Alpha-Tocopherol Supplementation in Healthy Individuals Reduces Low-Density Lipoprotein Oxidation but Not Atherosclerosis

The Vitamin E Atherosclerosis Prevention Study (VEAPS)

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Background—Epidemiological studies have demonstrated an inverse relationship between vitamin E intake and cardiovascular disease (CVD) risk. In contrast, randomized controlled trials have reported conflicting results as to whether vitamin E supplementation reduces atherosclerosis progression and CVD events.

Methods and Results—The study population consisted of men and women ≥40 years old with an LDL cholesterol level ≥3.37 mmol/L (130 mg/dL) and no clinical signs or symptoms of CVD. Eligible participants were randomized to DL-α-tocopherol 400 IU per day or placebo and followed every 3 months for an average of 3 years. The primary trial end point was the rate of change in the common carotid artery far-wall intima-media thickness (IMT) assessed by computer image–processed B-mode ultrasonograms. A mixed effects model using all determinations of IMT was used to test the hypothesis of treatment differences in IMT change rates. Compared with placebo, α-tocopherol supplementation significantly raised plasma vitamin E levels (P<0.0001), reduced circulating oxidized LDL (P=0.03), and reduced LDL oxidative susceptibility (P<0.01). However, vitamin E supplementation did not reduce the progression of IMT over a 3-year period compared with subjects randomized to placebo.

Conclusions—The results are consistent with previous randomized controlled trials and extend the null results of vitamin E supplementation to the progression of IMT in healthy men and women at low risk for CVD. (Circulation. 2002;106:1453-1459.)

Key Words: coronary disease ■ atherosclerosis ■ antioxidants ■ trials

A large body of laboratory and animal data suggest that atherosclerosis results from a series of oxidative processes.1 Epidemiological studies support these data, indicating an inverse relationship between antioxidant vitamin intake and cardiovascular disease (CVD) risk.1 Large observational and arterial imaging studies2–5 indicate that daily consumption of ≥100 IU of vitamin E for at least 2 years reduces atherosclerosis progression and event rates. Conflicting results regarding the effects of vitamin E supplementation on atherosclerosis progression and CVD events have been reported from randomized controlled trials.6–16 Plausible explanations for the conflicting results include timing of the intervention relative to the atherosclerotic process and preexisting antioxidant status of study participants. We report results from the Vitamin E Atherosclerosis Progression Study (VEAPS), a randomized clinical trial designed to determine the effects of DL-α-tocopherol supplementation on subclinical atherosclerosis progression in healthy low-risk individuals.

Methods

Study Design

Eligible subjects were men and women ≥40 years old with LDL cholesterol (LDL-C) ≥3.37 mmol/L (130 mg/dL) and no clinical signs or symptoms of CVD. Exclusion criteria were fasting triglycerides >5.64 mmol/L (500 mg/dL), diabetes mellitus or fasting serum glucose ≥3.62 mmol/L (140 mg/dL), regular vitamin E supplement intake >1 year, lipid standardized plasma vitamin E ≥35 μmol/L, diastolic blood pressure ≥100 mm Hg, untreated thyroid disease, serum creatinine ≥0.065 mmol/L (2.5 mg/dL), life-threatening disease with prognosis <5 years, or alcohol intake...
>5 drinks daily. All participants gave written informed consent. The University of Southern California Institutional Review Board approved the study protocol.

Computer-generated random numbers were used to assign participants to vitamin E (DL-α-tocopherol) supplementation at 400 IU daily or placebo in one of two strata defined by the screening visit carotid intima-media thickness (IMT) (<0.75 mm or ≥0.75 mm). Participants, clinical staff, imaging specialists, data monitor, and statistical analyses were blinded to treatment assignment. Participants were instructed to take study pills with their greatest fat-containing meal of the day.17

Participants were followed every 3 months, with clinic visits occurring every 6 months. At each clinic visit, carotid ultrasonography, vital signs, clinical events, compliance to study pills, diet, physical activity, present smoking habits, and nonstudy medication and dietary supplement/nutriceutical use were ascertained. Between clinic visits, participants were mailed study pills and returned dietary records and pill compliance forms. Dietary intake was monitored every 3 months with 3-day dietary booklets (Norton Scientific). All medical management, including management of lipid disorders and blood pressure, occurred with the participant’s primary physician.

The initial study design called for a 2-year treatment period. Based on evolving null results from other antioxidant clinical trials, the External Data and Safety Monitoring Board recommended after 2 years of initiation of the study that the treatment period be extended to 3 years. Interim analyses of the primary trial end point were not performed.

The primary trial end point was the rate of change in the right distal common carotid artery intima-media thickness (CCA IMT) in computer image–processed B-mode ultrasonograms. Sample size calculations for VEAPS required 150 subjects per treatment arm based on detecting a treatment effect size (ie, the standardized difference in progression rates between the 2 treatment arms) of 0.32 at the 0.05 significance level (2-sided) with 0.80 power. A total of 353 participants were recruited to accommodate the anticipated dropout rate.

Assessment of Atherosclerosis Progression

High-resolution B-mode ultrasound images of the right CCA were obtained with a 7.5-MHz linear array transducer attached to an ATL Ultramark-4 Plus Ultrasound System (Advanced Technology Laboratory). Participants were placed in a supine position with the head rotated to the left using a 45-degree head block. As described previously,18,19 the jugular vein and carotid artery were imaged transversely with the jugular vein stacked above the carotid artery. The transducer was rotated 90 degrees around the central line of the stacked jugular vein–carotid artery transverse image to obtain a longitudinal image while maintaining the vessels in the stacked position. All images contained internal anatomical landmarks for reproducing probe angulation. Each individual’s baseline image was used as an online guide for follow-up examinations on a split-screen system designed for repeat image acquisition for longitudinal studies (patent pending). For each individual, depth of field, gain, monitor intensity setting, and all other instrumentation settings used at baseline examination were maintained for all follow-up examinations. These techniques have resulted in significant reductions in measurement variability.18,19 All examinations were recorded with the ECG on super VHS videotape.

An image analyst measured the CCA far wall IMT by automated computerized edge detection using an in-house developed software package (Prosound, University of Southern California).18,19 Carotid IMT was determined as the average of 70 to 100 measurements between the intima-lumen and media-adventitia interfaces along a 1-cm length just distal to the carotid artery bulb. This method standardizes the location and the distance over which the IMT is measured, ensuring comparability within and across participants.18,19

Laboratory Measurements

Participants fasted for 8 hours before sample collections. Plasma total cholesterol, triglyceride, and HDL cholesterol levels were measured using an enzymatic method under the Standardization Program of the National Centers for Disease Control and Prevention, and LDL-C was calculated.20 Plasma vitamin E (α- and γ-tocopherol) was measured at baseline and every 6 months on trial by reversed-phase HPLC using UV detection.21 Vitamin C levels were measured spectrophotometrically.22

LDL oxidative susceptibility (baseline and annual) was measured as the length of time before the onset of conjugated diene accumulation (lag phase). Freshly prepared LDL samples in PBS were monitored spectrophotometrically23 up to 5 hours after addition of 10 μmol Cu++. The content of lipid peroxidation products was estimated from the ratio of OD0 to ODm before measurement of the oxidative lag phase. The lag phase (in minutes) was determined from the intercept of the tangent to the curve for conjugated diene propagation and the baseline representing no net accumulation of conjugated dienes.23,24

Circulating oxidized LDL (baseline and annual) was determined by separating unmodified LDL and oxidatively modified electronegative LDL (LDL−) using anion-exchange HPLC.24 LDL− was expressed as a percentage of total LDL-C.

Statistical Analysis

Demographic and baseline clinical and laboratory variables were compared between randomized groups using either an independent samples t test for means or a χ2 test for proportions. Compliance to study treatment was computed as percentage pill compliance (number of pills consumed divided by the number that should have been consumed) and plasma vitamin E levels at each clinic visit. Compliance variables were compared between treatment groups using an independent samples t test.

The intention-to-treat analysis of the primary trial end point, carotid IMT progression, was conducted for all evaluable randomized participants (those who had a baseline and at least one follow-up CCA IMT). To test the hypothesis of treatment differences in IMT change rates, we used a mixed-effects model using all available determinations of IMT.25 IMT was regressed on the follow-up time, adjusting for baseline IMT strata (<0.75 mm or ≥0.75 mm). The regression coefficient associated with follow-up time represents the average rate of change in IMT. Treatment group differences in the estimated IMT change rate were tested for significance by including a treatment × follow-up time interaction term in the mixed-effects model.

On-trial averages of the clinical, lipid, and oxidized LDL determinations were calculated using all available follow-up determinations for each evaluable participant. On-trial averages were compared between treatment groups using a t test for independent samples.

Major CVD events, cancer, and death were reported for all randomized participants. The proportions of participants experiencing events were compared between treatment groups using a Fisher’s exact test for independent samples.
TABLE 1. VEAPS Baseline Carotid Intima-Media Thickness, Lipid Levels, and Demographic and Medical History Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Evaluable Placebo (n = 170)</th>
<th>Evaluable Vitamin E (n = 162)</th>
<th>P*</th>
<th>Evaluable Total (n = 332)</th>
<th>Inevaluable Total (n = 21)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid IMT, mm</td>
<td>0.760 ± 0.131</td>
<td>0.746 ± 0.132</td>
<td>0.35</td>
<td>0.753 ± 0.131</td>
<td>0.781 ± 0.123</td>
<td>0.34</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.04 ± 0.67</td>
<td>6.11 ± 0.67</td>
<td>0.24</td>
<td>6.06 ± 0.67</td>
<td>6.19 ± 0.73</td>
<td>0.40</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.86 ± 0.54</td>
<td>3.99 ± 0.60</td>
<td>0.06</td>
<td>3.91 ± 0.57</td>
<td>3.96 ± 0.65</td>
<td>0.70</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.45 ± 0.36</td>
<td>1.45 ± 0.28</td>
<td>0.92</td>
<td>1.45 ± 0.31</td>
<td>1.45 ± 0.34</td>
<td>0.90</td>
</tr>
<tr>
<td>Total triglycerides, mmol/L</td>
<td>1.54 ± 0.63</td>
<td>1.50 ± 0.63</td>
<td>0.48</td>
<td>1.53 ± 0.63</td>
<td>1.67 ± 0.62</td>
<td>0.29</td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td>Single</td>
<td>26 (15)</td>
<td>22 (14)</td>
<td>0.32</td>
<td>48 (15)</td>
<td>2 (8)</td>
<td>0.55</td>
</tr>
<tr>
<td>Married</td>
<td>108 (64)</td>
<td>104 (64)</td>
<td>0.81</td>
<td>212 (64)</td>
<td>16 (76)</td>
<td></td>
</tr>
<tr>
<td>Divorced/separated/widow</td>
<td>36 (21)</td>
<td>36 (22)</td>
<td></td>
<td>72 (22)</td>
<td>3 (14)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>56.7 ± 8.6</td>
<td>55.7 ± 9.2</td>
<td>0.32</td>
<td>56.2 ± 8.9</td>
<td>56.0 ± 9.9</td>
<td>0.93</td>
</tr>
<tr>
<td>Non-Hispanic whites</td>
<td>132 (78)</td>
<td>118 (73)</td>
<td>0.46</td>
<td>250 (75)</td>
<td>10 (48)</td>
<td>0.03</td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>0.52</td>
</tr>
<tr>
<td>Single</td>
<td>26 (15)</td>
<td>22 (14)</td>
<td></td>
<td>48 (15)</td>
<td>2 (8)</td>
<td></td>
</tr>
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<td></td>
<td>72 (22)</td>
<td>3 (14)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
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<td>0.18</td>
</tr>
<tr>
<td>&lt; High school</td>
<td>5 (3)</td>
<td>2 (1)</td>
<td>0.37</td>
<td>7 (2)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>9 (5)</td>
<td>8 (5)</td>
<td></td>
<td>17 (5)</td>
<td>3 (14)</td>
<td></td>
</tr>
<tr>
<td>&gt; High school</td>
<td>156 (92)</td>
<td>152 (94)</td>
<td></td>
<td>308 (93)</td>
<td>18 (86)</td>
<td></td>
</tr>
<tr>
<td>Smoking History</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Current smoker</td>
<td>5 (3)</td>
<td>6 (4)</td>
<td>0.67</td>
<td>11 (3)</td>
<td>3 (14)</td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>58 (34)</td>
<td>52 (32)</td>
<td></td>
<td>110 (33)</td>
<td>3 (14)</td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>107 (63)</td>
<td>104 (64)</td>
<td></td>
<td>211 (64)</td>
<td>15 (71)</td>
<td></td>
</tr>
<tr>
<td>Weight, lb</td>
<td>176.4 ± 35.3</td>
<td>173.5 ± 37.6</td>
<td>0.46</td>
<td>175.0 ± 36.4</td>
<td>173.5 ± 44.0</td>
<td>0.86</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>0.85 ± 0.07</td>
<td>0.86 ± 0.08</td>
<td>0.57</td>
<td>0.86 ± 0.08</td>
<td>0.86 ± 0.08</td>
<td>0.72</td>
</tr>
<tr>
<td>Quetelet index, kg/m²</td>
<td>27.9 ± 4.4</td>
<td>27.6 ± 5.1</td>
<td>0.57</td>
<td>27.8 ± 4.7</td>
<td>28.4 ± 5.1</td>
<td>0.54</td>
</tr>
<tr>
<td>Pulse rate, bpm</td>
<td>63.9 ± 6.8</td>
<td>64.7 ± 7.0</td>
<td>0.31</td>
<td>64.3 ± 6.9</td>
<td>67.0 ± 5.5</td>
<td>0.08</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>128.4 ± 15.6</td>
<td>128.3 ± 17.1</td>
<td>0.98</td>
<td>128.3 ± 16.3</td>
<td>125.2 ± 19.9</td>
<td>0.41</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76.9 ± 9.0</td>
<td>76.4 ± 9.7</td>
<td>0.66</td>
<td>76.6 ± 9.3</td>
<td>77.0 ± 9.5</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Values are mean ± SD for continuous variables; frequency (%) for categorical variables.

To convert cholesterol values to mg/dL, multiply by 38.6; to convert triglycerides, multiply by 88.5.

*Group differences for continuous variables evaluated by Student’s t test; categorical variables by χ² test.

Results

Baseline Characteristics

Of 1833 telephone-prescreened individuals, 993 were invited for a clinic-screening visit and 353 were randomized (176 placebo, 177 vitamin E, Figure). The mean age was 56.2 years (range, 40 to 82 years).

Twenty-one participants (6 placebo, 15 vitamin E) did not have a follow-up IMT and were not evaluable on the primary trial end point. Reasons for dropout included the following: moved/lost contact (n = 2), lost interest (n = 14), medical problems/physician recommended discontinuing (n = 3), and death (n = 2).

A total of 318 (90% of randomized) participants completed the 2-year treatment period and were offered the opportunity to continue another year of their randomized and blinded treatment assignment. A total of 258 (81% of 2-year completors, 73% of randomized) elected to continue for a 3-year treatment period.

There were no significant differences between treatment groups at baseline in carotid IMT or any demographic, laboratory, or clinical characteristics (Table 1). Proportionately more unevaluable participants were ethnic minorities (P = 0.03) and smokers (P = 0.02) (Table 1). Because of a marginally significant treatment group difference in LDL-C (P = 0.06), the primary trial end point was also analyzed with baseline LDL-C and the interaction of baseline LDL-C and follow-up time as covariates.

IMT Progression Rates

Evaluable participants in the placebo and vitamin E groups had a mean ± SD of 7.3 ± 1.1 and 7.2 ± 1.3 carotid IMT measurements, respectively (P = 0.27). Baseline carotid IMT was similar in the placebo and vitamin E groups overall (0.760 ± 0.131 versus 0.746 ± 0.132 mm; P = 0.35), in females (0.738 ± 0.110 versus 0.747 ± 0.115 mm; P = 0.70), and in males (0.783 ± 0.145 versus 0.750 ± 0.150 mm; P = 0.16).

No difference in the average rates of progression between the 2 treatment groups was found overall (with and without...
adjusting for baseline LDL-C) or stratified by gender (Table 2). The difference in the average rates of progression between the 2 treatment groups overall and for females and males was as follows: −0.0017 mm/y (95% CI, −0.0036 to 0.0002 mm/y), −0.0010 mm/y (−0.0034 to 0.0014 mm/y), and −0.0024 mm/y (−0.0057 to 0.0006 mm/y), respectively. No treatment differences in IMT progression rates were found when stratifying by baseline plasma levels of vitamins E and C.

**On-Trial Variables**

Except for total cholesterol (P=0.04), there were no significant differences between treatment groups in on-trial variables (Table 2). Two assays, one in vivo and one in vitro, demonstrated that LDL was protected from oxidation by vitamin E supplementation. In the vitamin E group, mean±SEM LDL levels were significantly lower (1.3±1.5% versus 1.8±2.4%, P=0.03) and LDL oxidative susceptibility (lag time) was significantly greater (61.8±2.9 versus 51.3±2.9 minutes, P=0.01) compared with placebo.

**Compliance**

Mean pill compliance was 92% in the placebo-treated group and 91% in the vitamin E group (P=0.17). Pill compliance for the placebo-treated versus the active vitamin E participants was maintained throughout the trial, as follows: 89% versus 87%, 90% versus 89%, 92% versus 92%, 91% versus 93%, 94% versus 91%, and 93% versus 93% at 6, 12, 24, 30, and 36 months, respectively. There was an appropriate rise in the mean±SD plasma vitamin E level in the active vitamin E group from a baseline level of 22.1±6.3 to 53.3±12.7 μmol/L (P<0.0001). There was a small but significant increase in the plasma vitamin E level in the placebo-treated group (23.2±6.3 to 30.9±6.2 μmol/L, P<0.0001). The plasma vitamin E levels between treatment groups were significantly different during follow-up (P<0.0001).

**Clinical Events**

There were 3 deaths during the study, including 2 fatal myocardial infarctions (1 placebo and 1 vitamin E) and 1...
homicide (vitamin E). New cancer diagnoses occurred in 5 placebo and 9 vitamin E subjects \( (P=0.17) \). In the placebo group, the cancers included breast (1), bladder (1), prostate (1), melanoma (1), and non-Hodgkin’s lymphoma (1). In the vitamin E group, the cancers included breast (2), prostate (3), bile duct (1), renal (1), nasal (1), and ovarian (1). A total of 25 cardiovascular events occurred in 10 placebo participants (14 events) and 8 vitamin E participants (11 events), \( P=0.81 \). These included (placebo, vitamin E) fatal myocardial infarction (1, 1), nonfatal myocardial infarction (3, 4), non–Q-wave myocardial infarction (2, 0), coronary artery bypass graft surgery (3, 0), percutaneous transluminal coronary angioplasty (1, 3 in 2 vitamin E participants), unstable angina (1, 2), transient ischemic attack (1, 1), and cerebrovascular accident (2, 0).

Discussion

Summary of VEAPS Findings

Supplementation with DL-\( \alpha \)-tocopherol significantly raised plasma vitamin E levels and reduced LDL- and LDL oxidative susceptibility relative to placebo. However, \( \alpha \)-tocopherol supplementation did not reduce the progression of CCA IMT over a 3-year period, overall and stratified by sex.

Although plasma markers of LDL oxidation and LDL oxidative protection are routinely interpreted as indicators of an agent’s potential effectiveness in reducing atherosclerosis, this linkage has never been directly demonstrated. Our results call into question whether these plasma markers accurately reflect tissue oxidative processes and whether these parameters can be used to make decisions about which agents may have antiatherosclerosis activity. In most animal studies, vitamin E has been shown to reduce atherosclerosis.26 However, when administered at pharmacological dosages, vitamin E has been shown to be ineffective in inhibiting atherosclerosis.27

There may be problems with supplementation of vitamin E alone, because there seems to be a coregulation of metabolism or absorption of antioxidant supplements.27,28 For example, supplementation with vitamin E lowered the plasma levels of ubiquinol–10, another antioxidant.28 Even high doses of vitamin E failed to show antioxidant activity in healthy humans.29 It is possible that when other antioxidants are insufficient, vitamin E could act as a prooxidant,30 and under the right circumstances, supplementation with high doses of vitamin E could promote rather than reduce lipid peroxidation11 or offset the effect of other antioxidants. Vitamin E is oxidized to reactive \( \alpha \)-tocopheryl radicals that require reduction back to \( \alpha \)-tocopherol by other reducing agents, such as glutathione and vitamin C.32 Although an antioxidant action was found for LDL in this trial, this may not reflect metabolic processes in vascular tissues, where vitamin E exerts a myriad of regulatory effects that are not directly based on its antioxidant activity.33 In plasma, where other reducing agents such as vitamin C are ubiquitous, vitamin E acts as an antioxidant, as demonstrated by the significant reduction in circulating oxidized LDL and LDL-oxidative susceptibility in this trial. Although our findings showed that LDL-oxidative susceptibility was significantly decreased in vitamin–E–supplemented subjects, the effect was modest by comparison with the demonstrated effects of antioxidants on in vitro LDL oxidation. In other microenvironments, such as the arterial wall, where other compounds necessary for reduction of vitamin E may be in limited supply, oxidized vitamin E may exert untoward metabolic effects as a prooxidant.

VEAPS and Other Clinical Trials

Despite epidemiological studies that suggest an inverse relationship between vitamin E intake and CVD, randomized controlled trials have predominantly demonstrated no reduction in CVD or atherosclerosis progression with vitamin E supplementation.6–16 Two early trials testing the effects of antioxidant vitamin supplementation on primary cancer outcome with secondary CVD end points reported mixed results. In the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC), men with a previous myocardial infarction randomized to \( \alpha \)-tocopherol demonstrated a significant reduction in nonfatal myocardial infarction, but this was overshadowed by a 33% increase in fatal coronary heart disease.6,34 Subjects receiving the combination of \( \alpha \)-tocopherol and \( \beta \)-carotene had a 58% increase in fatal coronary heart disease.6 In the remaining subjects without a history of myocardial infarction, \( \alpha \)-tocopherol alone or in combination with \( \beta \)-carotene had no effect on fatal coronary heart disease or nonfatal myocardial infarction.7 In the second study conducted in 29 584 Chinese subjects 40 to 69 years of age without CVD living in the Linxian Province, subjects were randomized to several vitamin and mineral combinations. After a follow-up of 5.25 years, total mortality was reduced by 9% among those randomized to daily vitamin E, \( \beta \)-carotene, and selenium, but there was no significant reduction in CVD events.13 Several trials testing the effects of antioxidant vitamin supplementation on CVD events as the primary end point also reported mixed results. In the Cambridge Heart Antioxidant Study (CHAOS), subjects assigned to \( \alpha \)-tocopherol experienced a significant reduction in the risk for nonfatal myocardial infarction. However, similar to ATBC, there was an 18% increase in CVD death in the \( \alpha \)-tocopherol group.8 The GISSI-Prevenzione (GISSI), the Heart Outcomes Prevention Evaluation Study (HOPE), and the Primary Prevention Project (PPP), large 2×2 factorial randomized controlled trials, failed to demonstrate a reduction in CVD events with vitamin E supplementation.9–11 In contrast, each of these trials demonstrated a significant reduction in CVD events with the other therapies under study (n-3 polyunsaturated fatty acids,9 ACE inhibitor,10 and low-dose aspirin,11 respectively). Pooled analysis from the randomized controlled trials ATBC, CHAOS, GISSI, and HOPE indicated no evidence that vitamin E supplementation (50 to 400 mg) reduced CVD events or all-cause mortality compared with placebo over a 1.3- to 4.5-year time period.10 Other trials indicate possible patient-specific benefits. For example, in the Secondary Prevention with Antioxidants of Cardiovascular Disease in Endstage Renal Disease (SPACE) trial, vitamin E significantly reduced CVD events (myocardial infarction, but not cardiovascular and total mortality).12
The SPACE trial involved subjects with preexisting CVD, experiencing excess oxidizing conditions associated with hemodialysis. These results suggest that vitamin E may be beneficial under circumstances where antioxidant activity is compromised.

Vitamin E supplementation may require concomitant administration of other antioxidants to have a beneficial effect on atherosclerosis progression. In the Antioxidant Supplement in Atherosclerosis Prevention (ASAP) trial, vitamin E and vitamin C alone had no effect on the 3-year progression of CCA IMT in high-risk East Finnish men and women. However, the combination of α-tocopherol and vitamin C significantly reduced the progression of atherosclerosis in hypercholesterolemic smoking men who had low baseline serum vitamin E levels. In the HDL-Atherosclerosis Treatment Study (HATS), subjects were randomized to simvastatin-niacin were attenuated by concurrent antioxidant therapy.16,35 Antioxidant therapy alone reduced the HDL-C subfraction and did not significantly reduce atherosclerosis progression in atherosclerosis progression and CVD end points with simvastatin-niacin were attenuated by concurrent antioxidant therapy.16,35 Antioxidant therapy alone reduced the HDL-C subfraction and did not significantly reduce atherosclerosis progression and CVD events relative to placebo.16

Additional Research
Although serum levels of antioxidant vitamins were not determined in SPACE or in the Linxian study, hemodialysis patients have low intracellular vitamin levels, and the Linxian population was chosen because of low antioxidant vitamin intake. Compromised antioxidant status may exist in other populations, such as diabetics, where targeted therapy may be beneficial. Beneficial effects of vitamin E supplementation on atherosclerosis may be limited to persons with initially low serum levels. Whether antioxidant vitamin supplementation with vitamin E alone or in combination with other antioxidant vitamins can reduce atherosclerosis progression and CVD events in individuals with low serum or intracellular antioxidant vitamin levels needs to be determined.

The two studies showing a significant effect of vitamin E on CVD outcome used a higher dosage of vitamin E. In CHAOS, 800 IU per day of vitamin E was initially used, and in SPACE, 800 IU per day of vitamin E was used throughout the trial. Whether higher dosages of vitamin E have a beneficial effect on atherosclerosis progression and CVD events requires guarded consideration given the prooxidant potential of vitamin E and the negative trials that used this higher dosage (HATS).

Conclusions
The results from VEAPS are consistent with previous randomized controlled trials and extend the null results of vitamin E to the progression of subclinical atherosclerosis in healthy men and women at low risk for CVD. Although the accumulated evidence indicates that vitamin E does not have a perceptible effect on the reduction of atherosclerosis progression and CVD events in the general population, the data do not exclude the possibility of an effect in specific populations. Low plasma or intracellular vitamin E levels may be requisite for the effective application of vitamin E supplementation for specific populations. VEAPS indicates that in well-nourished healthy vitamin E replete individuals at low risk for CVD, vitamin E supplementation has no perceptible effect on the progression of atherosclerosis.

Appendix
The VEAPS Research Group was made up of the following members: Study Chairman: Howard N. Hodis, MD; Clinical Investigators: Peter R. Maher, MD and Alex Sevaniian PhD; Clinical Center Staff (USC): Mary Ann Spahn, MS, Sonia Moss, Steve LaBree, Frank Watcher, Tmirah Haselkorn, MS, Heather Gordish, MS, and Natalie Wong; Clinical Center Staff (Kaiser Permanente): Robert Browning, RN, Patricia Jackimowicz, RN, and Phyllis Scutella, RN; Image Acquisition and Processing Laboratory: Robert H. Selzer, MS (Director), Chao-ran Liu, MD, Ci-hua Liu, MD, Zenaida Lee; Data Coordinating Center: Wendy J. Mack, PhD (Director), Stanley P. 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