

## VITAMIN E SUPPLEMENTATION AND CARDIOVASCULAR EVENTS IN HIGH-RISK PATIENTS

THE HEART OUTCOMES PREVENTION EVALUATION STUDY INVESTIGATORS\*

### ABSTRACT

**Background** Observational and experimental studies suggest that the amount of vitamin E ingested in food and in supplements is associated with a lower risk of coronary heart disease and atherosclerosis.

**Methods** We enrolled a total of 2545 women and 6996 men 55 years of age or older who were at high risk for cardiovascular events because they had cardiovascular disease or diabetes in addition to one other risk factor. These patients were randomly assigned according to a two-by-two factorial design to receive either 400 IU of vitamin E daily from natural sources or matching placebo and either an angiotensin-converting–enzyme inhibitor (ramipril) or matching placebo for a mean of 4.5 years (the results of the comparison of ramipril and placebo are reported in a companion article). The primary outcome was a composite of myocardial infarction, stroke, and death from cardiovascular causes. The secondary outcomes included unstable angina, congestive heart failure, revascularization or amputation, death from any cause, complications of diabetes, and cancer.

**Results** A total of 772 of the 4761 patients assigned to vitamin E (16.2 percent) and 739 of the 4780 assigned to placebo (15.5 percent) had a primary outcome event (relative risk, 1.05; 95 percent confidence interval, 0.95 to 1.16;  $P=0.33$ ). There were no significant differences in the numbers of deaths from cardiovascular causes (342 of those assigned to vitamin E vs. 328 of those assigned to placebo; relative risk, 1.05; 95 percent confidence interval, 0.90 to 1.22), myocardial infarction (532 vs. 524; relative risk, 1.02; 95 percent confidence interval, 0.90 to 1.15), or stroke (209 vs. 180; relative risk, 1.17; 95 percent confidence interval, 0.95 to 1.42). There were also no significant differences in the incidence of secondary cardiovascular outcomes or in death from any cause. There were no significant adverse effects of vitamin E.

**Conclusions** In patients at high risk for cardiovascular events, treatment with vitamin E for a mean of 4.5 years has no apparent effect on cardiovascular outcomes. (N Engl J Med 2000;342:154-60.)

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**O**XIDATIVE modification of low-density lipoprotein is an important step in the development and progression of atherosclerosis in experimental studies,<sup>1,2</sup> and antioxidants such as vitamin E have been shown to slow atherosclerosis.<sup>3-5</sup> An inverse relation has been observed between coronary heart disease and the consumption of fruits, vegetables, and other foods containing vitamins, particularly vitamin E.<sup>6-9</sup> Observational studies have indicated that persons who con-

sume more than 100 IU of vitamin E a day for more than two years have lower rates of coronary events<sup>10,11</sup> and lower rates of progression of coronary artery lesions.<sup>12</sup> However, observational studies cannot distinguish whether the lower risk of coronary heart disease associated with higher levels of vitamin E consumption is due to the vitamin or to other associated lifestyle factors such as increased exercise and other aspects of diet. There have been four randomized, controlled trials of the relation between vitamin E and coronary heart disease,<sup>13-16</sup> but their results are conflicting, perhaps because of the low doses of vitamin E used in some studies,<sup>13,14</sup> the small numbers of events,<sup>15</sup> or the limited duration of treatment.<sup>15,16</sup>

We evaluated a high dose (400 IU per day) of vitamin E from natural sources, which has high bioavailability, in a large, five-year, prospective study of patients at high risk for cardiovascular events. The primary outcome was a composite of myocardial infarction, stroke, and death from cardiovascular causes. The secondary outcomes included death from any cause, hospitalization for unstable angina or congestive heart failure, revascularization or limb amputation, complications of diabetes, and cancer. The trial was also designed to evaluate the effects of an angiotensin-converting–enzyme inhibitor, ramipril, on the incidence of cardiovascular events. After nearly 4.5 years of follow-up, the collection of data on cardiovascular disease was stopped in April 1999 on the basis of a finding by the independent data and safety monitoring board that the trial had conclusively demonstrated the benefits of ramipril and a lack of effect of vitamin E on cardiovascular events. This report presents our findings relating to the effects of vitamin E on the primary and secondary cardiovascular outcomes. The study has been continued in the majority of centers to evaluate the effects of vitamin E on the incidence of cancer.

### METHODS

#### Study Design

The Heart Outcomes Prevention Evaluation (HOPE) Study is a double-blind, randomized trial with a two-by-two factorial de-

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sign, conducted to evaluate the effects of ramipril and vitamin E in 9541 patients at high risk for cardiovascular events. The results of the comparison of ramipril with placebo are reported in a companion article.<sup>17</sup> Details of the methods are given in that article<sup>17</sup> and in a previously published article.<sup>18</sup> Briefly, eligible patients at high risk were randomly assigned to receive either 400 IU of vitamin E from natural sources or an equivalent placebo daily for 4 to 6 years (mean, 4.5) and in addition to receive either 10 mg of ramipril or an equivalent placebo daily. Patients were evaluated every six months for a variety of outcomes.

**Outcomes**

The primary outcome was a composite of myocardial infarction, stroke, and death from cardiovascular causes. Deaths classified as due to cardiovascular causes were unexpected deaths presumed to be due to ischemic cardiovascular disease and occurring within 24 hours after the onset of symptoms without clinical or postmortem evidence of another cause; deaths from myocardial infarction or stroke that occurred within seven days after the myocardial infarction or stroke; and deaths from congestive heart failure, dysrhythmia, pulmonary embolism, or ruptured abdominal aortic aneurysm. Deaths for which the cause was uncertain were presumed to be due to cardiovascular disease. Myocardial infarction was diagnosed when two of the following three criteria were met: typical symptoms, increased cardiac enzyme levels (at least twice the upper limit of normal), and diagnostic electrocardiographic changes. Stroke was defined as a neurologic deficit lasting more than 24 hours. A computed tomographic or magnetic resonance imaging examination was recommended to define the type of stroke.

Secondary and other outcomes were death from any cause; unstable angina, defined as worsening angina or angina at rest requiring hospitalization; hospitalization for heart failure with clinical and radiologic signs of congestion; revascularization or limb amputation; the development of overt nephropathy or the need for dialysis or laser therapy among patients with diabetes; and the development of heart failure or new or worsening angina regardless of the need for hospitalization.

**RESULTS**

**Characteristics of the Patients**

The characteristics of the 9541 patients are shown in Table 1. The rate of compliance with the assigned regimen was high throughout the study. The percentages of patients who were taking vitamin E in the vitamin E and placebo groups, respectively, were 94.2 percent and 1.0 percent at one year, 93.3 percent and 1.7 percent at two years, 91.3 percent and 2.0 percent at three years, 90.2 percent and 2.7 percent at four years, and 89.2 percent and 3.4 percent at the final visit.

**Primary Cardiovascular Outcomes and Deaths from Any Cause**

A total of 772 of the 4761 patients who were assigned to receive vitamin E (16.2 percent) and 739 of the 4780 who were assigned to placebo (15.5 percent) had a primary cardiovascular event (relative risk, 1.05; 95 percent confidence interval, 0.95 to 1.16; P=0.33) (Table 2 and Fig. 1). There were no significant differences between the groups in the numbers of deaths from cardiovascular causes (342 in the vitamin E group vs. 328 in the placebo group; relative risk, 1.05), myocardial infarctions (532 vs. 524; relative risk, 1.02), deaths from coronary heart disease

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.\***

CHARACTERISTIC	VITAMIN E GROUP (N=4761)	PLACEBO GROUP (N=4780)
Age — yr	66±7	66±7
Blood pressure — mm Hg	139±20/79±11	139±20/79±11
Heart rate — beats/min	69±11	69±11
Body-mass index‡	28±4	28±4
Female sex — no. (%)	1263 (26.5)	1282 (26.8)
History of coronary artery disease — no. (%)	3857 (81.0)	3832 (80.2)
Myocardial infarction	2499 (52.5)	2535 (53.0)
Stable angina pectoris	2653 (55.7)	2668 (55.8)
Unstable angina pectoris	1205 (25.3)	1246 (26.1)
CABG	1229 (25.8)	1251 (26.2)
PTCA	851 (17.9)	863 (18.1)
Stroke or transient ischemic attacks — no. (%)	530 (11.1)	500 (10.5)
Peripheral vascular disease — no. (%)§	2109 (44.3)	2037 (42.6)
Hypertension — no. (%)	2219 (46.6)	2222 (46.5)
Diabetes — no. (%)	1838 (38.6)	1816 (38.0)
Known elevated total cholesterol — no. (%)	3109 (65.3)	3171 (66.3)
Known low HDL cholesterol — no. (%)	893 (18.8)	869 (18.2)
Current cigarette smoking — no. (%)	665 (14.0)	679 (14.2)
Medications — no. (%)		
Beta-blockers	1901 (39.9)	1870 (39.1)
Aspirin or other antiplatelet agents	3665 (77.0)	3616 (75.6)
Lipid-lowering agents	1352 (28.4)	1401 (29.3)
Diuretics	728 (15.3)	717 (15.0)
Calcium-channel blockers	2249 (47.2)	2236 (46.8)
Left ventricular hypertrophy on ECG — no. (%)	411 (8.6)	382 (8.0)
Microalbuminuria — no. (%)	1012 (21.3)	976 (20.4)

\*Plus-minus values are means ±SD.

‡CABG denotes coronary-artery bypass grafting, PTCA percutaneous transluminal coronary angioplasty, HDL high-density lipoprotein, and ECG electrocardiogram.

§The body-mass index is calculated as the weight in kilograms divided by the square of the height in meters.

§Peripheral vascular disease included claudication, a history of peripheral arterial disease, or a ratio of blood pressure in the ankle to blood pressure in the arm of less than 0.90.

(287 vs. 277; relative risk, 1.06), or strokes (209 vs. 180; relative risk, 1.17) (Fig. 2 and 3). The total numbers of deaths were similar in the two groups (535 vs. 537; relative risk, 1.00). Vitamin E had no significant effect on the primary outcome either among patients who were receiving ramipril (338 events among those who were receiving vitamin E and 313 events among those who were receiving placebo; relative risk, 1.08) or among patients who were not receiving ramipril (421 and 405 events, respectively; relative risk, 1.05).

**Secondary Cardiovascular and Combined Outcomes**

There were no differences between patients assigned to vitamin E and those assigned to placebo in the number of hospitalizations for unstable angina

**TABLE 2.** INCIDENCE OF THE PRIMARY OUTCOME AND OF DEATHS FROM ANY CAUSE.

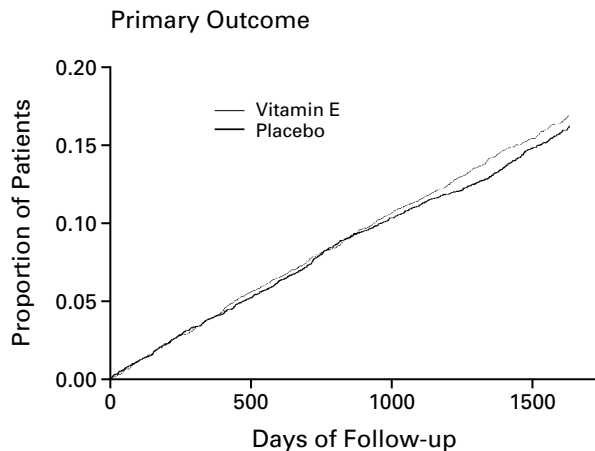
OUTCOME	VITAMIN E GROUP (N=4761)	PLACEBO GROUP (N=4780)	RELATIVE RISK (95% CI)*	P VALUE†
	no. (%)			
Myocardial infarction, stroke, or death from cardiovascular causes‡	772 (16.2)	739 (15.5)	1.05 (0.95–1.16)	0.33
Death from cardiovascular causes§	342 (7.2)	328 (6.9)	1.05 (0.90–1.22)	0.54
Myocardial infarction§	532 (11.2)	524 (11.0)	1.02 (0.90–1.15)	0.74
Stroke§	209 (4.4)	180 (3.8)	1.17 (0.95–1.42)	0.13
Death from any cause	535 (11.2)	537 (11.2)	1.00 (0.89–1.13)	0.99

\*CI denotes confidence interval.

†P values were calculated with use of the log-rank test.

‡The number of events among those receiving ramipril did not differ significantly between those assigned to receive vitamin E and those assigned to placebo (338 vs. 313). Similar results were observed among those who received matching placebo rather than ramipril (421 vs. 405).

§A patient may have had more than one event.



**Figure 1.** Kaplan–Meier Estimates of the Effect of Vitamin E on the Composite Outcome of Nonfatal Myocardial Infarction, Stroke, or Death from Cardiovascular Causes.

The relative risk of the composite outcome in the vitamin E group as compared with the placebo group was 1.05 (95 percent confidence interval, 0.95 to 1.16;  $P=0.33$ ).

(586 vs. 569; relative risk, 1.04), hospitalizations for heart failure (160 vs. 144; relative risk, 1.12), or revascularizations or limb amputations (848 vs. 787; relative risk, 1.09) (Table 3). There were no significant differences in the number of patients with angina of new onset (278 vs. 245; relative risk, 1.15) or microvascular complications of diabetes (340 vs. 325; relative risk, 1.06). A combined analysis of the proportion of patients who had any primary or secondary event found a nonsignificantly higher rate among those assigned to vitamin E (1630 vs. 1576; relative risk, 1.05; 95 percent confidence interval, 0.98 to 1.13;  $P=0.14$ ).

### Subgroup Analyses

There was no heterogeneity of results among subgroups defined according to sex, age, previous cardiovascular disease, or use of other drugs with respect to the primary or secondary outcomes (data not shown). Specifically, there was no significant difference in the incidence of the primary outcome among patients with diabetes (325 of those assigned to vitamin E vs. 313 of those assigned to placebo; relative risk, 1.04) or among smokers (135 vs. 139; relative risk, 1.02).

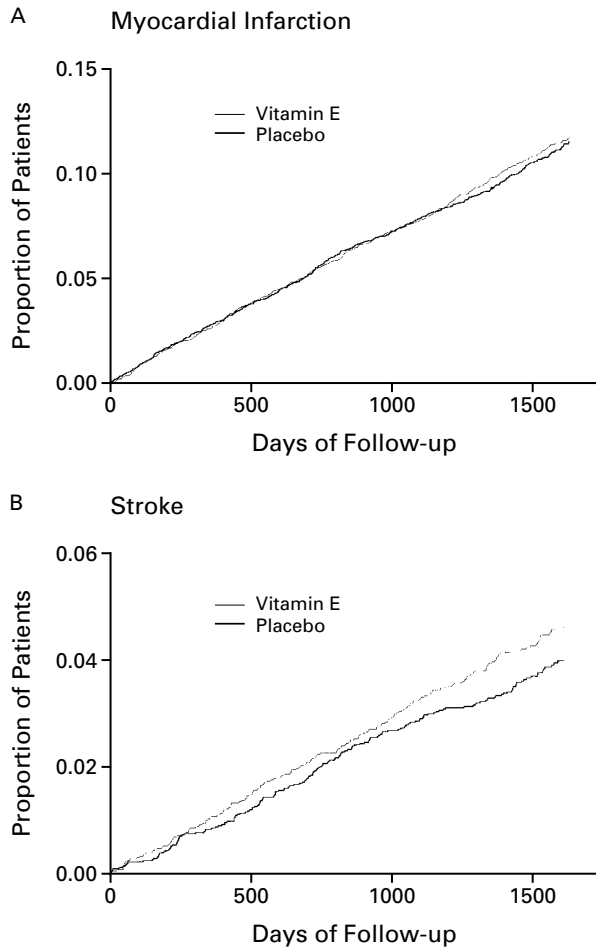
### Adverse Effects

There was no significant difference between groups in the incidence of adverse effects or in the number of patients who stopped taking the study medication. There was no increase in hemorrhagic stroke associated with vitamin E use (17 of those assigned to vitamin E had hemorrhagic stroke, as compared with 13 of those assigned to placebo) or among those who were also taking an antiplatelet agent (11 vs. 8).

### DISCUSSION

In our study, vitamin E did not reduce the incidence of cardiovascular events, as compared with the incidence among patients assigned to placebo, during a follow-up period of four to six years. Given the large number of events and the consistent lack of difference in all secondary cardiovascular outcomes, it is very unlikely that vitamin E had any clinically worthwhile beneficial effect on cardiovascular disease during four or five years of treatment.

Results have been reported from four randomized trials of the effects of vitamin E on cardiovascular events. In a Chinese study, 29,584 adults from Linxian Province, who did not have cardiovascular disease at entry, were randomly assigned to receive daily vita-

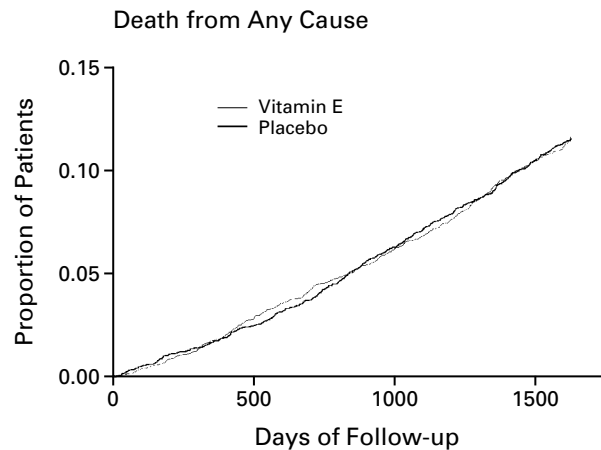


**Figure 2.** Kaplan–Meier Estimates of the Effect of Vitamin E on the Incidence of Myocardial Infarction (Panel A) and Stroke (Panel B).

The relative risk of myocardial infarction in the vitamin E group as compared with the placebo group was 1.02 (95 percent confidence interval, 0.90 to 1.15;  $P=0.74$ ), and the relative risk of stroke was 1.17 (95 percent confidence interval, 0.95 to 1.42;  $P=0.13$ ).

min E (30 mg), beta carotene, and selenium supplements or to receive placebo.<sup>13</sup> During the 5.2 years of follow-up, there was a 9 percent decrease in deaths from any cause without any significant reduction in cardiovascular events. The dose of vitamin E in this study was small, the nutritional status and cardiovascular risk of this population were very different from those of Western populations, and the beneficial effects on overall mortality cannot be attributed only to vitamin E.

The second trial was the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study, involving 29,133 male smokers who were 50 to 69 years of age.<sup>14</sup> Daily treatment with 50 mg of vitamin E for five to eight years had no effect on the risk of death from coronary heart disease. In a subgroup of 1862 men with a pre-



**Figure 3.** Kaplan–Meier Estimates of the Effect of Vitamin E on the Incidence of Death from Any Cause.

The relative risk in the vitamin E group as compared with the placebo group was 1.00 (95 percent confidence interval, 0.89 to 1.13;  $P=0.99$ ).

vious myocardial infarction at entry, there was a non-significant increase in the risk of death from coronary heart disease (relative risk, 1.33; 95 percent confidence interval, 0.86 to 2.05;  $P=0.20$ ). However, a reduction in the risk of nonfatal myocardial infarction was documented among men assigned to vitamin E only (40 vs. 55; relative risk, 0.62; 95 percent confidence interval, 0.41 to 0.96), but not among those receiving the combination of vitamin E and beta carotene, in comparison with those receiving placebo only.<sup>19</sup> In this subgroup, the number of events was small. In the remaining patients in this study, there was no significant effect of vitamin E on nonfatal or fatal myocardial infarction, despite large numbers of events (1204 and 907, respectively).<sup>20</sup> Thus, in this well-conducted trial, vitamin E had no effect on coronary heart disease. Although the trial used a low dose of synthetic vitamin E (50 mg per day), the median level of alpha-tocopherol increased significantly, from 28.5  $\mu\text{mol}$  per liter at base line to 42.5  $\mu\text{mol}$  per liter at three months.

The third trial was the Cambridge Heart Antioxidant Study, which randomly assigned 2002 patients with coronary atherosclerosis to receive either vitamin E or placebo.<sup>15</sup> The mean alpha-tocopherol levels increased from 34.2 to 51.1  $\mu\text{mol}$  per liter in patients receiving 400 IU of vitamin E per day and to 64.5  $\mu\text{mol}$  per liter in patients receiving 800 IU per day. The majority of the patients received 400 IU per day. After a median follow-up of 1.4 years, a large reduction in the number of patients with nonfatal myocardial infarction was observed (14 in the vitamin E group vs. 41 in the placebo group; relative risk, 0.53; 95 percent confidence interval, 0.11 to 0.47;  $P=0.005$ ), but there was no difference in deaths due to

**TABLE 3. INCIDENCE OF SECONDARY AND OTHER OUTCOMES.**

OUTCOME	VITAMIN E GROUP (N=4761)	PLACEBO GROUP (N=4780)	RELATIVE RISK (95% CI)*	P VALUE†
	no. (%)			
Revascularization or limb amputation	848 (17.8)	787 (16.5)	1.09 (0.99–1.20)	0.07
Hospitalization for unstable angina	586 (12.3)	569 (11.9)	1.04 (0.93–1.17)	0.52
New-onset angina	278 (5.8)	245 (5.1)	1.15 (0.97–1.37)	0.11
Worsening angina	1215 (25.5)	1186 (24.8)	1.02 (0.94–1.11)	0.63
Claudication	762 (16.0)	753 (15.8)	1.02 (0.92–1.13)	0.70
Hospitalization for heart failure	160 (3.4)	144 (3.0)	1.12 (0.90–1.41)	0.32
Heart failure	530 (11.0)	457 (9.6)	1.17 (1.03–1.32)	0.02
Complications of diabetes‡	340 (7.1)	325 (6.8)	1.06 (0.91–1.23)	0.47

\*CI denotes confidence interval.

†P values were calculated with use of the log-rank test.

‡Complications included nephropathy, dialysis, and laser therapy.

**TABLE 4. META-ANALYSIS OF THE EFFECTS OF VITAMIN E ON MYOCARDIAL INFARCTION, STROKE, OR DEATH FROM CARDIOVASCULAR CAUSES IN LARGE TRIALS.\***

STUDY	DAILY DOSE	DURATION OF STUDY	VITAMIN E	PLACEBO	RELATIVE RISK (95% CI)
	mg	yr	no. with events/total no. (%)		
ATBC <sup>14</sup>	50	5.0	1889/14,564 (13.0)	1970/14,569 (13.5)	0.96 (0.90–1.03)
CHAOS <sup>15</sup>	≥400	1.3	41/1035 (4.0)	64/967 (6.6)	0.60 (0.40–0.89)
GISSI <sup>16</sup>	300	3.5	571/5660 (10.1)	584/5664 (10.3)	0.98 (0.87–1.10)
Current study	400	4.5	772/4761 (16.2)	739/4780 (15.5)	1.05 (0.95–1.16)
Total			3273/26,020 (12.6)	3357/25,980 (12.9)	0.97 (0.92–1.02)†

\*CI denotes confidence interval, ATBC Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, CHAOS Cambridge Heart Antioxidant Study, and GISSI Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico.

†Relative risks and confidence intervals were derived by the method of Yusuf et al.<sup>21</sup>; P=0.27.

cardiovascular causes (27 vs. 23; relative risk, 1.18; 95 percent confidence interval, 0.62 to 2.27; P=0.61). In this trial, the number of events was small and there were imbalances in several base-line characteristics that call into question whether randomization resulted in truly comparable groups.

Furthermore, the very large reduction in nonfatal myocardial infarction within a relatively short time (median, 1.4 years) is inconsistent with the results of other interventions, such as lipid-lowering agents or antihypertensive medications, that reduce cardiovascular events. It is therefore likely that the results of the Cambridge Heart Antioxidant Study may have been due to chance. This possibility is supported by the results of a recent Italian trial,<sup>16</sup> in which 11,000 patients who had had myocardial infarctions were randomly assigned to receive 300 IU of vitamin E per day or placebo for a median of 3.5 years. The number of patients with nonfatal myocardial infarction was slightly higher in the vitamin E group than the

placebo group (295 vs. 284; relative risk, 1.02; 95 percent confidence interval, 0.87 to 1.21), and the number of deaths from coronary heart disease was slightly smaller (227 vs. 249; relative risk, 0.92; 95 percent confidence interval, 0.77 to 1.11). Neither difference was statistically significant.<sup>16</sup>

Our study used a high dose of vitamin E (400 IU per day), had high rates of compliance, and involved high-risk patients. The study had a large number of primary outcomes and therefore had high statistical power (more than 90 percent power to detect a 13 percent relative reduction in the risk of the primary outcome). Furthermore, a large number of secondary outcomes (e.g., revascularization or limb amputation, unstable angina, worsening angina, and heart failure) were examined. Such data are not available from most trials. Combining the data from all trials of vitamin E indicates that such treatment has little effect on the risk of death or cardiovascular events (Table 4), at least over a four-to-six-year period.

Steinberg has hypothesized that unlike agents that lower cholesterol or blood pressure, antioxidants may have to be used for more than five years to have a demonstrable benefit, since the primary mechanism of these agents may be the prevention of new lesions.<sup>22</sup> Therefore, in a population like the one we studied, it may take longer than five years to detect an effect on clinical outcomes. However, the Physicians' Health Study did not find a benefit of beta carotene (another antioxidant with a different action) after 12 years.<sup>23</sup> Similar data are not available for vitamin E, but observational studies that demonstrated a lower rate of coronary heart disease with vitamin E supplementation suggested that a lower risk should be evident after two years.<sup>10,11</sup> In a nested substudy, we are examining whether the thickness of the carotid intima and media (an indication of the risk of early atherosclerosis) can be favorably altered by vitamin E.<sup>24</sup> If so, Steinberg's hypothesis may be worth exploring with more prolonged follow-up or treatment to assess whether such changes in the development of atherosclerosis would translate into a benefit in terms of clinical outcomes.

Although the moderate duration of vitamin E supplementation (four to six years) and the characteristics of the population may explain our finding of a lack of benefit of vitamin E, another reason may be our use of vitamin E alone, without other antioxidants. In the epidemiologic studies that found an association between higher dietary intake of vitamin E and lower rates of coronary heart disease, higher vitamin E consumption was also associated with higher intake of a number of other antioxidants and micronutrients.<sup>6-9</sup> It is possible that vitamin E supplementation requires these cofactors to have a beneficial effect.<sup>25</sup> Although the existence of interactions between vitamin E and other vitamins,<sup>10</sup> beta carotene,<sup>6,14</sup> or selenium<sup>13</sup> is not supported by the findings of prospective observational studies or randomized trials, this hypothesis can be tested only in trials in which combinations of vitamins are given; some such trials are now in progress.<sup>26-28</sup>

In conclusion, 400 IU of vitamin E administered daily for four to six years had no beneficial effects on cardiovascular outcomes in a high-risk population of patients who were 55 years of age or older. Vitamin E was well tolerated, with no significant adverse events as compared with placebo. This finding provides some reassurance for the conduct of large, longer-term trials to address unanswered questions regarding vitamin E, such as its possible effects in preventing cancer.

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