Chapter 3. Results

Description of the Evidence

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

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

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

Details of the "Named" Clinical Trials Included in Analysis

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

Primary Prevention Trials

ATBC

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

Linxian

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

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

PPP

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

Trials of patients with risk factors for cardiovascular disease

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

HOPE

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

MASI

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

Secondary Prevention Trials

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

ASAP

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

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

MRC/BHF

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

GISSI

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

CHAOS

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

HATS

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

MVP

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

SPACE

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

Vitamin E Trials That Report Death as an Outcome

Trial Inclusion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Vitamin E Trials That Report on Myocardial Infarction as an Outcome

Trial Inclusion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Vitamin E Trials That Reported on Lipids as an Outcome

Trial Inclusion

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

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

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

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

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

Trials Using Vitamin E Alone vs. Placebo: Lipid Analysis

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Meta-Regression Analysis of Vitamin E Treatment Over Time

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

Trials Using Vitamin E in Combination vs. Placebo

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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