REVIEW

# Effect of Supplemental Vitamin E for the Prevention and Treatment of Cardiovascular Disease

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***OBJECTIVE:*** **To evaluate and synthesize the evidence on the effect of supplements of vitamin E on the prevention and treatment of cardiovascular disease.**

***DESIGN:*** **Systematic review of placebo-controlled randomized controlled trials; meta-analysis where justified.**

***MEASUREMENTS AND MAIN RESULTS:*** **Eighty-four eligible trials were identified. For the outcomes of all-cause mortality, cardiovascular mortality, fatal or nonfatal myocardial infarction, and blood lipids, neither supplements of vitamin E alone nor vitamin E given with other agents yielded a statistically significant beneficial or adverse pooled relative risk (for example, pooled relative risk of vitamin E alone = 0.96 [95% confidence interval (CI), 0.84 to 1.10]; 0.97 [95% CI, 0.80 to 1.90]; and 0.72 [95% CI, 0.51 to 1.02] for all-cause mortality, cardiovascular mortality, and nonfatal myocardial infarction, respectively.**

***CONCLUSIONS:*** **There is good evidence that vitamin E supplementation does not beneficially or adversely affect cardiovascular outcomes.**

***KEY WORDS:*** **vitamin E; antioxidants; meta-analysis; systematic review; cardiovascular disease.**
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Cardiovascular disease, 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, 1 in 5 Americans had cardiovascular disease, and 958,775 died from it that year. This figure represented 40% of all deaths in the United States that year, equal to the next 7 leading causes of death.[1] Globally, cardiovascular disease accounts for an estimated 31% of worldwide mortality and burden of disease from all noncommunicable diseases.[2]

The epidemiologic and observational literature have suggested a beneficial effect of antioxidant-rich foods, as well as specific antioxidants, on the risk of cardiovascular disease.[3–9] The purpose of this study was to conduct a systematic review and meta-analysis of randomized trials to assess the evidence for the efficacy of supplements of the antioxidant vitamin E for the prevention and treatment of cardiovascular disease.

## METHODS

### Identification of Literature

This report is part of a larger review of the literature regarding the antioxidants vitamin C, vitamin E, and coenzyme Q10.[10] This report deals only with vitamin E. Potential evidence for the report came from 3 sources: published reports listed in online databases and in the reference lists of relevant articles, and other sources such as experts in the field and the personal libraries of project staff and their associates. "Gray" literature was included (abstracts, etc.) but we did not specifically search for unpublished data.[11] We conducted 4 searches on the specific interventions of interest with no language restriction. The full search strategies and antioxidant terms are displayed in the Appendix (available at http://www.jgim.org). In brief, we searched Medline, Embase, MANTIS, Allied & Complementary Medicine, Biosis Previews, CAB Health, Cancerlit, the Cochrane Library, Social SciSearch, SciSearch Cited Ref Sci, and TGG Health & Wellness Database using supersensitive search terms for clinical trials and vitamin E, alpha-tocopherol, d-alpha-tocopherol, rrr-alpha-tocopherol, and all rac-alpha-tocopherol.

Two trained reviewers (a physician and a PhD) independently evaluated lists of titles and abstracts (from which duplicates were removed) generated by the online database searches, as well as the additional titles from other sources to identify clinical trials in humans that assessed the effect

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of supplements of vitamin C, vitamin E, or coenzyme Q10 and reported clinical outcomes or intermediate (surrogate) outcomes that are closely associated with clinical outcomes. Fifty-two abstracts or articles in 7 languages other than English were reviewed by physicians in the language, with the assistance of a member of the study team. Non-English language articles did not undergo dual review.

## Data Extraction

Detailed information from each study was collected on a specialized data collection instrument. The reviewers, working independently, extracted data in duplicate and resolved disagreements by consensus. A senior physician resolved any disagreements not resolved by consensus.

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.[12,13] A quality score was calculated for each trial using a system developed by Jadad.[12] Empirical evidence has shown that studies scoring 2 or less on the Jadad scale report exaggerated results compared with studies scoring 3 or more.[14] Whereas other elements of the design and execution of controlled trials have been proposed as quality measures, empiric evidence supporting their use as generic quality measures is lacking.

## Data Synthesis

For groups of studies that assessed interventions, populations, and outcomes that were sufficiently similar, we performed meta-analysis. We estimated the Dersimonian and Laird random effects[15] pooled log risk ratio if the outcome was binary, or effect size if the outcome was continuous, and associated 95% confidence interval. We applied a random effects model as it incorporates both within and between study variation. We transformed the pooled log risk ratio to the risk ratio scale for interpretability. For each subgroup of comparable studies, we calculated the $\chi^2$ test for heterogeneity based on Cochran's $Q$,[16] and the $I^2$ statistic and its 95% uncertainty interval.[17] This latter statistic represents the percentage of study variability due to heterogeneity rather than chance, and is independent of the number of studies and the effect size metric. We present a forest plot for each meta-analysis in which each individual trial intervention effect 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 its location. A vertical solid line either at 1 (for risk ratio analyses) or at 0 (for effect size analyses) indicates no treatment effect. We performed some posthoc sensitivity analyses motivated by the observed heterogeneity among the trials. These posthoc sensitivity analyses included removing any trials that appeared to have extreme estimates.

For each subgroup of trials for which we conducted a meta-analysis, we assessed the possibility of publication bias graphically by evaluating a funnel plot of the log risk ratios or effect sizes for asymmetry, which would result from the nonpublication of small trials with negative outcomes. Because graphical evaluation can be subjective, we also conducted an adjusted rank-correlation test[18] and a regression asymmetry test[19] as formal statistical tests for publication bias.

# RESULTS

## Description of the Evidence

Our literature search identified 8,173 titles, which yielded 156 articles that represented results from 144 unique trials (see Fig. 1). Of these, 84 trials concerned vitamin E. A number of articles reported on different aspects of several large clinical trials. These large trials are described in Table 1 and are categorized as primary or secondary prevention trials based on the population enrolled. All studies reviewed in depth are summarized in the evidence table in the Appendix.

## Vitamin E Trials that Report Death as an Outcome

Twenty trials reported on death as an outcome and were therefore considered for pooled analysis. We decided not to pool the primary prevention trials with the secondary prevention trials, as the death rates in the primary prevention trials are expected to be lower because the patients did not have known preexisting disease. We considered pooling primary prevention trials (ATBC, PPP, ASAP, Linxian)[20–23] but judged these 4 trials to be too heterogeneous in terms of interventions to support statistical pooling; thus the findings for these studies are reported narratively.

The follow-up of the included trials ranged from 2[24,25] to 7 years.[26] The interventions consisted of vitamin E alone or in combination with other antioxidants, typically vitamin C or beta-carotene. Four of the trials tested a relatively low-dose vitamin E supplement (i.e., less than or equal to 400 IU),[26–29] and the remaining 4 trials tested a higher dose of vitamin E (greater than 400 IU).[24,25,30,31] For details of these trials, please see the evidence table in the Appendix.

***Meta-analysis of Vitamin E Alone Versus Placebo: All-cause Mortality.*** Four large secondary prevention trials reported on all-cause mortality using vitamin E alone as an intervention: the SPACE trial,[24] the HOPE trial,[27] the GISSI trial,[28] and the CHAOS trial.[25] A fifth, smaller, trial by Haeger and colleagues is also included in this meta-analysis.[26] The random effects pooled estimate was a relative risk ratio of 0.96 (95% confidence interval [CI], 0.84 to 1.10) as shown in Fig. 2. The $\chi^2$ test did not demonstrate significant heterogeneity ($P = .22$). The $I^2$ statistic was 31% (with 95% uncertainty interval 0% to 74%). Sensitivity analyses did not alter these results. Neither formal test demonstrated evidence of publication bias (Appendix Table). The results of these tests are presented in the Appendix.

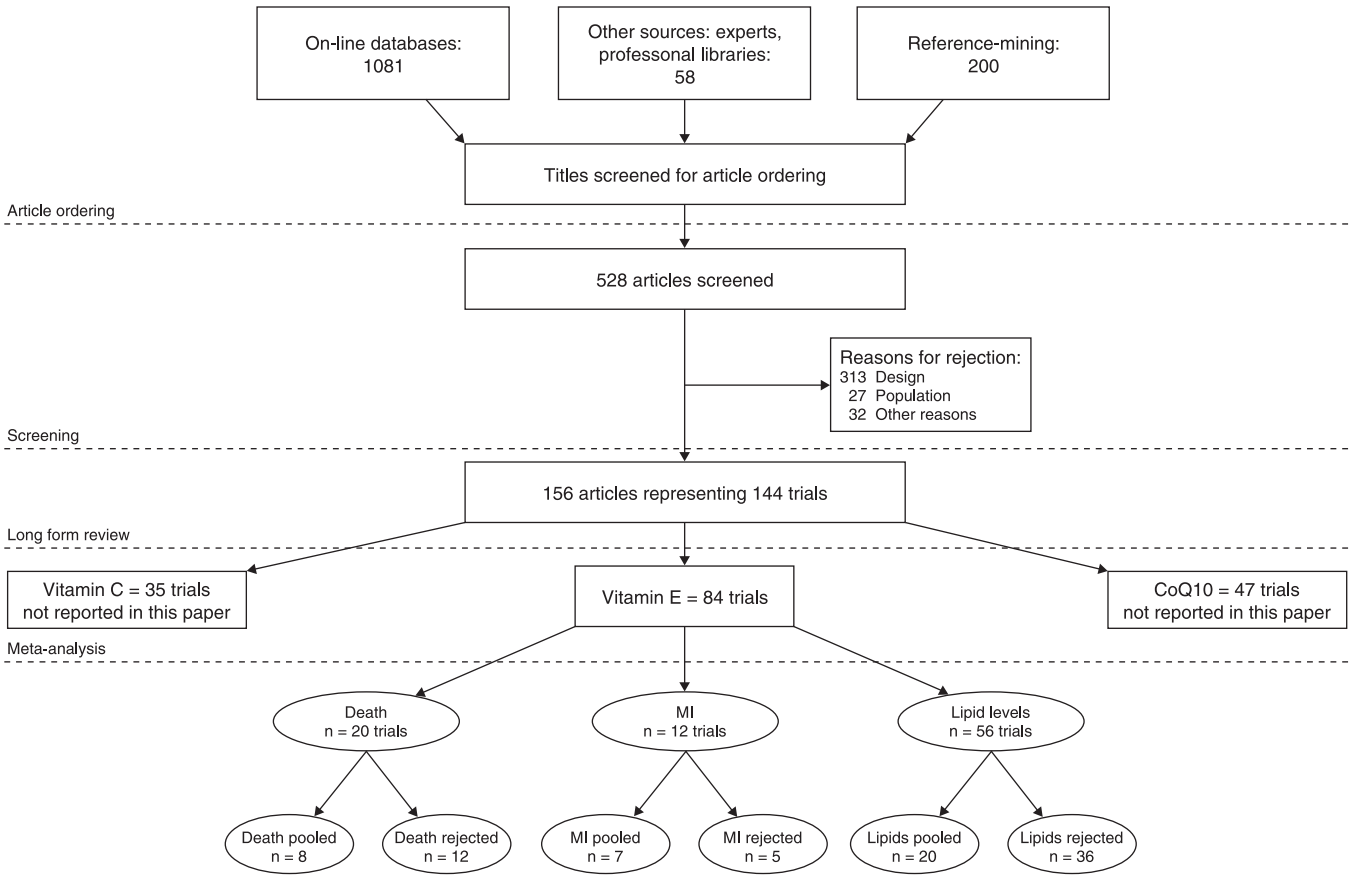


**FIGURE 1.** Flowchart of trials.

A small secondary prevention study by Gillian[32] that was excluded from the pooled analysis because of insufficient follow-up time (6 months) reported a relative risk ratio for all-cause mortality of 0.85 (95% CI, 0.13 to 5.52). The remaining 2 studies were primary prevention trials, and were therefore not included in the pooled analysis of the secondary prevention trials. The ASAP trial[22] reported a relative risk ratio of 3.00 (95% CI, 0.32 to 28.47) and the PPP trial[21] reported a relative risk ratio of 1.07 (95% CI, 0.78 to 1.49). Thus, the results of the 3 trials that were not included in the pooled analysis support the findings of the pooled analysis that there is no evidence of a significant effect of vitamin E alone on all-cause mortality, either in primary or secondary prevention trials.

***Meta-analysis of Vitamin E in Combination Versus Placebo: All-cause Mortality.*** Five trials were considered for this pooled analysis. Two of the trials were primary prevention trials, so they were not considered for pooling with the secondary prevention trials for the reasons previously listed.[22,23] Of the secondary prevention trials, one[33] had a follow-up time of 6 months, too short for pooling with the other studies. Eliminating those 3 trials left only 2 clinically similar trials, the GISSI trial[28] and the MRC/BHF Heart Protection Study,[30] an insufficient number for meta-analytic pooling. Therefore we describe the results for these 5 studies narratively.

The Linxian study[23] and the GISSI study[28] alone reported statistically significant benefits. The effect on all-cause mortality in the GISSI trial was almost certainly a result of the omega-3 polyunsaturated fatty acids that were given with vitamin E, with the former providing all of the benefits. In an analysis of the effect of the individual components in this $2 \times 2$ factorial trial, omega-3 polyunsaturated fatty acid supplementation was beneficial as measured by all-cause mortality (risk ratio [RR], 0.80; 95% CI, 0.68 to 0.95), whereas vitamin E supplementation was not (RR, 0.86; 95% CI, 0.73 to 1.01). Therefore, the beneficial effect reported for the combination of these 2 agents is most probably due to the omega-3 polyunsaturated fatty acids alone. The Linxian trial reported a statistically significant 9% reduction in all-cause mortality for subjects who received beta-carotene, selenium, and vitamin E (RR, 0.91; 95% CI, 0.84 to 0.99).[23] The other 3 studies all reported no statistically significant beneficial or adverse effect on all-cause mortality.[22,30,33]

***Meta-analysis of Vitamin E Alone Versus Placebo: Cardiovascular Deaths.*** Five trials were pooled.[24,25,27–29] The ATBC trial reported on the results at 2 different time intervals.[29,34,35] To avoid double-counting the data, only the results with the longer follow-up period[29] were pooled. The random effects pooled estimate for all studies was a relative risk

**Table 1. Large Clinical Trials Included in Various Pooled Analyses***

| | |
|---|---|
| **Primary Prevention Trials** | |
| 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.[20] The subjects ($N$ = 520) all had elevated lipid levels and included both smokers and nonsmokers. Serum lipids were measured as secondary outcomes. |
| 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 1 of 4 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 5 years and a maximum of 8 years.[32] |
| 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 CVD 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 1 of 5 treatments singly and in combination for 5.2 years. They were given either placebo or formula A (retinol [5,000 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 4 formulas were given together and a placebo group was included.[21] |
| 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.[42] |
| PPP | The Primary Prevention trial (PPP) involved 4,495 subjects in a $2 \times 2$ 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. Follow-up in this study was stopped after 3.6 years because of the proven benefit of aspirin supplementation in atherosclerosis (ASA) for cardiac patients.[19] |
| **Secondary Prevention Trials (testing the effects of antioxidants in preventing further disease in patients with preexisting cardiovascular disease) or persons judged to be at high risk for developing coronary artery disease.** | |
| ATBC (Subgroup) | The ATBC investigators also analyzed their trial for the subgroup of enrolled subjects with cardiovascular disease at the baseline examination.[27,33] The median time for follow-up was 510 days, this is the value used in this analysis. |
| CHAOS | The Cambridge Heart Antioxidant Study (CHAOS) assessed 2,002 subjects with angiographically proven coronary artery disease who 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.[23] |
| 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 g/day), both, or placebo for 3.5 years—and evaluated the risk of developing death, nonfatal MI, or nonfatal stroke as primary outcomes.[26] |
| 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.[34] 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 3 years. |
| HOPE | The Heart Outcomes Prevention Evaluation Study (HOPE)[25] enrolled 2,545 men and 6,996 women more than 55 years old who were judged at increased risk for CVD due to the presence of certain risk factors in a $2 \times 2$ 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. |
| MRC/BHF | The MRC/BHF trial enrolled 20,536 British adults with preexisting coronary artery disease, peripheral vascular disease, or diabetes in a 5-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.[28] |
| MVP | The Multi-vitamins and Probucol Study (MVP) enrolled 317 patients scheduled for percutaneous angioplasty and having preexisting coronary artery disease in a 6-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.[31] |
| SPACE | The Secondary Prevention with Antioxidants of Cardiovascular Disease in End-stage Renal Disease (SPACE) trial[22] 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. |

* *Data on vitamin E dosages, which were often in the form of alpha-tocopherol, are sometimes reported in milligrams and sometimes in international units (IU). One milligram of alpha-tocopherol is approximately equal to 1.5 IU of vitamin E.*

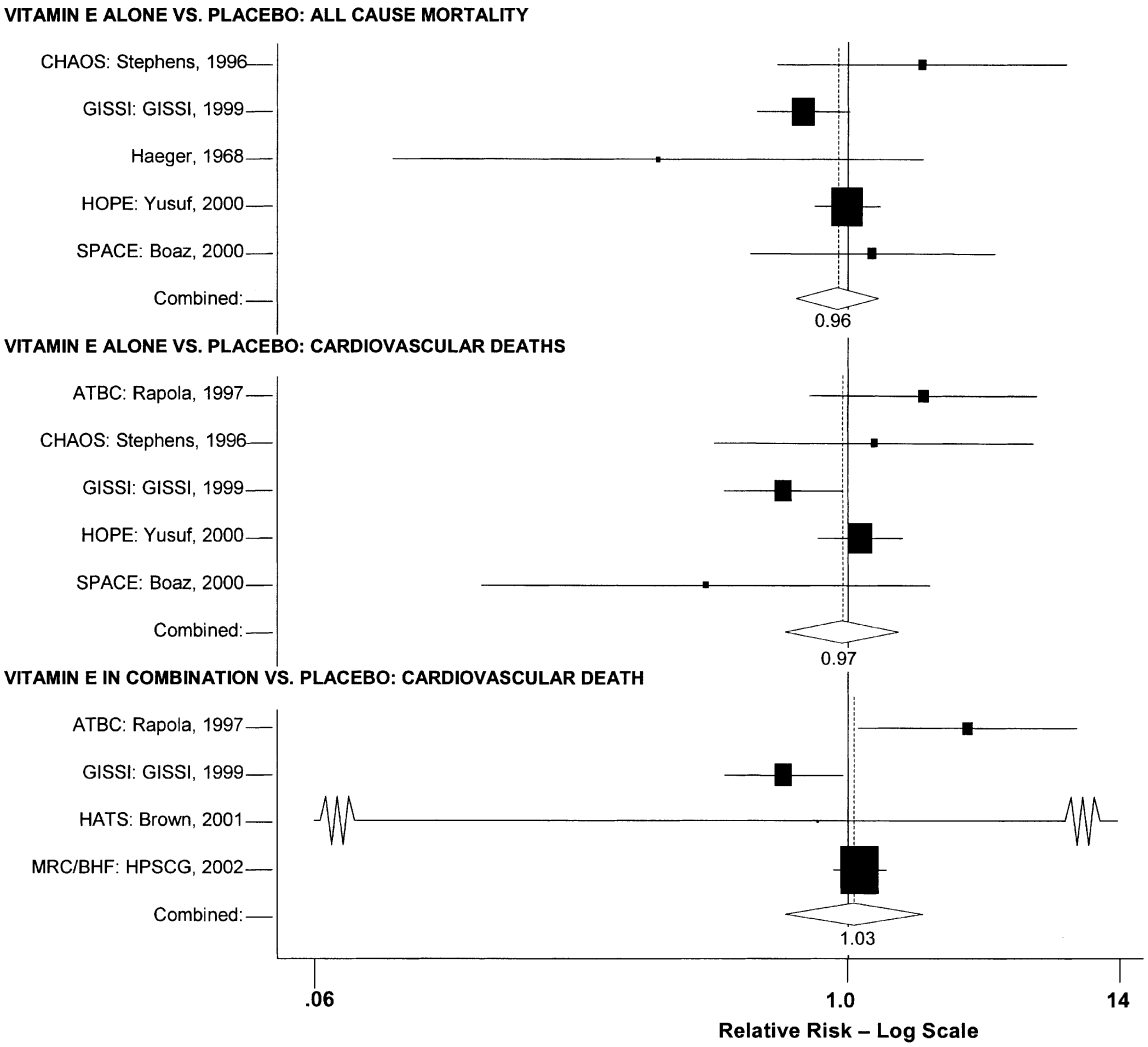


**FIGURE 2.** Pooled relative risk ratios for all-cause mortality.

ratio of 0.97 (95% CI, 0.80 to 1.19) as shown in Fig. 2. The $\chi^2$ test did not demonstrate significant heterogeneity with a $P$ value of .09. The $I^2$ statistic was 50% (with 95% uncertainty interval 0% to 82%). Sensitivity analyses did not alter these results. The GISSI study reported a significant benefit on mortality (RR, 0.80), whereas 3 of the other 4 studies actually reported nonsignificant increases in mortality in the treated groups. Neither formal test demonstrated evidence of publication bias (Appendix Table).

***Meta-analysis of Vitamin E in Combination Versus Placebo: Cardiovascular Death.*** Four trials were included in this analysis. A small secondary prevention trial, the HATS trial, was pooled[36] with 3 large secondary prevention trials: the ATBC trial[29] (cardiovascular disease subpopulation); the GISSI trial;[28] and the MRC/BHF trial.[30] The random effects pooled estimate for the 4 studies was a relative risk ratio of 1.03 (95% CI, 0.81 to 1.32) as shown in Fig. 2. The $\chi^2$ test did demonstrate significant heterogeneity ($P$ = .02). The $I^2$ statistic was 70% (with 95% uncertainty interval 12% to 89%). Similar to the findings for vitamin E alone, the GISSI trial reported a statistically significant benefit, while 2 of the other 3 trials reported increases in the numbers of negative outcomes in the vitamin E-treated group. There was no evidence of publication bias (Appendix Table).

The results of 2 analyses of the ATBC trial[34,35] that were not included in the pooled analysis demonstrated no evidence of a significant association of vitamin E in the combinations tested on the risk of mortality due to cardiovascular disease.

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

For the 4 preceding syntheses, the results did not generally support 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 all-cause mortality

and on cardiovascular mortality reported in the GISSI trial were observed only in the "four-way" analysis (that is, comparing each arm of the $2 \times 2$ factorial study separately), but not in the "two-way" analysis (comparing all subjects who received vitamin E to all those who did not). The GISSI investigators suggested that the results in the four-way analysis were likely due to chance and concluded that vitamin E supplementation conferred no benefit. The reduction in all-cause mortality reported in the Linxian study was primarily due to a decrease in cancer deaths, not cardiovascular deaths, although the relative risk reported for stroke deaths also achieved statistical significance (RR, 0.91; 95% CI, 0.84 to 0.99). Therefore, there is little evidence that vitamin E supplementation results in a reduction in cardiovascular mortality.

After we completed our analyses, results were reported for a new randomized controlled trial that assessed the effect of vitamin E, vitamin C, and estrogen in 423 postmenopausal women with preexisting cardiovascular disease. No benefit was reported for patients treated with vitamins E and C. A potential for increased mortality was reported in the antioxidant-treated group.[37]

## Vitamin E Trials that Report on Myocardial Infarction as an Outcome

Fifteen trials were considered for inclusion in this analysis. We judged the 2 primary prevention trials not clinically appropriate to pool with secondary prevention studies because of the differences in the populations studied.[21,34] We determined that 2 years of follow-up was the minimum appropriate for adequate assessment. Therefore, 4 studies were eliminated for insufficient follow-up time.[38–41] Seven trials were judged suitable for inclusion in the pooled analysis.[24,25,27–30,36] All of the included trials were secondary prevention trials; therefore, all the populations tested had a previous history of or significant risk factors for cardiovascular disease.

Three of the trials tested a low dose of vitamin E (i.e., less than or equal to 400 IU),[27–29] and the remaining 4 trials tested a high dose of vitamin E (greater than 400 IU). [24,25,30,31] The outcome of myocardial infarction (MI) was reported in 2 ways in these trials: as fatal MI or as nonfatal MI. We pooled these 2 outcomes separately. For details of these trials, please see the evidence table in the Appendix.

***Meta-analysis of Vitamin E Alone Versus Placebo: Fatal Myocardial Infarction.*** Five trials were included in the pooled analysis: the SPACE trial,[24] the HOPE trial,[27] the report of the ATBC subpopulation with preexisting cardiovascular disease,[29] the GISSI trial,[28] and the CHAOS trial.[25]

The random effects pooled estimate of the relative risk ratio was 0.97 (95% CI, 0.74 to 1.27) as shown in Fig. 3. The $\chi^2$ test did demonstrate significant heterogeneity ($P$ = .03). The $I^2$ statistic was 63% (with 95% uncertainty interval, 2% to 86%). Sensitivity analyses did not alter these results. No evidence of publication bias was demonstrated. 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, 0.59 to 0.96). However, this effect was seen only in the four-way analysis; in the two-way analysis the effect was not significant. Three of the remaining 4 trials reported nonsignificant results with the point estimates actually reflecting increased fatal MI in the vitamin E treated group.

Risk ratios were calculated for the primary prevention ATBC and PPP trials that were not included in the pooled analysis.[21,29,34,35] Neither of these primary prevention studies reported a statistically significant benefit for vitamin E on fatal MI.

***Meta-analysis of Vitamin E in Combination Versus Placebo: Fatal Myocardial Infarction.*** Four trials were included in this pooled analysis: a secondary prevention trial, HATS;[36] the longer version of the ATBC trial, which focused on patients with prior cardiovascular disease;[29] the GISSI trial;[28] and the MRC/BHF trial.[30] The random effects pooled estimate of the 4 studies was 1.02 (95% CI, 0.77 to 1.37) as shown in Fig. 3. This result was not significant, but the $\chi^2$ test did demonstrate significant heterogeneity ($P$ = .01). The $I^2$ statistic was 73% (with 95% uncertainty interval, 25% to 90%). Sensitivity analyses did not alter these results. No evidence of publication bias was demonstrated (Appendix Table).

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 to 0.96). Also similar to the previous case, in the two-way analysis of the GISSI data the effect on fatal MI was not statistically significant. In contrast to the results of previous analyses, 1 trial, the ATBC trial, which enrolled subjects with prior cardiovascular disease, reported a statistically significant adverse effect of vitamin E supplementation (RR, 1.51; 95% CI, 1.04 to 2.20). Although the GISSI trial used a higher dose of vitamin E than did the ATBC, it would be rare for 2 different doses of a supplement to have completely opposite effects and for each of those effects to be real. It is possible that the adverse effect reported for the ATBC and the beneficial effect reported for the GISSI result was due to chance.

An additional trial,[39] not included in the pooled analysis due to insufficient follow-up time, demonstrated no significant effect of vitamin E supplementation in the risk of fatal MI. The primary prevention sample of the ATBC trial[34] reported no effect on fatal MI.

***Meta-analysis Vitamin E Alone Versus Placebo: Nonfatal Myocardial Infarction.*** The same 5 trials included in a prior pooled analysis of fatal MI also reported on the outcome of nonfatal MI.[24,25,27–29] The random effects pooled estimate was 0.72 (95% CI, 0.51 to 1.02) as shown in Fig. 3. The $\chi^2$ test did demonstrate significant heterogeneity ($P$ = .001). The $I^2$ statistic was 78% (with 95% uncertainty interval, 47% to 91%). Sensitivity analyses did not alter these results. There was no evidence of publication bias (Appendix Table).

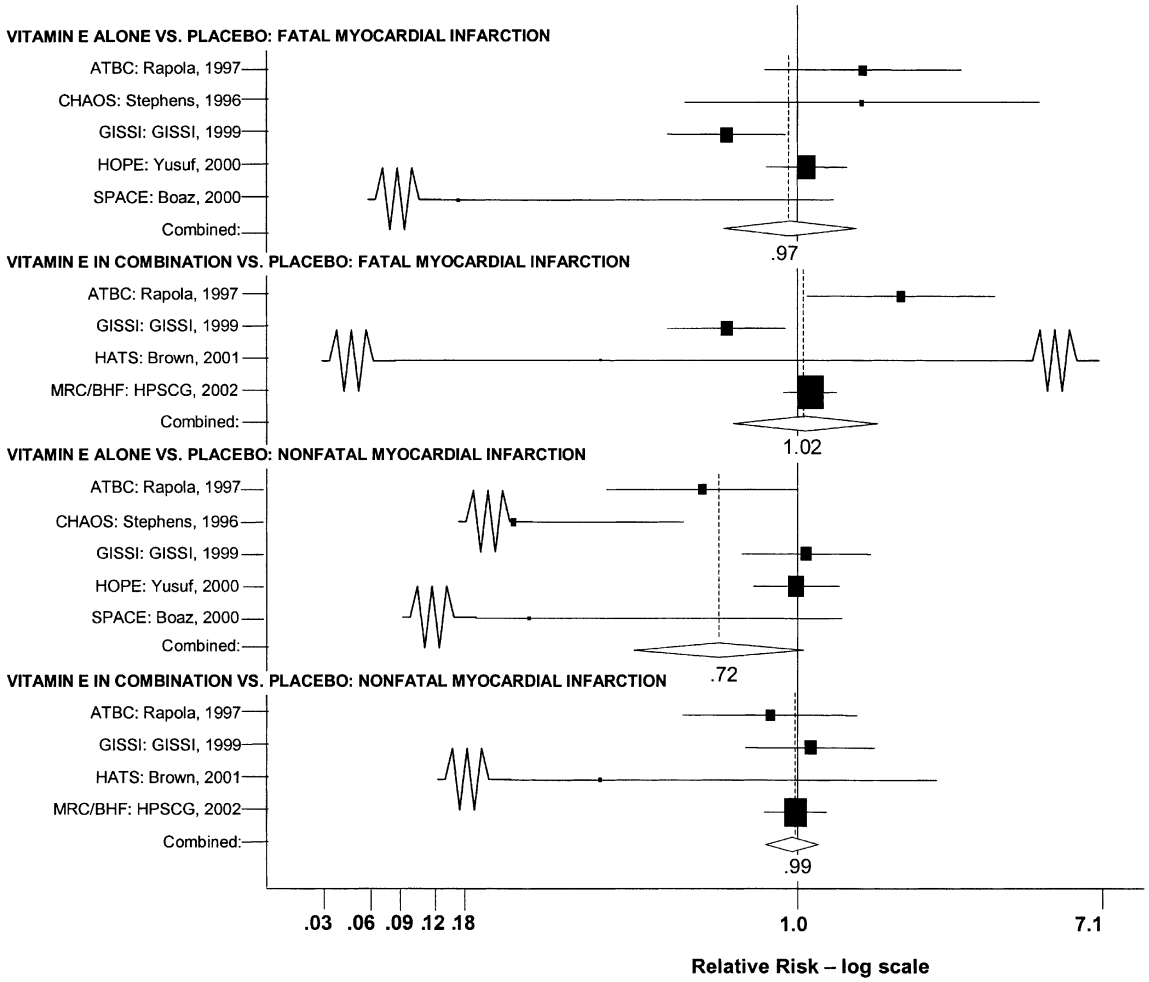


**FIGURE 3.** Pooled relative risk ratios for myocardial infarction.

In contrast to prior analyses, in this analysis the GISSI trial did not report a statistically significant effect of vitamin E. In fact, the point estimate of effect for nonfatal MI was in the opposite direction (RR, 1.04; 95% CI, 0.80 to 1.34). Surprisingly, in this analysis the ATBC trial, which reported a statistically significant adverse effect of vitamin E on fatal MI, reports a beneficial effect for nonfatal MI that just fails to reach conventional levels of statistical significance (RR, 0.68; 95% CI, 0.46 to 1.01).

The results of 2 primary prevention studies, the ATBC study and the PPP trial,[21,34] reported no significant effect of vitamin E alone for reducing the risk of nonfatal MI.

***Meta-analysis of Vitamin E in Combination Versus Placebo: Nonfatal Myocardial Infarction.*** Four trials were included in this pooled analysis: the HATS trial,[36] the longer version of the ATBC trial of subjects with prior cardiovascular disease,[29] the GISSI trial,[28] and the MRC/BHF trial.[30] The random effects pooled estimate was a relative risk ratio of 0.99 (95% CI, 0.89 to 1.10) as shown in Fig. 3. The $\chi^2$ test did not demonstrate significant heterogeneity ($P = .60$). The $I^2$ statistic was 0% (with 95% uncertainty interval, 0% to 89%). There was no evidence of publication bias.

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

The effects of treatment with vitamin E alone or in combination on the risk of MI, both fatal and nonfatal, 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 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 ATBC trials reported just the opposite results of the GISSI four-way analysis: a significant adverse effect of vitamin E on fatal myocardial infarction but a nearly significant beneficial effect of vitamin E on nonfatal MI. These trials had distinct differences (ATBC assessed 50 mg of vitamin E whereas the GISSI assessed 300 mg; but the baseline risk of both fatal and nonfatal MI was approximately equivalent in the 2 studies), but such disparities in results cast doubt on the observed effects being due to a causal relationship, because consistency of effect and a dose–response relationship are 2 important criteria of causality.

### Vitamin E Trials that Reported on Lipids as an Outcome

Fifty-six trials were identified that examined the effects of the antioxidants on the intermediate outcome of blood lipids. Intermediate outcomes that have a demonstrated relationship to cardiovascular disease 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 because no direct evidence links them to clinical cardiovascular disease outcomes such as mortality. Therefore, 4 trials that reported only on the indirect outcome of lipid oxidation were excluded from pooling.[42–45] A fifth trial[46] was excluded because none of the chosen lipid outcomes was identified. A sixth trial[47] was excluded because it was a pharmacokinetics study of coenzyme Q10.

Two trials, the GISSI[28] and the MRC/BHF trials,[30] were excluded from pooled analysis because their sample sizes were more than an order of magnitude larger than those of the rest of the trials and would have rendered the results of any smaller trials statistically meaningless in pooled analysis. Instead, we compared the results of these large trials with the pooled results of the smaller trials.

In the populations studied, interventions with vitamin E (alone and in combination with other antioxidants) in doses ranging from 100 IU to 1200 IU and treatment durations of 8 to 24 weeks did not demonstrate a statistically significant effect on serum lipids (effect sizes for vitamin E alone were −0.07, −0.07, and 0.01 for total cholesterol, LDL cholesterol, and HDL cholesterol, respectively; full results are in the Appendix.) The 2 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.

## DISCUSSION

The available scientific studies offer little evidence that supplementation with vitamin E has any benefit on cardiovascular disease prevention or treatment. Indeed, supplementation with vitamin E at the doses tested appears to provide no benefit: large placebo-controlled, randomized trials 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 benefits for vitamin E supplementation reported for specific outcomes in particular trials failed to be confirmed by other outcomes in the same trials or in other trials. Either these disparate results within and across trials are due to chance, or the mechanism of action of vitamin E with respect to MI is very complicated. This lack of consistency in the evidence casts doubt on any of the reported associations having a cause-and-effect relationship. There is good evidence that vitamin E supplementation has no clinically important effect on lipid levels.

After finishing our report, 2 new reviews have been published assessing the effect of vitamin E on cardiovascular disease. The first was a meta-analysis of vitamin E and beta-carotene.[48] This meta-analysis restricted its selection criteria to only very large studies, and therefore included fewer studies than ours and used somewhat different methods for assessing outcomes. However, despite these differences, this meta-analysis also concluded that vitamin E supplementation has no appreciable effect on mortality or cardiovascular outcomes. The second review was performed for the U.S. Prevention Services Task Force.[49] This review searched fewer databases, included cohort studies, and synthesized their evidence qualitatively rather than quantitatively. They included fewer RCTs assessing mortality and myocardial infarction outcomes than our review, but included studies assessing angina outcomes that we did not assess. This review concluded that the randomized trial evidence showed "no effect" on cardiovascular events or cardiovascular or all-cause mortality. Taken together, these 3 reviews, conducted independently, using somewhat different inclusion criteria and methods for synthesis, provide strong convergent validity that supplementary use of vitamin E has no effect on cardiovascular outcomes.

An explanation that has been proposed for the lack of effect reported in many of the reviewed trials is that the vitamin E 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 given to a population sufficiently likely to benefit. Both the GISSI study and the HOPE study were prematurely terminated due to evidence of benefits from other intervention arms. It has been suggested that if these studies had been allowed to continue for 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 selecting participants based on some measure of oxidative stress or low levels of antioxidants. Whether higher doses or different formulations or longer treatment durations will prove more effective is unknown. The findings we report here make it less likely, in our view, that a particular antioxidant intervention will be found that proves to be markedly beneficial.

Our review and meta-analysis have several limitations. The first, common to many systematic reviews, is the quality of the original studies. Only a third of our trials achieved a Jadad score of 3 or more. Other elements of the design and execution of the studies may also be important. For example, the Linxian trial was not designed to assess cardiovascular disease outcomes as its primary purpose, hence the baseline data on cardiovascular disease were not as complete as those from 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, proposed criteria and scales are not reproducible and do not distinguish studies based on their results.[50,51]

Heterogeneity existed in the trial design, populations, size, interventions, and outcomes and affected our ability to pool studies. We describe explicitly the clinical judgments we made about pooling studies. We tested other combinations of studies in sensitivity analyses; no differences 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 summary, there is good evidence that supplements of the antioxidant vitamin E do not substantially affect cardiovascular disease either positively or adversely.

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# Appendix

**Biomedical and other Databases Searched**

| Database | Years |
|---|---|
| Allied & Complementary Medicine | 1984–2001 Feb |
| Biosis Previews | 1969–2002 Jan |
| CAB Health | 1983–2001 Dec |
| Cancerlit | 1975–2001 Oct |
| Cochrane Library | 1922–2001 |
| Database of Systematic Reviews | |
| Controlled Trials Register | |
| **Elsevier Biobase** | 1994–2002 Jan |
| Embase | 1974–2002 Jan |
| MANTIS | 1880–2001 Oct |
| Medline | 1966–2002 Jan |
| **SciSearch Cited Ref Sci** | 1974–1989 Dec |
| Social SciSearch(R) | 1972–2002 Jan |
| SciSearch Cited Ref Sci | 1990–2002 Jan |
| TGG Health&Wellness DB | 1976–2002 Dec |

**Additional Search Terms for Antioxidants Studied**

| Vitamin E |
|---|
| **alpha tocopherol** |
| **d alpha tocopherol** |
| **rrr alpha tocopherol** |
| **all rac alpha tocopherol** |

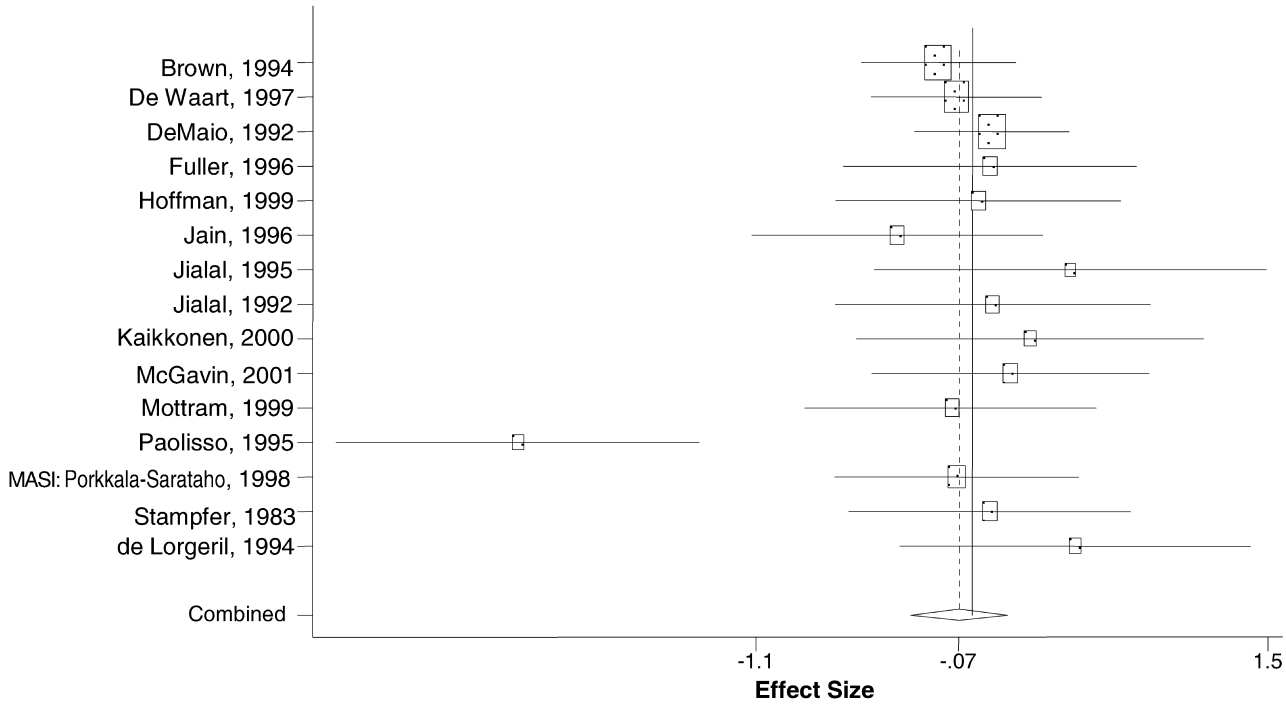
**Summary of Search Strategy**

| Name | Description | Number of References |
|---|---|---|
| Search 1 | Focused search on intervention (Coenzyme Q10), disease state (cardiovascular disease), and human in on-line databases. | 582 |
| Search 2a | Focused search on intervention (Vitamin C), disease state, and human in on-line databases. | 2228 |
| Search 2b | Search of Cochrane databases for intervention (Vitamin C) and disease state. | 169 |
| Search 3a | Focused search on intervention (Vitamin E), disease state, type of therapy, and human for on-line databases. | 3578 |
| Search 3b | Search of Cochrane databases for intervention (Vitamin E) and disease state. | 192 |
| Search 4 | Search of on-line databases for Coenzyme Q10 synonyms | 503 |
| Search 5 | Search on Cochrane databases for intervention (Coenzyme Q10). | 111 |
| **Total references found (duplicate articles included in total):** | | **8173** |

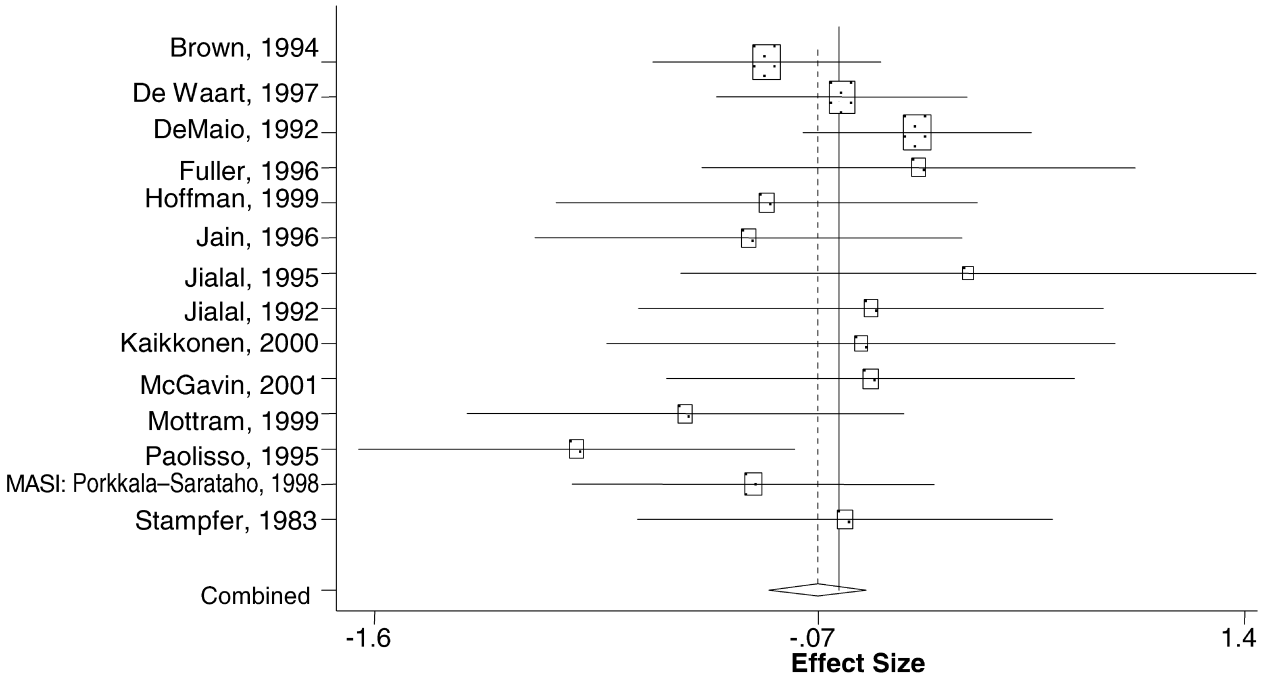
**Publication Bias Test Results**

| Study/Analysis | Number of Studies | Adjusted Rank Correlation Test | Regression Asymmetry Test |
|---|---|---|---|
| Vitamin E alone vs. placebo: all-cause mortality | 5 | p=1.00 | p=0.91 |
| Vitamin E alone vs. placebo: cardiovascular death | 5 | p=0.81 | p=0.88 |
| Vitamin E in combination vs. placebo: cardiovascular death | 4 | p=1.00 | p=0.95 |
| Vitamin E alone vs. placebo: fatal myocardial infarction | 5 | p=0.81 | p=0.77 |
| Vitamin E in combination vs. placebo: fatal myocardial infarction | 4 | p=1.00 | p=0.89 |
| Vitamin E alone vs. placebo: nonfatal myocardial infarction | 5 | p=0.09 | p=0.07 |
| Vitamin E in combination vs. placebo: nonfatal myocardial infarction | 4 | p=0.31 | p=0.26 |
| Vitamin E alone vs. placebo: total cholesterol | 15 | p=0.37 | p=0.81 |
| Vitamin E alone vs. placebo: low-density lipoprotein | 14 | p=0.91 | p=0.64 |
| Vitamin E alone vs. placebo: high-density lipoprotein | 15 | p=0.32 | p=0.02 |
| Vitamin E in combination vs. placebo: total cholesterol | 7 | p=0.37 | p=0.61 |
| Vitamin E in combination vs. placebo: low-density lipoprotein | 5 | p=0.22 | p=0.80 |
| Vitamin E in combination vs. placebo: high-density lipoprotein | 5 | p=0.81 | p=0.24 |

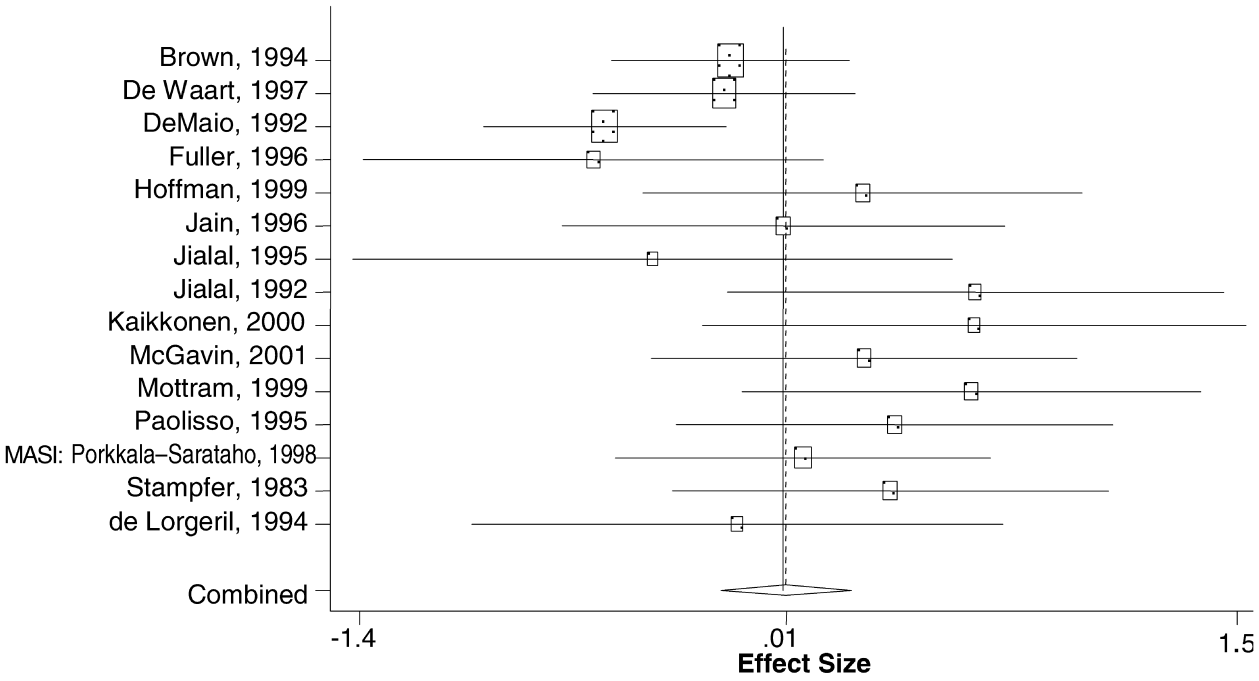
**Vitamin E alone vs. placebo: total cholesterol**



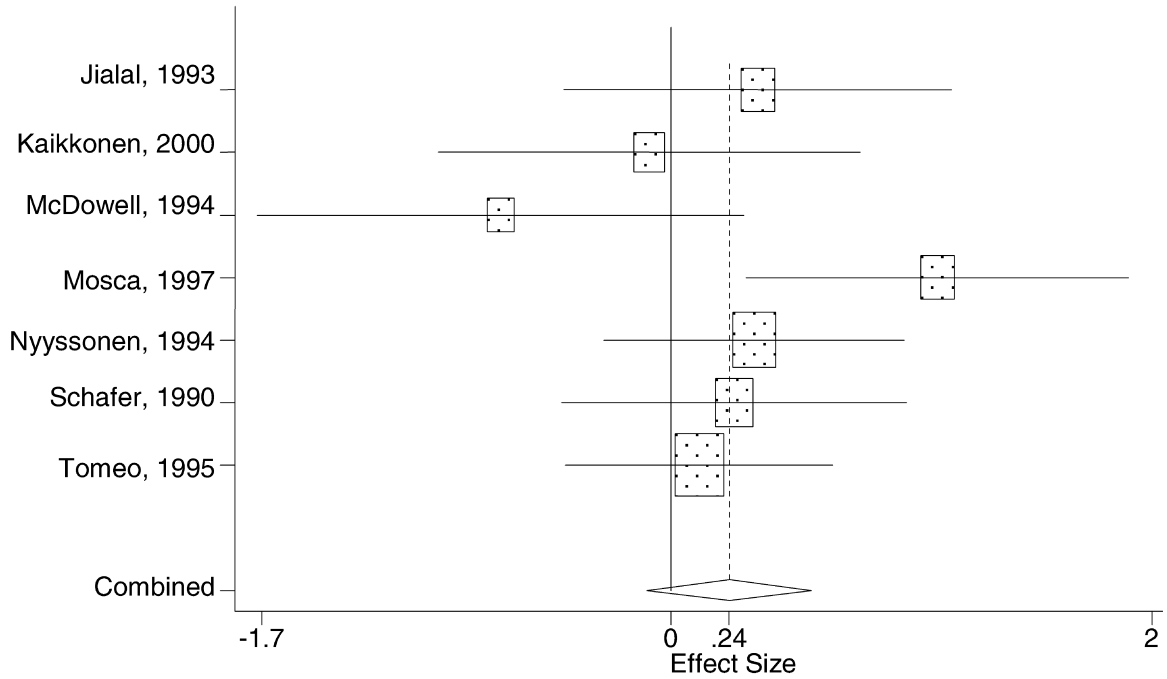

**Vitamin E alone vs. placebo: LDL cholesterol**



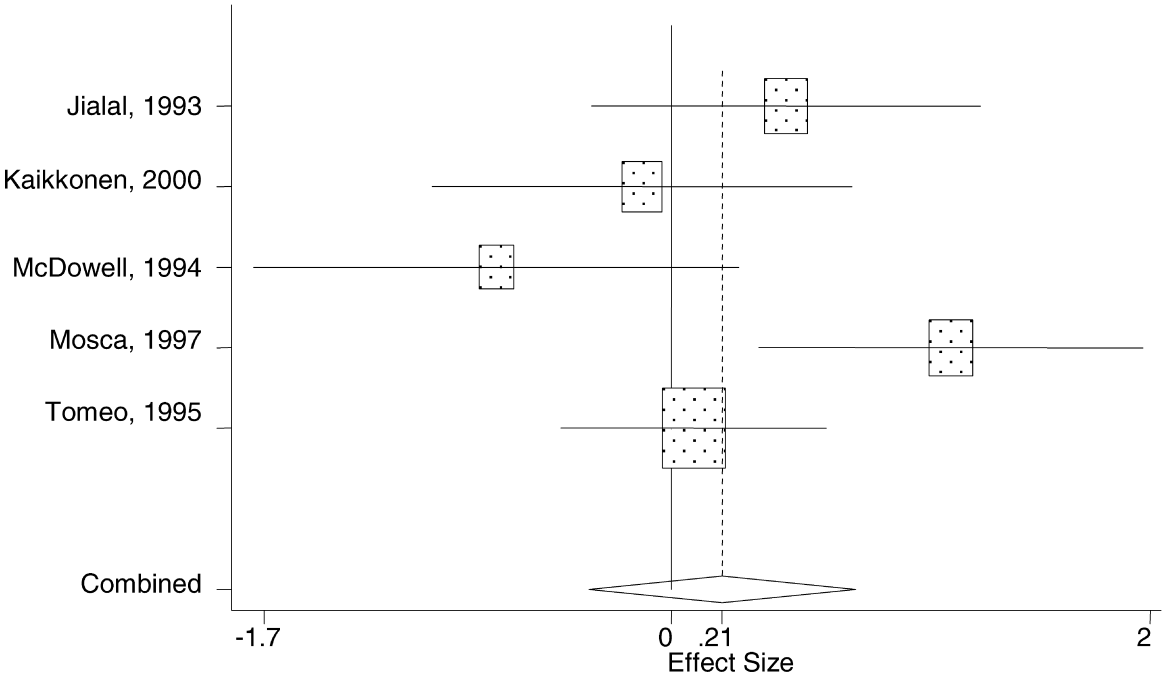
**Vitamin E alone vs. placebo: HDL cholesterol**



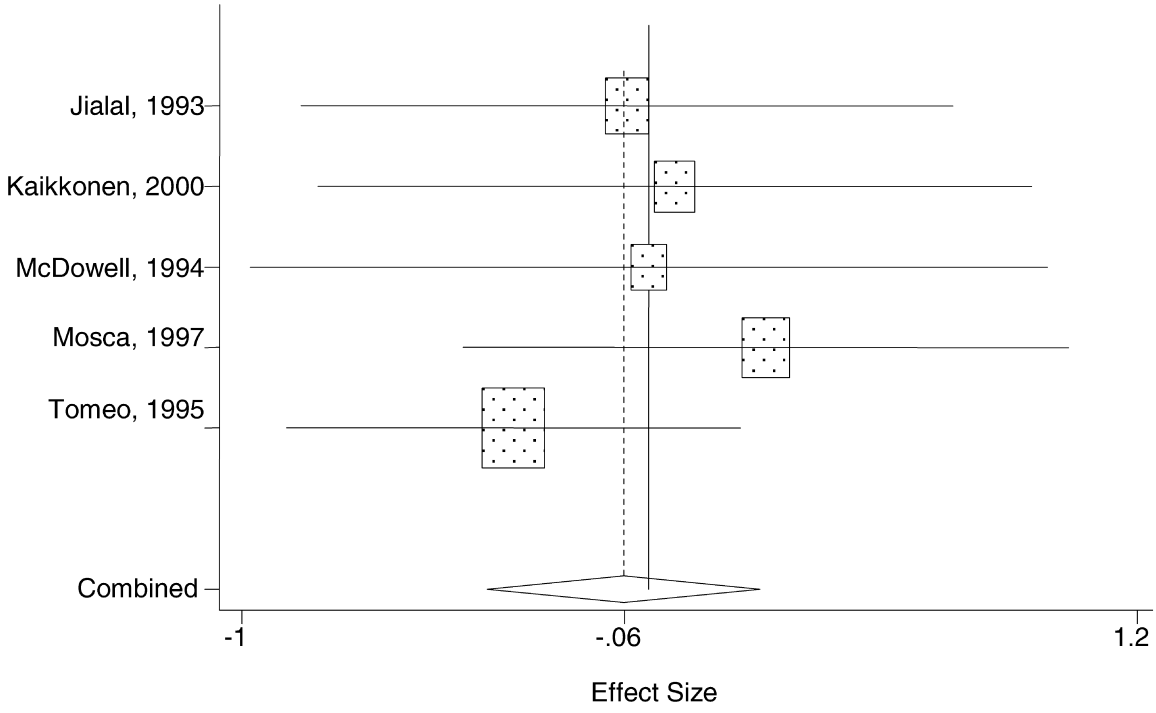

**Vitamin E in combination vs. placebo: total cholesterol**



**Vitamin E in combination vs. placebo: LDL cholesterol**




**Vitamin E in combination vs. placebo: HDL cholesterol**



| 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<br>Placebo for 9 Wks. | N entered:<br>N analyzed: | 24<br>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<br>3200 IU orally for 9 Wks. | N entered:<br>N analyzed: | 24<br>15 | |
| | Jadad: | 5 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | Angina | | | | | |
| Anderson 1974a Study 2 | Named trial: | Other | 1 | Placebo<br>Placebo for 9 Wks. | N entered:<br>N analyzed: | 10<br>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<br>Dose N/A orally for 9 Wks. | N entered:<br>N analyzed: | 10<br>6 | |
| | Jadad: | 5 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | Angina | | | | | |
| Anderson 1974b | Named trial: | Other | 1 | Placebo<br>Placebo for 9 Wks. | N entered:<br>N analyzed: | 18<br>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<br>3200 IU orally for 9 Wks. | N entered:<br>N analyzed: | 18<br>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

**Vitamin E for Cardiovascular Prevention and Treatment**

| 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 | 1 | Placebo<br>Placebo for 8 Wks. | N entered:<br>N analyzed: | 20<br>16 | Excluded from meta-analysis of lipids due to study design. Antioxidant combination group showed significant reduction in LDL oxidation as compared to placebo. |
| | Design: | CCT | 2 | Vitamin C<br>1000 mg orally for 12 Wks.<br>Vitamin E<br>800 IU orally for 12 Wks.<br>Beta-carotene<br>24 mg orally for 12 Wks. | N entered:<br>N analyzed: | 20<br>18 | |
| | Jadad: | 0 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD | | | | | |
| Boaz 2000 | Named trial: | SPACE | 1 | Placebo<br>Placebo for 26 Months | N entered:<br>N analyzed: | 99<br>99 | Included in meta-analysis of death and MI. |
| | Design: | RCT | 2 | Vitamin E<br>800 IU orally for 26 Months | N entered:<br>N analyzed: | 97<br>97 | |
| | Jadad: | 4 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD, CVA/TIA, PVD, angina | | | | | |
| Brown 1994 | Named trial: | Other | 1 | Placebo<br>Placebo for 10 Wks. | N entered:<br>N analyzed: | N/A<br>N/A | Included in meta-analysis of lipids. |
| | Design: | CCT | 2 | Vitamin E<br>280 mg orally for 10 Wks. | N entered:<br>N analyzed: | N/A<br>N/A | |
| | 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<br>Study Design and Quality<br>Population<br>Type of Disease | | Arm | Interventions<br>Dose Data | Sample Size | | Summary of Results |
|---|---|---|---|---|---|---|---|
| Brown 2001 | Named trial: | HATS | 1 | Placebo<br>Placebo for 3 Yrs. | N entered:<br>N analyzed: | N/A<br>34 | Included in meta-analysis of death and MI. Excluded from meta-analysis of lipids due to insufficient followup time. |
| | Design: | RCT | 2 | Niacin<br>Dose N/A orally for 3 Yrs.<br>Statin drug<br>Dose N/A orally for 3 Yrs. | N entered:<br>N analyzed: | N/A<br>33 | |
| | Jadad: | 4 | | | | | |
| | Population: | Unspecified | 3 | Vitamin E<br>800 IU orally for 3 Yrs.<br>Vitamin C<br>1000 mg orally for 3 Yrs.<br>Beta-carotene<br>25 mg orally for 3 Yrs.<br>Selenium<br>100 µg orally for 3 Yrs. | N entered:<br>N analyzed: | N/A<br>39 | |
| | Condition: | CAD, CVA/TIA, 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 |
|---|---|---|---|---|---|---|---|
| | | | 4 | Selenium<br>100 µg orally for 3 Yrs.<br>Beta-carotene<br>25 mg orally for 3 Yrs.<br>Vitamin E<br>800 IU orally for 3 Yrs.<br>Vitamin C<br>1000 mg orally for 3 Yrs.<br>Niacin<br>Dose N/A orally for 3 Yrs.<br>Statin drug<br>Dose N/A orally for 3 Yrs. | N entered:<br>N analyzed: | N/A<br>40 | |
| Chamiec 1996 | Named trial:<br>Design:<br>Jadad:<br>Population:<br>Condition: | Other<br>RCT<br>2<br>Unspecified<br>CAD | 1 | Control or Usual care<br>No dosage data reported | N entered:<br>N analyzed: | N/A<br>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<br>600 mg orally for 14 Days<br>Vitamin E<br>600 mg orally for 14 Days | N entered:<br>N analyzed: | N/A<br>33 | |
| de Lorgeril 1994 | Named trial:<br>Design: | Other<br>RCT | 1 | Control or Usual care<br>Control or Usual care for 2 Months | N entered:<br>N analyzed: | 10<br>10 | Included in meta-analysis of lipids. |

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 |
|---|---|---|---|---|---|---|
| | | 2 | Vitamin E | N entered: | 10 | |
| | Jadad: 1 | | 500 IU orally for 2 Months | N analyzed: | 10 | |
| | Population: Unspecified | | | | | |
| | Condition: CAD | | | | | |
| De Waart 1997 | Named trial: Other | 1 | Placebo | N entered: | 41 | Included in meta-analysis of lipids. |
| | | | Placebo for 3 Months | N analyzed: | 41 | |
| | Design: RCT | 2 | Vitamin E | N entered: | 42 | |
| | | | 100 IU orally for 3 Months | N analyzed: | 41 | |
| | Jadad: 3 | | | | | |
| | Population: Elderly (over 65) | | | | | |
| | Condition: CAD | | | | | |
| DeMaio 1992 | Named trial: Other | 1 | Placebo | N entered: | N/A | Included in meta-analysis of lipids. |
| | | | Placebo for 4 Months | N analyzed: | 48 | |
| | Design: RCT | 2 | Vitamin E | N entered: | N/A | |
| | | | 1200 IU orally for 4 Months | N analyzed: | 52 | |
| | Jadad: 2 | | | | | |
| | Population: Unspecified | | | | | |
| | Condition: CAD, reperfusion injury | | | | | |
| Dieber-Rotheneder 1991 | Named trial: Other | 1 | Placebo | N entered: | 4 | Excluded from meta-analysis of lipids due to insufficient statistics. Vitamin E group showed significant reduction in LDL oxidation as compared to placebo. |
| | | | Placebo for 21 Days | N analyzed: | 4 | |
| | Design: CCT | 2 | Vitamin E | N entered: | 2 | |
| | | | 150 IU orally for 21 Days | N analyzed: | 2 | |
| | Jadad: 0 | 3 | Vitamin E | N entered: | 2 | |
| | | | 225 IU orally for 21 Days | 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 |
|---|---|---|---|---|---|
| | Population: Unspecified<br>Condition:CAD, LDL oxidation | 4 | Vitamin E<br>800 IU orally for 21 Days | N entered: 2<br>N analyzed: 2 | |
| | | 5 | Vitamin E<br>1200 IU orally for 21 Days | N entered: 2<br>N analyzed: 2 | |
| Duthie 1991 | Named trial: Other<br>Design: CCT<br>Jadad: 0<br>Population: Unspecified<br>Condition: N/A | 1 | Placebo<br>Placebo for 14 Days | N entered: 10<br>N analyzed: 10 | Excluded from meta-analysis of lipids due to insufficient statistics. Vitamin E group showed no significant difference in total cholesterol among male smokers. |
| | | 2 | Vitamin E<br>1000 mg orally for 14 Days | N entered: 10<br>N analyzed: 10 | |
| Fuller 1996b | Named trial: Other<br>Design: RCT<br>Jadad: 1<br>Population: Unspecified<br>Condition:CAD, LDL oxidation | 1 | Placebo<br>Placebo for 8 Wks. | N entered: 13<br>N analyzed: 13 | Included in meta-analysis of lipids. |
| | | 2 | Vitamin E<br>1200 IU orally for 8 Wks. | N entered: 15<br>N analyzed: 15 | |
| Galley 1997 | Named trial: Other<br>Design: RCT<br>Jadad: 5<br>Population: Unspecified | 1 | Placebo<br>Placebo for 8 Wks. | N entered: 40<br>N analyzed: 38 | Excluded from statistical analysis because no outcomes of interest were reported. |
| | | 2 | Vitamin C<br>500 mg orally for 8 Wks.<br>Vitamin E<br>600 mg orally for 8 Wks.<br>Beta-carotene<br>30 mg orally for 8 Wks. | N entered: 40<br>N analyzed: 38 | Significantly reduced blood pressure levels among those in group receiving high-dose combinations of antioxidants including vitamins C and E. |

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<br>Study Design and Quality<br>Population<br>Type of Disease | | Arm | Interventions<br>Dose Data | Sample Size | | Summary of Results |
|---|---|---|---|---|---|---|---|
| | Condition: | HTN | | Multi-vitamin<br>Multi-vitamin orally for 8 Wks. | | | |
| Ghatak 1996 | Named trial: | Other | 1 | Placebo<br>Placebo for 4 Wks. | N entered:<br>N analyzed: | 7<br>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<br>400 mg orally for 4 Wks. | N entered:<br>N analyzed: | 5<br>5 | |
| | 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

**Vitamin E for Cardiovascular Prevention and Treatment**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Gillilan 1977 | Named trial: | Other | 1 | Placebo<br>Placebo for 6 Months | N entered:<br>N analyzed: | 52<br>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<br>1600 IU orally for 6 Months | N entered:<br>N analyzed: | 52<br>48 | |
| | Jadad: | 3 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD | | | | | |
| GISSI 1999 | Named trial: | GISSI/GIZZI | 1 | Placebo<br>Placebo for 3.5 Yrs. | N entered:<br>N analyzed: | 2828<br>2809 | Included in meta-analysis of death and MI. Excluded from meta-analysis of lipids due to heterogeneous sample-size. |
| | Design: | RCT | 2 | n3 PUFA<br>1 gm orally for 3.5 Yrs. | N entered:<br>N analyzed: | 2836<br>2065 | |
| | Jadad: | 3 | 3 | Vitamin E<br>300 mg orally for 3.5 Yrs. | N entered:<br>N analyzed: | 2830<br>2128 | |
| | Population: | Unspecified | 4 | Vitamin E<br>300 mg orally for 3.5 Yrs.<br>n3 PUFA<br>1 gm orally for 3.5 Yrs. | N entered:<br>N analyzed: | 2830<br>1170 | |
| | Condition: | CAD, CVA/TIA | | | | | |
| Guetta 1995 | Named trial: | Other | 1 | 17 beta estradiol<br>0.1 mg 3 for 3 Wks. | N entered:<br>N analyzed: | 9<br>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. |
| | Design: | RCT | 2 | Vitamin E<br>800 IU orally for 6 Wks. | N entered:<br>N analyzed: | 10<br>10 | |
| | Jadad: | 1 | 3 | Vitamin E<br>800 IU orally for 6 Wks.<br>17 beta estradiol<br>0.1 mg 3 for 3 Wks. | N entered:<br>N analyzed: | 19<br>19 | |
| | Population: | Female | | | | | |
| | 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

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Haeger 1968 | Named trial: | Other | 1 | Vasodilators<br>Dose N/A orally for 7 Yrs. | N entered:<br>N analyzed: | 37<br>N/A | Included in meta-analysis of death. |
| | Design: | CCT | 2 | Coumadin<br>Dose N/A orally for 7 Yrs. | N entered:<br>N analyzed: | 44<br>N/A | |
| | Jadad: | 0 | 3 | Multi-vitamin<br>Multi-vitamin orally for 7 Yrs. | N entered:<br>N analyzed: | 42<br>N/A | |
| | Population: | Unspecified | 4 | Vitamin E<br>300 mg orally for 7 Yrs. | N entered:<br>N analyzed: | 104<br>N/A | |
| | Condition: | PVD | | | | | |
| Haeger 1973 | Named trial: | Other | 1 | Control or Usual care<br>No dosage data reported | N entered:<br>N analyzed: | N/A<br>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. |
| | Design: | CCT | 2 | Vitamin E<br>300 mg orally for 5 Yrs. | N entered:<br>N analyzed: | N/A<br>33 | |
| | Jadad: | 0 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | PVD | | | | | |
| Haeger 1974 | Named trial: | Other | 1 | Control or Usual care<br>No dosage data reported | N entered:<br>N analyzed: | N/A<br>N/A | Excluded from statistical analysis because no outcomes of interest were reported. Significant improvement in claudication symptoms among vitamin E group. |
| | Design: | CCT | 2 | Vitamin E<br>300 mg orally for 3.5 Yrs. | N entered:<br>N analyzed: | N/A<br>N/A | |
| | Jadad: | 0 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD, PVD | | | | | |
| Harats 1990 | Named trial: | Other | 1 | Control or Usual care<br>Control or Usual care for 4 Wks. | N entered:<br>N analyzed: | 3<br>3 | Excluded from meta-analysis of lipids due to insufficient statistics. Both vitamin E and hormonal therapy groups showed significant reductions in LDL oxidation. |
| | Design: | CCT | 2 | Vitamin C<br>1.5 gm orally for 4 Wks. | N entered:<br>N analyzed: | 3<br>3 | |
| | Jadad: | 0 | 3 | Vitamin E<br>600 mg orally for 4 Wks. | N entered:<br>N analyzed: | 4<br>4 | |
| | Population: | Smokers | | | | | |
| | 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

**Vitamin E for Cardiovascular Prevention and Treatment**

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|---|---|---|---|---|---|---|---|
| Herbaczynska-Cedro 1995 | Named trial: | Other | 1 | Control or Usual care<br>Control or Usual care for 14 Days | N entered:<br>N analyzed: | 22<br>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<br>600 mg orally for 14 Days<br>Vitamin E<br>600 mg orally for 14 Days | N entered:<br>N analyzed: | 23<br>23 | |
| | Jadad: | 1 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD | | | | | |
| Hoffman 1999 | Named trial: | Other | 1 | Placebo<br>Placebo for 6 Mos. | N entered:<br>N analyzed: | 12<br>11 | Included in meta-analysis of lipids. |
| | Design: | RCT | 2 | Vitamin E<br>400 mg orally for 6 Mos. | N entered:<br>N analyzed: | 27<br>22 | |
| | Jadad: | 2 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD, LDL oxidation | | | | | |
| (HPSCG, Heart Protection Study Collaborative Group, 2002) | Named trial: | MRC/BHF | 1 | Placebo<br>Placebo for 5 Yrs. | N entered: 10267<br>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<br>600 mg orally for 5 Yrs.<br>Vitamin C<br>250 mg orally for 5 Yrs.<br>Beta-carotene<br>020 mg orally for 5 Yrs. | N entered: 10269<br>N analyzed: 10241 | | |
| | Jadad: | 5 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD | | | | | |
| Iino 1977 | Named trial: | Other | 1 | Placebo<br>Placebo for 4 Wks. | N entered:<br>N analyzed: | 48<br>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. |
| | Design: | CCT | 2 | Vitamin E<br>600 mg orally for 4 Wks. | N entered:<br>N analyzed: | 46<br>44 | |
| | Jadad: | 2 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CVA/TIA, 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

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Inagaki 1978 | Named trial: | Other | 1 | Placebo<br>Placebo for 5 Wks. | N entered:<br>N analyzed: | 37<br>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. |
| | Design: | CCT | 2 | Vitamin E<br>600 mg orally for 5 Wks. | N entered:<br>N analyzed: | 40<br>38 | |
| | Jadad: | 2 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD, CVA/TIA, PVD, HTN | | | | | |
| Inal 1997 | Named trial: | Other | 1 | 17 beta estradiol<br>0.05 gm 3 for 6 Mos. | N entered:<br>N analyzed: | 22<br>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<br>0.05 gm 3 for 6 Mos.<br>Progesterone<br>10 mg orally for 10 Days | N entered:<br>N analyzed: | 22<br>22 | |
| | Jadad: | 1 | | | | | |
| | Population: | Female | 3 | Vitamin E<br>600 mg orally for 6 Mos.<br>17 beta estradiol<br>0.05 gm 3 for 6 Mos.<br>Progesterone<br>10 mg orally for 10 Days | N entered:<br>N analyzed: | 22<br>22 | |
| | Condition: | CAD | | | | | |
| Jain 1996 | Named trial: | Other | 1 | Placebo<br>Placebo for 3 Mos. | N entered:<br>N analyzed: | N/A<br>16 | Included in meta-analysis of lipids. |
| | Design: | CCT | 2 | Vitamin E<br>100 IU orally for 3 Mos. | N entered:<br>N analyzed: | N/A<br>13 | |
| | 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

**Vitamin E for Cardiovascular Prevention and Treatment**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Jialal 1992 | Named trial: | Other | 1 | Placebo<br>Placebo for 12 Wks. | N entered:<br>N analyzed: | 12<br>12 | Included in meta-analysis of lipids. |
| | Design: | RCT | 2 | Vitamin E<br>800 IU orally for 12 Wks. | N entered:<br>N analyzed: | 12<br>12 | |
| | Jadad: | 1 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD | | | | | |
| Jialal 1993 | Named trial: | Other | 1 | Placebo<br>Placebo for 12 Wks. | N entered:<br>N analyzed: | 12<br>12 | Included in meta-analysis of lipids. |
| | Design: | RCT | 2 | Vitamin E<br>800 IU orally for 12 Wks.<br>Vitamin C<br>1 gm orally for 12 Wks.<br>Beta-carotene<br>30 mg orally for 12 Wks. | N entered:<br>N analyzed: | 12<br>12 | |
| | Jadad: | 1 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD | | | | | |
| Jialal 1995 | Named trial: | Other | 1 | Placebo<br>Placebo for 8 Wks. | N entered:<br>N analyzed: | 8<br>8 | Included in meta-analysis of lipids. |
| | Design: | RCT | 2 | Vitamin E<br>60 IU orally for 8 Wks. | N entered:<br>N analyzed: | 8<br>8 | |
| | Jadad: | 1 | 3 | Vitamin E<br>200 IU orally for 8 Wks. | N entered:<br>N analyzed: | 8<br>8 | |
| | Population: | Unspecified | 4 | Vitamin E<br>400 IU orally for 8 Wks. | N entered:<br>N analyzed: | 8<br>8 | |
| | Condition: | CAD, LDL oxidation | 5 | Vitamin E<br>800 IU orally for 8 Wks. | N entered:<br>N analyzed: | 8<br>8 | |
| | | | 6 | Vitamin E<br>1200 IU orally for 8 Wks. | N entered:<br>N analyzed: | 8<br>8 | |

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

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Kaikkonen 2000 Study 1 | Named trial: | Other | 1 | Placebo<br>Placebo for 3 Mos. | N entered:<br>N analyzed: | 10<br>10 | Included in meta-analysis of lipids. |
| | Design: | RCT | 2 | Vitamin E<br>700 mg orally for 3 Mos.<br>Co-Q10<br>200 mg orally for 3 Mos. | N entered:<br>N analyzed: | 10<br>10 | |
| | Jadad: | 2 | | | | | |
| | Population: | Unspecified | 3 | Co-Q10<br>200 mg orally for 3 Mos. | N entered:<br>N analyzed: | 10<br>10 | |
| | Condition: | CAD | 4 | Vitamin E<br>700 mg orally for 3 Mos. | N entered:<br>N analyzed: | 10<br>10 | |
| Keith 2000 | Named trial: | Other | 1 | Placebo<br>Placebo for 12 Wks. | N entered:<br>N analyzed: | N/A<br>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<br>1000 IU orally for 12 Wks. | N entered:<br>N analyzed: | N/A<br>N/A | |
| | Jadad: | 1 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CHF | | | | | |
| Keith 2001 | Named trial: | Other | 1 | Placebo<br>Placebo for 12 Wks. | N entered:<br>N analyzed: | 30<br>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<br>500 IU orally for 12 Wks. | N entered:<br>N analyzed: | 26<br>26 | |
| | 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

**Vitamin E for Cardiovascular Prevention and Treatment**

| | | | | | | |
|---|---|---|---|---|---|---|
| Leppala 2000a | Named trial: | ATBC | 1 | Placebo<br>Placebo for 6 Yrs. | N entered: 7153<br>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<br>50 mg orally for 6 Yrs. | N entered: 7120<br>N analyzed: 6869 | |
| | Jadad: | 3 | 3 | Beta-carotene<br>20 mg orally for 6 Yrs. | N entered: 7128<br>N analyzed: 6832 | |
| | Population: | Smokers | 4 | Vitamin E<br>50 mg orally for 6 Yrs.<br>Beta-carotene<br>20 mg orally for 6 Yrs. | N entered: 7118<br>N analyzed: 6860 | |
| | Condition: | CVA/TIA | | | | |
| Leppala 2000b | Named trial: | ATBC | 1 | Placebo<br>Placebo for 6 Yrs. | N entered: 7153<br>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<br>20 mg orally for 6 Yrs. | N entered: 7128<br>N analyzed: N/A | |
| | Jadad: | 3 | 3 | Vitamin E<br>50 mg orally for 6 Yrs. | N entered: 7120<br>N analyzed: N/A | |
| | Population: | Smokers | 4 | Vitamin E<br>50 mg orally for 6 Yrs.<br>Beta-carotene<br>20 mg orally for 6 Yrs. | N entered: 7118<br>N analyzed: N/A | |
| | Condition: | CVA/TIA | | | | |

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

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Mark 1998 | Named trial: | Linxian | 1 | Placebo<br>Placebo for 5.25 Yrs. | N entered:<br>N analyzed: | N/A<br>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<br>40 mg orally for 5.25 Yrs.<br>Multi-vitamin<br>Multi-vitamin orally for 5.25 Yrs. | N entered:<br>N analyzed: | N/A<br>N/A | |
| | Jadad: | 1 | 3 | Vitamin C<br>120 mg orally for 5.25 Yrs.<br>Multi-vitamin<br>Multi-vitamin orally for 5.25 Yrs. | N entered:<br>N analyzed: | N/A<br>N/A | |
| | Population: | Unspecified | 4 | Vitamin C<br>120 mg orally for 5.25 Yrs.<br>Multi-vitamin<br>Multi-vitamin orally for 5.25 Yrs. | N entered:<br>N analyzed: | N/A<br>N/A | |
| | Condition: | CVA/TIA, HTN | 5 | Vitamin E<br>30 mg orally for 5.25 Yrs.<br>Multi-vitamin<br>Multi-vitamin orally for 5.25 Yrs. | N entered:<br>N analyzed: | N/A<br>N/A | |
| | | | 6 | Vitamin C<br>120 mg orally for 5.25 Yrs.<br>Vitamin E<br>30 mg orally for 5.25 Yrs.<br>Multi-vitamin<br>Multi-vitamin orally for 5.25 Yrs. | N entered:<br>N analyzed: | N/A<br>N/A | |
| | | | 7 | Vitamin C<br>120 mg orally for 5.25 Yrs.<br>Vitamin E<br>30 mg orally for 5.25 Yrs.<br>Multi-vitamin<br>Multi-vitamin orally for 5.25 Yrs. | N entered:<br>N analyzed: | N/A<br>N/A | |
| | | | 8 | Vitamin E<br>30 mg orally for 5.25 Yrs.<br>Multi-vitamin<br>Multi-vitamin orally for 5.25 Yrs. | N entered:<br>N analyzed: | N/A<br>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

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| McDowell 1994 | Named trial: | Other | 1 | Placebo<br>Placebo for 8 Wks. | N entered:<br>N analyzed: | 8<br>8 | Included in meta-analysis of lipids. |
| | Design: | RCT | | Statin drug<br>20 mg orally for 8 Wks. | | | |
| | Jadad: | 2 | 2 | Probucol<br>1000 mg orally for 8 Wks. | N entered:<br>N analyzed: | 8<br>8 | |
| | Population: | Unspecified | | Statin drug<br>20 mg orally for 8 Wks. | | | |
| | Condition: | CAD, LDL oxidation | 3 | Vitamin E<br>400 IU orally for 8 Wks. | N entered:<br>N analyzed: | 8<br>8 | |
| | | | | Statin drug<br>20 mg orally for 8 Wks. | | | |
| McGavin 2001 | Named trial: | Other | 1 | Placebo<br>Placebo for 8 Wks. | N entered:<br>N analyzed: | 40<br>35 | Included in meta-analysis of lipids. |
| | Design: | RCT | 2 | Vitamin E<br>28 IU orally for 8 Wks. | N entered:<br>N analyzed: | 40<br>37 | |
| | Jadad: | 3 | 3 | Vitamin E<br>200 IU orally for 8 Wks. | N entered:<br>N analyzed: | 10<br>10 | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD | | | | | |
| Meagher 2001 | Named trial: | Other | 1 | Placebo<br>Placebo for 8 Weeks | N entered:<br>N analyzed: | 5<br>5 | Excluded from statistical analysis because no outcomes of interest were reported. No effect of vitamin E on lipid peroxidation. |
| | Design: | RCT | 2 | Vitamin E<br>200 IU orally for 8 Weeks | N entered:<br>N analyzed: | 5<br>5 | |
| | Jadad: | 3 | 3 | Vitamin E<br>400 IU orally for 8 Weeks | N entered:<br>N analyzed: | 5<br>5 | |
| | Population: | Unspecified | 4 | Vitamin E<br>800 IU orally for 8 Weeks | N entered:<br>N analyzed: | 5<br>5 | |
| | Condition: | CAD | 5 | Vitamin E<br>1200 IU orally for 8 Weeks | N entered:<br>N analyzed: | 5<br>5 | |
| | | | 6 | Vitamin E<br>2000 IU orally for 8 Weeks | N entered:<br>N analyzed: | 5<br>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

**Vitamin E for Cardiovascular Prevention and Treatment**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Mensink 1999 | Named trial: | Other | 1 | Vitamin E<br>80 mg orally for 6 Weeks | N entered:<br>N analyzed: | 20<br>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. |
| | Design: | RCT | | Palm olein<br>960 mg orally for 6 Weeks | | | |
| | Jadad: | 2 | | Tocotrienols in general<br>160 mg orally for 6 Weeks | | | |
| | Population: | Unspecified | 2 | Vitamin E<br>80 mg orally for 6 Weeks | N entered:<br>N analyzed: | 20<br>20 | |
| | Condition: | CAD, LDL oxidation | | Palm olein<br>1120 mg orally for 6 Weeks | | | |
| Meraji 1997 | Named trial: | Other | 1 | Beta-carotene<br>30 mg orally for 10 Weeks | N entered:<br>N analyzed: | 10<br>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. |
| | Design: | RCT | | Placebo<br>Placebo for 10 Weeks | | | |
| | Jadad: | 2 | 2 | Beta-carotene<br>30 mg orally for 10 Weeks | N entered:<br>N analyzed: | 11<br>9 | |
| | Population: | Unspecified | | Vitamin E<br>400 IU orally for 10 Weeks | | | |
| | Condition: | CAD | | | | | |
| Mosca 1996 | Named trial: | Other | 1 | Placebo<br>Placebo for 12 Weeks | N entered:<br>N analyzed: | 15<br>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. |
| | Design: | RCT | 2 | Vitamin E<br>400 IU orally for 12 Weeks | N entered:<br>N analyzed: | 15<br>N/A | |
| | Jadad: | 1 | | Vitamin C<br>500 mg orally for 12 Weeks | | | |
| | Population: | Unspecified | | Beta-carotene<br>12 mg orally for 12 Weeks | | | |
| | Condition: | CAD, LDL oxidation | 3 | Vitamin E<br>800 IU orally for 12 Weeks | N entered:<br>N analyzed: | 15<br>N/A | |
| | | | | Vitamin C<br>1000 mg orally for 12 Weeks | | | |
| | | | | Beta-carotene<br>24 mg orally for 12 Weeks | | | |

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

**Vitamin E for Cardiovascular Prevention and Treatment**

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|---|---|---|---|---|---|---|---|
| Mosca 1997 | Named trial: | Other | 1 | Placebo<br>Placebo for 12 Weeks | N entered:<br>N analyzed: | 15<br>14 | Included in meta-analysis of lipids. |
| | Design: | RCT | 2 | Vitamin E<br>400 IU orally for 12 Weeks<br>Vitamin C<br>500 mg orally for 12 Weeks<br>Beta-carotene<br>12 mg orally for 12 Weeks | N entered:<br>N analyzed: | 15<br>13 | |
| | Jadad: | 4 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD | 3 | Vitamin E<br>800 IU orally for 12 Weeks<br>Vitamin C<br>1000 mg orally for 12 Weeks<br>Beta-carotene<br>24 mg orally for 12 Weeks | N entered:<br>N analyzed: | 15<br>14 | |
| Mottram 1999 | Named trial: | Other | 1 | Placebo<br>Placebo for 8 Weeks | N entered:<br>N analyzed: | 14<br>14 | Included in meta-analysis of lipids. |
| | Design: | RCT | 2 | Vitamin E<br>400 IU orally for 8 Weeks | N entered:<br>N analyzed: | 14<br>14 | |
| | Jadad: | 3 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD | | | | | |
| Munday 1999 | Named trial: | Other | 1 | Garlic - whole<br>6 gm orally for 7 Days | N entered:<br>N analyzed: | 9<br>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<br>2.4 gm orally for 7 Days | N entered:<br>N analyzed: | 9<br>9 | |
| | Jadad: | 2 | 3 | Vitamin E<br>800 mg orally for 7 Days | N entered:<br>N analyzed: | 9<br>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

**Vitamin E for Cardiovascular Prevention and Treatment**

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|---|---|---|---|---|---|---|---|
| Nappo 1999 | Named trial: | Other | 1 | Placebo<br>Placebo for 1 Day | N entered:<br>N analyzed: | 20<br>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<br>100 mg/kg orally for 1 Day | N entered:<br>N analyzed: | 20<br>20 | |
| | Jadad: | 2 | 3 | Vitamin E<br>800 IU orally for 1 Day<br>Vitamin C<br>1000 mg orally for 1 Day<br>L-methionine<br>100 mg/kg orally for 1 Day | N entered:<br>N analyzed: | 20<br>20 | |
| | Population: | Unspecified | | | | | |
| | Condition: dysfunction | Endothelial | | | | | |
| | | | 4 | Vitamin E<br>800 IU orally for 1 Day<br>Vitamin C<br>1000 mg orally for 1 Day | N entered:<br>N analyzed: | 10<br>10 | |
| Ness 1999 | Named trial: | CHAOS | 1 | Placebo<br>No dosage data reported | N entered:<br>N analyzed: | N/A<br>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<br>No dosage data reported | N entered:<br>N analyzed: | N/A<br>1035 | |
| | Jadad: | 3 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD | | | | | |
| Nyyssonen 1994 | Named trial: | Other | 1 | Placebo<br>Placebo for 3 Months | N entered:<br>N analyzed: | 20<br>20 | Included in meta-analysis of lipids. |
| | Design: | RCT | 2 | Vitamin C<br>400 mg orally for 3 Months<br>Vitamin E<br>200 mg orally for 3 Months<br>Selenium<br>100 µg orally for 3 Months<br>Beta-carotene<br>30 mg orally for 3 Months | N entered:<br>N analyzed: | 20<br>20 | |
| | Jadad: | 2 | | | | | |
| | Population: | Smokers | | | | | |
| | 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

**Vitamin E for Cardiovascular Prevention and Treatment**

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|---|---|---|---|---|---|---|---|
| O'Byrne 2000 | Named trial: | Other | 1 | Placebo<br>Placebo for 8 Weeks | N entered:<br>N analyzed: | 13<br>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. |
| | Design: | RCT | 2 | Alpha tocotrienol<br>250 mg orally for 8 Weeks | N entered:<br>N analyzed: | 13<br>13 | |
| | Jadad: | 4 | 3 | Gamma tocotrienol<br>250 mg orally for 8 Weeks | N entered:<br>N analyzed: | 13<br>12 | |
| | Population: | Unspecified | 4 | Delta tocotrienol<br>250 mg orally for 8 Weeks | N entered:<br>N analyzed: | 13<br>N/A | |
| | Condition: | CAD, LDL oxidation | | | | | |
| Oda 1984 | Named trial: | Other | 1 | Vitamin E<br>.75 mg/kg orally duration N/A | N entered:<br>N analyzed: | N/A<br>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<br>1.2 mg/kg orally duration N/A | N entered:<br>N analyzed: | N/A<br>47 | |
| | Jadad: | 0 | 3 | Vitamin E<br>1.7 mg/kg orally duration N/A | N entered:<br>N analyzed: | N/A<br>51 | |
| | Population: | Children (under 18) | 4 | Vitamin E<br>2.2 mg/kg orally duration N/A | N entered:<br>N analyzed: | N/A<br>62 | |
| | Condition: | MVP | 5 | Vitamin E<br>2.7 mg/kg orally duration N/A | N entered:<br>N analyzed: | N/A<br>21 | |
| | | | 6 | Vitamin E<br>3.2 mg/kg orally duration N/A | N entered:<br>N analyzed: | N/A<br>62 | |
| Palumbo 2000 | Named trial: | PPP | 1 | Control or Usual care<br>No dosage data reported | N entered:<br>N analyzed: | N/A<br>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<br>300 mg orally for 12 Weeks | N entered:<br>N analyzed: | N/A<br>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

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|---|---|---|---|---|---|---|---|
| Paolisso 1995 | Named trial: | Other | 1 | Placebo<br>Placebo for 4 Months | N entered:<br>N analyzed: | 30<br>30 | Included in meta-analysis of lipids. |
| | Design: | RCT | 2 | Vitamin E<br>900 mg orally for 4 Months | N entered:<br>N analyzed: | 30<br>30 | |
| | Jadad: | 2 | | | | | |
| | Population: | Elderly (over 65) | | | | | |
| | Condition: | CAD | | | | | |
| Park 1999 | Named trial: | Other | 1 | Placebo<br>Placebo for 2 Years | N entered:<br>N analyzed: | N/A<br>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. |
| | Design: | RCT | 2 | Vitamin E<br>600 mg orally for 2 Years<br>Vitamin C<br>225 mg orally for 2 Years<br>Beta-carotene<br>18 mg orally for 2 Years | N entered:<br>N analyzed: | N/A<br>15 | |
| | Jadad: | 2 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD | | | | | |
| Porkkala-Sarataho 1998 | Named trial: | MASIT | 1 | Placebo<br>Placebo for 2 Months | N entered:<br>N analyzed: | 20<br>20 | Included in meta-analysis of lipids. |
| | Design: | RCT | 2 | Vitamin E<br>200 mg orally for 2 Months | N entered:<br>N analyzed: | 20<br>20 | |
| | Jadad: | 3 | 3 | Vitamin C<br>500 mg orally for 2 Months<br>Vitamin E<br>200 mg orally for 2 Months | N entered:<br>N analyzed: | 20<br>20 | |
| | Population: | Smokers | | | | | |
| | Condition: | CAD | | | | | |
| Porkkala-Sarataho 2000 | Named trial: | ASAP | 1 | Placebo<br>Placebo for 36 Months | N entered:<br>N analyzed: | 11<br>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<br>500 mg orally for 36 Months | N entered:<br>N analyzed: | 12<br>12 | |
| | Jadad: | 4 | 3 | Vitamin E<br>272 IU orally for 36 Months | N entered:<br>N analyzed: | 10<br>10 | |
| | Population: | Unspecified | 4 | Vitamin C<br>500 mg orally for 36 Months<br>Vitamin E<br>272 IU orally for 36 Months | N entered:<br>N analyzed: | 15<br>15 | |
| | 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

**Vitamin E for Cardiovascular Prevention and Treatment**

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|---|---|---|---|---|---|---|---|
| PPP 2001 | Named trial: | PPP | 1 | Placebo<br>Placebo for 3.6 Years | N entered:<br>N analyzed: | 2264<br>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<br>300 mg orally for 3.6 Years | N entered:<br>N analyzed: | 2231<br>1947 | |
| | Jadad: | 3 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD | | | | | |
| Qureshi 1995 | Named trial: | Other | 1 | Vitamin E<br>1 mg orally for 4 Weeks<br>Placebo<br>Placebo for 4 Weeks | N entered:<br>N analyzed: | 16<br>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<br>40 mg orally for 4 Weeks<br>Palm olein<br>940 mg orally for 4 Weeks<br>Alpha tocotrienol<br>48 mg orally for 4 Weeks<br>Gamma tocotrienol<br>112 mg orally for 4 Weeks<br>Delta tocotrienol<br>60 mg orally for 4 Weeks | N entered:<br>N analyzed: | 20<br>20 | |
| | Jadad: | 0 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD | | | | | |
| Rapola 1996 | Named trial: | ATBC | 1 | Placebo<br>Placebo for 4.7 Years | N entered:<br>N analyzed: | 5549<br>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<br>20 mg orally for 4.7 Years | N entered:<br>N analyzed: | 5602<br>N/A | |
| | Jadad: | 3 | 3 | Vitamin E<br>50 mg orally for 4.7 Years | N entered:<br>N analyzed: | 5570<br>N/A | |
| | Population: | Smokers | 4 | Vitamin E<br>50 mg orally for 4.7 Years | N entered:<br>N analyzed: | 5548<br>N/A | |
| | Condition: | Angina | | | | | |
| Rapola 1997 | Named trial: | ATBC | 1 | Placebo<br>Placebo for 5.3 Years | N entered:<br>N analyzed: | 438<br>N/A | Included in meta-analysis of death and MI. |
| | Design: | RCT | 2 | Beta-carotene<br>20 mg orally for 5.3 Years | N entered:<br>N analyzed: | 461<br>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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|---|---|---|---|---|---|---|---|
| | Jadad: | 3 | 3 | Vitamin E<br>50 mg orally for 5.3 Years | N entered:<br>N analyzed: | 466<br>N/A | |
| | Population: | Smokers | 4 | Vitamin E<br>50 mg orally for 5.3 Years<br>Beta-carotene<br>20 mg orally for 5.3 Years | N entered:<br>N analyzed: | 497<br>N/A | |
| | Condition: | CAD | | | | | |
| Reaven 1993 | Named trial: | Other | 1 | DL-alpha-tocopherol<br>1600 mg orally for 2 Months | N entered:<br>N analyzed: | 8<br>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<br>1600 mg orally for 2 Months | N entered:<br>N analyzed: | 8<br>7 | |
| | Jadad: | 3 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD, LDL oxidation | | | | | |
| Rokitzki 1994 | Named trial: | Other | 1 | Placebo<br>Placebo for 151 Days | N entered:<br>N analyzed: | N/A<br>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<br>330 mg orally for 151 Days | N entered:<br>N analyzed: | N/A<br>15 | |
| | Jadad: | 3 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD | | | | | |
| Salonen 2000 | Named trial: | ASAP | 1 | Placebo<br>Placebo for 3 Years | N entered:<br>N analyzed: | 130<br>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. |
| | Design: | RCT | 2 | Vitamin E<br>272 IU orally for 3 Years | N entered:<br>N analyzed: | 130<br>115 | |
| | Jadad: | 4 | 3 | Vitamin C<br>500 mg orally for 3 Years | N entered:<br>N analyzed: | 130<br>120 | |
| | Population: | Unspecified | 4 | Vitamin C<br>500 mg orally for 3 Years<br>Vitamin E<br>272 IU orally for 3 Years | N entered:<br>N analyzed: | 130<br>113 | |
| | Condition: | Carotid atherosclerosis | | | | | |

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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|---|---|---|---|---|---|---|---|
| Schafer 1990 | Named trial: | Other | 1 | Placebo<br>Placebo for 3 Months | N entered:<br>N analyzed: | 15<br>15 | Included in meta-analysis of lipids. |
| | Design: | RCT | 2 | Vitamin E<br>300 mg orally for 3 Months<br>Selenium<br>125 µg orally for 3 Months | N entered:<br>N analyzed: | 15<br>15 | |
| | Jadad: | 1 | | | | | |
| | Population: | Female<br>Elderly (Over 65) | | | | | |
| | Condition: | CAD, LDL oxidation | | | | | |
| Semple 1974 | Named trial: | Other | 1 | Control or Usual care<br>Control or Usual care for 6 Months | N entered:<br>N analyzed: | 14<br>14 | Excluded from statistical analysis because no outcomes of interest were reported. No impact of vitamin E on intermittent claudication symptoms. |
| | Design: | CCT | 2 | Vitamin E<br>400 mg orally for 6 Months | N entered:<br>N analyzed: | 12<br>12 | |
| | Jadad: | 0 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | PVD | | | | | |
| Simons 1996 | Named trial: | Other | 1 | Placebo<br>Placebo for 6 Weeks | N entered:<br>N analyzed: | 11<br>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. |
| | Design: | RCT | 2 | Vitamin E<br>500 IU orally for 6 Weeks | N entered:<br>N analyzed: | 11<br>11 | |
| | Jadad: | 3 | 3 | Vitamin E<br>1000 IU orally for 6 Weeks | N entered:<br>N analyzed: | 9<br>8 | |
| | Population: | Unspecified | 4 | Vitamin E<br>1500 IU orally for 6 Weeks | N entered:<br>N analyzed: | 11<br>11 | |
| | 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

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|---|---|---|---|---|---|---|---|
| Singh 1996 | Named trial: | Other | 1 | Placebo<br>Placebo for 3 Days<br>Placebo<br>Placebo for 28 Days<br>Placebo<br>Placebo for 25 Days | N entered:<br>N analyzed: | 62<br>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<br>50000 IU intravenously for 3 Days<br>Vitamin C<br>1000 mg intravenously for 3 Days<br>Vitamin E<br>400 mg orally for 28 Days<br>Beta-carotene<br>25 mg orally for 28 Days<br>Vitamin A<br>50000 IU orally for 25 Days<br>Vitamin C<br>1000 mg orally for 25 Days | N entered:<br>N analyzed: | 63<br>63 | |
| | Condition: | CAD | | | | | |
| Singhal 2001 | Named trial: | Other | 1 | Placebo<br>Placebo for 30 Days | N entered:<br>N analyzed: | 35<br>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<br>400 IU orally for 30 Days | N entered:<br>N analyzed: | 35<br>32 | |
| | Jadad: | 2 | 3 | Vitamin C<br>1000 mg orally for 30 Days | N entered:<br>N analyzed: | 35<br>31 | |
| | Population: | Unspecified | 4 | Vitamin A<br>25000 IU orally for 30 Days | N entered:<br>N analyzed: | 35<br>32 | |
| | Condition: | CAD, LDL oxidation | 5 | Fruit<br>400 gm orally for 30 Days | N entered:<br>N analyzed: | 35<br>30 | |

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

**Vitamin E for Cardiovascular Prevention and Treatment**

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|---|---|---|---|---|---|---|---|
| Sisto 1995 | Named trial: | Other | 1 | Control or Usual care<br>No dosage data reported | N entered:<br>N analyzed: | 25<br>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<br>600 mg orally for 28 Days<br>Vitamin C<br>2 gm orally for 3 Days<br>Allopurinol<br>600 mg orally for 3 Days | N entered:<br>N analyzed: | 20<br>N/A | |
| | Jadad: | 2 | 3 | Control or Usual care<br>No dosage data reported | N entered:<br>N analyzed: | 19<br>N/A | |
| | Population: | Unspecified | 4 | Vitamin E<br>600 mg orally for 2 Days<br>Vitamin C<br>2 gm orally for 3 Days<br>Allopurinol<br>600 mg orally for 3 Days | N entered:<br>N analyzed: | 17<br>N/A | |
| | Condition: | CAD | | | | | |
| Stampfer 1983 | Named trial: | Other | 1 | Placebo<br>Placebo for 16 Weeks | N entered:<br>N analyzed: | 15<br>15 | Included in meta-analysis of lipids. |
| | Design: | RCT | 2 | Vitamin E<br>800 IU orally for 16 Weeks | N entered:<br>N analyzed: | 15<br>15 | |
| | Jadad: | 2 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD | | | | | |
| Steiner 1995 | Named trial: | Other | 1 | Aspirin<br>325 mg orally for 2 Years | N entered:<br>N analyzed: | 48<br>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<br>400 IU orally for 2 Years<br>Aspirin<br>325 mg orally for 2 Years | N entered:<br>N analyzed: | 52<br>44 | |
| | Jadad: | 3 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CVA/TIA | | | | | |

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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|---|---|---|---|---|---|---|---|
| Stephens 1996 | Named trial: | CHAOS | 1 | Placebo<br>Placebo for 494 Days | N entered:<br>N analyzed: | 967<br>948 | Included in meta-analysis of death and MI. |
| | Design: | RCT | 2 | Vitamin E<br>800 IU orally for 737 Days | N entered:<br>N analyzed: | 546<br>N/A | |
| | Jadad: | 3 | 3 | Vitamin E<br>400 IU orally for 366 Days | N entered:<br>N analyzed: | 489<br>N/A | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD | | | | | |
| Takamatsu 1995 | Named trial: | Other | 1 | Vitamin E<br>3 mg orally for 6 Years | N entered:<br>N analyzed: | 73<br>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<br>100 mg orally for 6 Years | N entered:<br>N analyzed: | 74<br>69 | |
| | Jadad: | 5 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD | | | | | |
| Tardif 1997 | Named trial: | MVP | 1 | Placebo<br>Placebo for 7 Months | N entered:<br>N analyzed: | 79<br>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. |
| | Design: | RCT | 2 | Statin drug<br>500 mg orally for 7 Months | N entered:<br>N analyzed: | 80<br>58 | |
| | Jadad: | 3 | 3 | Vitamin C<br>500 mg orally for 7 Months<br>Vitamin E<br>700 IU orally for 7 Months<br>Beta-carotene<br>30000 IU orally for 7 Months<br>Vitamin E<br>2000 IU orally for 1 Day | N entered:<br>N analyzed: | 78<br>54 | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD | | | | | |
| | | | 4 | Statin drug<br>500 mg orally for 7 Months<br>Vitamin C<br>500 mg orally for 7 Months | N entered:<br>N analyzed: | 80<br>56 | |

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

**Vitamin E for Cardiovascular Prevention and Treatment**

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|---|---|---|---|---|---|---|---|
| Tomeo 1995 | Named trial: | Other | 1 | Palm olein<br>1200 mg orally for 18 Months | N entered:<br>N analyzed: | 25<br>25 | Included in meta-analysis of lipids. |
| | Design: | RCT | 2 | Vitamin E<br>64 mg orally for 18 Months | N entered:<br>N analyzed: | 25<br>25 | |
| | Jadad: | 4 | | Palm olein<br>960 mg orally for 18 Months | | | |
| | Population: | Unspecified | | Alpha tocotrienol<br>160 mg orally for 18 Months | | | |
| | Condition: | Carotid atherosclerosis | | Gamma tocotrienol<br>160 mg orally for 18 Months | | | |
| Toone 1973 | Named trial: | Other | 1 | Placebo<br>Placebo for 2 Years | N entered:<br>N analyzed: | 11<br>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<br>1600 IU orally for 2 Years | N entered:<br>N analyzed: | 11<br>N/A | |
| | Jadad: | 1 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD, angina | | | | | |
| Tornwall 1997 | Named trial: | ATBC | 1 | Placebo<br>Placebo for 4 Years | N entered:<br>N analyzed: | 6573<br>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<br>50 mg orally for 4 Years | N entered:<br>N analyzed: | 6605<br>4690 | |
| | Jadad: | 3 | 3 | Beta-carotene<br>20 mg orally for 4 Years | N entered:<br>N analyzed: | 6559<br>4591 | |
| | Population: | Smokers | 4 | Vitamin E<br>50 mg orally for 4 Years | N entered:<br>N analyzed: | 6552<br>4586 | |
| | Condition: | PVD | | Beta-carotene<br>20 mg orally for 4 Years | | | |

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

**Vitamin E for Cardiovascular Prevention and Treatment**

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|---|---|---|---|---|---|---|---|
| Tornwall 1999 | Named trial: | ATBC | 1 | Placebo<br>Placebo for 3.7 Years | N entered:<br>N analyzed: | 373<br>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<br>20 mg orally for 3.7 Years | N entered:<br>N analyzed: | 377<br>N/A | |
| | Jadad: | 3 | 3 | Vitamin E<br>50 mg orally for 3.7 Years | N entered:<br>N analyzed: | 344<br>N/A | |
| | Population: | Smokers | 4 | Vitamin E<br>50 mg orally for 3.7 Years<br>Beta-carotene<br>20 mg orally for 3.7 Years | N entered:<br>N analyzed: | 390<br>N/A | |
| | Condition: | PVD | | | | | |
| Tornwall 2001 | Named trial: | ATBC | 1 | Placebo<br>Placebo for 5.8 Years | N entered:<br>N analyzed: | 7287<br>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<br>50 mg orally for 5.8 Years | N entered:<br>N analyzed: | 7286<br>N/A | |
| | Jadad: | 3 | 3 | Beta-carotene<br>20 mg orally for 5.8 Years | N entered:<br>N analyzed: | 7282<br>N/A | |
| | Population: | Smokers | 4 | Vitamin E<br>50 mg orally for 5.8 Years<br>Beta-carotene<br>20 mg orally for 5.8 Years | N entered:<br>N analyzed: | 7278<br>N/A | |
| | Condition: | AAA | | | | | |
| Tsai 1978 | Named trial: | Other | 1 | Placebo<br>Placebo for 4 Weeks | N entered:<br>N analyzed: | 98<br>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<br>600 IU orally for 4 Weeks | N entered:<br>N analyzed: | 104<br>94 | |
| | 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

**Vitamin E for Cardiovascular Prevention and Treatment**

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|---|---|---|---|---|---|---|---|
| Upritchard 2000 | Named trial: | Other | 1 | Placebo<br>Placebo for 4 Weeks | N entered:<br>N analyzed: | 13<br>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<br>500 ml orally for 4 Weeks | N entered:<br>N analyzed: | 15<br>15 | |
| | Jadad: | 3 | 3 | Vitamin E<br>800 IU orally for 4 Weeks | N entered:<br>N analyzed: | 12<br>12 | |
| | Population: | Unspecified | 4 | Vitamin C<br>500 mg orally for 4 Weeks | N entered:<br>N analyzed: | 12<br>12 | |
| | Condition: | CAD | | | | | |
| Virtamo 1998 | Named trial: | ATBC | 1 | Placebo<br>Placebo for 6.1 Years | N entered:<br>N analyzed: | 6849<br>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<br>50 mg orally for 6.1 Years | N entered:<br>N analyzed: | 6820<br>N/A | |
| | Jadad: | 3 | 3 | Beta-carotene<br>20 mg orally for 6.1 Years | N entered:<br>N analyzed: | 6821<br>N/A | |
| | Population: | Smokers | 4 | Vitamin E<br>50 mg orally for 6.1 Years<br>Beta-carotene<br>20 mg orally for 6.1 Years | N entered:<br>N analyzed: | 6781<br>N/A | |
| | Condition: | CAD | | | | | |
| Wagdi 1996 | Named trial: | Other | 1 | Placebo<br>No dosage data reported | N entered:<br>N analyzed: | N/A<br>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<br>600 mg orally duration N/A<br>Vitamin C<br>1000 mg orally duration N/A<br>N-acetyl cysteine<br>200 mg orally duration N/A | N entered:<br>N analyzed: | N/A<br>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

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|---|---|---|---|---|---|---|---|
| Wen 1999 | Named trial: | Other | 1 | Placebo<br>Placebo for 30 Weeks | N entered:<br>N analyzed: | 22<br>17 | Excluded from meta-analysis of lipids due to insufficient statistics. Vitamin E group showed significant reduction in LDL oxidation as compared to placebo. |
| | Design: | RCT | 2 | Vitamin E<br>100 IU orally for 6 Weeks<br>Vitamin E<br>200 IU orally for 6 Weeks<br>Vitamin E<br>400 IU orally for 6 Weeks<br>Vitamin E<br>800 IU orally for 6 Weeks<br>Vitamin E<br>1600 IU orally for 6 Weeks | N entered:<br>N analyzed: | 27<br>20 | |
| | Jadad: | 3 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD, LDL oxidation | | | | | |
| Westhuyzen 1997 | Named trial: | Other | 1 | Placebo<br>Placebo for 10 Days<br>Placebo<br>Placebo for 1 Day | N entered:<br>N analyzed: | 38<br>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. |
| | Design: | RCT | 2 | Vitamin C<br>1000 mg orally for 1 Day<br>Vitamin E<br>750 IU orally for 10 Days | N entered:<br>N analyzed: | 38<br>38 | |
| | Jadad: | 2 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD, reperfusion injury | | | | | |
| Whittaker 1987 | Named trial: | Other | 1 | Control or Usual care<br>No dosage data reported | N entered:<br>N analyzed: | N/A<br>N/A | Excluded from statistical analysis because no outcomes of interest were reported. No cardioprotective effect of vitamin E among subjects receiving chemotherapy. |
| | Design: | RCT | 2 | Digoxin<br>0.25 mg orally duration N/A | N entered:<br>N analyzed: | N/A<br>N/A | |
| | Jadad: | 1 | 3 | Vitamin E<br>600 mg orally duration N/A | N entered:<br>N analyzed: | N/A<br>N/A | |
| | 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

**Vitamin E for Cardiovascular Prevention and Treatment**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Williams 1962 | Named trial: | Other | 1 | Placebo<br>No dosage data reported | N entered:<br>N analyzed: | 17<br>17 | Excluded from statistical analysis because no outcomes of interest were reported. |
| | Design: | RCT | 2 | Vitamin E<br>1600 mg orally duration N/A | N entered:<br>N analyzed: | 16<br>16 | Suggestions of improvement of claudication symptoms with Co-Q10 treatment without statistical significance. |
| | Jadad: | 2 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | PVD | | | | | |
| Williams 1971 | Named trial: | Other | 1 | Placebo<br>Placebo for 13.4 Months | N entered:<br>N analyzed: | 29<br>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<br>1600 mg orally for 26.8 Months | N entered:<br>N analyzed: | 45<br>N/A | |
| | Jadad: | 2 | | | | | |
| | Population: | Unspecified | | | | | |
| | 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

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|---|---|---|---|---|---|---|---|
| Woodside 1999 | Named trial: | Other | 1 | Placebo<br>Placebo for 8 Weeks | N entered:<br>N analyzed: | 33<br>26 | Excluded from statistical analysis because no outcomes of interest were reported. |
| | Design: | RCT | 2 | Multi-vitamin<br>Multi-vitamin orally for 8 Weeks | N entered:<br>N analyzed: | 32<br>22 | Combinations of antioxidants including vitamins C and E showed improvement in measures of LDL oxidation. |
| | Jadad: | 4 | 3 | Vitamin C<br>150 mg orally for 8 Weeks<br>Vitamin E<br>67 mg orally for 8 Weeks<br>Beta-carotene<br>9 mg orally for 8 Weeks | N entered:<br>N analyzed: | 33<br>25 | |
| | Population: | Unspecified | | | | | |
| | Condition: | Hyperhomocystinemia, LDL oxidation. | 4 | Vitamin C<br>150 mg orally for 8 Weeks<br>Vitamin E<br>67 mg orally for 8 Weeks<br>Beta-carotene<br>9 mg orally for 8 Weeks<br>Multi-vitamin<br>Multi-vitamin orally for 8 Weeks | N entered:<br>N analyzed: | 34<br>28 | |
| Yau 1994 | Named trial: | Other | 1 | Placebo<br>Placebo for 14 Days | N entered:<br>N analyzed: | 14<br>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. |
| | Design: | RCT | 2 | Vitamin E<br>300 mg orally for 14 Days | N entered:<br>N analyzed: | 14<br>14 | |
| | Jadad: | 4 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD, reperfusion injury | | | | | |

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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|---|---|---|---|---|---|---|---|
| Yusuf, 2000 | Named trial: | HOPE | 1 | Placebo<br>Placebo for 4.5 Years | N entered:<br>N analyzed: | 4780<br>N/A | Included in meta-analysis of death and MI. |
| | Design: | RCT | 2 | Vitamin E<br>400 IU orally for 4.5 Years | N entered:<br>N analyzed: | 4761<br>N/A | |
| | Jadad: | 3 | | | | | |
| | Population: | Unspecified | | | | | |
| | Condition: | CAD, CVA/TIA | | | | | |

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