REVIEW

The Antioxidant Vitamins and Cardiovascular Disease

A Critical Review of Epidemiologic and Clinical Trial Data

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■ *Purpose:* To review prospective epidemiologic studies and randomized trials regarding the role of antioxidant vitamins (vitamins E and C and β-carotene) in the prevention of cardiovascular disease, with emphasis on differences in results obtained by these two types of studies.

■ *Data Sources:* Computerized and manual searches of the literature on antioxidant vitamins and cardiovascular disease.

■ *Study Selection:* Prospective epidemiologic studies and randomized trials that included 100 or more participants and provided quantified estimates of antioxidant vitamin intake.

■ *Data Synthesis:* Comparisons of relative risk reductions (RRR) across observational studies and randomized trials, including assessment of dose–response relations.

■ *Results:* All three large epidemiologic cohort studies of vitamin E noted that high-level vitamin E intake or supplementation was associated with a significant reduction in cardiovascular disease (RRR range, 31% to 65%), as measured by various fatal and nonfatal cardiovascular end points. To obtain these reductions, vitamin E supplementation must last at least 2 years. Less consistent reductions were seen in studies of β-carotene (RRR range, −2% to 46%) and vitamin C (RRR range, −25% to 51%). Considerable biases in observational studies, such as different health behaviors of persons using antioxidants, may account for the observed benefit. By contrast, none of the completed randomized trials showed any clear reduction in cardiovascular disease with vitamin E, vitamin C, or β-carotene supplementation. The trials were not specifically designed to assess cardiovascular disease, did not provide data on nonfatal cardiovascular end points, may have had insufficient treatment durations, and used suboptimal vitamin E doses. The completed trials were of adequate size to indicate that the true therapeutic benefit of vitamin E and other antioxidants in reducing fatal cardiovascular disease (a survival benefit as long as 5 years) is probably more modest than the epidemiologic data suggest.

■ *Conclusion:* The epidemiologic data suggest that antioxidant vitamins reduce cardiovascular disease, with the clearest effect for vitamin E; however, completed randomized trials do not support this finding. Much of this controversy should be resolved by the ongoing large-scale and long-term randomized trials designed specifically to evaluate effects on cardiovascular disease.

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Cardiovascular disease is responsible for about 40% of the deaths in industrialized countries and many deaths in developing countries (1, 2). Simple, accessible, and cost-effective preventive therapies that decrease the incidence of cardiovascular disease could greatly affect public health. Substantial interest has recently focused on the hypothesis that the naturally occurring antioxidant vitamins such as vitamin E, vitamin C, and β-carotene may prevent myocardial infarction, progression of coronary heart disease, or strokes (3, 4). We critically review the human prospective observational studies and randomized clinical trials of antioxidant vitamins (vitamins E and C and β-carotene) in cardiovascular disease, highlighting the differences in the methods and results of the two study designs.

Methods

Data Sources

We searched the scientific literature for all epidemiologic studies (prospective cohort, prospective nested case–control, retrospective case–control, or geographic correlations) and randomized clinical trials of antioxidants (using the terms vitamin E, vitamin C, β-carotene, vitamins, and antioxidants) and cardiovascular disease (using the terms coronary heart disease, cerebrovascular disease, peripheral vascular disease, atherosclerosis, and mortality). We also examined all reports in the cancer literature to identify any studies of the effects of antioxidants on total mortality or other possible cardiovascular outcomes. We searched the MEDLINE database and the Science Citation Index for articles published from 1965 to 1994. We identified additional studies by examining bibliographies of original articles, review articles, and textbooks and by personally contacting the researchers. We also provide in the Appendix a list of the most relevant reviews as a supplement to the references.

Study Selection

We included only studies that specifically defined the type of intake of antioxidants, that is, studies that quantified the components of dietary intake or supplement use. We excluded studies that did not quantify intake (such as intake of fruits and vegetables or randomized trials of different diets). We used standard definitions to define epidemiologic studies (5) and did not consider case series. Randomized clinical trials were those in which previously established criteria (6) were used to randomly assign patients and to blind the investigators to treatment assignment.

See editorial comment on p 887.

Study Synthesis

We only selected prospective cohort studies; the rationale for this decision was consistent with discussions of epidemiologic causality (5). The epidemiologic cohort studies varied greatly in terms of study design, sample size, and assessment of antioxidant intake. To consistently summarize the results of these studies, we emphasized the consistency of the reductions in risk estimates across studies and antioxidant groups; when possible, we reviewed dose–response relations. We excluded retrospective studies because they cannot determine whether reported antioxidant intake or biological levels were altered by the development of cardiovascular disease. We also excluded broad geographic correlations of population-based intake of antioxidants and cardiovascular disease rates because such correlations are retrospective in nature; in addition, extrapolation of these results to individual clinical decisions is difficult. These two types of studies have been reviewed previously (7).

We included all randomized trials with more than 100 participants; only five randomized trials had fewer than 100 participants. These five trials consisted of a total of 268 patients, and all trials had a maximum treatment duration of 6 months. Thus, their exclusion did not alter our results. To consistently present results for randomized clinical trials, we used the one-step modified Mantel–Haenszel–Peto method (6) to estimate a relative risk reduction (RRR) for each trial.

Mechanisms of Antioxidants

Substantial laboratory, animal, and human data suggest that oxidation of low-density lipoprotein (LDL) cholesterol is an important step in the pathogenesis of atherosclerotic lesions. More extensive reviews have been published (4, 8, 9). Because oxidized LDL cholesterol is believed to have different properties than nonoxidized LDL cholesterol, LDL cholesterol accumulates in the cells that line the blood vessels. Various chemotactic and proliferative mechanisms lead to fatty streaks and later to atherosclerotic lesions. It is unknown whether oxidation of LDL cholesterol is important in both the initiation and progression of plaque or increases the risk for plaque rupture (10). The major lipid-soluble antioxidant vitamins are vitamin E (α-tocopherol) and β-carotene, a precursor of vitamin A. The major water-soluble antioxidant vitamin is vitamin C (ascorbic acid). Vitamin E is important in preventing oxidation of LDL cholesterol. In vitro studies have shown that this process does not begin until oxidative stress depletes the host vitamin E content (11). β-Carotene prevents oxidation of LDL cholesterol (12), although this finding is inconsistent (13). Vitamin C prevents oxidation of LDL cholesterol and preserves vitamin E and β-carotene levels during oxidative stress (14).

A combination of antioxidants is not believed to be clearly more efficacious in preventing oxidation of LDL cholesterol than any one antioxidant alone (13). Supplementation with daily doses greater than 200 IU of vitamin E, 1000 mg of vitamin C, and 25 mg of β-carotene increase blood levels of the corresponding vitamin to the same extent as do higher doses of these vitamins (15–17) (1.49 IU of vitamin E equals 1 mg; 10 IU of β-carotene equals 1 μg of retinol, which equals 1 retinol equivalent. Vitamin C is expressed in mg rather than IU). Antioxidant vitamins presumably exert their effects through protection of oxidation; however, some studies have shown that the vitamins may also preserve endothelial function (18), affect hemostasis (19), and lower both LDL cholesterol levels (20, 21) and blood pressure (22).

Epidemiologic Studies of Antioxidant Vitamins and Cardiovascular Disease

In the prospective observational studies, a large group of persons was followed over time and the incidence of cardiovascular disease in persons with high intakes (through diet or vitamin supplementation) or high blood levels of antioxidant vitamins was compared with the incidence in patients with lower intakes or levels. In the nested case–control studies, vitamin levels in blood samples collected at baseline were compared among persons who subsequently did and did not develop cardiovascular disease.

Vitamin E

Prospective Cohort Studies

In a large prospective cohort study, the U.S. Nurses' Health Study (23) (Table 1 and Figure 1), 87 000 female nurses were followed for an average of 8 years. About 13% of women regularly used vitamin E supplements. These women had a statistically significant RRR of 31% (95% CI, 3% to 51%) for nonfatal myocardial infarction and death from cardiovascular disease compared with women who did not use the supplements, after adjustment for age, smoking, alcohol use, menopausal status, hormone use, exercise, aspirin use, hypertension, cholesterol intake, diabetes, caloric intake, and vitamin C and β-carotene intake. The absolute risk reduction was 3.4 per 10 000 years of follow-up (8.5 compared with 5.2 per 10 000 years of follow-up).

Reduced risk was only seen with vitamin E supplementation (at least 100 IU/d) and not with multivitamin use (about 30 IU of vitamin E per day). No dose–response relation was seen with increasing duration of use, presumably because of the small numbers of women who used vitamin E for a prolonged period. However, only use of vitamin E beyond 2 years was associated with significant reductions in the risk for cardiovascular disease. A significantly reduced risk for myocardial infarction or death from cardiovascular disease was seen only with the fourth or highest quintile of vitamin E intake (mean intake for the fourth quintile, 17 IU/d) compared with the lowest quintile (mean intake, 3 IU/d); this corresponded to at least a fivefold difference in intake levels. Although persons using vitamin E more commonly took vitamin C or β-carotene, the effect of vitamin E was independent of these antioxidants. A nonsignificant reduction in ischemic stroke was seen with the use of vitamin E supplements (RRR, 29% [CI, −31% to 61%]).

Use of vitamin E supplements was found to offer similar protection in another cohort study in which 39 000 male health professionals were followed for 4 years (24). About 17% of the men took vitamin E supplements. Compared with men in the lower quintile of vitamin E intake (median intake, 6 IU/d), men in the upper quintile (median intake, 419 IU/d) had a 40% RRR (CI, 19% to 56%) for nonfatal myocardial infarction, death from coronary heart disease, or coronary revascularization after adjustment for age, smoking, body mass, caloric intake, fiber intake, alcohol use, hypertension, aspirin use, exercise, family history, profession, and vitamin C and β-carotene use. The absolute risk reduction was 6.0 per 10 000

Table 1. Prospective Observational Studies of Vitamin E and Cardiovascular Disease*

Study Participants and Location (Reference)	Age, *y*	Follow-up, *y*	Comparison Groups	Minimum Dose Difference between Groups	Outcomes	Results
87 245 female nurses; United States (23)	34–59	8	Vitamin E supplement and no supplement use	5.7-fold	437 nonfatal MIs, 115 deaths from CHD	RRR, 31% (3% to 51%)†‡
39 910 male health professionals; United States (24)	40–75	4	Upper and lower quintiles of intake	4.0-fold	360 CABGs or PTCAs, 201 nonfatal MIs, 106 deaths from CHD	RRR, 40% (19% to 56%)‡§
2748 men; Finland (25)	30–69	14	Upper and lower tertiles of intake	1.3-fold	186 deaths from CHD	RRR, 34% (−11% to 58%)‡‖
2385 women; Finland (25)	30–69	14	Upper and lower tertiles of intake	1.3-fold	58 deaths from CHD	RRR, 65% (12% to 86%)‡‖
84 patients who died of CHD, 168 community controls selected from 10 532 patients in general population; the Netherlands (26)	37–87	9	Serum vitamin E levels <645 μg/L and higher	Not provided	Nested case–control study	RR, 1.5 (0.6 to 3.5)‡¶
92 patients who died of CHD, 92 community controls selected from 12 000 patients in general population; Finland (27)	30–64	7	Not provided	Not provided	Nested case–control study	Mean tocopherol levels were 6.1 mg/L for case-patients and 5.8 mg/L for controls; P = NS**

* CABG = coronary artery bypass grafting; CHD = coronary heart disease; MI = myocardial infarction; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty; RR = relative risk; RRR = relative risk reduction.

† Adjusted for age, smoking, alcohol use, menopausal status, hormone use, exercise, aspirin use, hypertension, cholesterol level, diabetes, caloric intake, and vitamin C and β-carotene intake.

‡ Numbers in parentheses are 95% CIs.

§ Adjusted for age, smoking, body mass, caloric intake, fiber intake, alcohol use, hypertension, aspirin use, exercise, family history, profession, and vitamin C and β-carotene use.

‖ Adjusted for age, smoking, serum cholesterol level, hypertension, body mass index, and energy intake.

¶ Adjusted for sex, age, cholesterol level, blood pressure, smoking, body mass index, week of blood collection, and years of education.

** For differences between case-patients and controls; case-patients were matched for sex, age, tobacco use, cholesterol level, blood pressure, and history of cardiovascular disease.

years of follow-up (50.9 compared with 44.9 per 10 000 years of follow-up) among persons using vitamin E supplements. Use of vitamin E supplements for less than 2 years was not associated with a reduced risk for cardiovascular events (RRR, 5%; $P > 0.05$). As in the Nurses' Health Study, only the two upper quintiles of vitamin E intake were associated with significant risk reductions; the intakes in these quintiles were at least four times the intake in the lowest quintile.

In a prospective cohort study in Finland (25), 2748 men and 2385 women were followed for a mean of 14 years. During follow-up, 186 men and 58 women died of coronary heart disease. Only 3% of the study sample took vitamin supplements. Compared with men in the lowest tertile of intake (intake of vitamins through diet and supplements, <4.5 IU/d), men with the highest intake of vitamin E (mean, >6.0 IU/d) had a nonsignificant RRR of 34% (CI, −11% to 58%) after adjustment for age, smoking, serum cholesterol levels, hypertension, body mass index, and energy intake. Compared with women in the lowest tertile of vitamin E intake (mean, <3.5 IU/d), women in the highest tertile (mean, >4.7 IU/d) had an RRR of 65% (CI, 12% to 86%). The long follow-up period for this study (14 years) suggests that prolonged differences were seen in the intake of vitamin E between persons who died of coronary heart disease and those who did not; however, such differences were not reported.

Of note, the intake seen in the highest tertile in this study was similar to that in the lowest quintiles in the Nurses' (23) or Health Professionals (24) studies, suggesting that the association between vitamin E and coronary heart disease can be seen with both high and low intakes. The relative difference between the intake levels needed to observe benefit was only about 40% higher in the Finnish study (25). This percentage, however, refers to differences in tertile ranges; true differences in median levels of intake are probably higher. In addition, these investigators did not fully adjust for dietary factors and did not adjust for intake of vitamin C or β-carotene.

Nested Case–Control Studies

Two studies examined archived blood samples among patients who subsequently developed cardiovascular disease and those who did not (26, 27). Neither study found vitamin E levels to be significantly lower in persons who developed disease. However, these studies tested blood

more than 7 years after collection. Because antioxidant vitamin levels tend to decrease with time in archived blood (28, 29), these studies probably underestimate the strength of the association between antioxidant vitamins and cardiovascular disease. Moreover, single blood measurements cannot distinguish short-term use from long-term use, a distinction that seems to be necessary to measure the effect on cardiovascular disease (29).

β-Carotene

Prospective Cohort Studies

In the Health Professionals Study (24) (Table 2 and Figure 2), which included more than 39 000 men, participants in the highest quintile of carotene intake (mean, 19 034 IU/d) had a RRR of 29% (CI, 14% to 47%) for coronary revascularization, myocardial infarction, and death from coronary heart disease compared with those in the lowest quintile (mean, 3969 IU/d) after adjustment for cardiovascular risk factors and intake of vitamins E and C. Significantly reduced risk was seen only in the highest quintile compared with the lowest quintile, corresponding to a 4.8-fold difference. The benefit was largely confined to current smokers (RRR, 70%), with no benefit seen in nonsmokers (RRR, −9%). The reasons for this are unclear, although previous studies have shown that smoking reduces β-carotene levels (30).

In the Finnish study of 2748 men and 2385 women (25), risk for death from coronary heart disease was not significantly reduced in men in the highest tertile of carotene intake (mean, >258 μg) compared with those in the lowest tertile (mean, <147 μg) (RRR, −2% [CI, −48% to 30%]) after adjustment for cardiovascular risk factors. A nonsignificant reduction was seen for women (RRR, 38% [CI, −29% to 70%]) in the highest tertile (mean, 383 μg) compared with those in the lowest tertile (mean, <182 μg). No adjustment was made for vitamin E or C.

In another study of male pharmaceutical employees (31), mortality from coronary heart disease was nonsignificantly higher in men with low baseline carotene levels (relative risk, 1.53 [CI, 1.07 to 2.20]). Investigators of the Lipid Research Clinics follow-up study of 1899 middle-aged men with type IIa hyperlipidemia (32) found that patients with serum carotenoid levels in the highest quartile (mean, >3.2 μmol/L) had a RRR of 36% (CI, 8% to 56%) compared with those in the lowest quintile (mean, <2.3 μmol/L). In a small prospective study of 1299 elderly nursing home residents (33), risk for death from cardiovascular disease was reduced among residents with a high dietary intake of β-carotene (RRR, 46% [CI, 13% to 66%]). The Nurses' study did not show significant risk reductions associated with carotene intake once intake of vitamins E and C was considered (23).

Nested Case–Control Studies

In a study in which archived blood samples were used, β-carotene levels were lower among patients who had had myocardial infarction than among hospitalized controls (34). Investigators of two other similar studies did not find any association between death from coronary heart disease and baseline vitamin A levels (26, 27).

Vitamin C

In a prospective population-based study of 11 348 U.S. adults, investigators found a 34% lower standardized mortality rate (CI, 18% to 47%) among persons who received

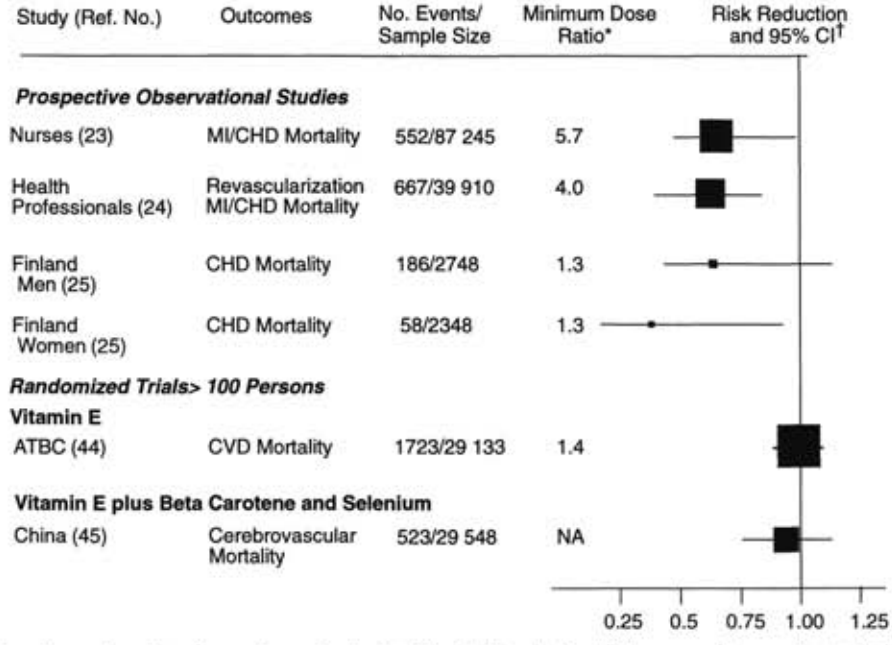

Figure 1. Prospective observational studies and randomized trials of vitamin E: effects on cardiovascular end points. The horizontal bars represent 95% CIs. The size of the square showing the reduction is approximately proportional to the square root of the overall sample size multiplied by the number of events. ATBC = Alpha-Tocopherol, Beta-Carotene and Cancer Prevention Study; CHD = coronary heart disease; CVD = cardiovascular disease; MI = myocardial infarction; NA = not applicable. *The minimum dose ratio refers to the minimum relative differences in intake levels or antioxidant vitamin doses between comparison groups (for observational studies) and between treatment groups (for randomized trials); *see* the tables for more details. †Risk reduction is the relative reduction in the odds ratio, standardized mortality ratio, or relative risk (*see* the tables for details).

Table 2. Prospective Observational Studies of β-Carotene and Cardiovascular Disease*

Study Participants and Location (Reference)	Age, y	Follow-up, y	Comparison Groups	Minimum Dose Difference between Groups	Outcomes	Results
39 910 male health professionals; United States (24)	40–75	4	Upper and lower quintiles of intake	4.8-fold	360 CABGs or PTCAs, 201 nonfatal MIs, 106 deaths from CHD	RRR, 29% (14% to 47%)†‡
2748 men; Finland (25)	30–69	14	Upper and lower tertiles of intake	1.8-fold	186 deaths from CHD	RRR, −2% (−48% to 30%)‡§
2385 women; Finland (25)	30–69	14	Upper and lower tertiles of intake	2.1-fold	58 deaths from CHD	RRR, 38% (−29% to 70%)‡§
2974 male pharmaceutical employees; Switzerland (31)	Middle-aged	12	Serum β-carotene levels <0.23 μmol/L and higher	Not provided	132 deaths from CHD	RR, 1.53 (1.07 to 2.20)‡‖
1899 men with hyperlipidemia; United States (32)	40–59	13	Upper and lower quartiles of serum β-carotene levels	1.5-fold	282 deaths from MI or CHD	RRR, 36% (8% to 56%)‡¶
1299 nursing home residents; United States (33)		5	Upper and lower quartiles of intake	Not provided	161 deaths from CVD	RRR, 46% (13% to 66%)‡**
125 patients with MI, 125 community controls, and 125 hospital controls selected from 12 000 blood donors; United States (34)	35–65	9	Highest and lowest quintiles of blood β-carotene levels	Not provided	Nested case–control study	Odds ratio (for hospital controls), 0.42 (0.19 to 0.89)‡††
84 patients who died of CHD, 168 community controls selected from 10 532 patients in general population; the Netherlands (26)	37–87	9	For blood vitamin A levels <0.45 μgl/L and higher	Not provided	Nested case–control study	RR, 1.2 (0.6 to 2.4)‡‡‡
92 patients who died of CHD, 92 community controls selected from 12 000 patients in general population; Finland (27)	30–64	7	Not provided	Not provided	Nested case–control study	Mean serum retinol levels were 651 g/L for case-patients and 613 g/L for controls; P = NS§§

* CABG = coronary artery bypass grafting; CHD = coronary heart disease; CVD = cardiovascular disease; MI = myocardial infarction; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty; RR = relative risk; RRR = relative risk reduction.

† Adjusted for age, smoking, body mass, caloric intake, fiber intake, alcohol use, hypertension, aspirin use, exercise, family history, profession, and vitamin C and E use.

‡ Numbers in parentheses are 95% CIs.

§ Adjusted for age, smoking, serum cholesterol level, hypertension, body mass index, and energy intake.

‖ Adjusted for age, smoking, blood pressure, and cholesterol level. Results for vitamin E were not reported.

¶ Adjusted for age, body mass index, high-density lipoprotein cholesterol level, low-density lipoprotein cholesterol level, systolic blood pressure, fasting glucose level, aspirin use, glucose tolerance test result, physical activity, current smoking, previous smoking, and education.

** Adjusted for age, sex, smoking, alcohol intake, cholesterol intake, and functional status; no results were given for vitamin E or C.

†† For case-patients matched for age and sex.

‡‡ Adjusted for sex, age cholesterol level, blood pressure, smoking, body mass index, week of blood collection, and years of education.

§§ For differences between case-patients and controls, case-patients were matched for sex, age, tobacco use, cholesterol level, blood pressure, and history of cardiovascular disease.

50 mg of vitamin C per day or more (by diet or supplements) compared with persons who received less vitamin C (35) (Table 3; Figure 3). However, these researchers did not consider vitamin E intake; the intake of this vitamin has been correlated with vitamin C intake (23). In a small cohort study of 730 elderly persons in the United Kingdom followed for 20 years (36), stroke among persons in the highest tertile of vitamin C intake (mean, >45 mg/d) was significantly reduced (RRR, 50% [CI, 20% to 70%]) compared with the lowest tertile (mean, <28 mg/d); however, no such reduction was seen in mortality from coronary heart disease (RRR, 20% [CI, −20% to 40%]). However, in the Nurses' study, persons using vitamin C did not have a significantly lower risk for myocardial

infarction or death from coronary heart disease once vitamin E was considered (23). Similarly, the Health Professionals study showed no reduced risk for coronary revascularization, myocardial infarction, or death from coronary heart disease among persons using vitamin C (excess RRR, −25% [CI, −71% to 9%]) after adjustment for cardiovascular disease risk factors and vitamin E intake (24).

In the Finnish study, vitamin C intake was associated with a significantly reduced risk for death from coronary heart disease among women (RRR, 51% [CI, 2% to 76%] for differences between persons receiving 91 mg/d and those receiving <61 mg/d) (25). However, no such reduction was seen for men (RRR, 0% [CI, −45% to 32%] for differences between men receiving 91 mg/d and those receiving <61 mg/d). The investigators of the Finnish study did not adjust for intake of vitamin E or carotene.

Three other small cohort study among adults in California (37), Switzerland (31), and Sweden (38) have shown no reductions in risk for death from coronary heart disease with vitamin C intake. Vitamin C has not been studied in nested case–control studies because vitamin C degrades quickly in stored samples (29).

Summary and Limitations of the Prospective Observational Studies

The magnitude of benefit from epidemiologic studies is difficult to precisely estimate because of differences in study design, assessment of intake of antioxidants, and end points. However, broad consistencies in risk reductions associated with high levels of antioxidant intake may be examined. On the basis of confirmation in all independent, large (>50 000 years of follow-up), and prospective cohort studies, the most consistent and reliable effect is seen with vitamin E, either with supplementation or relatively high levels of dietary intake. The RRR for various cardiovascular end points seems to range from 31% to 65%. This intake apparently needs to be sustained for at least 2 years before risk reductions may be detected. Use of β-carotene is less clearly associated with a reduced risk; β-carotene was found to provide significant protection in only one of the three large cohort studies. In that study, its benefits seemed to be largely confined to smokers. β-Carotene has provided inconsistent protection in the smaller cohort studies. The RRR for the large and small studies ranged from −2% to 46%). Vitamin C clearly reduced risk in only one of the large cohort studies, in which vitamin E intake was not ascertained, and in none of the small cohort studies. The RRR in these studies ranged from −25% to 51%.

These findings do not provide conclusive evidence that vitamin E reduces cardiovascular disease, because the studies have potentially important methodologic problems that limit their interpretation. First, lifestyle and dietary patterns probably differ significantly between persons who use and do not use antioxidant vitamins. For example, in four of the larger studies (23, 24, 35, 37), persons using antioxidant vitamins were, on aggregate and in relative percentages, 24% less likely to be current smokers, 29% more likely to exercise regularly, and 10% less likely to have hypertension than persons who did not use the vi-

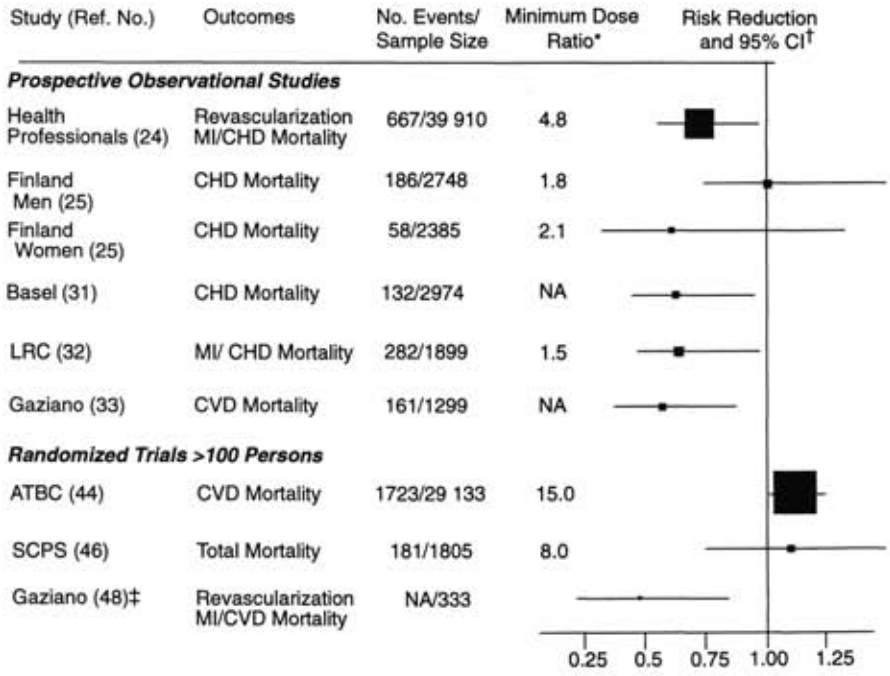

Figure 2. Prospective observational studies and randomized trials of β-carotene: effects on cardiovascular end points. The horizontal bars represent 95% CIs. The size of the square showing the reduction is approximately proportional to the square root of the overall sample size multiplied by the number of events. ATBC = Alpha-Tocopherol, Beta-Carotene and Cancer Prevention Study; CHD = coronary heart disease; CVD = cardiovascular disease; LRC = Lipids Research Clinic; NA = not applicable; MI = myocardial infarction; SCPS = Skin Cancer Prevention Study. *The minimum dose ratio refers to the minimum relative differences in intake levels or antioxidant vitamin doses between comparison groups (for observational studies) and between treatment groups (for randomized trials); *see* the tables for more details. †Risk reduction is the relative reduction in the odds ratio, standardized mortality ratio, or relative risk (*see* the tables for details). ‡The size of the square for the study by Gaziano and colleagues is estimated.

Table 3. Prospective Observational Studies of Vitamin C and Cardiovascular Disease*

Study Participants and Location (Reference)	Age, *y*	Follow-up, *y*	Comparison Groups	Minimum Dose Difference between Groups	Outcomes	Results
39 910 male health professionals; United States (24)	40–75	4	Upper and lower quintiles of intake	12.6-fold	360 CABGs or PTCAs, 201 nonfatal MIs, 106 deaths from CHD	RRR, −25% (−71% to 9%)†‡
11 348 adults; United States (35)	25–74	10	>50 mg and 0–49 mg of dietary or regular supplement use of vitamin C	Not provided	929 deaths from CVD	SMR, 0.66 (0.53 to 0.82)‡§
2748 men; Finland (25)	30–69	14	Upper and lower tertiles of intake	1.4-fold	186 deaths from CHD	RRR, 0% (−45% to 32%)‡‖
2385 women; Finland (25)	30–69	14	Upper and lower tertiles of intake	1.5-fold	58 deaths from CHD	RRR, 51% (2% to 76%)‡‖
3119 adults; United States (37)	16–74	10	>250 mg/d of vitamin C from intake and less	Not provided	127 deaths from CVD	SMR, 1.01 (0.61 to 1.39)‡¶
2974 male pharmaceutical company employees; Switzerland (31)	Middle-aged	12	<22.7 μmol/L blood levels of vitamin C and higher	Not provided	132 deaths from CHD	RR, 1.25 (0.77 to 2.01)‡**
730 elderly nursing home residents; United Kingdom (36)	≥65	20	Upper and lower tertiles of intake	1.6-fold	124 deaths from stroke	RRR, 50% (20% to 70%)‡††
730 elderly nursing home residents; United Kingdom (36)	≥65	20	Upper and lower tertiles of intake	1.6-fold	182 deaths from CHD	RRR, 20% (−20% to 40%)‡††
1462 women; Sweden (38)	38–60	5	Not provided	Not provided	23 MIs	*P* = NS‡‡

* CABG = coronary artery bypass grafting; CHD = coronary heart disease; CVD = cardiovascular disease; MI = myocardial infarction; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty; RR = relative risk; RRR = relative risk reduction; SMR = standardized mortality ratio.

† Adjusted for age, smoking, body mass, caloric intake, fiber intake, alcohol use, hypertension, aspirin use, exercise, family history, profession, and vitamin E and β-carotene use.

‡ Numbers in parentheses are 95% CIs.

§ No results were given for vitamin E or β-carotene.

‖ Adjusted for age, smoking, serum cholesterol level, hypertension, body mass index, and energy intake.

¶ Estimated CIs.

** Adjusted for smoking, blood pressure, and cholesterol level.

†† Adjusted for age, sex, diastolic blood pressure, and serum cholesterol level.

‡‡ No details were given.

tamins. Persons using antioxidant vitamins also consumed more alcohol.

These findings suggest that persons using antioxidant vitamins may have other health and lifestyle behaviors that reduce their risk for cardiovascular disease. The absolute difference in these behaviors is not large enough to significantly alter the risk reductions seen for vitamin E or vitamin C intake; in addition, these differences have been considered in most of the cohort studies we examined, either by stratification or adjustment in statistical models. However, such adjustment may be unreliable if these other variables were measured poorly (such as a single unreliable blood pressure reading). Moreover, it is impossible to adjust for unmeasured health behaviors that probably exist, given the more healthy profile of persons using antioxidant vitamins. The relative homogeneity of the Nurses' (23) and Health Professional (24) study samples was confirmed by the smaller differences in health behaviors between the persons in these samples who used and did not use vitamin supplements than among participants in the nationally representative study (35). Although this homogeneity tends to increase the internal validity of the risk reductions associated with vitamin E, it does limit generalization to broader populations (for example, the mortality rate in the Nurses' and Health Professionals studies was less than one third the U.S. national average [1]).

Second, vitamin E intake may only be a marker for the intake of another as-yet unidentified protective factor. However, that a benefit was seen specifically for vitamin E and not for vitamin C or β-carotene in the two largest studies partially argues against this theory. In addition, investigators of the two largest studies (the U.S. Nurses' and Health Professionals studies) adjusted their risk estimates for measured dietary factors such as fiber and caloric intake. However, vitamin E intake may still correlate best with intake of an undetermined protective factor.

In a prospective study of 805 men aged 65 years or

older, intake of flavonoids, the natural antioxidants found in many of the same foods as vitamin E, was inversely correlated with mortality from coronary heart disease ($P = 0.015$ for the trend) (39). Intake of vitamin E, vitamin C, and β-carotene was significantly higher in persons with the highest intake of flavonoids. Similarly, in a retrospective case–control study of antioxidants in persons with advanced age-related macular degeneration, intake of specific carotenoids—lutein and zeaxanthin (primarily obtained from dark green, leafy vegetables)—provided the most protection against macular degeneration, whereas the intake of preformed vitamin A (retinol) provided no protection (40). Although the significance of both flavonoids, lutein and zeaxanthin, in preventing cardiovascular disease is unclear, these two studies show that antioxidant vitamins may be markers for other protective factors. Further indirect evidence has been provided by observational studies of antioxidants and cancer, which have noted that whereas a broad intake of fresh fruits and vegetables offers protection, more specific intake of β-carotene and vitamin C offers less protection (41). Phyloestrogens, flavonoids, other carotenoid compounds, and phenol-derived substances have been less extensively studied (9, 42).

Self-reported diet questionnaires generally underestimate biological levels of antioxidant vitamins and have varying reproducibility within the same person (43). Both these factors would tend to underestimate the strength of the association between antioxidant vitamins and cardiovascular disease.

Completed Randomized Trials of Antioxidant Vitamins

Unbiased and reliable estimates of the efficacy of antioxidant vitamins as therapies can only be obtained from large-scale randomized trials. The completed large-scale randomized trials of antioxidants were specifically designed to address cancer, not cardiovascular disease. Only three trials enrolled more than 1000 patients; each of these has also reported on total mortality or fatal cardiovascular outcomes. The Alpha-Tocopherol, Beta-Carotene and Cancer Prevention Study (ATBC) of 29 133 middle-aged smokers in Finland followed for 6.1 years (44) was designed primarily to determine reductions in mortality from lung and other cancers. This trial evaluated intake of β-carotene (20 mg/d) and vitamin E (50 mg/d) in a 2×2 factorial design. A nutrition supplementation trial of 29 584 middle-aged adult residents in the Linxian province of China (45), who were followed for 5.25 years, evaluated different combinations of 10 nutritional substances in a variation of a partial 2×4 factorial design. One factor included 125 mg of vitamin C and 30 μg of molybdenum (an inhibitor of carcinogenic nitrosamines). Another factor included 15 mg of β-carotene plus 30 mg of vitamin E plus 50 μg of selenium, another antioxidant. The Skin Cancer Prevention Study (46) assessed recurrence of skin cancer in 1805 patients who were randomly assigned to receive either 50 mg of β-carotene or placebo and were followed for more than 5 years. We discuss the results of these and smaller trials by type of vitamin.

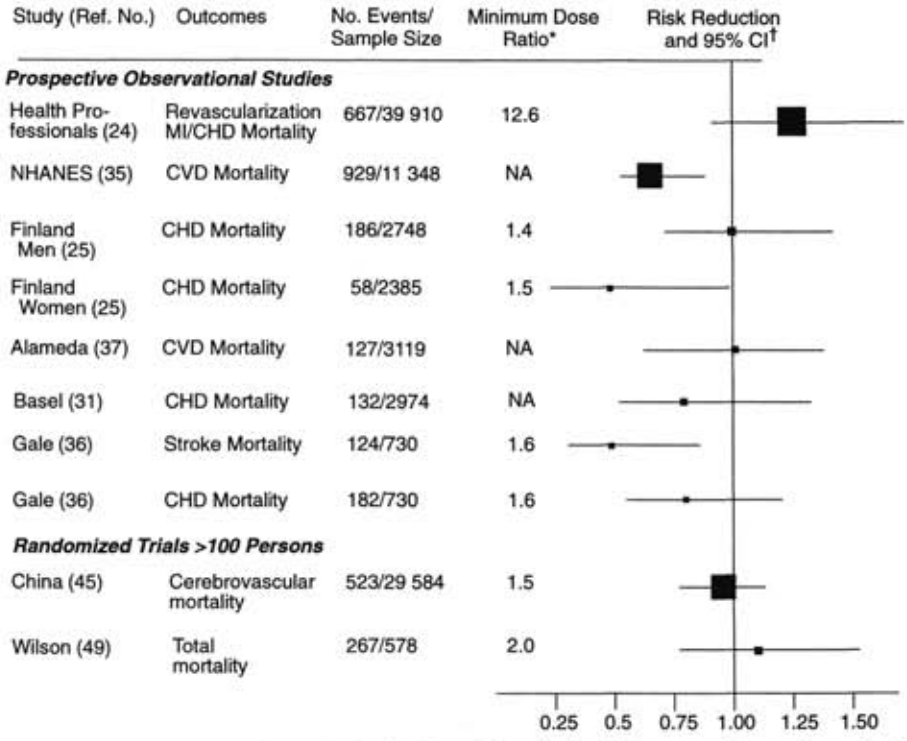

Figure 3. Prospective observational studies and randomized trials of vitamin C: effects on cardiovascular end points. The horizontal bars represent 95% CIs. The size of the square showing the reduction is approximately proportional to the square root of the overall sample size multiplied by the number of events. CHD = coronary heart disease; CVD = cardiovascular disease; MI = myocardial infarction; NA = not applicable; NHANES = National Health and Nutrition Examination Survey. *The minimum dose ratio refers to the minimum relative differences in intake levels or antioxidant vitamin doses between comparison groups (for observational studies) and between treatment groups (for randomized trials); *see* the tables for more details. †Risk reduction is the relative reduction in the odds ratio, standardized mortality ratio, or relative risk (*see* the tables for details).

Table 4. Randomized Clinical Trials of Vitamin E Alone or in Combination with Other Antioxidants, with an End Point of Total Mortality or Mortality from Cardiovascular Disease*

Trial (Reference)	Study Participants	Follow-up Period	Daily Vitamin Dose and Difference in Blood Levels between Comparison Groups	Outcomes	Events/Total Patients		Relative Risk Reduction (95% CI)
					Treatment Group	Control Group	
					n/n(%)		%
ATBC (44)	29 133 male smokers in Finland	6.1 years	50 mg; 1.4-fold	Total mortality	1798/14 564 (12.4)	1768/14 569 (12.1)	−2 (−9 to 5)
				Death from cardiovascular	853/14 564 (5.9)	870/14 569 (6.0)	2 (−8 to 11)
				Death from cancer	579/14 564 (4.0)	537/14 569 (3.7)	−8 (−22 to 4)
DeMaio et al. (47)	100 patients having angioplasty	4 months	1200 IU; 2.0-fold	Restenosis (angiographic plus thallium exercise)	18/52 (34.6)	24/48 (50.0)	46 (−18 to 76)
Chinese study (45)	29 584 adults in Linxian Province	5.25 years	β-carotene (15 mg) and vitamin E (30 mg) and selenium (50 μg); 15-fold for β-carotene	Total mortality	1018/14 792 (6.9)	1109/14 572 (7.5)	9 (0 to 17)
				Death from cerebrovascular disease	294/14 792 (1.7)	274/14 792 (1.9)	9 (−8 to 24)
				Death from cancer	369/14 792 (2.5)	423/14 792 (2.9)	13 (0 to 24)

* ATBC = Alpha-Tocopherol, Beta-Carotene and Cancer Prevention Study.

Vitamin E

In the ATBC trial (44) (Table 4; Figure 1), vitamin E did not significantly reduce total mortality (RRR, −2% [CI, −9% to 5%]) or mortality from cardiovascular disease (RRR, 2% [CI, −8% to 11%]). Vitamin E supplementation led to a marginally significant increase in mortality from hemorrhagic stroke (RRR, −49% [CI, −217% to −3%]) and a nonsignificant reduction in mortality from ischemic stroke (RRR, 16% [CI, −19% to 41%]). Both stroke outcomes were based on small numbers of events and may have arisen by chance. This trial did not report data on nonfatal cardiovascular disease events. The results of this large trial (more than 1700 deaths from cardiovascular disease) appear to directly contradict the findings that were based on the epidemiologic data.

This trial, however, had several limitations, primarily the low vitamin E dose used. The 50-mg vitamin E dose increased serum levels by only 1.4-fold, a much lower increase than the fourfold or greater differences that epidemiologic studies suggest are needed to see a reduction in cardiovascular disease (23, 24).

Second, the population studied, middle-aged male long-term smokers in Finland, is not representative of general populations or their state of atherosclerosis. In other studies, smoking has been shown to reduce antioxidant vitamin levels (30). Other completed trials of vitamin E in cardiovascular disease have been much smaller and have had treatment durations of less than 1 year. In a trial of 100 patients who had had angioplasty and were randomly assigned to receive 1200 IU of vitamin E daily or placebo for 4 months, the RRR for restenosis was 46% ($P = 0.06$; absolute risk reduction for restenosis, 15%: 50% in the placebo group compared with 35% in the vitamin E group) (47).

Vitamin E in Combination with Other Antioxidants

In the Chinese trial (45), the combination of vitamin E with β-carotene and selenium led to a marginally significant reduction in mortality (RRR, 9% [CI, 0% to 17%]); however, this reduction was largely due to reductions in the number of stomach cancers. A trend toward a reduction in mortality from cerebrovascular disease was also seen (RRR, 9% [CI, −8% to 24%]). It is impossible, however, to evaluate which substance—β-carotene, vitamin E, or selenium—contributed most to the trend toward lower mortality from cerebrovascular disease.

Significant 15-fold differences in serum levels were noted with 15 mg of β-carotene per day. Although vitamin E levels were not reported, it is probable that, as in the ATBC study, the 30-mg daily dose of vitamin E did not increase serum levels above 1.5-fold. A further limitation of this trial was that only 1% of the deaths in this population were caused by coronary heart disease (or only about 10% to 15% of the rate in the general population of that age group [2]); this finding limits the power of the trial to assess this coronary outcome. Finally, the Chinese trial was done in an area with low antioxidant intake, much less than that in Western populations, which limits the generalizability of the findings to populations with a higher intake of antioxidants.

β-Carotene

In the ATBC trial (44) (Table 5; Figure 2), β-carotene supplementation led to significant increases in total mortality (RRR, −9% [CI, −17% to −2%) and a nonsignificant increase in mortality from cardiovascular disease (RRR, −11% [CI, −23% to 1%]). No significant reductions were seen in mortality from stroke or other cardio-

Table 5. Randomized Clinical Trials of β-Carotene and Vitamin C with an Outcome of Total Mortality or Mortality from Cardiovascular Disease*

Trial (Reference)	Participants	Follow-up Period	Daily Vitamin Dose and Difference in Blood Levels between Comparison Groups	Outcomes	Events/Total Patients		Relative Risk Reduction (95% CI)
					Treatment Group	Control Group	
					n/n(%)		%
β-carotene							
ATBC (44)	29 133 male smokers in Finland	6.1 years	20 mg; 15-fold	Total mortality	1850/14 560 (12.7)	1716/14 573 (11.9)	−9 (−17 to −2)
				Death from cardiovascular disease	905/14 560 (6.2)	818/14 573 (5.6)	−11 (−23 to 1)
				Death from cancer	582/14 560 (4.0)	534/14 573 (3.7)	−9 (−23 to 3)
SCPS (46)	1805 patients with skin cancer	5 years	50 mg; 8-fold	Total mortality	79/913 (8.7)	72/892 (8.1)	−8 (−51 to 23)
Gaziano et al. (48)†	333 men with angina	5 years	50 mg every other day; not provided	Myocardial infarction, revascularization, stroke, or death from cardiovascular disease	NA	NA	54 (15 to 76)
Vitamin C							
Chinese study (45)	29 584 adults in Linxian Province	5.25 years	120 mg plus 30 μg of molybdenum; 1.5-fold	Total mortality	1018/14 792 (6.9)	1109/14 572 (7.5)	−1 (−10 to 7)
				Death from cerebrovascular disease	249/14 792 (1.7)	274/14 792 (1.9)	−4 (−24 to 12)
				Death from cancer	369/14 792 (2.5)	423/14 792 (2.9)	−6 (−22 to 8)
Wilson et al. (49)‡	578 patients admitted to a geriatric hospital	6 months	200 mg; 2-fold	Total mortality	137/271 (50.6)	130/267 (48.7)	−8 (−51 to 23)

* ATBC = Alpha-Tocopherol, Beta-Carotene and Cancer Prevention Study; NA = not available; SCPS = Skin Cancer Prevention Study.
† Subgroup of the larger Physicians Health Study of 21 000 men.
‡ Not an intention-to-treat analysis.

vascular disease. The 20-mg β-carotene dose increased serum levels 15-fold, suggesting that suboptimal dosing did not cause the lack of benefit. A possible limitation of this trial may have been the unblinding of β-carotene use. Yellowing of the skin was seen in 34% of persons in the β-carotene group and in 7% of persons in the placebo group. The group assigned to receive β-carotene may have felt protected and therefore increased their tobacco use or other adverse behaviors, which in turn led to cardiovascular disease. In the smaller trial of β-carotene in 1805 patients with skin cancer, total mortality was not reduced, even though only 151 patients died (46). According to a Physicians Health Study subgroup analysis in 333 men with evidence of angina at baseline, supplementation with 50 mg of β-carotene every other day for a mean of 5 years reduced the incidence of cardiovascular events by 54% (CI, 15% to 76%) (48). Although interesting, this was a data-derived finding in a subgroup of the larger sample of 21 000 men; the larger study is continuing, and the investigators should report its results in 1996 or 1997.

Vitamin C

In the Chinese trial (45) (Table 5; Figure 2), the combination of vitamin C and molybdenum did not reduce total mortality (RRR, −1% [CI, −10% to 7%]) or mortality from cerebrovascular disease (RRR, −4% [CI, −24% to 12%]). The 120-mg vitamin C dose led to significant fivefold increases in serum levels of vitamin C, suggesting that suboptimal dosing did not cause the lack of benefit. In a small trial of 578 patients admitted to a geriatric hospital, supplementation with 200 mg of vitamin C did not reduce total mortality at 6 months (49).

Summary of Completed Randomized Trials

Completed randomized trials, primarily designed for cancer outcomes, have shown no clear reduction in mortality from cardiovascular disease with supplementation lasting as long as 6 years for vitamin E, β-carotene, or vitamin C. Several factors can explain these "negative" findings. First, the vitamin E doses used in the larger trials were probably not large enough to detect plausible reductions in the risk for cardiovascular disease. In contrast, the β-carotene and vitamin C doses used in these trials were sufficient, yielding substantial increases in blood levels.

Second, in the epidemiologic studies, benefit was seen for both nonfatal and fatal end points. The trials were of sufficient size and statistical power to detect reductions in risk for death from cardiovascular disease that were as large as those found in epidemiologic studies (approximately 30%). However, unlike the epidemiologic studies,

the trials did not report findings on nonfatal myocardial infarction or strokes.

Third, none of the trials was specifically designed to detect differences in cardiovascular outcomes. The outcome measures and sample size determination were not designed for cardiovascular end points, and the proportion of cardiovascular end points to total end points in these trials may be lower than ideal. In addition, the mechanism of the benefit of antioxidants may differ between cancer and cardiovascular disease.

Finally, it is important to note that randomized trials evaluate the reduction in cardiovascular disease when supplementary antioxidant vitamins are used for a specified duration (usually a few years), usually starting in middle age; by this time atherosclerosis may be well established. By contrast, the epidemiologic studies address the relation of reduction in disease when high dietary intake (including supplementation) of antioxidant vitamins is sustained for much longer periods (at least several years or even decades), often starting at much younger ages, that is, the early part of atherosclerotic progression. Thus, the epidemiologic results probably also reflect differences in health behaviors and dietary habits between persons who use and do not use antioxidant vitamins. These results may also reflect differing effects of antioxidant supplementation on the initiation or progression or rupture of atherosclerotic plaques (10). These data suggest that the magnitude of benefit seen in the epidemiologic data (range, 20% to 60%) is probably larger than the magnitude of plausible therapeutic benefit expected from vitamin E, β-carotene, and vitamin C supplementation of a few years' duration. This may further indicate that the duration of supplementation may have to extend beyond 6 years before reductions can be detected.

Safety of Antioxidant Vitamins

In most countries, vitamins have been commonly available for many years and are associated with few major side effects (50). Previous short-term trials and epidemiologic studies suggest that antioxidant vitamin supplementation (at doses much lower than those being tested in trials) is safe. However, nonrandomized assessments of safety are prone to bias. In the ATBC trial (44), an apparent excess of lung cancer and deaths from cardiovascular disease was seen with β-carotene supplementation, and an excess of hemorrhagic stroke was seen with vitamin E supplementation. However, it is unclear whether these are real or spurious findings. Future trials should help address the safety and efficacy of higher-dose antioxidants.

Ongoing Randomized Trials

Several large-scale randomized trials have already started recruitment or are near completion; these trials will specifically address the efficacy of various antioxidant vitamins on cardiovascular disease (Table 6). The Physicians Health Study (51) is comparing β-carotene and placebo for an average of 12 years in 21 100 healthy male physicians, and the Carotene and Retinol Efficacy Trial (52) is comparing β-carotene and vitamin A in a factorial design in 17 700 long-term smokers or men with asbestos exposure followed for an average of 9 years. Results from these trials should be available in the next 2 years and will help resolve the controversy about β-carotene supplementation that surfaced with the ATBC trial.

The UK Heart Protection Study (Peto R. Personal communication) will assess a combination of vitamin E, β-carotene, and vitamin C in 20 000 patients with established cardiovascular disease. The Heart Outcomes Protection Study (53) is assessing vitamin E in 9000 similar patients. The Women's Antioxidant Cardiovascular Study will assess a factorial of vitamin E, vitamin C, and β-carotene in 8000 nurses with established cardiovascular disease (Hennekens CH. Personal communication). The GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Acuto) prevention trial will assess vitamin E in 12 000 patients who have had recent myocardial infarction (Tognoni GT. Personal communication). The Women's Health Study (54) is assessing vitamin E and β-carotene in a factorial design among 40 000 postmenopausal nurses. In all trials of vitamin E, doses greater than 300 IU/d are being used; such doses should be sufficient to increase serum levels at least two- to threefold (17). A future meta-analysis or a systematic overview of the cumulative numbers from these trials (an estimated 40 000 patients receiving secondary prevention and 86 000 patients receiving primary prevention) should, by the end of the decade, provide clear answers about the efficacy and safety of the various antioxidant vitamins. Such an overview would also provide data on the size of the effect, the treatment duration needed, and effects in different groups (for example, men compared with women, older patients compared with younger patients, smokers compared with nonsmokers, diabetic patients compared with nondiabetic patients).

Summary and Current Clinical Implications

The epidemiologic data suggest that high levels of intake of vitamin E either from diet or, more likely, from vitamin supplementation that are sustained for 2 or more years are associated with a reduced risk for fatal and nonfatal cardiovascular disease. Use of β-carotene or vitamin C is less clearly associated with a reduced risk. However, the limitations of the epidemiologic evidence, such as the differences in health behavior and dietary intake between persons using antioxidant vitamins and persons not using them, may explain much of the observed reduction in risk.

The completed randomized trials suggest that no antioxidant beneficially affects total mortality or mortality from cardiovascular disease. However, these trials have probably used suboptimal doses of vitamin E, and none was specifically designed to assess fatal or nonfatal cardiovascular disease outcomes. Within a few years, ongoing and planned randomized trials will help resolve many of these uncertainties. The combined evidence currently does not support the *routine* use of antioxidant vitamins as prevention against cardiovascular disease. Individual choices and public policy guidelines should await the result of the large trials, which will provide more information on the efficacy and safety of antioxidant vitamins as protection against cardiovascular disease (55).

Table 6. Ongoing Trials of Antioxidant Vitamins in Cardiovascular Disease Involving More Than 1000 Middle-Aged Patients*

Trial Name	Study Participants	Antioxidant and Daily Dose	Primary Cardiovascular End Point
PHS	21 100 male physicians	β-carotene, 50 mg every other day	Myocardial infarction and death from cardiovascular disease
CARET	17 700 male and female smokers and male smokers with asbestos exposure	β-carotene, 30 mg/d Retinyl palmitate, 25 000 U/d (2 × 2 factorial)	Myocardial infarction, stroke, and sudden death
WHS	40 000 postmenopausal U.S. nurses	Vitamin E, 600 IU/d β-carotene, 50 mg every other day (3 × 2 factorial with aspirin)	Myocardial infarction, stroke, and death from cardiovascular disease
HPS	20 000 persons with previous angina, stroke, claudication, or diabetic patients	Vitamin E, 600 mg/d, plus β-carotene, 20 mg/d, plus vitamin C, 250 mg/d	Total mortality
HOPE	9000 persons with previous myocardial infarction, stroke, or peripheral vascular disease and diabetic patients	Vitamin E, 400 IU/d	Myocardial infarction, stroke, and death from cardiovascular disease
WACS	8000 female nurses with previous cardiovascular disease	Vitamin C, 1 g/d, or vitamin E, 400 IU/d, or β-carotene, 20 mg/d (2 × 2 × 2 factorial)	Myocardial infarction, stroke, coronary revascularization, and death from cardiovascular disease
GISSI prevention	12 000 persons who had recently had myocardial infarction (<3 months)	Vitamin E, 300 mg/d	Total mortality
WHS	40 000 postmenopausal female U.S. nurses	Vitamin E, 600 IU/d β-carotene, 50 mg every other day (3 × 2 factorial with aspirin)	Myocardial infarction, stroke, and death from cardiovascular disease
Totals	86 000 patients receiving primary prevention 40 000 patients receiving secondary prevention 126 000 total		

* CARET = Carotene and Retinyl Palmitate Efficacy Trial; GISSI prevention = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Acuto; HOPE = Heart Outcomes Prevention Evaluation; HPS = Heart Protection Study; PHS = Physicians Health Study; WACS = Women's Atherosclerosis Cardiovascular Study; WHS = Women's Health Study.

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