analyzed:	15 13	
	Jadad:	4					
	Population:	Unspecified					
	Condition:	CAD	3	Vitamin E 800 IU orally for 12 Weeks Vitamin C 1000 mg orally for 12 Weeks Beta-carotene 24 mg orally for 12 Weeks	N entered: N analyzed:	15 14	
Mottram 1999	Named trial:	Other	1	Placebo Placebo for 8 Weeks	N entered: N analyzed:	14 14	Included in meta-analysis of lipids.
	Design:	RCT	2	Vitamin E 400 IU orally for 8 Weeks	N entered: N analyzed:	14 14	
	Jadad:	3					
	Population:	Unspecified					
	Condition:	CAD					
Munday 1999	Named trial:	Other	1	Garlic - whole 6 gm orally for 7 Days	N entered: N analyzed:	9 9	Excluded from meta-analysis of lipids due to insufficient followup time. Vitamin E group showed significant reduction in LDL oxidation as compared to placebo.
	Design:	RCT	2	Garlic - AGE 2.4 gm orally for 7 Days	N entered: N analyzed:	9 9	
	Jadad:	2	3	Vitamin E 800 mg orally for 7 Days	N entered: N analyzed:	9 9	
	Population:	Unspecified					
	Condition:	CAD					

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Munkholm 1999	Named trial:	Other	1	Placebo Placebo for 12 Weeks	N entered: N analyzed:	11 11	Excluded from statistical analysis because no outcomes of interest were reported. Co-Q10 group showed statistically significant improvement in some, but not all, measures of hemodynamics.
	Design:	RCT	2	Co-Q10 200 mg orally for 12 Weeks	N entered: N analyzed:	11 11	
	Jadad:	2					
	Population:	Unspecified					
	Condition:	CHF					
Nappo 1999	Named trial:	Other	1	Placebo Placebo for 1 Day	N entered: N analyzed:	20 20	Excluded from meta-analysis of lipids as not relevant intervention. No significant change in blood pressure among any of the groups.
	Design:	RCT	2	L-methionine 100 mg/kg orally for 1 Day	N entered: N analyzed:	20 20	
	Jadad:	2	3	Vitamin E 800 IU orally for 1 Day Vitamin C 1000 mg orally for 1 Day L-methionine 100 mg/kg orally for 1 Day	N entered: N analyzed:	20 20	
	Population:	Unspecified					
	Condition: dysfunction	Endothelial	4	Vitamin E 800 IU orally for 1 Day Vitamin C 1000 mg orally for 1 Day	N entered: N analyzed:	10 10	
Ness 1999	Named trial:	CHAOS	1	Placebo No dosage data reported	N entered: N analyzed:	N/A 967	Excluded from meta-analysis of death and MI due to insufficient followup time. The ATBC trial and the CHAOS trial showed non-significant increases in all-cause mortality and coronary deaths with vitamin E treatment.
	Design:	RCT	2	Vitamin E No dosage data reported	N entered: N analyzed:	N/A 1035	
	Jadad:	3					
	Population:	Unspecified					
	Condition:	CAD					

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1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
Nyyssonen 1994	Named trial: Other Design: RCT Jadad: 2 Population: Smokers Condition: CAD	1	Placebo Placebo for 3 Months	N entered: 20 N analyzed: 20	Included in meta-analysis of lipids.
		2	Vitamin C 400 mg orally for 3 Months Vitamin E 200 mg orally for 3 Months Selenium 100 µg orally for 3 Months Beta-carotene 30 mg orally for 3 Months	N entered: 20 N analyzed: 20	
Nyyssonen 1997	Named trial: MASIT Design: RCT Jadad: 3 Population: Smokers Condition:CAD, LDL oxidation	1	Placebo Placebo for 2 Months	N entered: N/A N analyzed: 19	Excluded from meta-analysis of lipids as not relevant intervention. Vitamin C showed no significant effect on lipid oxidation among smokers.
		2	Vitamin C 500 mg orally for 3 Months	N entered: N/A N analyzed: 20	
		3	Vitamin C 500 mg orally for 2 Months	N entered: N/A N analyzed: 20	
O'Byrne 2000	Named trial: Other Design: RCT Jadad: 4 Population: Unspecified Condition:CAD, LDL oxidation	1	Placebo Placebo for 8 Weeks	N entered: 13 N analyzed: 13	Excluded from meta-analysis of lipids as not relevant intervention. Vitamin E group showed no significant difference in total lipid levels, but did show significant reductions in lipid oxidation.
		2	Alpha tocotrienol 250 mg orally for 8 Weeks	N entered: 13 N analyzed: 13	
		3	Gamma tocotrienol 250 mg orally for 8 Weeks	N entered: 13 N analyzed: 12	
		4	Delta tocotrienol 250 mg orally for 8 Weeks	N entered: 13 N analyzed: N/A	

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1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Oda 1984	Named trial:	Other	1	Vitamin E .75 mg/kg orally duration N/A	N entered: N analyzed:	N/A 4	Excluded from statistical analysis because no outcomes of interest were reported. Significant association found between Co-Q10 dose and measures of cardiac dysfunction among subjects with mitral valve prolapse.
	Design:	CCT	2	Vitamin E 1.2 mg/kg orally duration N/A	N entered: N analyzed:	N/A 47	
	Jadad:	0	3	Vitamin E 1.7 mg/kg orally duration N/A	N entered: N analyzed:	N/A 51	
	Population:	Children (under 18)	4	Vitamin E 2.2 mg/kg orally duration N/A	N entered: N analyzed:	N/A 62	
	Condition:	MVP	5	Vitamin E 2.7 mg/kg orally duration N/A	N entered: N analyzed:	N/A 21	
			6	Vitamin E 3.2 mg/kg orally duration N/A	N entered: N analyzed:	N/A 62	
Oda 1985 Study 1	Named trial:	Other	1	Co-Q10 0.6-0.9 mg/kg orally duration N/A	N entered: N analyzed:	N/A 11	Excluded from statistical analysis because no outcomes of interest were reported. Positive dose response seen for Co-Q10 in measures of stress induced cardiac dysfunction among pediatric subjects with mitral valve prolapse.
	Design:	CCT	2	Co-Q10 1.0-1.4 mg/kg orally duration N/A	N entered: N analyzed:	N/A 44	
	Jadad:	1	3	Co-Q10 1.5-1.9 mg/kg orally duration N/A	N entered: N analyzed:	N/A 80	
	Population:	Children (under 18)	4	Co-Q10 2.0-2.4 mg/kg orally duration N/A	N entered: N analyzed:	N/A 166	
	Condition:	MVP	5	Co-Q10 2.5-2.9 mg/kg orally duration N/A	N entered: N analyzed:	N/A 54	
			6	Co-Q10 3.0-3.4 mg/kg orally duration N/A	N entered: N analyzed:	N/A 45	

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Oda 1985 Study 2	Named trial:	Other	1	ATP 0.6-0.9 mg/kg orally duration N/A	N entered: N analyzed:	8 8	Excluded from statistical analysis because no outcomes of interest were reported. Improvement seen in Co-Q10 group for stress induced cardiac dysfunction among pediatric subjects with mitral valve prolapse.
	Design:	RCT	2	Co-Q10 1.0-1.4 mg/kg orally duration N/A	N entered: N analyzed:	8 8	
	Jadad:	1					
	Population:	Children (under 18)					
	Condition:	MVP					

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Oda 1986a	Named trial:	Other	1	Co-Q10 0.75 mg/kg orally duration N/A	N entered: N analyzed:	N/A 11	Excluded from statistical analysis because no outcomes of interest were reported. Significant association found between Co-Q10 dose and measures of cardiac dysfunction among pediatric subjects with mitral valve prolapse.
	Design:	CCT	2	Co-Q10 1.2 mg/kg orally duration N/A	N entered: N analyzed:	N/A 44	
	Jadad:	0	3	Co-Q10 1.7 mg orally duration N/A	N entered: N analyzed:	N/A 81	
	Population:	Children (under 18)	4	Co-Q10 2.2 mg orally duration N/A	N entered: N analyzed:	N/A 58	
	Condition:	MVP	5	Co-Q10 2.7 mg orally duration N/A	N entered: N analyzed:	N/A 112	
			6	Co-Q10 3.2 mg/kg orally duration N/A	N entered: N analyzed:	N/A 166	
Oda 1986b	Named trial:	Other	1	Co-Q10 0.6-0.9 mg/kg orally duration N/A	N entered: N analyzed:	N/A 11	Excluded from statistical analysis because no outcomes of interest were reported. Strong correlation was shown between dose of Co-Q10 and normalization of a test of cardiac dysfunction in children with mitral valve prolapse.
	Design:	RCT	2	Co-Q10 1.0-1.4 mg/kg orally duration N/A	N entered: N analyzed:	N/A 44	
	Jadad:	1	3	Co-Q10 1.5-1.9 mg/kg orally duration N/A	N entered: N analyzed:	N/A 81	
	Population:	Children (under 18)	4	Co-Q10 2.0-2.4 mg/kg orally duration N/A	N entered: N analyzed:	N/A 166	
	Condition:	MVP	5	Co-Q10 2.5-2.9 mg/kg orally duration N/A	N entered: N analyzed:	N/A 54	
			6	Co-Q10 3.0-3.4 mg/kg orally duration N/A	N entered: N analyzed:	N/A 45	

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Oda 1990	Named trial:	Other	1	Co-Q10 6.5 mg/kg orally for 7 Days	N entered: N analyzed:	20 20	Excluded from statistical analysis because no outcomes of interest were reported. Co-Q10 group exhibited improvement in cardiac dysfunction among subjects with mitral valve prolapse.
	Design:	RCT	2	Co-Q10 6.5 mg/kg orally for 14 Days	N entered: N analyzed:	40 40	
	Jadad:	2					
	Population:	Children (under 18)					
	Condition:	CHF					
Okamura 1983	Named trial:	Other	1	Control or Usual care Control or Usual care for 2 Days	N entered: N analyzed:	18 18	Excluded from statistical analysis because no outcomes of interest were reported. Co-Q10 group showed significant improvement in myocardial damage following cardiac surgery.
	Design:	CCT	2	Co-Q10 5 mg/kg intravenously for 2 Days	N entered: N analyzed:	21 21	
	Jadad:	0					
	Population:	Unspecified					
	Condition:	CAD					
Okamura 1984	Named trial:	Other	1	Control or Usual care No dosage data reported	N entered: N analyzed:	27 N/A	Excluded from statistical analysis because no outcomes of interest were reported. There was increased ability to be weaned from intra-aortic balloon pump following aorto-coronary bypass surgery among the Co-Q10 group.
	Design:	RCT	2	Co-Q10 5-10 mg/kg intravenously duration N/A Aprontin 5000-10000 ku/kg intravenously duration N/A	N entered: N analyzed:	14 N/A	
	Jadad:	1					
	Population:	Unspecified					
	Condition:	CAD, CHF					

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Osilesi 1991	Named trial:	Other	1	Placebo Placebo for 6 Weeks	N entered: N analyzed:	20 20	Excluded from meta-analysis of lipids due to study design. Reduction in systolic blood pressure was noted in vitamin C group with no change found in lipid levels.
	Design:	RCT	2	Vitamin C 1000 mg orally for 6 Weeks	N entered: N analyzed:	20 20	
	Jadad:	2					
	Population:	Unspecified					
	Condition:	HTN					
Palomaki 1998	Named trial:	Other	1	Statin drug 60 mg orally for 6 Weeks Placebo Placebo for 6 Weeks	N entered: N analyzed:	20 19	Excluded from meta-analysis of lipids as not relevant intervention. Small but significant improvement in LDL oxidation by Co-Q10 as compared to control among subjects receiving statin therapy.
	Design:	RCT					
	Jadad:	3	2	Co-Q10 180 mg orally for 6 Weeks Statin drug 60 mg orally for 6 Weeks	N entered: N analyzed:	20 19	
	Population:	Unspecified					
	Condition:	CAD					
Palumbo 2000	Named trial:	PPP	1	Control or Usual care No dosage data reported	N entered: N analyzed:	N/A 67	Excluded from statistical analysis because no outcomes of interest were reported. No effect of vitamin E on blood pressure.
	Design:	RCT	2	Vitamin E 300 mg orally for 12 Weeks	N entered: N analyzed:	N/A 75	
	Jadad:	3					
	Population:	Unspecified					
	Condition:	HTN					

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
Paolisso 1995	Named trial: Other Design: RCT Jadad: 2 Population: Elderly (over 65) Condition: CAD	1	Placebo Placebo for 4 Months	N entered: 30 N analyzed: 30	Included in meta-analysis of lipids.
		2	Vitamin E 900 mg orally for 4 Months	N entered: 30 N analyzed: 30	
Park 1999	Named trial: Other Design: RCT Jadad: 2 Population: Unspecified Condition: CAD	1	Placebo Placebo for 2 Years	N entered: N/A N analyzed: 16	Excluded from statistical analysis because no outcomes of interest were reported. Antioxidant combination including vitamins C and E was associated with decreased cardiac allograft vasculopathy among transplant recipients.
		2	Vitamin E 600 mg orally for 2 Years Vitamin C 225 mg orally for 2 Years Beta-carotene 18 mg orally for 2 Years	N entered: N/A N analyzed: 15	
Permanetter 1992	Named trial: Other Design: RCT Jadad: 4 Population: Unspecified Condition: CHF	1	Placebo Placebo for 4 Months	N entered: 26 N analyzed: 25	Excluded from statistical analysis because no outcomes of interest were reported. No effect of Co-Q10 on any hemodynamic measurements among subjects with idiopathic dilated cardiomyopathy.
		2	Co-Q10 100 mg orally for 4 Months	N entered: 26 N analyzed: 25	

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1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Poggesi 1991	Named trial:	Other	1	Placebo Placebo for 60 Days	N entered: N analyzed:	20 18	Excluded from statistical analysis because no outcomes of interest were reported. Co-Q10 group showed statistically significant improvement in some, but not all, measures of hemodynamics among subjects with dilated cardiomyopathy.
	Design:	RCT	2	Co-Q10 100 mg orally for 60 Days	N entered: N analyzed:	20 18	
	Jadad:	4					
	Population:	Unspecified					
	Condition:	CHF					
Porkkala-Sarataho 1998	Named trial:	MASIT	1	Placebo Placebo for 2 Months	N entered: N analyzed:	20 20	Included in meta-analysis of lipids.
	Design:	RCT	2	Vitamin E 200 mg orally for 2 Months	N entered: N analyzed:	20 20	
	Jadad:	3	3	Vitamin C 500 mg orally for 2 Months Vitamin E 200 mg orally for 2 Months	N entered: N analyzed:	20 20	
	Population:	Smokers					
	Condition:	CAD					
Porkkala-Sarataho 2000	Named trial:	ASAP	1	Placebo Placebo for 36 Months	N entered: N analyzed:	11 11	Excluded from meta-analysis of lipids as not relevant outcome. Vitamin E alone and in combination with vitamin C reduced lipid oxidation whereas vitamin C alone had no effect.
	Design:	RCT	2	Vitamin C 500 mg orally for 36 Months	N entered: N analyzed:	12 12	
	Jadad:	4	3	Vitamin E 272 IU orally for 36 Months	N entered: N analyzed:	10 10	
	Population:	Unspecified	4	Vitamin C 500 mg orally for 36 Months Vitamin E 272 IU orally for 36 Months	N entered: N analyzed:	15 15	
	Condition:	CAD					

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1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
PPP 2001	Named trial:	PPP	1	Placebo Placebo for 3.6 Years	N entered: N analyzed:	2264 2242	Excluded from meta-analysis of death and MI as primary prevention study. Vitamin E showed no effect on the prevention of cardiovascular events among subjects at high risk.
	Design:	RCT	2	Vitamin E 300 mg orally for 3.6 Years	N entered: N analyzed:	2231 1947	
	Jadad:	3					
	Population:	Unspecified					
	Condition:	CAD					
Qureshi 1995	Named trial:	Other	1	Vitamin E 1 mg orally for 4 Weeks Placebo Placebo for 4 Weeks	N entered: N analyzed:	16 16	Excluded from meta-analysis of lipids due to insufficient followup time. Vitamin E led to significant reductions in lipid levels among hypercholesterolemic subjects.
	Design:	RCT	2	Vitamin E 40 mg orally for 4 Weeks Palm olein 940 mg orally for 4 Weeks Alpha tocotrienol 48 mg orally for 4 Weeks Gamma tocotrienol 112 mg orally for 4 Weeks Delta tocotrienol 60 mg orally for 4 Weeks	N entered: N analyzed:	20 20	
	Jadad:	0					
	Population:	Unspecified					
	Condition:	CAD					
Raitakari 2000a	Named trial:	Other	1	Placebo Placebo for 4 Weeks	N entered: N analyzed:	12 12	Excluded from meta-analysis of lipids as not relevant outcome. Co-Q10 led to a significant decrease in LDL oxidation among subjects with moderate hypercholesterolemia.
	Design:	RCT	2	Co-Q10 150 mg orally for 4 Weeks	N entered: N analyzed:	12 12	
	Jadad:	2					
	Population:	Unspecified					
	Condition:	N/A					

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1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Raitakari 2000b	Named trial:	Other	1	Placebo Placebo for 2 Hours Placebo Placebo for 8 Weeks	N entered: N analyzed:	20 20	Excluded from meta-analysis of lipids due to insufficient statistics. No effect of vitamin C on lipid levels among smokers.
	Design:	RCT	2	Vitamin C 2 gm orally for 2 Hours Vitamin C 1 gm orally for 8 Weeks	N entered: N analyzed:	20 20	
	Jadad:	2					
	Population:	Smokers					
	Condition:	Endothelial dysfunction					
Rapola 1996	Named trial:	ATBC	1	Placebo Placebo for 4.7 Years	N entered: N analyzed:	5549 N/A	Excluded from statistical analysis because no outcomes of interest were reported. Small, but statistically significant, decrease in risk of angina symptoms with vitamin E among male smokers.
	Design:	RCT	2	Beta-carotene 20 mg orally for 4.7 Years	N entered: N analyzed:	5602 N/A	
	Jadad:	3	3	Vitamin E 50 mg orally for 4.7 Years	N entered: N analyzed:	5570 N/A	
	Population:	Smokers	4	Vitamin E 50 mg orally for 4.7 Years	N entered: N analyzed:	5548 N/A	
	Condition:	Angina					
Rapola 1997	Named trial:	ATBC	1	Placebo Placebo for 5.3 Years	N entered: N analyzed:	438 N/A	Included in meta-analysis of death and MI.
	Design:	RCT	2	Beta-carotene 20 mg orally for 5.3 Years	N entered: N analyzed:	461 N/A	
	Jadad:	3	3	Vitamin E 50 mg orally for 5.3 Years	N entered: N analyzed:	466 N/A	
	Population:	Smokers	4	Vitamin E 50 mg orally for 5.3 Years Beta-carotene 20 mg orally for 5.3 Years	N entered: N analyzed:	497 N/A	
	Condition:	CAD					

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1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Reaven 1993	Named trial:	Other	1	DL-alpha-tocopherol 1600 mg orally for 2 Months	N entered: N analyzed:	8 8	Excluded from meta-analysis of lipids due to no placebo arm. Vitamin E groups showed significant reductions in LDL oxidation.
	Design:	RCT	2	RRR-alpha-tocopherol 1600 mg orally for 2 Months	N entered: N analyzed:	8 7	
	Jadad:	3					
	Population:	Unspecified					
	Condition:	CAD, LDL oxidation					
Rokitzki 1994	Named trial:	Other	1	Placebo Placebo for 151 Days	N entered: N analyzed:	N/A 15	Excluded from statistical analysis because no outcomes of interest were reported. No improvement in performance, but significant reduction in oxidative stress measures among athletes in vitamin E group.
	Design:	RCT	2	Vitamin E 330 mg orally for 151 Days	N entered: N analyzed:	N/A 15	
	Jadad:	3					
	Population:	Unspecified					
	Condition:	CAD					
Rossi 1991	Named trial:	Other	1	Placebo Placebo for 90 Days	N entered: N analyzed:	10 N/A	Excluded from statistical analysis because no outcomes of interest were reported. Improved exercise tolerance, but no change in resting hemodynamics, among Co-Q10 subjects.
	Design:	RCT	2	Co-Q10 200 mg orally for 90 Days	N entered: N analyzed:	10 N/A	
	Jadad:	2					
	Population:	Unspecified					
	Condition:	CAD, CHF					

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1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
Salonen 2000	Named trial: ASAP Design: RCT Jadad: 4 Population: Unspecified Condition: Carotid atherosclerosis	1	Placebo Placebo for 3 Years	N entered: 130 N analyzed: 110	Excluded from meta-analysis of death as primary prevention study. Significant reduction in progression of carotid atherosclerosis in vitamin combination group as compared to placebo.
		2	Vitamin E 272 IU orally for 3 Years	N entered: 130 N analyzed: 115	
		3	Vitamin C 500 mg orally for 3 Years	N entered: 130 N analyzed: 120	
		4	Vitamin C 500 mg orally for 3 Years Vitamin E 272 IU orally for 3 Years	N entered: 130 N analyzed: 113	
Samman 1997	Named trial: Other Design: RCT Jadad: 2 Population: Smokers Condition:CAD, LDL oxidation	1	Placebo Placebo for 2 Weeks	N entered: 10 N analyzed: 8	Excluded from meta-analysis of lipids as not relevant intervention. Vitamin C showed no significant effect on lipid levels or on LDL oxidation among smokers.
		2	Vitamin C 1 gm orally for 2 Weeks	N entered: 10 N analyzed: 8	
Schafer 1990	Named trial: Other Design: RCT Jadad: 1 Population: Female Elderly (Over 65) Condition:CAD, LDL oxidation	1	Placebo Placebo for 3 Months	N entered: 15 N analyzed: 15	Included in meta-analysis of lipids.
		2	Vitamin E 300 mg orally for 3 Months Selenium 125 µg orally for 3 Months	N entered: 15 N analyzed: 15	

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1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Schardt, 1991	Named trial:	Other	1	Placebo Placebo for 4 Days	N entered: N analyzed:	15 15	Excluded from statistical analysis because no outcomes of interest were reported. Statistically significant improved ST-segment depression in Co-Q10 group.
	Design:	RCT	2	Co-Q10 600 mg orally for 4 Days	N entered: N analyzed:	15 15	
	Jadad:	2					
	Population:	Female					
	Condition:	CAD, angina					
Schardt 1986	Named trial:	Other	1	Placebo Placebo for 4 Days	N entered: N analyzed:	15 N/A	Excluded from statistical analysis because no outcomes of interest were reported. Significant effect of Co-Q10 on ischemia-related ECG changes.
	Design:	RCT	2	Co-Q10 600 mg orally for 4 Days	N entered: N analyzed:	15 N/A	
	Jadad:	2					
	Population:	Female					
	Condition:	CAD					
Schneeberger 1986	Named trial:	Other	1	Placebo Placebo for 15 Weeks	N entered: N analyzed:	12 6	Excluded from statistical analysis because no outcomes of interest were reported. Co-Q10 group showed significantly improved measures of cardiac function.
	Design:	CCT	2	Co-Q10 100 mg orally for 15 Weeks	N entered: N analyzed:	12 6	
	Jadad:	1					
	Population:	Unspecified					
	Condition:	CHF					

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1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
Semple 1974	Named trial: Other Design: CCT Jadad: 0 Population: Unspecified Condition: PVD	1	Control or Usual care Control or Usual care for 6 Months	N entered: 14 N analyzed: 14	Excluded from statistical analysis because no outcomes of interest were reported. No impact of vitamin E on intermittent claudication symptoms.
		2	Vitamin E 400 mg orally for 6 Months	N entered: 12 N analyzed: 12	
Serra 1991	Named trial: Other Design: RCT Jadad: 2 Population: Unspecified Condition:CAD, CHF, angina	1	Placebo Placebo for 4 Weeks	N entered: 20 N analyzed: 20	Excluded from statistical analysis because no outcomes of interest were reported. Co-Q10 group showed statistically significant improvement in some, but not all, measures of hemodynamics.
		2	Co-Q10 60 mg orally for 4 Weeks	N entered: 20 N analyzed: 20	
Simons 1996	Named trial: Other Design: RCT Jadad: 3 Population: Unspecified Condition: CAD	1	Placebo Placebo for 6 Weeks	N entered: 11 N analyzed: 11	Excluded from statistical analysis because no outcomes of interest were reported. Significant reduction in LDL oxidation among all doses of vitamin E as compared to placebo.
		2	Vitamin E 500 IU orally for 6 Weeks	N entered: 11 N analyzed: 11	
		3	Vitamin E 1000 IU orally for 6 Weeks	N entered: 9 N analyzed: 8	
		4	Vitamin E 1500 IU orally for 6 Weeks	N entered: 11 N analyzed: 11	

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1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Singh 1996	Named trial:	Other	1	Placebo Placebo for 3 Days Placebo Placebo for 28 Days Placebo Placebo for 25 Days	N entered: N analyzed:	62 62	Excluded from meta-analysis of death and MI due to insufficient followup time. Antioxidant group showed significantly smaller infarction size after acute MI and significantly lower rates of lipid oxidation and most, but not all, cardiac end points.
	Design:	RCT					
	Jadad:	4					
	Population:	Unspecified	2	Vitamin A 50000 IU intravenously for 3 Days Vitamin C 1000 mg intravenously for 3 Days Vitamin E 400 mg orally for 28 Days Beta-carotene 25 mg orally for 28 Days Vitamin A 50000 IU orally for 25 Days Vitamin C 1000 mg orally for 25 Days	N entered: N analyzed:	63 63	
	Condition:	CAD					
Singh 1998	Named trial:	Other	1	Placebo Placebo for 28 Days	N entered: N analyzed:	71 71	Excluded from meta-analysis of death as not relevant intervention. Excluded from meta-analysis of MI due to insufficient followup time. Co-Q10 group showed significant reductions in all adverse cardiovascular measures following acute MI compared to placebo.
	Design:	RCT	2	Co-Q10 120 mg orally for 28 Days	N entered: N analyzed:	73 73	
	Jadad:	1					
	Population:	Unspecified					
	Condition:	CAD, angina					

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1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Singh 1999a	Named trial:	Other	1	Placebo Placebo for 28 Days	N entered: N analyzed:	24 22	Excluded from meta-analysis of lipids as not relevant intervention. Co-Q10 led to significant reduction over placebo in serum lipoproteins and lipid oxidation and significant elevation in HDL cholesterol among subjects with coronary artery disease.
	Design:	RCT	2	Co-Q10 120 mg orally for 28 Days	N entered: N analyzed:	27 25	
	Jadad:	4					
	Population:	Unspecified					
	Condition:	CAD					
Singh 1999b	Named trial:	Other	1	Multi-vitamin Multi-vitamin orally for 8 Weeks	N entered: N analyzed:	32 29	Excluded from meta-analysis of lipids as not relevant intervention. Co-Q10 group showed significant decrease in blood pressure, blood glucose levels, triglyceride levels in subjects with CAD and HTN with no change in placebo group.
	Design:	RCT	2	Co-Q10 120 mg orally for 8 Weeks	N entered: N analyzed:	32 30	
	Jadad:	4					
	Population:	Unspecified					
	Condition:	CAD					
Singhal 2001	Named trial:	Other	1	Placebo Placebo for 30 Days	N entered: N analyzed:	35 32	Excluded from meta-analysis of lipids due to insufficient followup time. No significant change in lipids in vitamin E or vitamin C groups. Vitamin E group showed the strongest reduction in lipid oxidation among all treatment groups.
	Design:	RCT	2	Vitamin E 400 IU orally for 30 Days	N entered: N analyzed:	35 32	
	Jadad:	2	3	Vitamin C 1000 mg orally for 30 Days	N entered: N analyzed:	35 31	
	Population:	Unspecified	4	Vitamin A 25000 IU orally for 30 Days	N entered: N analyzed:	35 32	
	Condition:	CAD, LDL oxidation	5	Fruit 400 gm orally for 30 Days	N entered: N analyzed:	35 30	

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1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Sisto 1995	Named trial:	Other	1	Control or Usual care No dosage data reported	N entered: N analyzed:	25 N/A	Excluded from meta-analysis of MI due to insufficient followup time. Significant improvements in cardiac event rates were noted in the intervention groups as compared to control groups among subjects status post cardiovascular surgery.
	Design:	RCT	2	Vitamin E 600 mg orally for 28 Days Vitamin C 2 gm orally for 3 Days Allopurinol 600 mg orally for 3 Days	N entered: N analyzed:	20 N/A	
	Jadad:	2					
	Population:	Unspecified					
	Condition:	CAD	3	Control or Usual care No dosage data reported	N entered: N analyzed:	19 N/A	
			4	Vitamin E 600 mg orally for 2 Days Vitamin C 2 gm orally for 3 Days Allopurinol 600 mg orally for 3 Days	N entered: N analyzed:	17 N/A	
Stampfer 1983	Named trial:	Other	1	Placebo Placebo for 16 Weeks	N entered: N analyzed:	15 15	Included in meta-analysis of lipids.
	Design:	RCT	2	Vitamin E 800 IU orally for 16 Weeks	N entered: N analyzed:	15 15	
	Jadad:	2					
	Population:	Unspecified					
	Condition:	CAD					

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Steiner 1995	Named trial:	Other	1	Aspirin 325 mg orally for 2 Years	N entered: 48 N analyzed: 40		Excluded from meta-analysis of death due to insufficient statistics. Significant reduction in ischemic event rates among aspirin plus vitamin E group was found.
	Design:	RCT	2	Vitamin E 400 IU orally for 2 Years Aspirin 325 mg orally for 2 Years	N entered: 52 N analyzed: 44		
	Jadad:	3					
	Population:	Unspecified					
	Condition:	CVA/TIA					
Stephens 1996	Named trial:	CHAOS	1	Placebo Placebo for 494 Days	N entered: 967 N analyzed: 948		Included in meta-analysis of death and MI.
	Design:	RCT	2	Vitamin E 800 IU orally for 737 Days	N entered: 546 N analyzed: N/A		
	Jadad:	3	3	Vitamin E 400 IU orally for 366 Days	N entered: 489 N analyzed: N/A		
	Population:	Unspecified					
	Condition:	CAD					
Taggart 1996	Named trial:	Other	1	Placebo Placebo for 12 Hours	N entered: 10 N analyzed: 10		Excluded from statistical analysis because no outcomes of interest were reported. No improvement in myocardial protection following bypass surgery among subjects pretreated with Co-Q10.
	Design:	RCT	2	Co-Q10 600 mg orally for 12 Hours	N entered: 10 N analyzed: 10		
	Jadad:	4					
	Population:	Unspecified					
	Condition:	CAD					

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Takamatsu 1995	Named trial:	Other	1	Vitamin E 3 mg orally for 6 Years	N entered: N analyzed:	73 63	Excluded from meta-analysis of MI due to insufficient statistics. Excluded from meta-analysis of lipids due to no placebo arm. Higher rates of myocardial disease were found among subjects receiving the higher dose of vitamin E.
	Design:	RCT	2	Vitamin E 100 mg orally for 6 Years	N entered: N analyzed:	74 69	
	Jadad:	5					
	Population:	Unspecified					
	Condition:	CAD					
Tanaka 1982	Named trial:	Other	1	Control or Usual care No dosage data reported	N entered: N analyzed:	25 25	Excluded from statistical analysis because no outcomes of interest were reported. Statistically significant reduction in low cardiac output state following cardiac valve replacement in Co-Q10 group.
	Design:	RCT	2	Co-Q10 30-60 mg orally for 6 Days	N entered: N analyzed:	25 25	
	Jadad:	1					
	Population:	Unspecified					
	Condition:	CHF					

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
Tardif 1997	Named trial: MVP Design: RCT Jadad: 3 Population: Unspecified Condition: CAD	1	Placebo Placebo for 7 Months	N entered: 79 N analyzed: 62	Included in meta-analysis of death. Excluded from meta-analysis of MI as not relevant outcome. No statistically significant difference in outcomes following angioplasty between antioxidant and no antioxidant groups.
		2	Statin drug 500 mg orally for 7 Months	N entered: 80 N analyzed: 58	
		3	Vitamin C 500 mg orally for 7 Months Vitamin E 700 IU orally for 7 Months Beta-carotene 30000 IU orally for 7 Months Vitamin E 2000 IU orally for 1 Day	N entered: 78 N analyzed: 54	
		4	Statin drug 500 mg orally for 7 Months Vitamin C 500 mg orally for 7 Months	N entered: 80 N analyzed: 56	
Tomeo 1995	Named trial: Other Design: RCT Jadad: 4 Population: Unspecified Condition: Carotid atherosclerosis	1	Palm olein 1200 mg orally for 18 Months	N entered: 25 N analyzed: 25	Included in meta-analysis of lipids.
		2	Vitamin E 64 mg orally for 18 Months Palm olein 960 mg orally for 18 Months Alpha tocotrienol 160 mg orally for 18 Months Gamma tocotrienol 160 mg orally for 18 Months	N entered: 25 N analyzed: 25	

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size	Summary of Results
Toone 1973	Named trial:	Other	1	Placebo Placebo for 2 Years	N entered: 11 N analyzed: N/A	Excluded from statistical analysis because no outcomes of interest were reported. Significant reduction in nitroglycerin use among subjects with ischemic heart disease given vitamin E.
	Design:	CCT	2	Vitamin E 1600 IU orally for 2 Years	N entered: 11 N analyzed: N/A	
	Jadad:	1				
	Population:	Unspecified				
	Condition:	CAD, angina				
Tornwall 1997	Named trial:	ATBC	1	Placebo Placebo for 4 Years	N entered: 6573 N analyzed: 4667	Excluded from statistical analysis because no outcomes of interest were reported. No preventative effect of vitamin E on intermittent claudication found from among male smokers.
	Design:	RCT	2	Vitamin E 50 mg orally for 4 Years	N entered: 6605 N analyzed: 4690	
	Jadad:	3	3	Beta-carotene 20 mg orally for 4 Years	N entered: 6559 N analyzed: 4591	
	Population:	Smokers	4	Vitamin E 50 mg orally for 4 Years Beta-carotene 20 mg orally for 4 Years	N entered: 6552 N analyzed: 4586	
	Condition:	PVD				
Tornwall 1999	Named trial:	ATBC	1	Placebo Placebo for 3.7 Years	N entered: 373 N analyzed: N/A	Excluded from statistical analysis because no outcomes of interest were reported. No effect of vitamin E on claudication symptoms among men with baseline claudication.
	Design:	RCT	2	Beta-carotene 20 mg orally for 3.7 Years	N entered: 377 N analyzed: N/A	
	Jadad:	3	3	Vitamin E 50 mg orally for 3.7 Years	N entered: 344 N analyzed: N/A	
	Population:	Smokers	4	Vitamin E 50 mg orally for 3.7 Years Beta-carotene 20 mg orally for 3.7 Years	N entered: 390 N analyzed: N/A	
	Condition:	PVD				

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Tornwall 2001	Named trial:	ATBC	1	Placebo Placebo for 5.8 Years	N entered: N analyzed:	7287 N/A	Excluded from meta-analysis of death due to insufficient statistics. No significant preventive effect of vitamin E on abdominal aortic aneurysm formation or rupture.
	Design:	RCT	2	Vitamin E 50 mg orally for 5.8 Years	N entered: N analyzed:	7286 N/A	
	Jadad:	3	3	Beta-carotene 20 mg orally for 5.8 Years	N entered: N analyzed:	7282 N/A	
	Population:	Smokers	4	Vitamin E 50 mg orally for 5.8 Years Beta-carotene 20 mg orally for 5.8 Years	N entered: N analyzed:	7278 N/A	
	Condition:	AAA					
Tsai 1978	Named trial:	Other	1	Placebo Placebo for 4 Weeks	N entered: N analyzed:	98 90	Excluded from meta-analysis of lipids due to insufficient followup time. No significant change in lipids with vitamin E except for small but statistically significant increase in serum triglycerides among female subjects.
	Design:	RCT	2	Vitamin E 600 IU orally for 4 Weeks	N entered: N analyzed:	104 94	
	Jadad:	3					
	Population:	Unspecified					
	Condition:	CAD					
Upritchard 2000	Named trial:	Other	1	Placebo Placebo for 4 Weeks	N entered: N analyzed:	13 13	Excluded from statistical analysis because no outcomes of interest were reported. Decrease in LDL oxidation found among vitamin E group, but not among vitamin C group.
	Design:	RCT	2	Tomato juice 500 ml orally for 4 Weeks	N entered: N analyzed:	15 15	
	Jadad:	3	3	Vitamin E 800 IU orally for 4 Weeks	N entered: N analyzed:	12 12	
	Population:	Unspecified	4	Vitamin C 500 mg orally for 4 Weeks	N entered: N analyzed:	12 12	
	Condition:	CAD					

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Vanfraechem 1986	Named trial:	Other	1	Placebo Placebo for 12 Weeks	N entered: N analyzed:	N/A N/A	Excluded from statistical analysis because no outcomes of interest were reported. Improvement in physical performance found in Co-Q10 group.
	Design:	RCT	2	Co-Q10 99 mg orally for 12 Weeks	N entered: N analyzed:	N/A N/A	
	Jadad:	2					
	Population:	Unspecified					
	Condition:	CHF					
Virtamo 1998	Named trial:	ATBC	1	Placebo Placebo for 6.1 Years	N entered: N analyzed:	6849 N/A	Excluded from meta-analysis of death and MI as primary prevention study. No statistically significant effect of vitamin E on fatal coronary heart disease or nonfatal myocardial infarction among male smokers.
	Design:	RCT	2	Vitamin E 50 mg orally for 6.1 Years	N entered: N analyzed:	6820 N/A	
	Jadad:	3	3	Beta-carotene 20 mg orally for 6.1 Years	N entered: N analyzed:	6821 N/A	
	Population:	Smokers	4	Vitamin E 50 mg orally for 6.1 Years Beta-carotene 20 mg orally for 6.1 Years	N entered: N analyzed:	6781 N/A	
	Condition:	CAD					
Wagdi 1996	Named trial:	Other	1	Placebo No dosage data reported	N entered: N analyzed:	N/A 13	Excluded from statistical analysis because no outcomes of interest were reported. No statistically significant effects of vitamins E and C on cardioprotection among subjects receiving toxic chemotherapy.
	Design:	RCT	2	Vitamin E 600 mg orally duration N/A Vitamin C 1000 mg orally duration N/A N-acetyl cysteine 200 mg orally duration N/A	N entered: N analyzed:	N/A 12	
	Jadad:	3					
	Population:	Unspecified					
	Condition:	Cardiotoxicity					

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
Watanabe 1998	Named trial: Other Design: RCT Jadad: 2 Population: Unspecified Condition: CHF	1	Placebo Placebo for 24 Hours Nitroglycerine Dose N/A intravenously for 24 Hours	N entered: 10 N analyzed: 10	Excluded from statistical analysis because no outcomes of interest were reported. Vitamin C group exhibited lower tolerance to intravenous nitrates among subjects with heart failure.
		2	Vitamin C 55 microgram/kg intravenously for 24 Hours Nitroglycerine Dose N/A intravenously for 24 Hours	N entered: 10 N analyzed: 10	
Watson 1999	Named trial: Other Design: RCT Jadad: 2 Population: Unspecified Condition: CHF	1	Placebo Placebo for 12 Weeks	N entered: 30 N analyzed: 27	Excluded from statistical analysis because no outcomes of interest were reported. No effect of Co-Q10 found on systolic function or quality of life measures among subjects with heart failure.
		2	Co-Q10 99 mg orally for 12 Weeks	N entered: 30 N analyzed: 27	
Wen 1997	Named trial: Other Design: CCT Jadad: 0 Population: Unspecified Condition:CAD, LDL oxidation	1	Control or Usual care No dosage data reported	N entered: 9 N analyzed: 9	Excluded from meta-analysis of lipids as not relevant outcome. Vitamin C showed no significant effect on lipid oxidation.
		2	Vitamin C 1000 mg orally for 4 Weeks	N entered: 11 N analyzed: 11	

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
Wen 1999	Named trial: Other Design: RCT Jadad: 3 Population: Unspecified Condition: CAD, LDL oxidation	1	Placebo Placebo for 30 Weeks	N entered: 22 N analyzed: 17	Excluded from meta-analysis of lipids due to insufficient statistics. Vitamin E group showed significant reduction in LDL oxidation as compared to placebo.
		2	Vitamin E 100 IU orally for 6 Weeks Vitamin E 200 IU orally for 6 Weeks Vitamin E 400 IU orally for 6 Weeks Vitamin E 800 IU orally for 6 Weeks Vitamin E 1600 IU orally for 6 Weeks	N entered: 27 N analyzed: 20	
Westhuyzen 1997	Named trial: Other Design: RCT Jadad: 2 Population: Unspecified Condition: CAD, reperfusion injury	1	Placebo Placebo for 10 Days Placebo Placebo for 1 Day	N entered: 38 N analyzed: 38	Excluded from statistical analysis because no outcomes of interest were reported. No reduction in myocardial injury following cardiac surgery among vitamin E or vitamin C groups.
		2	Vitamin C 1000 mg orally for 1 Day Vitamin E 750 IU orally for 10 Days	N entered: 38 N analyzed: 38	
Whittaker 1987	Named trial: Other Design: RCT Jadad: 1 Population: Unspecified Condition: Cardiotoxicity	1	Control or Usual care No dosage data reported	N entered: N/A N analyzed: N/A	Excluded from statistical analysis because no outcomes of interest were reported. No cardioprotective effect of vitamin E among subjects receiving chemotherapy.
		2	Digoxin 0.25 mg orally duration N/A	N entered: N/A N analyzed: N/A	
		3	Vitamin E 600 mg orally duration N/A	N entered: N/A N analyzed: N/A	

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease		Arm	Interventions Dose Data	Sample Size		Summary of Results
Williams 1962	Named trial:	Other	1	Placebo No dosage data reported	N entered: N analyzed:	17 17	Excluded from statistical analysis because no outcomes of interest were reported. Suggestions of improvement of claudication symptoms with Co-Q10 treatment without statistical significance.
	Design:	RCT	2	Vitamin E 1600 mg orally duration N/A	N entered: N analyzed:	16 16	
	Jadad:	2					
	Population:	Unspecified					
	Condition:	PVD					
Williams 1971	Named trial:	Other	1	Placebo Placebo for 13.4 Months	N entered: N analyzed:	29 N/A	Excluded from statistical analysis because no outcomes of interest were reported. Vitamin E showed significant improvement among some, but not all, subjects with peripheral vascular occlusive disease.
	Design:	RCT	2	Vitamin E 1600 mg orally for 26.8 Months	N entered: N analyzed:	45 N/A	
	Jadad:	2					
	Population:	Unspecified					
	Condition:	PVD					
Wilson 1991	Named trial:	Other	1	Placebo Placebo for 4 Weeks	N entered: N analyzed:	17 17	Excluded from statistical analysis because no outcomes of interest were reported. Statistically significant improvement in exercise duration with Co-Q10 among subjects with angina symptoms.
	Design:	CCT	2	Co-Q10 150 mg orally for 4 Weeks	N entered: N analyzed:	20 20	
	Jadad:	1	3	Co-Q10 300 mg orally for 4 Weeks	N entered: N analyzed:	21 21	
	Population:	Unspecified					
	Condition:	CAD, angina					

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
Woodside 1999	Named trial: Other Design: RCT Jadad: 4 Population: Unspecified Condition: Hyperhomocystinemia, LDL oxidation.	1	Placebo Placebo for 8 Weeks	N entered: 33 N analyzed: 26	Excluded from statistical analysis because no outcomes of interest were reported.
		2	Multi-vitamin Multi-vitamin orally for 8 Weeks	N entered: 32 N analyzed: 22	Combinations of antioxidants including vitamins C and E showed improvement in measures of LDL oxidation.
		3	Vitamin C 150 mg orally for 8 Weeks Vitamin E 67 mg orally for 8 Weeks Beta-carotene 9 mg orally for 8 Weeks	N entered: 33 N analyzed: 25	
		4	Vitamin C 150 mg orally for 8 Weeks Vitamin E 67 mg orally for 8 Weeks Beta-carotene 9 mg orally for 8 Weeks Multi-vitamin Multi-vitamin orally for 8 Weeks	N entered: 34 N analyzed: 28	
Yamagami 1986	Named trial: Other Design: RCT Jadad: 3 Population: Unspecified Condition: HTN	1	Placebo Placebo for 12 Weeks	N entered: 10 N analyzed: 10	Excluded from statistical analysis because no outcomes of interest were reported. Statistically significant reduction of systolic blood pressure found among Co-Q10 group.
		2	Co-Q10 100 mg orally for 12 Weeks	N entered: 10 N analyzed: 10	

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

1st Author Year	Trial name Study Design and Quality Population Type of Disease	Arm	Interventions Dose Data	Sample Size	Summary of Results
Yamamura 1977	Named trial: Other Design: CCT Jadad: 0 Population: Unspecified Condition: CHF	1	Co Q7 75 mg intravenously for 98 Days	N entered: 21 N analyzed: 21	Excluded from statistical analysis because no outcomes of interest were reported. No significant effect on severity of heart failure in Co-Q10 group.
		2	Co Q7 60 mg orally for 98 Days	N entered: 17 N analyzed: 17	
		3	Co-Q10 30 mg orally for 98 Days	N entered: 17 N analyzed: 17	
Yau 1994	Named trial: Other Design: RCT Jadad: 4 Population: Unspecified Condition: CAD, reperfusion injury	1	Placebo Placebo for 14 Days	N entered: 14 N analyzed: 14	Excluded from statistical analysis because no outcomes of interest were reported. Significant functional and metabolic improvements were found post cardiac surgery among vitamin E group.
		2	Vitamin E 300 mg orally for 14 Days	N entered: 14 N analyzed: 14	
Yusuf, 2000	Named trial: HOPE Design: RCT Jadad: 3 Population: Unspecified Condition: CAD, CVA/TIA	1	Placebo Placebo for 4.5 Years	N entered: 4780 N analyzed: N/A	Included in meta-analysis of death and MI.
		2	Vitamin E 400 IU orally for 4.5 Years	N entered: 4761 N analyzed: N/A	

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CCT = clinical controlled trial; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; DM = diabetes melitus; HTN = hypertension; LDL = low density lipoprotein; MI = myocardial infarction; MVP = mitral valve prolapse; N/A = not applicable/not available; PVD = peripheral vascular disease; RCT = randomized controlled trial

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Appendix A
Acknowledgments

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We gratefully acknowledge the following individuals who reviewed the initial draft of this report and provided us with constructive feedback. Acknowledgments are made with the explicit statement that this does not constitute endorsement of the report.

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Appendix B

Search Methodology

SEARCH #1 (PERFORMED 11/16/01)

DATABASES SEARCHED/TIME PERIOD COVERED:

MEDLINE	1966-2001/Dec W2
MANTIS	1880-2001/Aug
Allied & Complementary Medicine	1984-2001/Dec
Cancerlit	1975-2001/Oct
CAB HEALTH	1983-2001/Oct
TGG Health&Wellness DB	1976-2001/Nov W1
Biosis Previews	1969-2001/Nov W2
EMBASE	1974-2001/Nov W2
Social SciSearch	1972-2001/Nov W3
SciSearch Cited Ref Sci	1990-2001/Nov W3
SciSearch Cited Ref Sci	1974-1989/Dec
ELSEVIER BIOBASE	1994-2001/Nov W2

SEARCH STRATEGY:

ubiquinone OR ubidecarenone OR coenzyme q10 OR co-enzyme q10 OR coenzyme q 10 OR co-enzyme q 10 OR coenzyme q-10 OR co-enzyme q-10

AND

cardiovascular diseases(exploded) from Medline,CancerLit
OR cardiovascular disease(exploded) from EMBASE
OR cardiovascular disease* OR coronary artery disease*
OR coronary atherosclerosis OR heart disease*
OR congestive heart failure OR myocardial OR coronary ischemia
OR acute coronary syndrome OR coronary plaque OR heart plaque
OR arter* plaque

AND

(prevention OR preventive OR therapy OR therapeutic OR treatment) in title,subject heading fields

AND

Human

NOT

(cell OR cells) in subject heading field

TOTAL NUMBER OF ITEMS RETRIEVED: 582

SEARCH #2a (PERFORMED 11/27/01)

DATABASES SEARCHED/TIME PERIOD COVERED:

MEDLINE	1966-2001/Dec W4
MANTIS	1880-2001/Aug
Allied & Complementary Medicine	1984-2001/Dec
Cancerlit	1975-2001/Oct
CAB HEALTH	1983-2001/Oct
TGG Health&Wellness DB	1976-2001/Nov W2
Biosis Previews	1969-2001/Nov W3
EMBASE	1974-2001/Nov W3
Social SciSearch	1972-2001/Nov W4
SciSearch Cited Ref Sci	1990-2001/Nov W4
SciSearch Cited Ref Sci	1974-1989/Dec
ELSEVIER BIOBASE	1994-2001/Nov W4

SEARCH STRATEGY:
ascorbic acid(exploded)from Medline, Embase OR ascorbic acid OR dehydroascorbic acid* OR ascorbate OR vitamin c OR antiscorbutic vitamin* OR cevitamic acid*

AND

cardiovascular diseases(exploded) from Medline,CancerLit
OR cardiovascular disease(exploded) from EMBASE
OR cardiovascular disease* OR coronary artery disease*
OR coronary atherosclerosis OR heart disease*
OR congestive heart failure OR myocardial OR coronary ischemia
OR acute coronary syndrome OR coronary plaque OR heart plaque
OR arter* plaque

AND

(prevention OR preventive OR therapy OR therapeutic OR treatment) in title,subject heading fields

AND

human

NOT

(cell OR cells) in subject heading field

TOTAL NUMBER OF ITEMS RETRIEVED: 2228 [NOTE: NOT ALL DUPLICATE RECORDS WERE DELETED FROM THESE RESULTS – RS]

SEARCH #2b (PERFORMED 11/7/01)

DATABASES SEARCHED:

Cochrane Library

SEARCH STRATEGY:

vitamin c OR ascorbic acid OR ascorbate OR antiscorbutic vitamin OR cevitamic acid OR dehydroascorbic acid

AND

cardiovascular diseases(exploded)

TOTAL NUMBER OF ITEMS RETRIEVED:

The Cochrane Database of Systematic Reviews
Complete reviews - 11

Database of Abstracts of Reviews of Effectiveness
Abstracts of quality assessed systematic reviews - 3

The Cochrane Controlled Trials Register (CENTRAL/CCTR)
References - 155

SEARCH #3a (PERFORMED 12/4/01)

DATABASES SEARCHED/TIME PERIOD COVERED:

MEDLINE	1966-2001/Dec W5
MANTIS	1880-2001/Aug
Allied & Complementary Medicine	1984-2001/Jan
Cancerlit	1975-2001/Oct
CAB HEALTH	1983-2001/Oct
TGG Health&Wellness DB	1976-2001/Nov W3
Biosis Previews	1969-2001/Nov W4
EMBASE	1974-2001/Nov W4
Social SciSearch	1972-2001/Dec W1
SciSearch Cited Ref Sci	1990-2001/Dec W1
SciSearch Cited Ref Sci	1974-1989/Dec
ELSEVIER BIOBASE	1994-2001/Dec W1

SEARCH STRATEGY:

vitamin e (exploded) from Medline OR vitamin e OR alpha tocopherol* OR d1 alpha tocopherol* OR d alpha tocopherol OR rrr alpha tocopherol* OR all rac alpha tocopherol*

AND

cardiovascular diseases(exploded) from Medline,CancerLit
OR cardiovascular disease(exploded) from EMBASE
OR cardiovascular disease* OR coronary artery disease*
OR coronary atherosclerosis OR heart disease*
OR congestive heart failure OR myocardial OR coronary ischemia
OR acute coronary syndrome OR coronary plaque OR heart plaque
OR arter* plaque

AND

(prevention OR preventive OR therapy OR therapeutic OR treatment) in title,subject heading fields

AND

human

TOTAL NUMBER OF ITEMS RETRIEVED: 3578

SEARCH #3b (PERFORMED 12/19/01)

DATABASES SEARCHED/TIME PERIOD COVERED:

Cochrane Library	1922-2001

SEARCH STRATEGY:
vitamin-e

AND

cardiovascular diseases(exploded) OR coronary
OR heart OR myocardial

TOTAL NUMBER OF ITEMS RETRIEVED:

The Cochrane Database of Systematic Reviews - Complete reviews: 1

Database of Abstracts of Reviews of Effectiveness
Abstracts of quality assessed systematic reviews: 1
Other reviews: bibliographic details only: 3

The Cochrane Controlled Trials Register (CENTRAL/CCTR) – References: 187

SEARCH #4 (PERFORMED 1/25/02)

DATABASES SEARCHED/TIME PERIOD COVERED:

MEDLINE	1966-2002/JAN W3
MANTIS	1880-2001/Oct
Allied & Complementary Medicine	1984-2002/Feb
Cancerlit	1975-2001/Oct
CAB HEALTH	1983-2001/Dec
TGG Health&Wellness DB	1976-2002/Jan W1
Biosis Previews	1969-2002/Jan W3
EMBASE	1974-2002/Jan W3
Social SciSearch	1972-2002/Jan W4
SciSearch Cited Ref Sci	1990-2002/Jan W4
SciSearch Cited Ref Sci	1974-1989/Dec
ELSEVIER BIOBASE	1994-2002/Jan W3

SEARCH STRATEGY:
ubidecarenon* OR isoprostane* OR f2 isoprostane*

AND

cardiovascular diseases (exploded) from Medline, CancerLit, Embase OR cardiovascular disease* OR coronary artery disease* OR coronary atherosclerosis OR heart disease* OR congestive heart failure OR myocardial OR coronary ischemia OR acute coronary syndrome OR coronary plaque OR heart plaque OR arter* plaque

AND

Human

NOT

(coenzyme OR co enzyme) within 2 words of (q10 or q 10)

TOTAL NUMBER OF ITEMS RETRIEVED: 503

SEARCH #5 PERFORMED 11/7/01

DATABASE SEARCHED:

Cochrane Library

SEARCH STRATEGY:

coenzyme q10 or coenzyme q 10 OR co enzyme q10 OR co enzyme q 10 OR co q10 OR co q 10 OR ubiquinone

TOTAL NUMBER OF ITEMS RETRIEVED:

The Cochrane Database of Systematic Reviews - Complete reviews - 1
The Cochrane Controlled Trials Register (CENTRAL/CCTR) References - 110

Appendix C

Article# **Antioxidant Screener** **RAND EPC Alternative Medicine**

Reviewers: _____ mm/dd/yy
_____ mm/dd/yy

Assigned on:

[article author, title, journal, date, vol, pages]

1. Data Source: **Circle One**
   - Article 1
   - Abstract of article 2
   - Conference proceeding 3
   - Other (Specify_____) 4

2. What topic does the article study: **Check all that apply**
   - Vitamin C .....
   - Vitamin E .....
   - Co-Enzyme Q10 .....
   - Other (Specify_____) .. (STOP)
   - Unclear .....

3. Condition(s) and/or disease(s) studied in article: **Check all that apply**
   - Cancer .....
   - Cardiovascular Disease .....
   - No condition/disease ..... (STOP)
   - Other (Specify_____) .... (STOP)
   - Unclear .....

4. Subject Population: **Check all that apply**
   - Human .....
   - In vitro / In vivo ..... (STOP)
   - Animal ..... (STOP)
   - Other (Specify_____) .... (STOP)
   - Unclear .....

5. Article Type: **Check all that apply**
   - Historical/Descriptive/System/Bkgrd .....
   - Review/Meta-analysis .....
   - Pharmacological .....
   - Clinical Study
     - Trial .....
     - Cohort .....
     - Other clinical study .....
   - Other (Specify_____) ....
   - Unclear .....

6. How is the intervention being used in the study? **Circle One**
   - Treatment 1
   - Primary prevention 2
   - Secondary prevention 3
   - Adjunct to conventional treatment 4
   - Other (Specify_____) .. 5
   - Unclear 6

7. Language of Article: **Circle One**
   - English 1
   - Foreign 2

NOTES:

Abstract:

RAND EPC, CAM Project

Quality Review Form, Topic = ANTIOXIDANT

Article ID:_____ Reviewer:_____

First Author: _____
(Last Name Only)

Study Number: ___of____Description:_____
(Enter '1of 1' if only one) (if more than one study)

1. Design: (circle one)
   - RCT 1
   - CCT 2
   - Other ..... 3 **(STOP)**

(If not RCT or CCT, change study design on cover sheet and STOP)

2. What topic(s) does the study report on? ..... (check all that apply)
   - Vitamin C ..... ❑
   - Vitamin E ..... ❑
   - Co-Q10 ..... ❑
   - None of the above ..... ❑ **(STOP)**

2. What condition(s) does the study report on? (circle one)
   - Cardiovascular 1
   - Cancer 2
   - Both 3
   - None ..... 4 **(STOP)**

3. Is the study described as randomized? (circle one)
   - Yes 1
   - No 2

4. If the study was randomized, was method of randomization appropriate? (circle one)
   - Yes 1
   - No 2
   - Method not described 8
   - Not applicable 9

5. Is the study described as: (circle one)
   - Double blind 1
   - Single blind, patient 2
   - Single blind, outcome assessment 3
   - Open 4
   - Blinding not described 8
   - Not applicable 9

6. If reported, was the method of double blinding appropriate? (circle one)
   - Yes 1
   - No 2
   - Double blinding method not described 8
   - Not applicable 9

7. If study was randomized, did the method of randomization provide for concealment of allocation? (circle one)
   - Yes 1
   - No 2
   - Concealment not described 8
   - Not applicable 9

8. Are withdrawals (W) and dropouts (D) described? (circle one)
   - Yes, reason described for **all** W and D 1
   - Yes, reason described for **some** W and D 2
   - Not described 8
   - Not applicable 9

9. Is this a cross-over study design? (circle one)
   - Yes 1
   - No 2
   - Not described 8

10. Does the study population include a purposefully selected group of individuals chosen because they have any of the following characteristics? (check all that apply)

Race:
- African-American ..... ❑ (01)
- Asian ..... ❑ (02)
- Hispanic ..... ❑ (03)

Gender:
- Male ..... ❑ (04)
- Female ..... ❑ (05)

Age:
- Children (under 18) ..... ❑ (06)
- Elderly (over 65) ..... ❑ (07)

Miscellaneous:
- Smokers ..... ❑ (08)

Other:
- (Enter code: ____ ____, ____ ____, ____ ___, ____ ____, ____ ____)

None of the above ..... ❑ (97)

11. Does the study population include a purposefully selected group of individuals chosen because they have any of the following comorbidities? (enter code or circle)

Code: ____ ____, ____ ____, ____ ___, ____ ____, ____ ____

Not applicable 99

12. Does the study population include a purposefully selected group of individuals chosen because they have any of the following predisposing factors? (enter code or circle)

Code: ____ ____, ____ ____, ____ ___, ____ ____, ____ ____

Not applicable 99

13. If this study is from a larger trial, please note the name of original trial. (circle one or enter code)

- ADMT ..... ❑ (01)
- ATBC ..... ❑ (02)
- CGPPP ..... ❑ (03)
- CHAOS ..... ❑ (04)
- GISSI/GIZZI ..... ❑ (05)
- HOPE ..... ❑ (06)
- MRC/BHF ..... ❑ (07)
- PHS II ..... ❑ (08)
- SPACE ..... ❑ (09)
- SU.VI.MAX ..... ❑ (10)
- WHI ..... ❑ (11)
- WHS ..... ❑ (12)

Code: ____ ____

Not from a larger trial ..... ❑ (99)

Patient Characteristics – CARDIOVASCULAR

14.…What type of cardiovascular disease did the study report on?
(check all that apply and/or add code)

CAD ..... (01)
CVA/TIA..... (02)
PVD..... (03)
CHF ..... (04)
Angina ..... (05)

Code: ____ ____

____ ____

____ ____

____ ____

Not Applicable..... (99)

15.…What was the severity of the disease?

Enter code: ____ ____
(enter 99 if not applicable)

Patient Characteristics – CANCER

16. What type of cancer did the study report on?
(check all that apply and/or add code)

Breast..... (01)
Lung ..... (02)
Prostate..... (03)
Oral..... (04)
Cervix ..... (05)
Gastric ..... (06)
Colon ..... (07)

Code: ____ ____

____ ____

____ ____

____ ____

Not Applicable 99

17. What was the severity of the disease? (check all that apply and/or add code)

Pre-cancerous ..... (01)
Localized ..... (02)
Metastatic ..... (03)

Other code: ____ ____

Not Applicable 99

RAND EPC, CAM Project
Quality Review Form, Topic = ANTIOXIDANT

If the study has a control/usual care arm, enter that data in arm 1.
Otherwise, enter data for the groups in order of first mention.

Arm 1 of Description:

18. What type of arm is this? (circle one)
    - Placebo 1
    - Usual care 2
    - Primary Antioxidant 3
    - Other active treatment 4

19. What was the sample size in this arm?

___ ___ ___ , ___ ___ ___ Entering ___ ___ ___ , ___ ___ ___ Completing

(Enter 999,999 if not reported.)

20. Intervention:

Intervention	Daily Dose	Units		Route of administration	Duration	Units	
1 _____	_____	_____	taken	_____	_____	_____	
2 _____	_____	_____	taken	_____	_____	_____	
3 _____	_____	_____	taken	_____	_____	_____	
4 _____	_____	_____	taken	_____	_____	_____	
Enter code	Enter a number	1. µg 2. mg 998. ND 999. NA 3. gm 4. IU 8. ND 9. NA		1. PO 2. IV 8. ND 9. NA	Enter a number 998. ND 999. NA	1. Hour 2. Day 3. Week 4. Month 5. Year 6. Mean Month 7. Median Month	8. Mean Year 9. Median Year 10. Maximum Month 11. Minimum Month 12. Maximum Year 13. Minimum Year 98. ND 99. NA

If the study has a control/usual care arm, enter that data in arm 1.
Otherwise, enter data for the groups in order of first mention.

Arm 2 of Description:

18. What type of arm is this? (circle one)
    - Placebo 1
    - Usual care 2
    - Primary Antioxidant 3
    - Other active treatment 4

19. What was the sample size in this arm?

___ ___ ___ , ___ ___ ___ Entering ___ ___ ___ , ___ ___ ___ Completing

(Enter 999,999 if not reported.)

20. Intervention:

	Intervention	Daily Dose	Units		Route of administration	Duration	Units
1	_____	_____	_____	taken	_____	_____	_____
2	_____	_____	_____	taken	_____	_____	_____
3	_____	_____	_____	taken	_____	_____	_____
4	_____	_____	_____	taken	_____	_____	_____
	Enter code	Enter a number	1. µg 2. mg 998. ND 999. NA 3. gm 4. IU 8. ND 9. NA		1. PO 2. IV 8. ND 9. NA	Enter a number 998. ND 999. NA	1. Hour 2. Day 3. Week 4. Month 5. Year 6. Mean Month 7. Median Month 8. Mean Year 9. Median Year 10. Maximum Month 11. Minimum Month 12. Maximum Year 13. Minimum Year 98. ND 99. NA

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Quality Review Form, Topic = ANTIOXIDANT

If the study has a control/usual care arm, enter that data in arm 1.
Otherwise, enter data for the groups in order of first mention.

Arm 3 of Description:

19. What was the sample size in this arm?

___ ___ ___ , ___ ___ ___ Entering ___ ___ ___ , ___ ___ ___ Completing

(Enter 999,999 if not reported.)

18. What type of arm is this? (circle one)

- Placebo.....1
- Usual care.....2
- Primary Antioxidant.....3
- Other active treatment.....4

---

20. Intervention:

Intervention	Daily Dose	Units		Route of administration	Duration	Units
1 _____	_____	_____	taken	_____	_____	_____
2 _____	_____	_____	taken	_____	_____	_____
3 _____	_____	_____	taken	_____	_____	_____
4 _____	_____	_____	taken	_____	_____	_____
Enter code	Enter a number	1. µg 2. mg 3. gm 4. IU 8. ND 9. NA		1. PO 2. IV 8. ND 9. NA	Enter a number 998. ND 999. NA	1. Hour 2. Day 3. Week 4. Month 5. Year 6. Mean Month 7. Median Month 8. Mean Year 9. Median Year 10. Maximum Month 11. Minimum Month 12. Maximum Year 13. Minimum Year 98. ND 99. NA

RAND EPC, CAM Project
Quality Review Form, Topic = ANTIOXIDANT

If the study has a control/usual care arm, enter that data in arm 1.
Otherwise, enter data for the groups in order of first mention.

Arm 4 of Description:

19. What was the sample size in this arm?

___ ___ ___ , ___ ___ ___ Entering ___ ___ ___ , ___ ___ ___ Completing

(Enter 999,999 if not reported.)

18. What type of arm is this? (circle one)

- Placebo 1
- Usual care 2
- Primary Antioxidant 3
- Other active treatment 4

20. Intervention:

	Intervention	Daily Dose	Units		Route of administration	Duration	Units
1	_____	_____	_____	taken	_____	_____	_____
2	_____	_____	_____	taken	_____	_____	_____
3	_____	_____	_____	taken	_____	_____	_____
4	_____	_____	_____	taken	_____	_____	_____
	Enter code	Enter a number	1. µg 2. mg 3. gm 4. IU 8. ND 9. NA		1. PO 2. IV 8. ND 9. NA	Enter a number 998. ND 999. NA	1. Hour 2. Day 3. Week 4. Month 5. Year 6. Mean Month 7. Median Month 8. Mean Year 9. Median Year 10. Maximum Month 11. Minimum Month 12. Maximum Year 13. Minimum Year 98. ND 99. NA

Outcomes

21. Type of outcomes measured:

Enter the code for each outcome measured.
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____

Evaluation

22. When, relative to the start of the intervention, were outcomes reported?

Enter the number and letters in the appropriate box

	Number	Unit
1st follow-up		
2nd follow-up		
3rd follow-up		
4th follow-up		
5th follow-up		
6th follow-up		
Additional follow-ups:		

Use the following abbreviations for units:

MI	minute
HR	hour
DY	day
WK	week
MO	month
YR	year
YRMN	mean for year
YRME	median for year
YRMX	maximum for year
YRMI	minimum for year
MOMN	mean for month
MOME	median for month
MOMX	maximum for month
MOMI	minimum for month
ND	not described
NA	not applicable

23. Is there a sub-group analysis? (circle one)

Yes 1
No 2

If yes, code

____ ____ ____ ____
____ ____ ____ ____
____ ____ ____ ____

RAND EPC, CAM Project

Quality Review Form, Topic = ANTIOXIDANT

Article ID:_____ Reviewer:_____

First Author: _____
(Last Name Only)

Study Number: ___of____Description:_____
(Enter '1of 1' if only one) (if more than one study)

1. Design: (circle one)
   - RCT 1
   - CCT 2
   - Other ..... 3 **(STOP)**

(If not RCT or CCT, change study design on cover sheet and STOP)

2. What topic(s) does the study report on? ..... (check all that apply)
   - Vitamin C ..... ❑
   - Vitamin E ..... ❑
   - Co-Q10 ..... ❑
   - None of the above ..... ❑ **(STOP)**

2. What condition(s) does the study report on? (circle one)
   - Cardiovascular 1
   - Cancer 2
   - Both 3
   - None ..... 4 **(STOP)**

3. Is the study described as randomized? (circle one)
   - Yes 1
   - No 2

4. If the study was randomized, was method of randomization appropriate? (circle one)
   - Yes 1
   - No 2
   - Method not described 8
   - Not applicable 9

5. Is the study described as: (circle one)
   - Double blind 1
   - Single blind, patient 2
   - Single blind, outcome assessment 3
   - Open 4
   - Blinding not described 8
   - Not applicable 9

6. If reported, was the method of double blinding appropriate? (circle one)
   - Yes 1
   - No 2
   - Double blinding method not described 8
   - Not applicable 9

7. If study was randomized, did the method of randomization provide for concealment of allocation? (circle one)
   - Yes 1
   - No 2
   - Concealment not described 8
   - Not applicable 9

8. Are withdrawals (W) and dropouts (D) described? (circle one)
   - Yes, reason described for **all** W and D 1
   - Yes, reason described for **some** W and D 2
   - Not described 8
   - Not applicable 9

9. Is this a cross-over study design? (circle one)
   - Yes 1
   - No 2
   - Not described 8

10. Does the study population include a purposefully selected group of individuals chosen because they have any of the following characteristics? (check all that apply)

Race:
- African-American ..... ❑ (01)
- Asian ..... ❑ (02)
- Hispanic ..... ❑ (03)

Gender:
- Male ..... ❑ (04)
- Female ..... ❑ (05)

Age:
- Children (under 18) ..... ❑ (06)
- Elderly (over 65) ..... ❑ (07)

Miscellaneous:
- Smokers ..... ❑ (08)

Other:
- (Enter code: ____ ____, ____ ____, ____ ___, ____ ____, ____ ____)

None of the above ..... ❑ (97)

11. Does the study population include a purposefully selected group of individuals chosen because they have any of the following comorbidities? (enter code or circle)

Code: ____ ____, ____ ____, ____ ___, ____ ____, ____ ____

Not applicable 99

12. Does the study population include a purposefully selected group of individuals chosen because they have any of the following predisposing factors? (enter code or circle)

Code: ____ ____, ____ ____, ____ ___, ____ ____, ____ ____

Not applicable 99

13. If this study is from a larger trial, please note the name of original trial. (circle one or enter code)

- ADMT ..... ❑ (01)
- ATBC ..... ❑ (02)
- CGPPP ..... ❑ (03)
- CHAOS ..... ❑ (04)
- GISSI/GIZZI ..... ❑ (05)
- HOPE ..... ❑ (06)
- MRC/BHF ..... ❑ (07)
- PHS II ..... ❑ (08)
- SPACE ..... ❑ (09)
- SU.VI.MAX ..... ❑ (10)
- WHI ..... ❑ (11)
- WHS ..... ❑ (12)

Code: ____ ____

Not from a larger trial ..... ❑ (99)

Patient Characteristics – CARDIOVASCULAR

14.…What type of cardiovascular disease did the study report on?
(check all that apply and/or add code)

CAD ..... (01)
CVA/TIA..... (02)
PVD..... (03)
CHF ..... (04)
Angina ..... (05)

Code: ____ ____

____ ____

____ ____

____ ____

Not Applicable..... (99)

15.…What was the severity of the disease?

Enter code: ____ ____
(enter 99 if not applicable)

Patient Characteristics – CANCER

16. What type of cancer did the study report on?
(check all that apply and/or add code)

Breast..... (01)
Lung ..... (02)
Prostate..... (03)
Oral..... (04)
Cervix ..... (05)
Gastric ..... (06)
Colon ..... (07)

Code: ____ ____

____ ____

____ ____

____ ____

Not Applicable 99

17. What was the severity of the disease? (check all that apply and/or add code)

Pre-cancerous ..... (01)
Localized ..... (02)
Metastatic ..... (03)

Other code: ____ ____

Not Applicable 99

RAND EPC, CAM Project
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If the study has a control/usual care arm, enter that data in arm 1.
Otherwise, enter data for the groups in order of first mention.

Arm 1 of Description:

18. What type of arm is this? (circle one)
    - Placebo 1
    - Usual care 2
    - Primary Antioxidant 3
    - Other active treatment 4

19. What was the sample size in this arm?

___ ___ ___ , ___ ___ ___ Entering ___ ___ ___ , ___ ___ ___ Completing

(Enter 999,999 if not reported.)

20. Intervention:

Intervention	Daily Dose	Units		Route of administration	Duration	Units	
1 _____	_____	_____	taken	_____	_____	_____	
2 _____	_____	_____	taken	_____	_____	_____	
3 _____	_____	_____	taken	_____	_____	_____	
4 _____	_____	_____	taken	_____	_____	_____	
Enter code	Enter a number	1. µg 2. mg 998. ND 999. NA 3. gm 4. IU 8. ND 9. NA		1. PO 2. IV 8. ND 9. NA	Enter a number 998. ND 999. NA	1. Hour 2. Day 3. Week 4. Month 5. Year 6. Mean Month 7. Median Month	8. Mean Year 9. Median Year 10. Maximum Month 11. Minimum Month 12. Maximum Year 13. Minimum Year 98. ND 99. NA

If the study has a control/usual care arm, enter that data in arm 1.
Otherwise, enter data for the groups in order of first mention.

Arm 2 of Description:

18. What type of arm is this? (circle one)
    - Placebo 1
    - Usual care 2
    - Primary Antioxidant 3
    - Other active treatment 4

19. What was the sample size in this arm?

___ ___ ___ , ___ ___ ___ Entering ___ ___ ___ , ___ ___ ___ Completing

(Enter 999,999 if not reported.)

20. Intervention:

	Intervention	Daily Dose	Units		Route of administration	Duration	Units
1	_____	_____	_____	taken	_____	_____	_____
2	_____	_____	_____	taken	_____	_____	_____
3	_____	_____	_____	taken	_____	_____	_____
4	_____	_____	_____	taken	_____	_____	_____
	Enter code	Enter a number	1. µg 2. mg 998. ND 999. NA 3. gm 4. IU 8. ND 9. NA		1. PO 2. IV 8. ND 9. NA	Enter a number 998. ND 999. NA	1. Hour 2. Day 3. Week 4. Month 5. Year 6. Mean Month 7. Median Month 8. Mean Year 9. Median Year 10. Maximum Month 11. Minimum Month 12. Maximum Year 13. Minimum Year 98. ND 99. NA

RAND EPC, CAM Project
Quality Review Form, Topic = ANTIOXIDANT

If the study has a control/usual care arm, enter that data in arm 1.
Otherwise, enter data for the groups in order of first mention.

Arm 3 of Description:

19. What was the sample size in this arm?

___ ___ ___ , ___ ___ ___ Entering ___ ___ ___ , ___ ___ ___ Completing

(Enter 999,999 if not reported.)

18. What type of arm is this? (circle one)

- Placebo.....1
- Usual care.....2
- Primary Antioxidant.....3
- Other active treatment.....4

---

20. Intervention:

Intervention	Daily Dose	Units		Route of administration	Duration	Units
1 _____	_____	_____	taken	_____	_____	_____
2 _____	_____	_____	taken	_____	_____	_____
3 _____	_____	_____	taken	_____	_____	_____
4 _____	_____	_____	taken	_____	_____	_____
Enter code	Enter a number	1. µg 2. mg 3. gm 4. IU 8. ND 9. NA		1. PO 2. IV 8. ND 9. NA	Enter a number 998. ND 999. NA	1. Hour 2. Day 3. Week 4. Month 5. Year 6. Mean Month 7. Median Month 8. Mean Year 9. Median Year 10. Maximum Month 11. Minimum Month 12. Maximum Year 13. Minimum Year 98. ND 99. NA

RAND EPC, CAM Project
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If the study has a control/usual care arm, enter that data in arm 1.
Otherwise, enter data for the groups in order of first mention.

Arm 4 of Description:

19. What was the sample size in this arm?

___ ___ ___ , ___ ___ ___ Entering ___ ___ ___ , ___ ___ ___ Completing

(Enter 999,999 if not reported.)

18. What type of arm is this? (circle one)

- Placebo 1
- Usual care 2
- Primary Antioxidant 3
- Other active treatment 4

20. Intervention:

	Intervention	Daily Dose	Units		Route of administration	Duration	Units
1	_____	_____	_____	taken	_____	_____	_____
2	_____	_____	_____	taken	_____	_____	_____
3	_____	_____	_____	taken	_____	_____	_____
4	_____	_____	_____	taken	_____	_____	_____
	Enter code	Enter a number	1. µg 2. mg 3. gm 4. IU 8. ND 9. NA		1. PO 2. IV 8. ND 9. NA	Enter a number 998. ND 999. NA	1. Hour 2. Day 3. Week 4. Month 5. Year 6. Mean Month 7. Median Month 8. Mean Year 9. Median Year 10. Maximum Month 11. Minimum Month 12. Maximum Year 13. Minimum Year 98. ND 99. NA

Outcomes

21. Type of outcomes measured:

Enter the code for each outcome measured.
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____
____ ____

Evaluation

22. When, relative to the start of the intervention, were outcomes reported?

Enter the number and letters in the appropriate box

	Number	Unit
1st follow-up		
2nd follow-up		
3rd follow-up		
4th follow-up		
5th follow-up		
6th follow-up		
Additional follow-ups:		

Use the following abbreviations for units:

MI	minute
HR	hour
DY	day
WK	week
MO	month
YR	year
YRMN	mean for year
YRME	median for year
YRMX	maximum for year
YRMI	minimum for year
MOMN	mean for month
MOME	median for month
MOMX	maximum for month
MOMI	minimum for month
ND	not described
NA	not applicable

23. Is there a sub-group analysis? (circle one)

Yes 1
No 2

If yes, code

____ ____ ____ ____
____ ____ ____ ____
____ ____ ____ ____

Appendix E

Reviewers' Critique	Authors' Response to Comments
I found the decisions about whether/where to combine/report primary and secondary prevention trials very confusing. Primary prevention trials were not included in the pooled analysis, but were included in the discussion as a reported individual study. Thus, comparisons were made between secondary and primary prevention without explicitly labeling it as such. For example, on p 4 it states that "we did not find evidence in the pooled analysis of smaller trials that vitamin E . . . had a significant effect on all cause mortality. However, a 20% reduction in mortality was reported in the ATBC and Linxian trials . . ." When I first read this I assumed the distinction was being made on the basis of size: by what was seen in smaller trials versus larger trials. But later I realized that the "pooled analysis of smaller trials" included only secondary prevention trials, and ATBC and Linxian are primary prevention trials; thus the distinction was really by type of study.	We have tried to make these distinctions clearer in their revision. The decisions were based on sample size. However, this also had the effect of segregating the primary prevention trials from the secondary prevention trials.
It appears a serious oversight that the definition of antioxidant nutrients and the evaluative criteria necessary for determining antioxidant activity developed by the Institute of Medicine (IOM) Food and Nutrition Board was omitted from the report. Incorporate note into.	Added description of antioxidants and supplements based on IOM and added reference.
Definition of antioxidants. I am not familiar with the reference cited (Ternay, 1997) and wonder whether a more appropriate definition might be the one developed by the IOM (IOM, 2000 – DRIs for Vitamin C, Vitamin E, Selenium, and Carotenoids).	Added description of antioxidants and supplements based on IOM and added reference.
Similarly, the discussion on the Safety of Antioxidant Supplementation ignores the IOM establishment of the DRI Tolerable Upper Intake Levels (UL), their value in clinical and CAM practice, and their implication for future research studies.	Change made to the Introduction section.
First paragraph under "Safety". Suggest qualifying the number of reports (few, several, many?) that have been cited as a true potential interaction from those of documented interactions. 100-800 IU/day are considered safe in short-term; long-term doses >800 IU/day may adversely affect platelet function and doses >1200 IU/day may interfere with vitamin K functions. IOM upper tolerable limit is set at 1000 IU.	We were unclear of the reviewer's distinction between true potential interaction and documented interaction and could not respond to this comment. We did add a sentence about IOM upper tolerable limit.

There is literature suggesting a risk for vitamin E that is not described and that is probably due to increased bleeding. Particularly the ATBC study quoted to provide benefit of vitamin E. In that study vitamin E was associated with increase risk of hemorrhagic strokes by 50% (p=0.07) and fatal subarachnoid bleeding (Leppala JM, et al. Art Thromb Vasc Biol. 2000;20:230). Additionally, an increase in colorectal adenomas was found in ATBC possibly related to bleeding and increase use of colonoscopy (Malila et al. Cancer Epidemiol, Biomarkers and Prevention. 1999;8:489).	Malila article not in this report's bibliography. Change made.
It is clear what was done and I am able to understand what it is you did in order to produce the report. I agree with some but not all of the methods, findings, and conclusions.	No response.
My main issue is that I feel there is too much focus on the few suggestions of benefit, with recommendations that trials be done to confirm these findings, without acknowledgement that in the context of the totality of the evidence, these could well be due to chance. In addition, I still have a philosophic disagreement about such an emphasis on meta-analysis. It just felt disappointing in terms of the amount of information provided to think from the title we'd get a review of all cardiovascular disease and risk factors for three agents, and get only vitamin E, death and MI, and lipids.	We have endeavored to keep the conclusions balanced between the negative and positive findings/results. We have also included in this revision a narrative review of studies on vitamin C and coenzyme Q10.
It was never stated explicitly why supplements of vitamin C, vitamin E, and coenzyme Q10 are considered under the purview of Complementary and Alternative Medicine. If the vitamin C or E were, for example, being obtained by consuming foods rich in these vitamins, they would not, I assume, be considered CAM. Are they considered CAM then, solely because they are being taken as supplements? This should be clarified.	The sponsor (NCCAM) identified for us that the use of these antioxidants as supplements were CAM.
Purpose: Opening sentences. I do not consider the use of antioxidants, notably vitamin C and E, necessarily as CAM treatments. These "nutrients" have been studied for decades and Dietary Reference Intakes (DRIs) have been established for them. Perhaps if you wish to describe them as a CAM modality, include additional text to the effect "in mega-doses" or in doses greatly exceeding the recommended intakes."	See previous reply.
The just-published WAVE trial (*JAMA*, 11/10/02) should be included in the report.	A brief description of results of this study added to results section.
While this reviewer appreciates the requirement to impose a cut-off period in preparing a document such as this, inclusion of the WAVE trial results (Waters et al. *JAMA* 2002;288:2432-40) would further strengthen the null conclusions of this report.	See previous reply.
It would have been useful to know the gender distribution of the participants of the major studies.	We did not collect these data at the time of data extraction and cannot go back and collect it at this time.

I could not find notations on the formulation of agent used in the trial (eg., for vitamin E, was it synthetic or natural source). This would be helpful when you start talking about this issue under Future Research.	Not all of the included reports specify the source of the agent used in the trial. We included in future research that it would be desirable for any new studies to contain this information.
It would be easier to follow if the text and the relevant tables and figures were presented together.	AHRQ requires in their formatting guidelines that we present all tables and figures at the ends of each chapter.
The major strength of this report is its exhaustive and detailed review of the available literature of clinical trials of vitamins C and E and CVD. The major limitation is the absence of a qualitative assessment of this literature, including the distinction between the mechanisms of antioxidant action which may be pertinent to primary prevention of the initiation and progression of CVD lesions versus secondary prevention (maintenance or regression) of established lesions and recurrent event outcomes and death. Within the specific objectives of this report, the available information on vitamin C and coQ was so limited as to make sound conclusions (beyond the need for more research) impossible.	This revision now includes more information about vitamin C and coenzyme Q10. The mechanism of action was not given to us as one of the key questions from the sponsor.
I think it is unfortunate that the investigators chose to limit their analyses to the effects of the 3 antioxidants on mortality, MIs, or lipids. Although this is fine for vitamin E, for which there were an adequate number of studies to address these outcomes, the value of the report is limited with regard to vitamin C and coenzyme Q, for which few (if any) relevant studies were identified. Given the lack of mortality trials, it would have been helpful to review and analyze available data for other outcomes. For example, there have recently been 2 randomized trials of coenzyme Q in patients with heart failure (Khatta et al, Ann Intern Med 2000;132:636-40; Watson et al J Am Coll Cardiol 1999;33:1549-52), both of which provide clinically relevant data.	We included in the revision an expanded description of the vitamin C and coenzyme Q trials in the results section.
The major strengths of this report are that it is comprehensive, thorough, sophisticated in its methodology and statistical approach, and clearly written. The major limitation is that no insights are provided about the current state of knowledge regarding vitamin C and coenzyme Q. Although this limitation is related principally to the lack of published data, it is also in part related to the relatively narrow focus of the report with regard to clinically relevant outcomes.	See previous reply.
The selection of relevant studies of vitamin E in CVD appears appropriate and complete. However, the descriptions of studies with vitamin C and coenzyme Q10 are either very brief or altogether absent. While the report makes clear there are a limited number of such studies, the Results listings in the Table of Contents reveals not a single section is devoted to these two nutrients.	See previous reply.

The title that infers the review will include coenzyme Q10. It is unclear why you did not summarize the results of studies of coenzyme Q10 as used in congestive heart failure, state your opinion of the evidence or lack of evidence, and recommend future studies.	See previous reply.
The title suggests that the report will address the effects of vitamin C, vitamin E and coenzyme Q10 in cardiovascular disease. It does give an excellent overview of our understanding of the antioxidant activities of all three but then concentrates exclusively on the clinical trials of vitamin E. This is not made clear in the structured abstract or introduction.	See previous reply.
Selection Criteria: "Studies were also included if they affected known risk factors for cardiovascular disease such as blood lipids or hypertension." Suggest the inclusion of left ventricular hypertrophy (LVH) and ejection fraction is included as an outcome for the coenzyme Q10 heart failure studies as the literature would not suggest that coenzyme Q10 plays a significant role in reducing stroke or CAD. Your reference 88 (Soja and Mortensen, 1997) cited on page 21 indicates such.	See previous reply.
Description of coenzyme Q10 studies. Do not understand the comment that trials could not be pooled due to heterogeneity in population type when the referenced studies are in patients with heart failure and the data tables (page 93) list the population as "unspecified." Two studies had insufficient follow-up time (less than six months). If a more appropriate outcome measure were used, such as LVH, or ejection fraction, or possibly change in New York Heart Association Class function, three months might be a sufficient time period for study. (Franklin Rosenfeldt, Victoria, Australia has recently performed a meta-analysis on 7 trials that were double blind and placebo-controlled using a three month time point).	See previous reply.
Looking at the Conclusions on p. viii and the Findings on p 4, they only mention vitamin E. Nothing is said about the other two agents of interest (vitamin C and coenzyme Q10), even to say that there were no trials of these agents that could be reviewed. I think an explicit statement about each agent needs to be included in the Summary, and the Conclusions.	See previous reply.
The stated objective of the report included a review of the efficacy of the three antioxidants for the prevention and treatment of cardiovascular disease (CVD) or its risk factors. However, virtually the entire focus of this effort is devoted to three outcomes: death, MI, and/or blood lipid levels. Thus, other research approaches involving human studies (or even cell cultures and animal models) and examining other biomarkers of CVD risk (such as resistance to LDL oxidation, vascular reactivity, No production, hypertension, anti-platelet activity, carotid artery intima-media thickness, smooth muscle cell proliferation, oxidative stress, etc.), although briefly mentioned in some sections of the report, were absent from the equation for evaluating potential benefits and risks.	Within the resources available for this project, we focused on patient outcomes death, MI, and only the intermediate outcomes that were the best evidence supporting a direct relationship with patient outcomes. Other intermediate outcomes were not assessed. We did not assess animal studies or *in vivo* studies.

Elevated blood lipids are an established risk factor for CVD and are thus a reasonable risk factor to consider. However, even a cursory pre-review of the literature would have indicated that antioxidants do not have any significant effect on blood lipids.	These were a commonly reported intermediate outcome and a biological rationale from *in vivo* work, hence we included this in our analysis.
While the selection of the three antioxidants was determined by the contracting Agency for Healthcare Research and Quality, more detail should be provided concerning the large body of evidence indicating a putative beneficial role for the carotenoids and plant polyphenolics (such as the flavonoids). This information would help provide a better context for the question of why antioxidants are an appropriate area of focus for CVD research, especially future research.	Change made to future research.
As the objective of the report concerns antioxidant supplements, particularly in the context of CAM, it is not clear why so much effort was expended in the report detailing the relationship between dietary antioxidant intakes and CVD risk.	This material was included in the Introduction section so that readers could understand the context for the clinical trials.
Regarding safety, in contrast to the statement that: "For vitamin E, few adverse events have been reported in clinical trials for doses up to 1000 IU", it should be noted that large scale, long-term, randomized clinical trials have employed doses of 2000 IU daily without indication of toxicity (e.g., Parkinson Study Group. *Ann Neurol* 1998;43:318-25 and Sano et al. *N Engl J Med* 1997;336:1216-22).	Change made to the Introduction section.
Discussion of the potential adverse consequence of vitamin C supplementation in enhancing the bioavailability of iron fails to note the absence of data indicating this is actually a speculation unsupported by *in vivo* clinical studies or other reports.	This sentence was deleted.
Little consideration is given to such critical issues as antioxidant dose or form, rationale of antioxidant nutrient combinations, use of intermediary biomarkers of compliance and therapeutic action, and duration of the studies. The differential bioavailability and biopotency of the *RRR* - and all-*rac* forms of *a*-tocopherol are barely considered in the report. It is disturbing to note the report provides obsolete and inaccurate nomenclature for vitamin E (i.e., discussing the D isomers), fails to mention the new RDA redefined vitamin E requirements to be met only by 2*R* forms of *a*-tocopherol, and does not describe the central role of the hepatic *a*-tocopherol transport protein.	These concerns are limitations of the empiric data regarding what makes a study of antioxidants "good quality" and we have noted in the limitations and future research that more attention should be paid to these issues to determine if they are critical to the action of antioxidants in CVD.
Discussion of dose-response relationships concerning coenzyme Q10 is absent although the compelling data from Shults et al. (*Arch Neurol* 2002;59:1541-50) suggests that the null results from clinical trials of coenzyme Q10 in CVD and Parkinson Disease may be due to too low doses.	We did not do pooled analysis of coenzyme Q10 for reasons stated in the text. The Schults article was published after we submitted the report.
Please revise text and tables to consistently refer to each trial by a consistent identifier (trial name) and use reference numbers/author name to identify specific studies associated with each trial.	Change made.

Was vitamin E given with food in the trials as is necessary since it is better absorbed? The GISSI trial was performed in Italy and a benefit was found in a population consuming a relatively fatty breakfast not seen in the US.	This information was generally not stated in the published reports.
This is a very clear and comprehensive analysis and as with the cancer report, I am left with the feeling that your analysis is far more rigorous and well executed than the actual clinical studies being analyzed. The major strength of the report is its comprehensiveness and rigor, while the major limitation lies in the limitations of the clinical studies being analyzed. There are a few studies that use vitamin C alone, and few that include vitamin C in high enough pharmacologic doses to reasonably expect a clinically observable result. The conclusions starting on page 61 and the summary therefore, speak mainly to vitamin E and to vitamin E "in combination".	Only response is to add one sentence in the Limitations regarding vitamin C dose.
The major strengths of this report include question formulation and study identification. The major limitations are study selection and data synthesis.	No response.
However, there was a critical lack of discussion on the dose, formulation and quality of the antioxidant interventions used in the studies that were included in the final analysis.	We have added to the Limitations that a potential explanation for negative studies is that a beneficial dose and formulation of antioxidants has not yet been studied.
Middle paragraph line 4 and elsewhere – you use the words "unique trials". What does unique mean in this context?	Change made in Summary and Methods.
Were the coronary artery disease regression studies not appropriate for inclusion as a separate category? You mentioned the HATS study and another one. Two additional studies have recently been reported which may be beneficial to incorporate – the VEAPS and WAVE studies. Others ongoing are the SECURE, SMARTFED and MCBIT.	We could not find VEAPS study; the WAVE study has now been included.
You state that there is a 20% reduction in all cause mortality in ATBC and Linxian trials. I think this is incorrect. There is a 9% reduction in Linxian; you cite no results from ATBC on all-cause mortality although I don't believe it was reduced (there may not have been a 4 way analysis of these results). You ignore the findings of GISSI on all-cause mortality.	This was a typographical error and has been corrected.
Under all-cause mortality, I think both GISSI and Linxian reported a 20% (not 70%) reduction. And the same for CV death with GISSI (20%, not 70%). The 20% figures are given on p vii, so if that is wrong, it will have to be changed there instead.	See previous reply.
The statements (p. 63) specifying the 70% reduction in risk of all cause mortality and CVD death from the GISSI and Linxian trials is presumably a typographical error.	See previous reply.

There are, however, some errors in the summary statements, the most important of which are on page 63, in which all-cause and cardiovascular mortality are reported as being reduced “70%” in the GISSI trial (it should say 20%).	See previous reply.
Provide one overview table describing the major trials, separated by primary and secondary trials, which summarize the patient population, interventions, follow-up and outcomes reported (combining the various publications from each trial). The trials should be organized by primary and secondary prevention. Within each category they should be organized by interventions and size (or whoever you choose).	Table added that summarizes studies based on primary or secondary categorizations has been included at the beginning of the Results section.
Finally, there are no references attached to large sections of text (the Linxian trial).	Change made and reference added.
On page 36 the ATBC sub-population with coronary disease is described to have been given 400 or 800 IU of vitamin E. I believe they were given the same 2X2 factorial design with 50mg Vitamin E and beta carotene or placebo as the remainder. The description of vitamin E dosing is that in CHAOS (Stevens, Lancet 1996, and page 36).	Change made and reference added.
The purpose of this evidence report is stated to be to identify and assess the evidence for the efficacy of three antioxidants to affect cardiovascular disease or modification of known risk factors. On p 8, cardiovascular disease was defined as a number of conditions, and risk factors were defined as hypertension, hypercholesteremia, smoking and diabetes. Yet for the rest of the report, clinical outcomes of interest were limited to death, cardiovascular mortality and myocardial infarction, and the only risk factor discussed was lipid levels. The reason for limiting to this subset of the original purpose needs to be stated.	For the vitamin E studies, there was a sufficient number of clinically similar studies to justify meta-anlaysis. The three outcomes - death, MI, and lipid levels - were the most commonly reported outcomes in the vitamin E studies, and therefore, they were chosen for the meta-analysis. For vitamin C and coenzyme Q10, we limited our review to studies that reported clinical outcomes or intermediate outcomes with good evidence of a relationship to clinical outcomes. We have added at several points to the text new language to try and make this reasoning clear.
6 lines up from the bottom – 6% deaths from heart failure – seems a very low number. It may be important to quote lifetime risk of developing heart failure (see Lloyd-Jones et al. Circulation 2002;106:3068-72)	The 6% number is accurate. We also added the lifetime risk and Lloyd-Jones citation.
1st paragraph line 4 – 5-9 servings – is this per day, week, year?	Interval should be per day and change has been made to the Introduction.

Selecting another popular antioxidant, such as selenium, would be useful. I am surprised that selenium is repeatedly omitted from these reports. It may be even more important in terms of the antioxidant network and interactions among antioxidants than the examples used in the discussion of antioxidants on pages 14 – 16, for example. Although glutathione is important in the network, it is an endogenous component that may or may not be influenced by supplements. However, selenium clearly interacts with and complements the action of vitamin E, and in turn vitamin C. The evidence for this is quite strong and may be among the most potent interactions in terms of LDL oxidation. Such discussion may be superfluous given that selenium was not selected among the supplements studied, but it is certainly an important antioxidant to consider for future evaluation of the data pertaining to antioxidants and disease prevention.	We cannot add new topics at peer review stage. The topics were set by the sponsor. This is a good suggestion and has been added to future research.
Second paragraph, reference #76 (Aberg, 1998) does not appear to be an article related to statins but to Gemfibrozil – a different class of lipid lowering drugs.	This reference has been deleted.
12 lines down - ? compared with similar patients – without clinical evidence of atheroma.	Change has been made.
Second paragraph under “Safety” first sentence, qualify what you mean by “higher doses of vitamin C”.	Change made.
I am very uncomfortable with the exclusion on p 21 under “Safety of Antioxidant Supplementation” of the observed increase in risk of hemorrhagic stroke with vitamin E seen in the ATBC trial. To omit this at all, but especially after referring to vitamin E’s effects on platelets, seems inappropriate.	Change made.
Qualify what you mean higher doses of coenzyme Q10.	This editing error has been corrected in this revision. Change made.
On p. 36 there is a mention of two different doses of vitamin E in the ATBC trial – I don’t think this is correct.	The reviewer is correct. This typographical error has been corrected.
I could find no description of the Primary Prevention Trial, although I think one sentence describing ceasing trial due to benefits of ASA on p. 37 bottom refers to it.	Description of the Primary Prevention Trial added.
You say PPP and ASAP are secondary prevention – I think you mean primary prevention.	This sentence with this typographical error has been deleted.
First paragraph, sentence beginning “The former trials (PPP and ASAP) are secondary prevention trials” on page 38 you include the PPP and ASAP in the list of four primary prevention trials. Were they both? Which is correct?	This sentence with this typographical error has been deleted.

I disagree with the inclusion and exclusion criteria used to select articles. In fact, I believe selection criteria are applied in a manner that does not limit bias. Specifically, it is unclear to me why studies of lipids and blood pressure are included. Further, it is also unclear why lipids and not blood pressure are selected for further analysis.	Lipids and blood pressure were initially included as acceptable outcomes as they are intermediate outcomes with good evidence of a selection to clinical outcomes. Lipids alone were used in the meta-analysis as they were the most commonly reported intermediate outcome with a biologic rationale for an effect.
The important parameters are systematically addressed but I believe randomized design is under emphasized and other features over emphasized in data synthesis (see below). In the decision to conduct meta-analyses, I believe the key feature is the randomized design. I believe that the decision regarding randomized trials of vitamin E to separate small from large trials is poorly defended, in part, because I believe it is poorly defensible. For coenzyme Q10 also the key is randomization not length of follow-up or use of placebo. Furthermore, ATBC was a randomized, double-blind, placebo-controlled, 2x2 factorial trial of vitamin E and Beta-carotene. The most appropriate comparison is all vitamin E against all vitamin E placebo. In addition, the GISSI trial tested vitamin E and omega-3-fatty acid supplementation in a 2x2 factorial trial. To the best of my knowledge, no other antioxidants were randomized in that trial. Finally, evaluating all vitamin E against all no vitamin E in GISSI yields largely null results.	The stratification of trials of vitamin E based on sample size was done because pooling all together would make the overall pooled results totally based on the one or two very large studies, i.e. the smaller studies would be statistically meaningless. Rather than lose this information, we pooled the smaller studies and compared these results with the large studies. Regarding coenzyme Q10, we agree randomization is important, but disagree with respect to blinding (since this can introduce bias) and duration of treatment or follow-up (since the effects may be transient). We are now more cautious in the conclusions drawn from GISSI.
Many studies were excluded because outcomes of interest were not reported, and it does not appear that there was any effort to contact the study investigators in order to elicit supplemental data. While it seems unlikely that these additional data would materially affect the analyses, the report and its conclusions would be considerably more robust had these data been included.	The resources available precluded us from seeking unpublished data from the original researchers.

There is, however, one aspect of the data synthesis that I find troublesome, and this relates to the analysis and reporting of the vitamin E data from GISSI. GISSI was a prospective RCT utilizing a 2x2 factorial design to evaluate the effects of vitamin E and n-3 PUFA on major cardiovascular outcomes. A total of 11,324 subjects were enrolled, and in the vitamin E allocation, 5666 were assigned to vitamin E and 5668 were assigned to placebo. In the primary paper from GISSI (Lancet 1999;354:447-55), it is stated that there was no interaction between vitamin E and n-3 PUFA; therefore it seems that the fundamental criterion for a 2x2 factorial design was satisfied (i.e., independence of the 2 interventions), and that it is thus most appropriate to analyze the data for the entire population of subjects randomized to vitamin E or placebo. As reported in the GISSI publication, there was no suggestion of a beneficial effect of vitamin E on any major primary or secondary cardiovascular outcome in two-way analysis considering the entire population, a finding wholly consistent with the results of the analyses conducted as part of this Evidence Report. When 4-way analysis was performed, however (i.e. comparing outcomes across the 4 subgroups created by the 2x2 factorial design), there suddenly appeared an apparent beneficial effect of vitamin E on several secondary outcomes. I have difficulty understanding how this could happen, and I am skeptical about the validity of these findings. Therefore, I think that additional discussion of the GISSI data, and its potential limitations, is warranted, so as to avoid giving the impression that this large randomized trial of vitamin E showed improved cardiovascular outcomes, a conclusion that is in fact at odds with how the GISSI group itself interpreted their results.	We have noted in the results and summary that the two way analysis of vitamin E did not show an effect and that the GISSI investigators did not consider their data to prove that vitamin E supplementation is beneficial.
Also, an important limitation of the report is that individual patient data were not available, thus limiting exploratory analyses of relevant subgroups.	The resources are not available for us to seek unpublished data from the original researchers.
Within the confines of the objectives for study identification, no crucial pieces of information were missed. However, isoprostane should not be employed as a search term for coenzyme Q10 (coQ).	This term was included in our search strategy, but no titles or articles were selected based on this term, so this comment is moot.
Search terms. Is isoprostane and appropriate search term for coenzyme Q10? Should ubiquinol (the reduced form as it is present in the blood and on the lipoproteins) and neuquinon be added to the list?	See previous reply.

It appears that the intent to conduct a meta-analysis on the three pre-specified endpoints distracted the authors from extracting other relevant information from most of these studies.	The three outcomes selected for meta-analysis were chosen after examining our list of all outcomes measured in all reports. The three outcomes selected were those that were mose relevant to patients and most commonly reported. So, while we assessed whether other outcomes were reported, our findings indicated the data were too sparse to support a summary analysis either quantitative or qualitative.
I think the meta-analysis is a useful contribution to this literature. However, in isolating individual outcomes from trials, not all of which reported the identical outcomes, one loses the context provided by looking across outcomes for a trial. I also think that information from the 2x2 analyses, which may be inappropriate for meta-analysis, should be retained somehow. I would like the authors to consider how they might incorporate the results of their meta-analysis into a discussion that addresses the more complete data and context more thoroughly. The organization of the text is completely driven by the desire to conduct a meta-analysis of specific endpoints. While that is understandable, it defeats the purpose of conveying any overall sense of the consistency of findings within a trial. For example, the findings in GISSI that CVD mortality was significantly reduced looks a lot less impressive when one sees that there was no effect on overall CVD event rate. Moreover, the significant result on CVD mortality in the 4 way analysis (vit E only vs. placebo only) disappears in the 2 way analysis (comparing all patients who got vitamin E to all those who didn't). Similarly, the trend towards a benefit on non-fatal MI in a subgroup of ATBC with prior CHD is similarly undermined by observing that fatal MIs were increased, and that there was no benefit on total CVD events. The insistence on using only the 4 way results in the 2X2 factorial trials seems to have excluded potentially useful information. Again, it was so hard to follow what was included, when and why that maybe those results got mentioned but I can't be sure. Lastly, one could take issue with the decision not to pool primary and secondary prevention trials for MI outcomes – some trials included in the secondary prevention like HOPE had some patients without prior CHD. And some primary prevention trials had some patients with underlying vascular disease (at least in some analyses).	We have incorporated into this revision more information about both GISSI and ATBC so readers can get a better understanding of these trials. We also have tried to revise the organization to be more clear.
Composition of the Technical Expert Panel. Noted absence of a nutritionist, expert in biochemistry/metabolism and/or cardiovascular medicine.	The TEP for the NCCAM project was consistent from project to project and inevitably did not include all the relevant disciplines. These persons were included at the peer review stage to ensure that their expertise were incorporated into the report.

The searching strategies appeared appropriate. Reference was made to the Technical Expert Panel (p 25) that advised on search and inclusion criteria and appropriate analysis. However, the expertise of the Panel as listed did not include either cardiovascular disease or antioxidants, so their relevance to the design of this report is unclear.	See previous reply.
Extraction of Data, second paragraph. Comment on the equivalence of units for data extraction. I'm very pleased to see this but would like to see it taken a step further to equivalence in terms of supplement formulations, i.e., synthetic vs. natural. I feel very strongly that an attempt to standardize (for statistical analysis) the doses used in these trials should be made, as levels of bioactive ingredients are key. It has been shown that synthetic all rac-alpha-tocopherol increased plasma alpha-tocopherol concentrations only half as much as the natural form of RRR-alpha-tocopherol, and degradation of the synthetic form is 3-4 times that of the natural form (see Brigelius-Flohe, Am. J. Clin. Nutr. 2002;76:703-16 as well as IOM, 2000 DRI report for vitamin C, vitamin E and carotenoids). It would be helpful to incorporate this information in the data analysis tables (Tables 3-17) under the Intervention column.	While available for many trials, this information is not available for all trials. We were also unclear how we might adjust for differences in formulation or potency over time, so while we agree in principle with this comment, we did not think we could do this in our analysis.
First paragraph. I don't believe we know the most clinically relevant dose for the antioxidants, and again, dose and formulation do matter. The dose and formulation used in one study, i.e. HOPE 400 IU of natural alpha-tocopherol, may not equate with 300 mg of synthetic alpha-tocopherol used in the GISSI study. Similar problems exist for coenzyme Q10 formulations as the fat-soluble preparations have higher absorbability, which for CoQ10 is extremely low. CoQ prepared in soybean oil is the preparation regarded as the standard for clinical trials. Doses over 100 mg/day need to be delivered in divided doses, preferably with meals.	Change made: added to Limitations. That knowledge about dose and formulation is inadequate at this point in time.
I believe that the methods of study selection and data synthesis in this report could potentially bias the overall conclusions. In these instances, however, virtually all the data on clinical cardiovascular disease outcomes from individual trials are null (with the possible exception of CHAOS) so the conclusions are not materially affected.	No response.
I have trouble with the quality of the trials being reflected in the "Jadad" score. While this is a formal methodologic definition of quality, I do not see it as directly addressing the issue of quality of the science or scientific design. It does not appear that many, if any, high quality scientific trials have been performed to examine vitamin C in cardiovascular disease. If that is the case, it may be somewhat misleading to say that there is "no evidence" for a beneficial effect when the clinical experiments are biologically so unlikely to provide a positive result.	Perhaps not to examine vitamin C alone in the prevention of cardiovascular disease, but we judge the MRC/BHF study of vitamin C in combination with other agents to be both a high quality study and to report good evidence of no benefit.

The discussion among the scientific community regarding the outcome of AO studies and CVD prevention is that we may have approached the question incorrectly and studied (or compared) the wrong subject groups. Perhaps the draft should incorporate somewhere in its conclusions the idea that when subjects with relatively low antioxidant levels are studied, a stronger treatment effect may be found.	Change made to future research and Limitations.
One of the objectives of this report was to determine if statistical results from various studies could be pooled. This was shown in most instances to be true with some important provisions. As in the case of the SPACE study discussed above, there may be problems with pooling some primary or secondary intervention trials. When the results of studies such as VEAPS, GISSI or SPACE are to be compared, it is clear that the subjects are very different. Pooling such data may be too results confounding and is misleading.	All of the following comments concern the suitability of pooling certain studies. We agree that this is always a source of concern, with no "right" answer. To deal with these concerns, we performed sensitivity analyses, dropping the SPACE Study and the study by Haeger. This did not effect our results. We also note that the event rate in the placebo group in the GISSI and HOPE Study are similar, and this supports our decision to pool these studies.
There are problems with inclusion and exclusion criteria for selected articles that introduce bias for meta-analysis. For example, the SPACE study (Table 3, 5, 6, 8,10) (Boaz, Lancet 2001) specifically addresses vitamin E in patients with coronary disease and end stage renal disease on dialysis. The results should be mentioned as evidence of potential benefit of vitamin E, but not included in tables of secondary prevention or included in pooled analysis.	See previous reply.
The appraisal of studies is an area of concern. The outcome parameters are addressed ignoring clinical status of the subjects that limit the appropriateness of meta-analysis and lumping. For example, in GISSI Provenzione (Lancet, 1999) all 11,000+ patients had a myocardial infarction (MI) within the previous 3 months, in CHAOS patients had angiographic CAD and not necessarily previous MI (page 36), and HOPE did not require coronary disease and included diabetics and hypertensives without known disease. While each is a “secondary prevention” trial, I don’t think they can be lumped without inducing a possible dilution bias. I appreciate the Evidence Report Study Group would have considerable difficulty with these differing entry criteria and thus the weakness of meta-analysis.	See previous reply.

Data synthesis is the area I am most concerned about. There is lumping of studies for primary and secondary prevention that introduces bias. For example, the SPACE study by Boaz, Lancet 2000 (Table 3) evaluates vitamin E in a population with end-stage renal disease on dialysis. The effects of dialysis on CV outcome are so important this study should not have been included, albeit it did not influence outcomes. Similarly, the study by Haeger in 1968 (Table 3) using vitamin E in peripheral vascular disease was conducted in a time in which therapy and diagnosis was so limited I would not include it.	See previous reply.
The report indicates that evidence of benefit was not obtained in the pooled analysis of smaller trials of vitamin E (alone or in combination) and contrasts this null outcome with the reduction in mortality found in the ATBC and Linxian trials. The repeated comparative reference to these results suggests a less than adequate appreciation of the difference between the secondary prevention intent of the smaller trials and the primary prevention objective of the larger trials.	We revised our text to be more guarded in our conclusions regarding the mortality differences seen in ATBC and Linxian. Normally we would expect a secondary prevention trial to be more likely to show an effect than a primary prevention trial, all other things besides patient risk being equal (which is the opposite seen here). The "difference" in the results in this collection of studies may be more a consequence of the ability to test multiple subgroups in the larger trials.
Little mention or consideration is given to the increase in fatal MI observed in the CHAOS trial or the increase in hemorrhagic stroke found in the ATBC. While these results may be explained as spurious or described as unconfirmed by other studies, these data must be provided appropriate emphasis in this report.	Change made in the Safety section of Introduction for ATBC and the increase in fatal MI in the CHAOS study is already indicated in Table 12 and Figure 12.
I don't think there was any bias, but the clinical differences between studies are so great I don't believe a meta-analysis or lumping is appropriate. From my perspective I could see lumping the results of the British Primary Prevention Program and BMC/Heart Protection Study. While HOPE and GISSI were both secondary prevention studies, the HOPE study would dilute the GISSI results because patients were lower risk.	Our calculation shows that the event rates in the HOPE study were comparable to the rates in GISSI trial, supporting a decision to pool.
Meta-analysis of Vitamin E Alone vs. Placebo: first paragraph, second sentence notes that "a fifth smaller trial is also included in this meta-analysis" however this trial is not identified by name or author in the text (but is referenced). This study was performed in 1968, were comparable design methods and antioxidant formulations utilized?	Change made and results redone dropping this study as a sensitivity analysis.
You include the vit E + PUFA results under the table vitamin E + other vitamins. PUFA is not a vitamin, however, and if it has any benefit it is probably not as an antioxidant but through effects on thrombogenesis.	Correct, we changed the names of this category to "vitamin E in combination".

In the first paragraph on p 35, the MASIT trial was referred to, but there was no description of the trial in the next section on “Details of Named Trials”.	Change made.
The Linxian Nutrition Intervention Trial (page 36) was conducted in a population of Chinese who were known to be vitamin deficient to determine the value of micronutrients on esophageal cancer. As stated the CVD outcomes were not the primary goal of the study. The baseline clinical examinations and measures of CVD at outcome are not at the same standards of the other studies.	This limitation of the Linxian study was added to the Limitations section.
Details of the “Named” Clinical Trials… In the text description, if the details regarding formulation are not added to the data tables, then you may want to provide the specific formulation of the interventional agent (natural, synthetic, lipid soluble, etc) in the text.	Change made. Descriptions added.
There is an error on page 37, last sentence regarding the MRC/BHF study: ASA should have been simvastatin.	Editing mistake has been fixed.
Benefits of ASA? – is this aspirin?	See previous reply.
Trial Inclusion. Perhaps some explanation on the rationale for six months as the minimal appropriate time for adequate assessment. If this were a statin trial, would six months be a minimal appropriate time for adequate assessment for an outcome of MI? Most statin regression trials run for at least two years. Why would we expect vitamin E to be more powerful than a statin in preventing MI?	As it turned out, mostly all of the studies had two years duration of treatment, so this comment is moot.
The description of the different ATBC analyses is confusing. The text on p. 46 implies you used the primary prevention analysis in the pooled analysis but I don’t think that is true but there aren’t references attached with specific statements in the text.	Change made.
Third paragraph, first sentence. Please identify “an additional trial” and its text by name or author and its respective risk ratio as well as providing the reference citation.	Change made.
You state the largest study was the ATBC – that is not true for the subanalysis you rely on. The table and forest plot on non-fatal MI make it clear that the two largest studies showed no benefit on non-fatal MI. Only a subgroup analysis of ATBC suggests a benefit, along with some other small studies.	The reviewer is correct. We changed the text to reflect this.
It is not clear why the ATBC results for primary prevention portion are not included in tables but are described in text. My understanding is that one of the analyses eliminated those with prior CVD, so you could avoid overlap. Even if not, it is worth including in table (not meta-analysis) with footnote if there is an issue of overlap.	Change made to the "not-pooled" section of relevant tables.

Second paragraph, seventh sentence describing the other study (not identified in text by name), which is a study in patients following PTCA. Is this patient population considered comparable to those in the other secondary prevention trials as PTCA increases vascular reactivity and can enhance the disease process?	While the patient population was at high risk, we did not consider this study further because of follow-up time. 3-28 days was not comparable to the other studies.
Summary – I think this section is inaccurate. You state that the benefits of ATBC suggest a benefit for vitamin E alone for fatal MI, when it is GISSI (according to your tables) not ATBC suggesting benefits against fatal MI. For non fatal MIS, both CHAOS and ATBC subgroups suggest possible benefit, but you state on page 50 that the ATBC results for the general population suggest a benefit on nonfatal MIs. There was a trend toward benefit only in a subgroup with prior MI, but no benefit in the larger population of ATBC participants.	Corrected in text. Factual errors were corrected in the results section.
Last line paragraph 2 – "heterogeneous sample size" – meaning?	Large differences between trials in sample size text. Revised to make this clear.
First paragraph. Last sentence – "attempts to stratify the analysis by vitamin E dose level were not helpful." This is important, could the same be done for formulation: synthetic vs. natural at high and low doses? Same comment for analysis of HDLs and meta-analysis parameters.	The data are insufficient to support this analysis.
Second sentence is unclear as written. "A small negative effect not favor of treatment was shown."	This sentence was revised.
The decision to pool clearly heterogeneous results seems problematic, especially without some attempt to explore reasons for the heterogeneity. The two largest studies show no benefit, but the pooled result is driven by small, outlier studies. The text could do a better job of explaining this result as it may be misinterpreted.	We revised the text to try and better explain this.
The tables in Table 6 and 7 cite the identical number of deaths for GISSI results under vitamin E alone and Vitamin E + other vitamins. This is presumably an error. My suggestion is to delete the vitamin E + PUFA results altogether but if you keep them (there may be a case for doing so I don't know this area intimately) you need the correct figures for that arm.	These numbers have been double-checked for accuracy.
The report's overall conclusion is that the three antioxidants alone or in combination do not have a significant effect on the treatment and prevention of CVD. However, these conclusions cannot be made categorically as evidence from some studies suggest that some protection is conferred and in some instances AO use can confound or even worsen the effects of other interventions. It is important to emphasize that further studies are needed, especially using specific populations, to better understand the effects of AO supplements. This is clearly indicated in this draft and I find it to be among the most important conclusions or recommendations of this report.	No response.

There is insufficient comment about the potential positive outcomes from intermediate trials or studies that were complicated by multiple interventions or other complexities. This is especially true for studies that used subjects with disease that predispose to cardiovascular disease (e.g. SPACE trial).	This limitation was added to the Limitations and Conclusion sections.
Drawing conclusions on the potential role of antioxidants in CVD prevention and treatment, as noted above, by using only death, MI, and/or blood lipid levels as evaluative criteria likely underestimates their true value by ignoring their impact on other relevant parameters such as antiplatelet actions, vascular reactivity, antihypertensive capacity, and impact on the risk for related diseases like diabetes.	The intermediate outcomes listed by this reviewer were not assessed in this report because their relation to clinical outcomes (death, MI) are not firmly established. Within the resources available to us, we concentrated on clinical outcomes and intermediate outcomes with strong evidence of an association with clinical outcomes. Whether lack of assessment of these other intermediate outcomes underestimates or overestimates the effect of antioxidants on patient outcomes is unknown.
I agree with your conclusions but am doubtful surrogate endpoints will be of any value. They encourage extrapolation to the positive and don't address risk adequately. Physicians Health Study 2 will address long term use of vitamins. I favor targeting well-defined high risk populations such as diabetics with CAD, a high risk group that can be studied over a relatively short period.	Added to future research.
The major issue with antioxidants is that studies were stopped early because of outcome of other arms such as omega 3 fatty acids in GISSI, ramipril in HOPE, and simvastatin in BMC/HPS. There is a reasonable possibility that the benefit of antioxidants won't be reached for 10 years. Hopefully, the Woman's Health Initiative that is looking at vitamins will continue that arm regardless of other results.	Change made in Limitations.
The other issue is the potential for pro-oxidant effects of vitamin E and the need for combining vitamin E with a tissue antioxidant such as coenzyme Q-10.	This was added to future research.
Also, on page 62, line 5, seven outcomes are listed (not eight), and on page 64, line 14, it appears that the authors mean "fatal myocardial infarction" (not "all cause mortality").	Change made.
Similarly, on page 67, line 19, "total cholesterol" is incorrect; it should read "HDL cholesterol".	Change made.
I also disagree that further research on antioxidants is needed with surrogate endpoint. Finally, as regards coenzyme Q10 depletion does not imply that supplementation will lead to clinical benefit. For these reasons, rather than simply state further research is needed, I would emphasize that randomized trials, not observational studies are needed to avoid previous pitfalls with other antioxidants.	Agreed

First, since the population of RCTs is overwhelmingly comprised of middle-aged white males, there is a need for studies evaluating the effects of antioxidants in the elderly, women, and racial/ethnic minority groups (esp. blacks and Hispanics).	Added to future research.
Second, although this report focuses on mortality and major cardiovascular events, other endpoints may be relevant in selected patient populations; e.g. it is conceivable that coenzyme Q10 improves symptoms in patients with heart failure but does not reduce mortality, or that vitamin E has a favorable effect on preserving cognitive function in the elderly (as suggested by one study) without affecting mortality or cardiovascular events.	Agreed, although for the purposes of their report a presentation of cognitive function would fall outside our scope.
While it is evident that research focused on understanding the conflict between the largely consistent and compelling CVD primary prevention data with supplements and the largely null and discouraging CVD secondary prevention results with supplements, this "paradox" does not include the "beneficial effects of fruit and vegetable consumption". Contrary to the statement in the report that "It was postulated that the antioxidant component of fruits and vegetables accounted for the observed protection" (my emphasis), antioxidants have always been considered only as contributing factors in this context, along with other associated nutritional relationships associated with this dietary pattern (e.g., B vitamins, fat, and fiber).	Changes made to reflect this.
Further research is proposed to test "formulas which showed benefit in larger trials", however, none of these trials (as chosen for this report with its selected evaluation endpoints) provided sufficient evidence or magnitude of benefit to justify such an investment in new research. Similarly, trial interventions employing food concentrates fails to provide any guidance or priority, e.g.: what foods? what ingredients? concentrated how? administered for how long and to whom?	We have resolved this section of future research.
The recommendation to determine if fruit consumption is associated with other behaviors which cause benefit for which fruit consumption is a marker is reasonable. However, it is not clear why a similar recommendation is not proffered for vegetable consumption.	Vegetables have been added.
The recommendation to repeat the interventions which did show positive results is confusing as these studies (e.g., CHAOS and SPACE) have already essentially been replicated (e.g., HOPE and HPS) and shown a null outcome.	Agreed. Change made to future research.
No suggestions for future research are offered which prioritize single antioxidants or combinations for study.	We think this is best left to an expert panel assembled by the sponsor and considering the results in this report.

Similarly, although the need for “appropriate surrogate endpoints or intermediate outcomes” for CVD is emphasized, no suggestions are offered as to which ones might prove most likely to be successful, e.g., biochemical markers, lesion indices, physiological responsiveness, etc.	See previous reply.
Importantly, it should be noted that none of the large clinical trials have employed relevant biomarkers either to validate them or to test the efficacy of the intervention (e.g., increasing antioxidant defenses or lowering oxidative stress).	Added to future research.
Suggestions for future research should include recommendations as well for: [i] documenting full dose-response relationships of the selected antioxidants (N.B.: doses of 1200 IU vitamin E appear required to affect biomarkers of oxidative stress and inflammation relevant to atherogenesis [Devaraj & Jialal. *Free Radic Biol Med*. 2000;29:790-2]), [ii] determining polymorphisms relevant to CVD pathogenesis (including endothelial nitric oxide synthase, 12/15-lipoxygenase, and macrophage scavenger receptors) as well as to redox states, and oxidative stress status (and employing them as inclusion/exclusion criteria), [iii] employing lower risk groups (presumably whom utilize fewer concomitant drug therapies), [iv] exploring the relationship between antioxidant and B vitamin status (as homocysteine is a pro-oxidant), [v] the potential for adverse interactions with pharmacotherapy (e.g., see Cheung et al. *Arterioscler Thromb Vasc Biol*. 2001;21:1320-6).	Most of these have been added to future research.
I believe the statement to be unwarranted that further research is necessary to explain the apparent paradox between results of observational studies and randomized trials. In fact, it should be stated clearly in this report that for many, if not most, expose and disease hypothese randomized trials are neither necessary nor desirable. When searching for small to moderate effects, however, (20-50%) the amount of uncontrolled and uncontrollable confounding inherent in observational studies is as big as the most plausible benefits or harm. In such circumstances, reliable data can only derive from randomized trials of sufficient size, dose, and duration. In my view, observational studies have been misleading for vitamin E, beta-carotene, and postmenopausal hormones.	Agreed. The Future Research section focuses on RCTs.
Perhaps one of the most critical research needs is to identify and standardize the test agent and administer it under the most appropriate conditions.	Agreed. This is included in future research.

The future research sections beginning on page 5 and page 71 might benefit from some revisions. The meaning of the following sentence at the end of "Future Research" on page 5 escapes my understanding; "the observation that higher levels of vitamin C were associated with lower death rate has not been confirmed yet in clinical studies. The explanation of this apparent paradox requires additional investigation as well". By higher levels, I presume you are referring to the serum concentration of vitamin C. If so when one says "higher levels", what is being referred to, higher than what? Likewise, I do not see the apparent paradox. What serum concentration of vitamin C do you think would be associated with a lower death rate?	This section has been revised.
In the Future Research section on p 5, it is stated that a possible avenue of future research would include testing of formulas which showed benefit in larger trials. There was no discussion of formulas in the report, nor any information on what formulation of agent was used by what trial. It sounds like you are suggesting that, for example, trials with promising results all used synthetic vitamin E not natural source (or vice versa). Is this true?	This has been clarified.
It is also stated on p 5 that additional research is needed for vitamin C on risk factor modification and lower death rate, and for co-Q10 on heart failure and cardiac surgery. It felt like these recommendations were coming out of the blue, since there were no statements in the preceding body of the Summary that even mentioned C or coenzyme Q10, and no full discussion in the actual report of an assessment of the status of the evidence of these agents.	This revision now includes data about vitamin C and coenzyme Q10.
It was also stated that surrogate or intermediate outcomes could be useful to do trials more quickly – trials of what? For vitamin E, for example, I can't see any place to go with another trial in CVD.	We have eliminated the suggestion to assess intermediate endpoints.
On page 71 I do not see the scientific logic of the suggestion of using supplements such as food concentrates with respect to vitamin C. Why would taking ascorbic acid in a food concentrate be more beneficial than ascorbic acid? I strongly favor the suggestion to perform studies to ascertain if favorable dietary compositions are markers for other beneficial behaviors. Again on page 71, is the issue of "higher levels" of vitamin C and decreased risk of death would benefit from restatement. I don't see the nature of the apparent paradox, nor is there any specificity of how this should be tested. Should one give very large pharmacologic doses of vitamin C and measure cellular and tissue accumulation?	This recommendation has been deleted.
Bullet 1 it is said to consider interventions which are intermediate between foods and isolated chemical supplements such as food concentrates, etc. I was just unclear what that meant – could you add an example of what that means for vitamin E and C, for example.	This recommendation has been deleted.

The third bullet says to perform careful "cohort trials to determine if fruit consumption is associated with other behaviors . . ." First, it is cohort studies, not trials, and second, did you mean vegetable consumption? – or fruit and vegetable consumption?	This recommendation has been deleted.
In bullet 4, it is stated that in observational studies, vitamin C is associated with decreased risk of death, but that this result "has not been reported in the clinical trials literature using supplemental vitamin C. Further trials could investigate this apparent paradox as well". A "paradox" implies that trials of vitamin C supplements were conducted and did not show a benefit on death. From your report, it appears there were no trials of vitamin C supplementation, which means they have to be done, not that there is a paradox. This needs to be clarified.	This text has been revised.
Bullet 5 says that the interventions that did show positive results need to be repeated to see if they can be replicated – I think it has to be added "to see if the findings were real or due to chance".	Agreed.
Top of p 72 says the most effective formulations for some antioxidants, e.g. vitamin E, have not been clearly determined. Again, this was not discussed in the report in terms of linking results to formulations in completed trials.	This has been deleted.
Comment: Since there are a number of ongoing primary (PHS II, WHS, SU.VI.MAX) and secondary (HPS, WACS) studies, as well as regression studies evaluating antioxidant use and CVD outcomes how should the research recommendations be prioritized or qualified so as to avoid duplication of effort or inappropriate or premature recommendations for future research? Should all future studies be required to utilize the same formulation of test preparation (antioxidant)?	Change made to future research.