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Vitamins E and C in the Prevention of Cardiovascular Disease in Men

The Physicians' Health Study II Randomized Controlled Trial

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DESPITE UNCERTAINTY REGARDING long-term health benefits, most US adults have taken a vitamin supplement in the past year.¹ In the 1999-2000 National Health and Nutrition Examination Survey, 12.7% and 12.4% of US adults took vitamin E and C supplements, respectively.² With annual vitamin supplement sales in the billions of US dollars,³ vitamin supplementation has broad public health implications.

Basic research studies suggest that vitamin E, vitamin C, and other antioxidants reduce cardiovascular disease by trapping organic free radicals, by deactivating excited oxygen molecules, or both, to prevent tissue damage.⁴ Antioxidants may slow or prevent atherosclerotic plaque formation by inhibiting low-density lipoprotein cholesterol oxidation,⁵ modifying platelet activity,^{6,7} reducing thrombotic potential,⁸ and modifying vascular reactivity.^{9,10} Some,¹¹⁻¹³ but not all,¹⁴ prospective cohort studies support a role for vitamin E in

Context Basic research and observational studies suggest vitamin E or vitamin C may reduce the risk of cardiovascular disease. However, few long-term trials have evaluated men at initially low risk of cardiovascular disease, and no previous trial in men has examined vitamin C alone in the prevention of cardiovascular disease.

Objective To evaluate whether long-term vitamin E or vitamin C supplementation decreases the risk of major cardiovascular events among men.

Design, Setting, and Participants The Physicians' Health Study II was a randomized, double-blind, placebo-controlled factorial trial of vitamin E and vitamin C that began in 1997 and continued until its scheduled completion on August 31, 2007. There were 14 641 US male physicians enrolled, who were initially aged 50 years or older, including 754 men (5.1%) with prevalent cardiovascular disease at randomization.

Intervention Individual supplements of 400 IU of vitamin E every other day and 500 mg of vitamin C daily.

Main Outcome Measures A composite end point of major cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, and cardiovascular disease death).

Results During a mean follow-up of 8 years, there were 1245 confirmed major cardiovascular events. Compared with placebo, vitamin E had no effect on the incidence of major cardiovascular events (both active and placebo vitamin E groups, 10.9 events per 1000 person-years; hazard ratio [HR], 1.01 [95% confidence interval {CI}, 0.90-1.13]; $P = .86$), as well as total myocardial infarction (HR, 0.90 [95% CI, 0.75-1.07]; $P = .22$), total stroke (HR, 1.07 [95% CI, 0.89-1.29]; $P = .45$), and cardiovascular mortality (HR, 1.07 [95% CI, 0.90-1.28]; $P = .43$). There also was no significant effect of vitamin C on major cardiovascular events (active and placebo vitamin E groups, 10.8 and 10.9 events per 1000 person-years, respectively; HR, 0.99 [95% CI, 0.89-1.11]; $P = .91$), as well as total myocardial infarction (HR, 1.04 [95% CI, 0.87-1.24]; $P = .65$), total stroke (HR, 0.89 [95% CI, 0.74-1.07]; $P = .21$), and cardiovascular mortality (HR, 1.02 [95% CI, 0.85-1.21]; $P = .86$). Neither vitamin E (HR, 1.07 [95% CI, 0.97-1.18]; $P = .15$) nor vitamin C (HR, 1.07 [95% CI, 0.97-1.18]; $P = .16$) had a significant effect on total mortality but vitamin E was associated with an increased risk of hemorrhagic stroke (HR, 1.74 [95% CI, 1.04-2.91]; $P = .04$).

Conclusions In this large, long-term trial of male physicians, neither vitamin E nor vitamin C supplementation reduced the risk of major cardiovascular events. These data provide no support for the use of these supplements for the prevention of cardiovascular disease in middle-aged and older men.

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cardiovascular disease prevention. Dietary and supplemental vitamin C have been inconsistently associated with cardiovascular disease, including significant¹⁵ and nonsignificant¹⁶ inverse associations as well as no association.^{17,18} In a pooled analysis of 9 cohorts, vitamin C supplement use exceeding 700 mg/d was significantly associated with a 25% reduction in coronary heart disease risk.¹⁹

Initial clinical trials of vitamin E alone among male smokers in the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) trial showed both possible benefits on prostate cancer²⁰ and risks on hemorrhagic stroke,²¹ in addition to secondary prevention trials such as the Cambridge Heart Antioxidant Study (CHAOS),²² which indicated possible cardiovascular disease reductions. Yet even as largely negative trials of vitamin E later emerged among patients with multiple coronary risk factors or preexisting cardiovascular disease,²³⁻²⁸ vitamin E and other supplement use has remained surprisingly prevalent among healthy individuals who report its regular use as part of their routine health regimen.²⁹ There have been fewer long-term primary prevention trials of vitamin E alone among participants at initially low risk of cardiovascular disease, for which there has been no effect on cardiovascular disease,^{30,31} with comparatively less data in men.³⁰

Vitamin C has typically been incorporated into antioxidant combinations with vitamin E, beta carotene, and other vitamins and minerals in large-scale clinical trials that reported no significant cardiovascular effects.³²⁻³⁵ Vitamin C alone has only been evaluated among 8171 women at high risk for cardiovascular disease,²⁸ and no effect on cardiovascular disease was found with use of 500 mg/d of vitamin C. Therefore, the clinical utility of vitamin C alone in preventing cardiovascular disease among those at low initial risk of cardiovascular disease remains uncertain. Further, because vitamin C may potentially interact with vitamin E,³⁶ it is important to

evaluate the effect of their interaction on cardiovascular disease.

Given these persistent gaps in knowledge and the ongoing debate regarding the roles of vitamin E and vitamin C for cardiovascular disease prevention, we designed the Physicians' Health Study II (PHS II) to provide novel and clinically relevant information on the individual effects of vitamin E and vitamin C supplementation on the risk of major cardiovascular events over a median follow-up of 8 years among 14 641 male physicians at lower initial risk of cardiovascular disease compared with participants in most previous trials.

METHODS

Study Design

The PHS II was a randomized, double-blind, placebo-controlled, 2×2×2×2 factorial trial evaluating the balance of risks and benefits of vitamin E (400 IU synthetic α -tocopherol or its placebo every other day; BASF Corporation, Florham Park, New Jersey), vitamin C (500 mg synthetic ascorbic acid or its placebo daily; BASF Corporation), and a multivitamin (Centrum Silver or its placebo daily; Wyeth Pharmaceuticals, Madison, New Jersey) in the prevention of cancer and cardiovascular disease among 14 641 male physicians aged 50 years or older.³⁷ A fourth randomized component, beta carotene (50 mg of Lurotin or placebo on alternate days; BASF Corporation), was scheduled to stop in March 2003, while the data and safety monitoring board recommended that the vitamin E, vitamin C, and multivitamin components continue.

The PHS II study design has previously been described.³⁷ Recruitment, enrollment, and randomization of men into PHS II occurred in 2 phases (FIGURE 1). Starting in July 1997, 18 763 PHS I participants^{38,39} were invited to participate in PHS II. Men were ineligible if they reported a history of cirrhosis, active liver disease, were taking anticoagulants, or reported a serious illness that might

preclude participation. Men with a history of myocardial infarction (MI), stroke, or cancer were eligible to enroll in PHS II. Individuals also must have been willing to forgo during the course of PHS II any current use of multivitamins or individual supplements containing more than 100% of the recommended daily allowance of vitamin E, vitamin C, beta carotene, or vitamin A. A total of 7641 willing participants (41%) from PHS I were randomized into PHS II and retained their original beta carotene treatment assignment.

In 1999, invitation letters and baseline questionnaires were mailed to 254 597 US male physicians aged 50 years or older identified from a list provided by the American Medical Association, excluding PHS I participants. Between July 1999 and July 2001, 42 165 men completed a baseline questionnaire. Of these, 16 743 individuals were willing to participate in PHS II, of whom 11 128 were eligible following the same eligibility criteria as PHS I participants. A 12-week run-in period excluded noncompliers who typically emerge during the first several months of participation.⁴⁰ Of 11 128 physicians who entered the run-in phase, 7000 willing and eligible men (63%) took at least two-thirds of their pills and were randomized into PHS II.

Thus, 14 641 men (7641 from PHS I and 7000 new physicians) were randomized into PHS II in blocks of 16, stratified by age, prior diagnosis of cardiovascular disease, prior diagnosis of cancer, and, for the 7641 PHS I participants, their original beta carotene treatment assignment. Men were randomly assigned to vitamin E or its placebo, to vitamin C or its placebo, to beta carotene or its placebo, and to a multivitamin or its placebo. There were 754 men (5.1%) with prevalent cardiovascular disease (nonfatal MI and stroke) randomized into PHS II. All participants provided written informed consent and the institutional review board at Brigham and Women's Hospital approved the research protocol.

Study Treatment, Follow-up, and Adherence

Participants were sent monthly calendar packs, containing vitamin E or placebo (taken every other day), and vitamin C or placebo (taken daily), every 6 months for the first year and annually thereafter. Participants also were sent annual questionnaires asking about adherence, potential adverse events, the occurrence of new end points, and updated risk factors. Treatment and follow-up continued in a blinded fashion through August 31, 2007, the scheduled end of the vitamin E and C components of PHS II. The multivitamin component is still ongoing.

Morbidity and mortality follow-up were extremely high at 95.3% and

97.7%, respectively. Morbidity and mortality follow-up as a percentage of person-time each exceeded 99.9%, with only 1055 and 289 person-years of morbidity and mortality follow-up, respectively, lost through August 31, 2007.

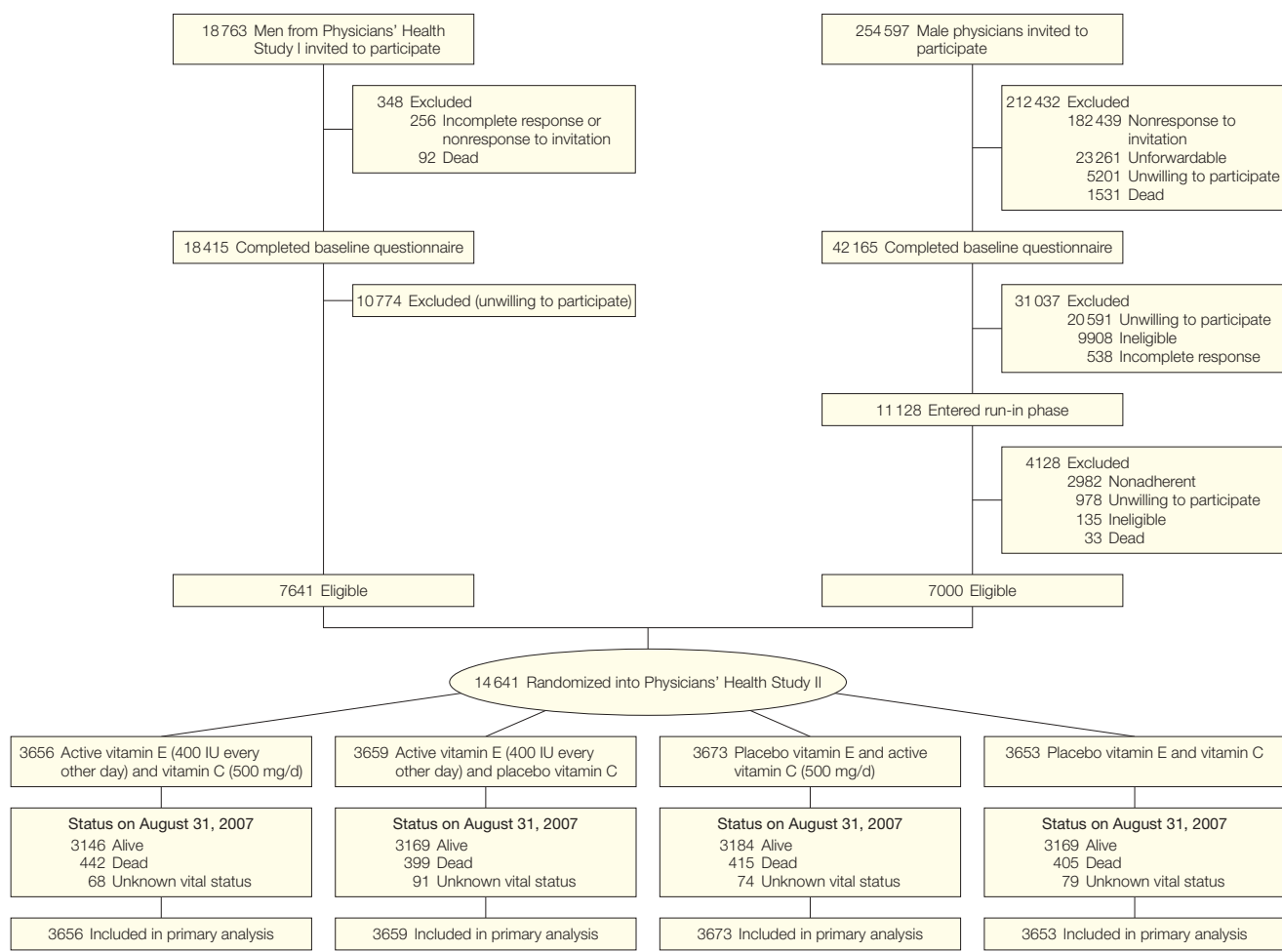
Adherence was defined from participant self-reports as taking at least two-thirds of the study agents. For active vitamin E and its placebo, adherence among participants at 4 years was 78% and 77%, respectively ($P = .12$), and at the end of follow-up (mean of 8 years), 72% and 70% ($P = .004$). For active vitamin C and its placebo, adherence among participants at 4 years was 78% and 78%, respectively ($P = .99$), and at the end of follow-up, 71% and 71% ($P = .54$). There were no differences be-

tween groups in the average rates of individual nontrial vitamin E supplement use (3.2% active and 3.1% placebo) or vitamin C supplement use (3.8% active and 4.4% placebo) for 31 days per year or more (drop-ins) at the end of the trial (each $P > .05$).

Confirmation of End Points

The primary cardiovascular end point, major cardiovascular events, was a composite end point that included nonfatal MI, nonfatal stroke, and cardiovascular mortality. For each end point reported by participants in the follow-up questionnaire, letter, telephone call, and other correspondence, permission was requested from the participant to examine relevant

Figure 1. Flow of Individuals Through the Vitamin E and Vitamin C Components of the Physicians' Health Study II



medical records. Once consent was obtained, records were requested from the hospital or attending physician and reviewed by an end points committee of physicians blinded to randomized treatment assignment.

The diagnosis of MI was confirmed by evidence of symptoms in the presence of either diagnostic elevations of cardiac enzymes or diagnostic changes on electrocardiograms. For fatal events, the diagnosis of MI also was accepted based on autopsy findings.³⁸ Diagnoses of stroke were confirmed that were defined as a typical neurological deficit of sudden or rapid onset and vascular origin, and lasted longer than 24 hours. Stroke was classified according to National Survey of Stroke criteria into ischemic, hemorrhagic, and unknown subtype,⁴¹ with high interobserver agreement.⁴²

Participant deaths were usually reported by family members or postal authorities. Following a report of a participant death, permission was requested to obtain death certificates and/or autopsy reports from next of kin or from the state vital records bureau in which the participant died. Total mortality was confirmed by the end points committee or by death certificate. Cardiovascular disease mortality was additionally documented by convincing evidence of a cardiovascular mechanism from all available sources, including death certificates, hospital records, and for deaths outside the hospital, observers' impressions. For men with unknown vital status, we used Web searches to identify deaths along with National Death Index searches that included data through 2006. By the end of the vitamin E and vitamin C components of PHS II, mortality follow-up as a percentage of person-time exceeded 99.9%. End point data also were collected on participant self-reports of congestive heart failure, angina pectoris, and revascularization (including coronary artery bypass graft and percutaneous coronary intervention).

Statistical Analyses

All primary analyses were based on the intention-to-treat principle, in which all

14 641 randomized participants were classified according to their randomized vitamin E or vitamin C treatment assignments and were followed up until the occurrence of a disease end point, death, loss to follow-up, or the end of the vitamin E and vitamin C components of PHS II on August 31, 2007, whichever came first. All data were analyzed using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina), with statistical significance set at $P < .05$ using 2-sided tests. The PHS II was designed to have 80% power to detect a 16% relative reduction in the hazard of our primary end point of major cardiovascular events, based on historical event rates of cardiovascular disease observed in PHS physicians.

Baseline characteristics were first compared by vitamin E or vitamin C treatment assignment to evaluate whether randomization equally distributed baseline characteristics. Cox proportional hazards models were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) comparing event rates in the vitamin E and placebo groups, and the vitamin C and placebo groups, for each prespecified end point, adjusting for variables in the PHS II study design of age, PHS cohort (original PHS I participant, new PHS II participant), and randomized beta carotene, vitamin E or vitamin C, and multivitamin assignments. The proportional hazards assumption was tested by modeling interaction terms separately for vitamin E or vitamin C with the logarithm of time, and these assumptions were not violated ($P > .05$).

Whether vitamin E or C adherence affected our primary results was then investigated through sensitivity analyses that censored follow-up when a participant reported taking less than two-thirds of either vitamin E or vitamin C during the previous year. The effect of vitamin E or vitamin C on major cardiovascular events also was examined separately among 13 887 men without and 754 with baseline cardiovascular disease (including MI or stroke). Finally, subgroup analyses were conducted, stratified by major coronary risk

factors, and effect modification was assessed by using interaction terms between subgroup indicators and either vitamin E or vitamin C assignment.

RESULTS

The PHS II randomized 14 641 men with a mean (SD) age of 64.3 (9.2) years, with a mean follow-up of 8 years (median [interquartile range], 7.6 [7.1-9.6] years; maximum, 10 years; total follow-up, 117 711 person-years). Randomization equally distributed all baseline characteristics between vitamin E or vitamin C and their placebo groups (TABLE 1; all $P > .05$). At the end of PHS II, there were 1245 confirmed major cardiovascular events, including 511 total MIs, 464 total strokes, and 509 cardiovascular deaths, with some men experiencing multiple events. A total of 1661 men died during follow-up.

Vitamin E and Major Cardiovascular Events

The overall rates of major cardiovascular events were 10.8 and 10.9 per 1000 person-years in the active and placebo vitamin E groups, respectively. There was no effect of vitamin E on the primary end point of major cardiovascular events (HR, 1.01 [95% CI, 0.90-1.13]; $P = .86$; TABLE 2). The cumulative incidence curves indicate that this lack of effect did not vary throughout treatment and follow-up (log-rank $P = .94$) (FIGURE 2). Compared with placebo, vitamin E did not reduce the incidence of individual cardiovascular events, including total MI (HR, 0.90 [95% CI, 0.75-1.07]; $P = .22$) and total stroke (HR, 1.07 [95% CI, 0.89-1.29]; $P = .45$). Among stroke subtypes, however, there were 39 hemorrhagic strokes in the active vitamin E group and 23 hemorrhagic strokes in the placebo vitamin E group (HR, 1.74 [95% CI, 1.04-2.91]; $P = .04$).

Based on concerns raised in the Heart Outcomes Prevention Evaluation-The Ongoing Outcomes (HOPE-TOO) trial,²⁷ we examined the rates of congestive heart failure by treatment group, finding no effect (HR, 1.02 [95% CI, 0.87-1.20]; $P = .80$). There was no significant effect of vitamin E on cardio-

vascular mortality (HR, 1.07 [95% CI, 0.90-1.28]; $P=.43$) or total mortality (HR, 1.07 [95% CI, 0.97-1.18]; $P=.15$). Censoring participants at the time of vitamin E nonadherence did not affect our results for major cardiovascular events (HR, 0.97 [95% CI, 0.85-1.11]; $P=.68$).

The association between vitamin E and major cardiovascular events was examined among 13 887 men without and 754 men with a baseline history of cardiovascular disease (including MI or stroke). Vitamin E had no effect on the primary prevention of major cardiovascular events (532 events in the active vi-

tamin E group and 520 events in the placebo vitamin E group) (HR, 1.05 [95% CI, 0.93-1.19]; $P=.42$), total MI (HR, 0.90 [95% CI, 0.75-1.08]; $P=.25$), total stroke (HR, 1.15 [95% CI, 0.95-1.41]; $P=.16$), cardiovascular mortality (HR, 1.16 [95% CI, 0.95-1.42]; $P=.13$), and total mortality (HR, 1.10 [95% CI, 0.99-

Table 1. Baseline Characteristics According to Vitamin E and Vitamin C Treatment Assignment in 14 641 Men in the Physicians' Health Study II

| Self-reported Baseline Characteristics | No. (%) of Men ^a | | | |
|--|-----------------------------|-----------------------|------------------------|-----------------------|
| | Vitamin E ^b | | Vitamin C ^b | |
| | Active (n = 7315) | Placebo (n = 7326) | Active (n = 7329) | Placebo (n = 7312) |
| Age, mean (SD), y | 64.2 (9.1) | 64.3 (9.2) | 64.3 (9.2) | 64.3 (9.1) |
| Age group, y | | | | |
| 50-59 | 2940 (40.2) | 2951 (40.3) | 2953 (40.3) | 2938 (40.2) |
| 60-69 | 2349 (32.1) | 2347 (32.0) | 2348 (32.0) | 2348 (32.1) |
| ≥70 | 2026 (27.7) | 2028 (27.7) | 2028 (27.7) | 2026 (27.7) |
| Body mass index, mean (SD) | 26.0 (3.6) | 26.0 (3.7) | 26.0 (3.6) | 26.0 (3.7) |
| Body mass index ^c | | | | |
| <25 | 3055 (41.8) | 2996 (40.9) | 3019 (41.2) | 3032 (41.5) |
| 25-<30 | 3433 (47.0) | 3499 (47.8) | 3479 (47.5) | 3453 (47.3) |
| ≥30 | 815 (11.2) | 823 (11.3) | 823 (11.2) | 815 (11.2) |
| Cigarette smoking | | | | |
| Never | 4104 (56.1) | 4148 (56.7) | 4135 (56.5) | 4117 (56.4) |
| Former | 2967 (40.6) | 2885 (39.4) | 2908 (39.7) | 2944 (40.3) |
| Current | 239 (3.3) | 285 (3.9) | 280 (3.8) | 244 (3.3) |
| Exercise ≥1 time/wk | | | | |
| No | 2739 (38.4) | 2766 (38.7) | 2759 (38.5) | 2746 (38.6) |
| Yes | 4389 (61.6) | 4383 (61.3) | 4408 (61.5) | 4364 (61.4) |
| Alcohol consumption | | | | |
| Rarely or never | 1372 (18.9) | 1358 (18.7) | 1364 (18.7) | 1366 (18.8) |
| ≥1 drink/mo | 5893 (81.1) | 5923 (81.4) | 5920 (81.3) | 5896 (81.2) |
| Current aspirin use | | | | |
| No | 1627 (22.6) | 1634 (22.6) | 1638 (22.6) | 1623 (22.6) |
| Yes | 5578 (77.4) | 5589 (77.4) | 5605 (77.4) | 5562 (77.4) |
| History of hypertension ^d | | | | |
| No | 4219 (58.0) | 4187 (57.5) | 4252 (58.3) | 4154 (57.1) |
| Yes | 3058 (42.0) | 3098 (42.5) | 3039 (41.7) | 3117 (42.9) |
| History of high cholesterol ^e | | | | |
| No | 4490 (63.4) | 4476 (63.2) | 4494 (63.1) | 4472 (63.5) |
| Yes | 2589 (36.6) | 2601 (36.8) | 2624 (36.9) | 2566 (36.5) |
| History of diabetes | | | | |
| No | 6850 (93.7) | 6871 (93.9) | 6880 (94.0) | 6841 (93.7) |
| Yes | 461 (6.3) | 444 (6.1) | 442 (6.0) | 463 (6.3) |
| Parental history of MI <60 y ^f | | | | |
| No | 5928 (89.5) | 5941 (89.9) | 5954 (89.5) | 5915 (89.9) |
| Yes | 697 (10.5) | 665 (10.1) | 700 (10.5) | 662 (10.1) |
| Self-reported history of cardiovascular disease ^g | | | | |
| No | 6940 (94.9) | 6947 (94.8) | 6945 (94.8) | 6942 (94.9) |
| Yes | 375 (5.1) | 379 (5.2) | 384 (5.2) | 370 (5.1) |

Abbreviation: MI, myocardial infarction.

^aUnless otherwise indicated. The numbers do not always sum to group totals due to missing information for some variables.

^b $P > .05$ for all comparisons between active and placebo groups of vitamin E and vitamin C.

^cCalculated as weight in kilograms divided by height in meters squared.

^dDefined as self-reported systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or past or current treatment for hypertension.

^eDefined as self-reported total cholesterol of 240 mg/dL or higher or past or current treatment for high cholesterol.

^fExcludes 1410 men with missing information on parental history of MI before age 60 years.

^gIncluded nonfatal MI or nonfatal stroke.

1.22]; *P* = .07). A statistically significant increased risk of hemorrhagic stroke remained (HR, 1.99 [95% CI, 1.13-3.52]; *P* = .02). In analyses among the 754 men with baseline cardiovascular disease, there was a nonsignificant reduction in risk of major cardiovascular events (HR, 0.82 [95% CI, 0.62-1.09]; *P* = .18), total MI (HR,

0.88 [95% CI, 0.50-1.55]; *P* = .67), total stroke (HR, 0.74 [95% CI, 0.47-1.16]; *P* = .18), cardiovascular mortality (HR, 0.83 [95% CI, 0.57-1.19]; *P* = .31), and total mortality (HR, 0.91 [95% CI, 0.70-1.17]; *P* = .45). There were only 4 and 5 cases of hemorrhagic stroke in the active and placebo vitamin E groups, respectively (*P* = .62). Expanding the defi-

nition of baseline cardiovascular disease to add angina pectoris or revascularization among 1419 men taking vitamin E still had no effect on major cardiovascular events (HR, 0.88 [95% CI, 0.70-1.10]; *P* = .26).

We also evaluated whether coronary risk factors and each of the other randomized interventions from PHS II

Table 2. Association Between Randomized Vitamin E and Vitamin C Assignment and the Risk of Major Cardiovascular Events and Mortality in the Physicians' Health Study II^a

| Outcome | Vitamin E | | | Vitamin C | | |
|--|-------------------|--------------------|-----------------------------------|-------------------|--------------------|-----------------------------------|
| | No. of Events | | Adjusted HR (95% CI) ^b | No. of Events | | Adjusted HR (95% CI) ^b |
| | Active (n = 7315) | Placebo (n = 7326) | | Active (n = 7329) | Placebo (n = 7312) | |
| Major cardiovascular events ^c | 620 | 625 | 1.01 (0.90-1.13) | 619 | 626 | 0.99 (0.89-1.11) |
| Total myocardial infarction ^d | 240 | 271 | 0.90 (0.75-1.07) | 260 | 251 | 1.04 (0.87-1.24) |
| Myocardial infarction death | 22 | 30 | 0.75 (0.43-1.31) | 30 | 22 | 1.37 (0.79-2.38) |
| Total stroke ^d | 237 | 227 | 1.07 (0.89-1.29) | 218 | 246 | 0.89 (0.74-1.07) |
| Stroke death | 45 | 56 | 0.86 (0.58-1.27) | 44 | 57 | 0.77 (0.52-1.14) |
| Ischemic stroke ^e | 191 | 196 | 1.00 (0.82-1.22) | 180 | 207 | 0.87 (0.71-1.07) |
| Hemorrhagic stroke ^e | 39 | 23 | 1.74 (1.04-2.91) | 30 | 32 | 0.95 (0.57-1.56) |
| Cardiovascular death | 258 | 251 | 1.07 (0.90-1.28) | 256 | 253 | 1.02 (0.85-1.21) |
| Congestive heart failure ^f | 289 | 294 | 1.02 (0.87-1.20) | 293 | 290 | 1.02 (0.87-1.20) |
| Angina ^f | 718 | 765 | 0.95 (0.85-1.05) | 718 | 765 | 0.93 (0.84-1.03) |
| Revascularization ^{f,g} | 675 | 709 | 0.96 (0.86-1.07) | 678 | 706 | 0.96 (0.86-1.06) |
| Total mortality | 841 | 820 | 1.07 (0.97-1.18) | 857 | 804 | 1.07 (0.97-1.18) |

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aMean follow-up of 8 years for all 14 641 men through August 31, 2007.

^bAdjusted for age, Physicians' Health Study cohort (original Physicians' Health Study I participant, new Physicians' Health Study participant), randomized beta carotene assignment, randomized multivitamin assignment, and either randomized vitamin E or vitamin C assignment, and stratified on baseline cardiovascular disease.

^cDefined as a composite end point consisting of the first of any of the following individual events: nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death. The individual events do not sum to the total because each individual analysis assesses the first event that occurs during follow-up. Therefore, a participant who has a myocardial infarction and then dies of cardiovascular disease would be counted for both individual events, but only once for the primary end point of major cardiovascular events.

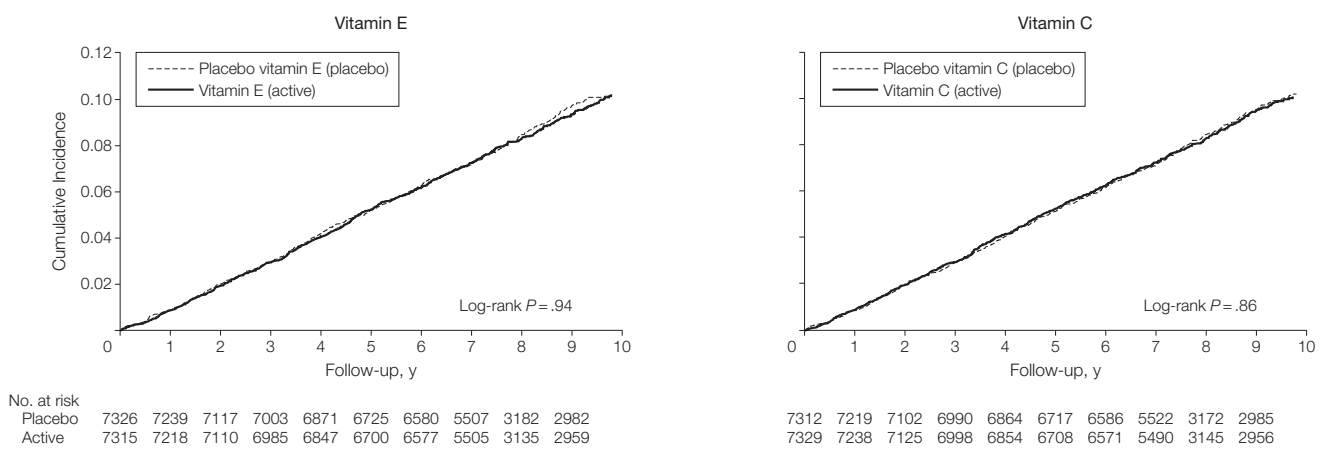
^dIncludes both nonfatal and fatal events.

^eStroke type was unknown for 7 men in the active vitamin E group and 8 men in the placebo vitamin E group, as well as 8 men in the active vitamin C group and 7 men in the placebo vitamin C group.

^fSelf-reported.

^gIncludes both coronary artery bypass graft and percutaneous transluminal coronary angioplasty.

Figure 2. Cumulative Incidence Rates of Major Cardiovascular Events in the Physicians' Health Study II



modified the effect of vitamin E on major cardiovascular events (TABLE 3). Parental history of MI before age 60 years significantly modified (P for interaction = .04) the effect of vitamin E on major cardiovascular events, with nonsignificant reductions among men who took vitamin E and had a parental history of MI before age 60 years. Otherwise, no

Table 3. Association Between Randomized Vitamin E and Vitamin C Assignment and Risk of Major Cardiovascular Events According to Baseline Characteristics and Treatment Assignment in the Physicians' Health Study II^a

| Group | Vitamin E | | | | Vitamin C | | | |
|--|---------------|---------|-----------------------------------|-------------------------|---------------|---------|-----------------------------------|-------------------------|
| | No. of Events | | Adjusted HR (95% CI) ^b | P Value for Interaction | No. of Events | | Adjusted HR (95% CI) ^b | P Value for Interaction |
| | Active | Placebo | | | Active | Placebo | | |
| Age group, y | | | | | | | | |
| 50-59 | 70 | 87 | 0.81 (0.59-1.10) | .21 | 78 | 79 | 0.98 (0.72-1.34) | .67 |
| 60-69 | 166 | 162 | 1.03 (0.83-1.28) | | 159 | 169 | 0.95 (0.76-1.18) | |
| ≥70 | 384 | 376 | 1.05 (0.91-1.21) | | 382 | 378 | 1.02 (0.89-1.18) | |
| Body mass index ^c | | | | | | | | |
| <25 | 242 | 267 | 0.92 (0.77-1.10) | .42 | 249 | 260 | 0.98 (0.82-1.17) | .73 |
| 25-29 | 307 | 285 | 1.13 (0.96-1.33) | | 297 | 295 | 0.99 (0.84-1.16) | |
| ≥30 | 67 | 71 | 0.88 (0.63-1.23) | | 70 | 68 | 1.08 (0.77-1.51) | |
| Smoking status | | | | | | | | |
| Never | 290 | 300 | 1.01 (0.86-1.19) | .76 | 294 | 296 | 1.02 (0.87-1.19) | .45 |
| Former | 302 | 286 | 1.04 (0.88-1.22) | | 294 | 294 | 1.00 (0.85-1.17) | |
| Current | 28 | 39 | 0.91 (0.56-1.48) | | 31 | 36 | 0.72 (0.45-1.18) | |
| Exercise ≥1 time/wk | | | | | | | | |
| No | 269 | 268 | 1.02 (0.86-1.21) | .94 | 267 | 270 | 0.98 (0.83-1.17) | .84 |
| Yes | 330 | 330 | 1.03 (0.88-1.20) | | 331 | 329 | 1.01 (0.87-1.18) | |
| Alcohol consumption | | | | | | | | |
| Rarely or never | 136 | 134 | 1.02 (0.81-1.30) | .94 | 132 | 138 | 0.93 (0.74-1.19) | .51 |
| ≥1 drink/mo | 477 | 486 | 1.01 (0.89-1.14) | | 481 | 482 | 1.01 (0.89-1.14) | |
| Current aspirin use | | | | | | | | |
| No | 130 | 123 | 1.10 (0.86-1.41) | .48 | 128 | 125 | 1.07 (0.83-1.36) | .47 |
| Yes | 470 | 483 | 0.99 (0.87-1.13) | | 474 | 479 | 0.98 (0.87-1.12) | |
| History of hypertension ^d | | | | | | | | |
| No | 214 | 211 | 1.02 (0.85-1.24) | .92 | 219 | 206 | 1.03 (0.85-1.25) | .68 |
| Yes | 403 | 414 | 1.00 (0.88-1.15) | | 399 | 418 | 0.99 (0.86-1.13) | |
| History of high cholesterol ^e | | | | | | | | |
| No | 360 | 359 | 1.00 (0.87-1.16) | .98 | 360 | 359 | 1.01 (0.88-1.17) | .76 |
| Yes | 250 | 257 | 1.03 (0.86-1.22) | | 253 | 254 | 0.98 (0.82-1.16) | |
| History of diabetes | | | | | | | | |
| No | 527 | 540 | 1.00 (0.89-1.13) | .69 | 532 | 535 | 0.99 (0.88-1.12) | .84 |
| Yes | 92 | 85 | 1.07 (0.80-1.44) | | 87 | 90 | 1.04 (0.77-1.40) | |
| Parental history of MI <60 y ^f | | | | | | | | |
| No | 494 | 473 | 1.07 (0.94-1.21) | .04 | 482 | 485 | 0.99 (0.88-1.13) | .86 |
| Yes | 57 | 73 | 0.79 (0.56-1.12) | | 67 | 63 | 0.99 (0.70-1.40) | |
| History of cardiovascular disease ^g | | | | | | | | |
| No | 532 | 520 | 1.05 (0.93-1.19) | .10 | 525 | 527 | 1.00 (0.89-1.13) | .85 |
| Yes | 88 | 105 | 0.82 (0.62-1.09) | | 94 | 99 | 0.96 (0.72-1.27) | |
| Randomized to vitamin C or E ^h | | | | | | | | |
| Placebo | 310 | 316 | 1.00 (0.85-1.17) | .77 | 309 | 316 | 0.97 (0.83-1.14) | .77 |
| Active | 310 | 309 | 1.03 (0.88-1.21) | | 310 | 310 | 1.01 (0.86-1.18) | |
| Randomized to beta carotene | | | | | | | | |
| Placebo | 304 | 317 | 0.97 (0.83-1.14) | .41 | 309 | 312 | 1.00 (0.85-1.17) | .82 |
| Active | 316 | 308 | 1.06 (0.91-1.24) | | 310 | 314 | 0.99 (0.84-1.15) | |

Abbreviations: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

^a Mean follow-up of 8 years for all 14 641 men through August 31, 2007.

^b Adjusted for age, Physicians' Health Study cohort (original Physicians' Health Study I participant, new Physicians' Health Study participant), randomized beta carotene assignment, randomized multivitamin assignment, and either randomized vitamin E or vitamin C assignment.

^c Calculated as weight in kilograms divided by height in meters squared.

^d Defined as self-reported systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or past or current treatment for hypertension.

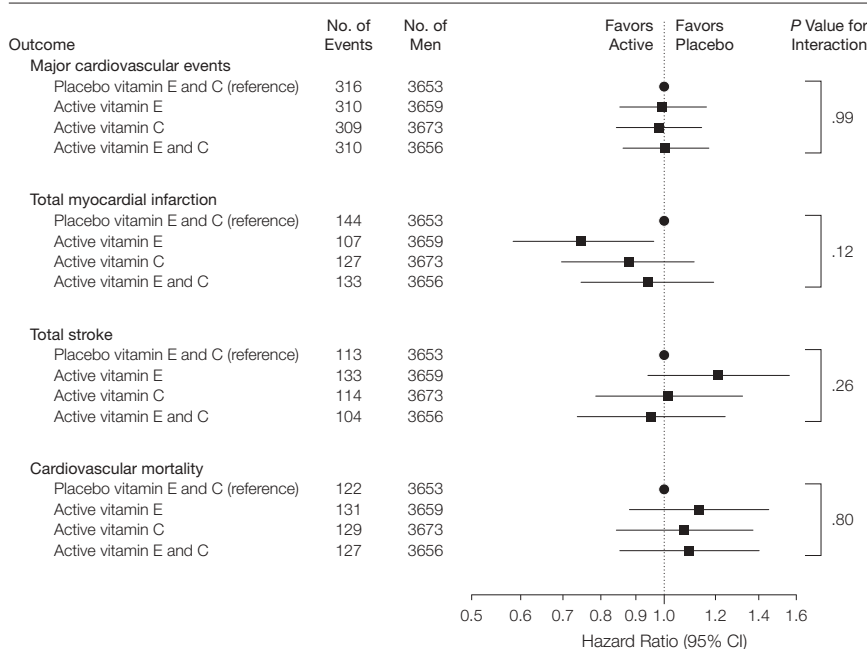
^e Defined as self-reported total cholesterol of 240 mg/dL or higher or past or current treatment for high cholesterol.

^f Excludes 1410 men with missing information on parental history of MI before age 60 years.

^g Included nonfatal MI or nonfatal stroke.

^h For analyses of vitamin E, stratified by vitamin C; for analyses of vitamin C, stratified by vitamin E.

Figure 3. Hazard Ratios and 95% Confidence Intervals of Major Cardiovascular Events, Total Myocardial Infarction, Total Stroke, and Cardiovascular Mortality in the Physicians' Health Study II



Error bars indicate 95% confidence intervals (CIs).

other significant effect modification by coronary risk factors was found on major cardiovascular events. In addition, there was no effect modification by randomized beta carotene or the ongoing multivitamin treatment assignment.

Vitamin C and Major Cardiovascular Events

The overall rates of major cardiovascular events for the active and placebo vitamin C groups were 10.8 and 10.9 per 1000 person-years, respectively. There was no effect of vitamin C on the primary end point of major cardiovascular events (HR, 0.99 [95% CI, 0.89-1.11]; *P* = .91; Table 2). The cumulative incidence curves showed no difference between groups in the HRs over time (log-rank *P* = .86; Figure 2). Vitamin C also had no effect on individual cardiovascular end points, including total MI (HR, 1.04 [95% CI, 0.87-1.24]; *P* = .65), total stroke (HR, 0.89 [95% CI, 0.74-1.07]; *P* = .21), and cardiovascular mortality (HR, 1.02 [95% CI, 0.85-1.21]; *P* = .86), as well as total mortality (HR,

1.07 [95% CI, 0.97-1.18]; *P* = .16). There also was no effect of vitamin C on hemorrhagic stroke. Censoring for nonadherence with vitamin C did not appreciably affect our findings for major cardiovascular events (HR, 0.98 [95% CI, 0.86-1.13]; *P* = .81).

When vitamin C use was examined among 13 887 men without and 754 men with a baseline history of cardiovascular disease, the lack of effect of vitamin C on major cardiovascular events remained. Vitamin C had no effect on the primary prevention of major cardiovascular events (525 events in those receiving active vitamin C and 527 events in those receiving placebo vitamin C) (HR, 1.00 [95% CI, 0.88-1.13]; *P* = .98), total MI (HR, 1.47 [95% CI, 0.82-2.63]; *P* = .19), total stroke (HR, 0.86 [95% CI, 0.69-1.07]; *P* = .18), cardiovascular mortality (HR, 0.99 [95% CI, 0.81-1.20]; *P* = .88), and total mortality (HR, 1.08 [95% CI, 0.97-1.20]; *P* = .15). In the 754 men with a history of cardiovascular disease at baseline, vitamin C did not affect incident major

cardiovascular events (HR, 0.96 [95% CI, 0.72-1.27]; *P* = .77). For total MI, there were 18 and 31 cases in the active and placebo vitamin C groups, respectively (HR, 0.57 [95% CI, 0.32-1.02]; *P* = .06). Adding angina and revascularization to our definition of baseline cardiovascular disease did not change the lack of effect on major cardiovascular events (HR, 1.03 [95% CI, 0.82-1.29]; *P* = .81), and the effect on total MI weakened somewhat (HR, 0.71 [95% CI, 0.47-1.07]; *P* = .10).

We then considered whether the effect of vitamin C on major cardiovascular events was modified by baseline coronary risk factors or other PHS II randomized interventions (Table 3). No significant effect modification was found between vitamin C and various baseline factors, randomized beta carotene, or the ongoing multivitamin treatment assignment on major cardiovascular events. When we examined the 2-way interaction between randomized vitamin E and vitamin C assignments, no significant interactions were found for major cardiovascular events (*P* for interaction = .99), total MI (*P* for interaction = .12), total stroke (*P* for interaction = .26), or cardiovascular disease mortality (*P* for interaction = .80) (FIGURE 3). Men assigned to active vitamin E only had a lower risk of total MI than those assigned to placebo vitamins E and C (HR, 0.74; 95% CI, 0.58-0.96), but no reduction was seen in those receiving both active vitamins E and C (HR, 0.94; 95% CI, 0.74-1.19).

Adverse Effects

We assessed whether vitamin E or vitamin C treatment increased potential adverse effects such as bleeding (including hematuria, easy bruising, and epistaxis) because vitamin E may potentially inhibit platelet function,⁶ along with gastrointestinal tract symptoms (peptic ulcer, constipation, diarrhea, gastritis, and nausea), fatigue, drowsiness, skin discoloration or rashes, and migraine. No significant differences were observed in adverse effects, including hematuria, easy bruising, and

epistaxis for both active vitamins E and C compared with placebo.

COMMENT

In this large-scale, randomized controlled trial among middle-aged and older men, long-term vitamin E and vitamin C supplement use did not reduce the primary end point of incident major cardiovascular events. We also found that neither vitamin E nor vitamin C reduced total MI, total stroke, cardiovascular death, congestive heart failure, total mortality, angina, or coronary revascularization. We did find an increase in hemorrhagic stroke with vitamin E use.

Randomized Trials of Vitamin E

Our finding that vitamin E has no effect on major cardiovascular events, including among a small subgroup of 754 men with a baseline history of cardiovascular disease, is consistent with the majority of previous clinical trials conducted among higher risk individuals with^{22,24,26,28} or without^{20,25,26,28} preexisting cardiovascular disease. Although some of these trials report possible reductions in composite cardiovascular end points,^{22,25,28} meta-analyses indicate no overall benefit for vitamin E in the secondary prevention of cardiovascular disease.⁴³⁻⁴⁵

The strength of PHS II is that the majority of participants (94.9%) were of low initial risk of cardiovascular disease, a previously understudied population. Primary prevention trials such as the Chinese Cancer Prevention Study³² and the Supplementation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study³⁵ included 30 mg/d of vitamin E as part of a combination of vitamins and minerals, with no effect found on cardiovascular disease. The Primary Prevention Project examined the individual effect of 300 mg/d of vitamin E among 1912 men and 2583 women (mean age, 64.4 years) with at least 1 cardiovascular risk factor for 3.6 years, and found no effect on prespecified cardiovascular end points.⁴⁶ The Women's Health Study tested 600 IU of vitamin E every other day among

39 876 women at low or usual risk of cardiovascular disease for 10 years and also reported no overall effect on major cardiovascular events.³¹ Moreover, results in PHS II did not corroborate the significant 24% reduction in cardiovascular death or the significant 26% reduction in major cardiovascular events among women aged 65 years or older in the Women's Health Study. At present, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) is the only ongoing, large-scale clinical trial testing 400 IU/d of vitamin E, with cardiovascular disease as a secondary end point.⁴⁷

Although vitamin E has appeared relatively safe with few documented adverse effects,⁴⁸ we observed a 74% increase in the risk of hemorrhagic stroke in the vitamin E treatment group consistent with results among the male smokers in the ATBC trial,²¹ but not observed in other primary^{30,31} and secondary^{24,26-28} prevention trials testing individual vitamin E supplement use. Vitamin E did not increase the incidence of reported congestive heart failure in PHS II, in contrast to increased risk reported by HOPE-TOO.²⁷ While meta-analyses of clinical trials have reinforced the lack of effect between vitamin E and cardiovascular disease,⁴³ possible slight but significant increases in total mortality⁴³⁻⁴⁵ have been reported. However, in PHS II we found no significant effect between vitamin E and total mortality after up to 10 years of treatment and follow-up.

The source, type, and dose of vitamin E used in PHS II warrant discussion. We used synthetic vitamin E (all-rac-alpha-tocopheryl acetate) in PHS II, similar to earlier trials,^{20,24} whereas more recent trials have used natural source vitamin E (*d*-alpha-tocopheryl acetate).^{26-28,31} However, neither form of vitamin E appears more or less associated with cardiovascular disease, consistent with the observation that both vitamin E sources have similar antioxidant properties.⁴⁹ Moreover, PHS II and other prevention trials have used α -tocopherol, whereas the γ -tocopherol isomer also may have a role

in cardiovascular disease prevention⁵⁰ because it has greater efficacy than α -tocopherol to inhibit lipid peroxidation⁵¹ and it may be suppressed in the presence of α -tocopherol.⁵² In addition, our dose of 400 IU/d of vitamin E is lower than that used in some other trials of vitamin E alone, but remains far greater than usual dietary levels and can only be achieved through supplementation.⁵³

Randomized Trials of Vitamin C

The PHS II represents the first large-scale, long-term trial of individual vitamin C supplementation in the prevention of cardiovascular disease in men. The Women's Antioxidant Cardiovascular Study (WACS) also tested 500 mg/d of vitamin C in 8171 women at higher risk of cardiovascular disease, and there was no effect on major cardiovascular end points.²⁸ Other primary and secondary prevention trials have considered vitamin C as part of a vitamin combination, in which no cardiovascular benefits were observed.³²⁻³⁵

Trials of intermediate cardiovascular end points have yielded inconsistent results. A combination of vitamins that included vitamin C had no effect on the rate and severity of restenosis in one trial.⁵⁴ In contrast, 500 mg/d of vitamin C given to patients with percutaneous transluminal coronary angioplasty reduced restenosis rates.⁵⁵ In 520 patients with hypercholesterolemia, 6 years of a combination of vitamin C and E reduced the progression of atherosclerosis.⁵⁶ Yet among postmenopausal women, a combination of vitamin E and vitamin C provided no cardiovascular benefits.⁵⁷ Our observation that vitamin C use among 754 men with preexisting cardiovascular disease nonsignificantly reduced total MI by 46% was interesting, but confined to a small subgroup. Among 5238 women with prior cardiovascular disease in WACS, there was no effect of vitamin C on major cardiovascular disease (HR, 1.05 [95% CI, 0.93-1.18]; $P = .43$).²⁸ Moreover, in PHS II long-term vitamin C supplementation had no significant effect on total and cardiovascular mortality.

The dose of vitamin C used in PHS II, 500 mg/d, greatly exceeds usual dietary vitamin C levels⁵⁸ and can only be achieved through supplementation. While even higher doses of vitamin C, generally tolerated up to a level of 2000 mg/d,⁵⁹ may be considered for cardiovascular disease prevention, limits in gastrointestinal tract absorption and other physiological restrictions may hinder vitamin C bioavailability attainable by dietary and supplemental vitamin C intake.⁶⁰ Despite the lack of effect for vitamin C on cardiovascular disease in PHS II, more comprehensive clinical trial data on vitamin C alone at different doses and in other populations remain lacking.

Potential Limitations

Adherence is of potential concern in any clinical trial. However, adherence remained high in PHS II during up to 10 years of follow-up, with low drop-in use in all of the study groups. Sensitivity analyses that censored follow-up time based on nonadherence did not alter our findings. Although PHS II represents one of the longest trials to date of individual vitamin E and vitamin C use on cardiovascular disease, an even longer period of vitamin supplementation may be necessary to cover the critical etiologic window or provide a sufficient cumulative dose capable of preventing cardiovascular disease. Vitamins E and C represent 2 parts of a broader spectrum of essential vitamins and minerals with possible roles in cardiovascular disease prevention. The randomized multivitamin component of PHS II still continues, with total treatment and follow-up planned to last more than a decade.

CONCLUSION

In this large-scale trial, after a mean of 8 years of treatment and follow-up in 14 641 men, neither vitamin E nor vitamin C supplementation reduced the risk of major cardiovascular events. These data provide no support for the use of these supplements in the prevention of cardiovascular disease in middle-aged and older men.

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Acquisition of data: Sesso, Buring, Kurth, Belanger, MacFadyen, Bubes, Manson, Gaziano.

Analysis and interpretation of data: Sesso, Buring, Christen, Kurth, Bubes, Manson, Glynn, Gaziano.

Drafting of the manuscript: Sesso, Buring.

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Study supervision: Sesso, Kurth, Belanger, MacFadyen, Bubes, Manson, Gaziano.

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