Randomized Trials of Vitamin E in the Treatment and Prevention of Cardiovascular Disease

Rachel S. Eidelman, MD; Danielle Hollar, PhD; Patricia R. Hebert, PhD; Gervasio A. Lamas, MD; Charles H. Hennekens, MD, DrPH

Background: Observational epidemiological studies consistently show that individuals who choose to take high amounts of vitamin E through diet or supplements experience cardiovascular benefits, for which basic research provides plausible mechanisms. However, because the size of the postulated benefit is small to moderate, the confounding inherent in observational studies is as great as the effect size. Before the availability of randomized evidence, about 1 in 4 adults was taking vitamin E supplements in the United States.

Methods: We conducted a computerized search of the English-language literature from 1990 to the present and found 7 large-scale randomized trials of the effectiveness vitamin E in the treatment and prevention of cardiovascular disease. Data were available on myocardial infarction, stroke, or cardiovascular death.

Results: Six of the 7 trials showed no significant effect of vitamin E on cardiovascular disease. In an overview, vitamin E had neither a statistically significant nor a clinically important effect on any important cardiovascular event (odds ratio [OR], 0.98; 95% confidence interval [CI], 0.94-1.03) or its components: nonfatal myocardial infarction (OR, 1.00; 95% CI, 0.92-1.09), nonfatal stroke (OR, 1.03; 95% CI, 0.93-1.14), or cardiovascular death (OR, 1.00; 95% CI, 0.94-1.05).

Conclusions: The ORs and CIs provide strong support for a lack of statistically significant or clinically important effects of vitamin E on cardiovascular disease. The use of agents of proven lack of benefit, especially those easily available over the counter, may contribute to underuse of agents of proven benefit and failure to adopt healthy lifestyles.

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Original Investigation

Author affiliations are listed at the end of this article.

Basic research has provided plausible mechanisms for benefits—including inhibition of oxidation of low-density lipoprotein cholesterol in plasma—and observational epidemiologic studies have consistently shown that individuals who choose to take high amounts of vitamin E through diet or supplements have decreased risks of cardiovascular disease.1,7 Because the postulated benefit is small to moderate, the uncontrolled and uncontrollable confounding inherent in all observational epidemiologic studies is as great as the effect size. Thus, reliable evidence must derive from large-scale randomized trials.8 There are published large-scale randomized trials of the effectiveness of vitamin E, alone or in combination, in the treatment and prevention of cardiovascular disease.9-15 In this report, we review the results of these trials both individually and in an overview or meta-analysis.
Table 1 lists the design features of the 7 randomized trials of vitamin E and cardiovascular disease.

The nutrition intervention trials in Linxian, China, evaluated the effects of dietary supplementation with specific vitamins and minerals in lowering mortality from cancer or other diseases. This trial randomized 29,584 apparently healthy men and women aged from 40 through 69 years in a one-half replicate of a 2x2 factorial design using various combinations of nutrients. One arm of the trial was an antioxidant vitamin combination of 30 mg of vitamin E, 15 mg of beta carotene, and 0.05 mg of selenium. Participants assigned to this combination had a possible but nonsignificant 10% reduction in mortality from cardiovascular disease (OR, 0.90; 95% CI, 0.76-1.07).

The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study randomized 29,133 smoking men aged from 50 through 69 years and without diagnosed coronary heart disease in a 2 x 2 factorial design to 50 mg of α-tocopherol, 20 mg of beta carotene, both active agents, or either of 2 placebos. Participants assigned to vitamin E had no significant change in risk of cardiovascular disease, including myocardial infarction or stroke, except for a significant 50% increase in risk of death from hemorrhagic stroke.

The Cambridge Heart Antioxidant Study randomized 20,536 men and women aged between 40 and 80 years who had coronary heart disease or other vascular disease in a 2 x 2 factorial design to 400 IU of vitamin E, 10 mg of ramipril, both active agents, or either of 2 placebos. Vitamin E showed no significant benefit for a combined end point of death, nonfatal myocardial infarction, or nonfatal stroke (OR, 0.95; 95% CI, 0.86-1.05).

Table 1. Design Features of the 7 Randomized Trials of Vitamin E and Cardiovascular Disease

<table>
<thead>
<tr>
<th>Subjects randomized, No.</th>
<th>Follow-up, y</th>
<th>Patient health status</th>
<th>Age range, y</th>
<th>Women, %</th>
<th>Vitamin E dose, mg</th>
<th>Vitamin E type</th>
<th>Vitamin type</th>
<th>Placebo</th>
<th>Placebo</th>
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<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Linxian, China (1983)</td>
<td>29,584</td>
<td>Apparently healthy</td>
<td>40-69</td>
<td>55</td>
<td>30</td>
<td>Synthetic</td>
<td>Synthetic</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>ATBC Study (1994)</td>
<td>29,133</td>
<td>Heavy cigarette smoking</td>
<td>50-69</td>
<td>55</td>
<td>50</td>
<td>Synthetic</td>
<td>Synthetic</td>
<td>6.1</td>
<td>6.1</td>
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</tr>
<tr>
<td>CHAOS (1996)</td>
<td>2002</td>
<td>Angiographically proven CAD</td>
<td>53-71</td>
<td>0</td>
<td>800,000</td>
<td>Natural</td>
<td>Natural</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>GISSI-P (1999)</td>
<td>11,324</td>
<td>Post-MI</td>
<td>49-70</td>
<td>0</td>
<td>400</td>
<td>Synthetic</td>
<td>Synthetic</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>HOPE (2000)</td>
<td>9,541</td>
<td>At high risk, undergoing primary and secondary prevention</td>
<td>59-73</td>
<td>0</td>
<td>400</td>
<td>Natural</td>
<td>Natural</td>
<td>4.5</td>
<td>4.5</td>
<td>4.5</td>
<td>4.5</td>
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<tr>
<td>PPP (2001)</td>
<td>4,495</td>
<td>At high risk (≥1 major CV risk factors)</td>
<td>57-72</td>
<td>0</td>
<td>400</td>
<td>Synthetic</td>
<td>Synthetic</td>
<td>3.6</td>
<td>3.6</td>
<td>3.6</td>
<td>3.6</td>
</tr>
<tr>
<td>HPS (2002)</td>
<td>20,536</td>
<td>At high risk (DM), undergoing primary and secondary prevention</td>
<td>40-80</td>
<td>0</td>
<td>400</td>
<td>Synthetic</td>
<td>Synthetic</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviations: ATBC, Alpha-Tocopherol, Beta Carotene Cancer Prevention Study; CAD, coronary artery disease; CHAOS, Cambridge Heart Antioxidant Study; CV, cardiovascular; DM, diabetes mellitus; GISSI-P, Gruppo Italiano per lo Studio della Sopravivenza nell’Infarto miocardico Prevenzione trial; HOPE, Heart Outcomes Prevention Evaluation Study; HPS, Heart Protection Study; PPP, Primary Prevention Project.

(2 + b)/(2 − b). For ORs between 0.5 and 2, these 2 methods give almost identical answers. For each OR we calculated a 95% confidence interval (CI).16

RESULTS

Table 1 lists the design features of the 7 randomized trials of vitamin E and cardiovascular disease.

The nutrition intervention trials in Linxian, China, evaluated the effects of dietary supplementation with specific vitamins and minerals in lowering mortality from cancer or other diseases. This trial randomized 29,584 apparently healthy men and women aged from 40 through 69 years in a one-half replicate of a 2x2 factorial design using various combinations of nutrients. One arm of the trial was an antioxidant vitamin combination of 30 mg of vitamin E, 15 mg of beta carotene, and 0.05 mg of selenium. Participants assigned to this combination had a possible but nonsignificant 10% reduction in mortality from cardiovascular disease (OR, 0.90; 95% CI, 0.76-1.07).

The Alpha-Tocopherol, Beta Carotene Cancer Prevention study randomized 29,133 smoking men aged from 50 through 69 years and without diagnosed coronary heart disease in a 2 x 2 factorial design to 50 mg of α-tocopherol, 20 mg of beta carotene, both active agents, or either of 2 placebos. Participants assigned to vitamin E had no significant change in risk of cardiovascular disease, including myocardial infarction or stroke, except for a significant 50% increase in risk of death from hemorrhagic stroke.

The Cambridge Heart Antioxidant Study randomized 20,536 men and women aged between 50 and 73 years in a 2 x 2 factorial design to an antioxidant vitamin combination of 30 mg of vitamin E, n-3 polyunsaturated fatty acids, both active agents, or either of 2 placebos. The subjects randomized to vitamin E showed no significant benefit for a combined end point of death, nonfatal myocardial infarction, or nonfatal stroke (OR, 0.95; 95% CI, 0.86-1.05).

The Heart Outcomes Prevention Evaluation trial randomized 95,411 high-risk (ie, known cardiovascular disease or diabetes plus 1 other risk factor) men and women between 59 and 73 years in a 2 x 2 factorial design to 400 IU of vitamin E, 10 mg of ramipril, both active agents, or either of 2 placebos. There was no apparent effect on a composite of myocardial infarction, stroke, and death from cardiovascular disease (OR, 1.05; 95% CI, 0.95-1.16).

The Primary Prevention Project randomized 44,955 men and women aged from 57 to 72 with one or more major risk factors for cardiovascular disease in a 2 x 2 factorial design to 300 mg of vitamin E, 100 mg of aspirin, both active agents, or either of 2 placebos. Vitamin E had no significant effect on the primary combined end point nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death (OR, 1.07; 95% CI, 0.74-1.56).

The Heart Protection Study randomized 20,536 men and women aged between 40 and 80 years who had coronary heart disease, other vascular disease, or diabetes in a 2 x 2 factorial design to an antioxidant vitamin combination (600 mg of vitamin E, 250 mg of ascorbic acid, and 20 mg of beta carotene), 40 mg of simvastatin, both active agents, or either of 2 placebos. There were no significant reductions in cardiovascular mortality (OR, 1.06; 95% CI, 0.95-1.18) or incidence of any type of cardiovascular disease (OR, 1.00; 95% CI, 0.94-1.06).

These 7 trials of vitamin E and cardiovascular disease randomized 106,625 participants in secondary and primary prevention who experienced a total of 97,279 cardiovascular disease end points. Table 2 shows the numbers of any important cardiovascular events and cardiovascular deaths in these 7 trials. There was no significant evidence of heterogeneity among the trials. In the overview, there were 4,832 important cardiovascular events (combined end point of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) among pa-
patients assigned to vitamin E and 4895 in those assigned to placebo (OR, 0.98; 95% CI, 0.94-1.03). Similarly, there were 2683 cardiovascular deaths in the vitamin E group and 2689 in the placebo group (OR, 1.00; 95% CI, 0.94-1.05).

Table 3 shows the numbers of participants who experienced nonfatal myocardial infarction or nonfatal stroke. For nonfatal myocardial infarction, there were 1255 participants in the vitamin E group and 1254 in the placebo group (OR, 1.00; 95% CI, 0.92-1.09). For nonfatal stroke, there were 742 in the vitamin E group and 723 in the placebo group (OR, 1.03; 95% CI, 0.93-1.14).

With respect to stroke subtypes, Table 4 shows that there was no significant difference in the vitamin E and the placebo groups for ischemic events (OR, 1.01; 95% CI, 0.90-1.14) or hemorrhagic events (OR, 1.24; 95% CI, 0.96-1.59).

This overview of 7 large-scale randomized trials of vitamin E supplementation in the secondary and primary prevention of cardiovascular disease provides conclusive evidence of a lack of statistically significant or clinically important benefit or harm regarding any important cardiovascular events or its components, namely, nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. With respect to stroke subtypes, the Alpha-Tocopherol, Beta Carotene Cancer Prevention trial reported a significant 50% increase in mortality from hemorrhagic stroke due to vitamin E. In this overview, the point estimate is compatible with a 24% increase in hemorrhagic stroke due to vitamin E, but the finding is not statistically significant. Furthermore, the width of the 95% CI for vitamin E and hemorrhagic stroke indicates that the data are compatible with a range of possibility going from a 4% benefit to a 59% increase in risk. The latter possibility is supported by basic research suggesting clinically relevant antiplatelet effects of vitamin E.

Our overview of the 7 published large-scale randomized trials of vitamin E increases the sample size and numbers of end points, thus providing far more stable estimates of the most likely magnitudes of effect. For example, for any important cardiovascular event, the narrow width of the 95% CI indicating that benefits greater than 6% are unlikely, which virtually eliminates any important clinical or public health impact attributable to vitamin E supplementation. It is interesting to note the similar lack of benefit on cardiovascular outcomes even in the largest individual trials, regardless of whether the natural form of vitamin E was used, as in the Heart Outcomes Prevention Evaluation Study, or a synthetic form, as in the Heart Protection Study. Furthermore, a similar lack of benefit was found whether vitamin E was tested alone or in combination. Nonetheless, it is possible that differing properties of the various forms of vitamin E used in the trials may have—at least in theory—played a role in the observed results.

Several potential limitations of this overview merit consideration. First, while an overview of randomized trials decreases the possible role of chance in interpreting the findings, it is possible that a small amount of confounding is introduced. In this instance, this possibility seems unlikely as compliance and follow-up in the individual randomized trials were high and the methods of ascertainment of outcomes were similar. In addition, it is not valid to directly compare individual subjects in multiple trials and reanalyze the data as if they all came from 1 large trial, as differences in factors involved may affect the risk of the outcomes under study. It is, however, as we have done, possible to compare the overall effect observed in 1 trial with that observed in another, as each is internally randomized. Although a small but clinically important effect could be obscured or reversed by the play of chance in any one trial, the grand total of observed minus expected events from all the trials is far more likely to reveal a benefit if one truly exits. The results of this overview strongly support the crucial need for data from randomized trials and their overviews to detect reliably the most plausible postulated small to moderate benefits of interventions. As had been the case with
beta carotene and hormone replacement therapy, for vitamin E, basic research suggested plausible mechanisms of benefit on cardiovascular disease, including inhibition of oxidation of low-density lipoprotein cholesterol in plasma. In addition, numerous large, well-designed, and well-conducted observational epidemiologic studies, both case-control and prospective cohort, consistently demonstrate that individuals who choose to take vitamin E supplements have lower risks of cardiovascular disease. For moderate to large benefits, randomized trials are neither necessary nor desirable. For lung cancer, regular lifelong smokers have about a 20-fold risk and for cardiovascular disease, current smokers have about a 2-fold risk. The US Surgeon General deemed smoking a cause of cardiovascular disease based on a totality of evidence that included basic research, clinical investigation, and observational epidemiologic studies, both case-control and cohort. This was possible because the effect sizes were relatively larger (ORs were 20 for lung cancer and 2 for cardiovascular disease). For a condition as common and serious as cardiovascular disease, small to moderate effects (10%-50%) are clinically worthwhile and would have an important public health impact, but these effects are difficult to detect reliably except in data from large-scale randomized trials and their overviews. This is because the amount of uncontrolled and, indeed, uncontrollable confounding inherent in observational epidemiologic studies is as large as the most plausible small to moderate effect size. Thus, for small to moderate effects, observational epidemiologic studies may be useful to support the need for randomized trials, but not to test hypotheses. Despite these conclusive data from randomized trials of vitamin E, the low-density lipoprotein oxidation hypothesis remains plausible. Moreover, the totality of evidence is insufficient to show any benefit for other chronic diseases such as prostate cancer and macular degeneration, and cardiovascular disease in patients with end-stage renal disease.

Table 3. Nonfatal Myocardial Infarction and Nonfatal Stroke in the 7 Randomized Trials of Vitamin E and Cardiovascular Disease

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Vitamin E</td>
<td>Placebo</td>
<td>Vitamin E</td>
</tr>
<tr>
<td>Linxian, China</td>
<td>14 792</td>
<td>3698</td>
<td>3698</td>
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<tr>
<td>ATBC</td>
<td>14 564</td>
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<td>967</td>
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<td>5668</td>
<td>5666</td>
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<tr>
<td>PPP</td>
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<td>2264</td>
<td>2231</td>
</tr>
<tr>
<td>HPS</td>
<td>10 269</td>
<td>10 267</td>
<td>10 269</td>
</tr>
<tr>
<td>Total</td>
<td>53 318</td>
<td>42 213</td>
<td>53 318</td>
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</tbody>
</table>

Abbreviations: ATBC, Alpha-Tocopherol, Beta Carotene Cancer Prevention Study; CHAOS, Cambridge Heart Antioxidant Study; GISSI-P, Gruppo Italiano per lo Studio della Sopravivenza nell’Infarto miocardico Prevenzione trial; HOPE, Heart Outcomes Prevention Evaluation Study; HPS, Heart Protection Study; PPP, Primary Prevention Project.

*Ellipses indicate that data were not available.
†Typical odds ratio (95% confidence interval), 1.00 (0.92-1.09).
‡Typical odds ratio (95% confidence interval), 1.03 (0.93-1.14).
§Fatal and nonfatal myocardial infarction.
¶Fatal and nonfatal stroke.

Table 4. Ischemic vs Hemorrhagic Stroke (Fatal and Nonfatal) in the 7 Randomized Trials of Vitamin E and Cardiovascular Disease

<table>
<thead>
<tr>
<th>Trial</th>
<th>Subjects Randomized, No.</th>
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<th>Hemorrhagic Stroke, No.</th>
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<tr>
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<td>Vitamin E</td>
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<td>Vitamin E</td>
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<td>Linxian, China</td>
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<td>ATBC</td>
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<tr>
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</tr>
<tr>
<td>HPS</td>
<td>10 269</td>
<td>10 267</td>
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*Ellipses indicate that data were not available.
†Typical odds ratio (95% confidence interval), 1.01 (0.90-1.14).
‡Typical odds ratio (95% confidence interval), 1.24 (0.96-1.59).
§Fatal events only.
In summary, the findings from this overview, including the magnitude of the OR estimates and the width of their 95% CIs, provide strong support that vitamin E supplementation has no statistically significant or clinically important effects on cardiovascular disease. The importance of this conclusion is enhanced by a recent survey indicating that 24% of adults in the United States are taking vitamin E supplements. Furthermore, the use of agents of proven lack of benefit, which are readily available over the counter, such as vitamin E, may be contributing to the underuse of agents of proven benefit in cardiovascular disease such as aspirin, statins, β-blockers, and angiotensin-converting enzyme inhibitors. Finally, rather than avoiding lifestyles proven harmful, many individuals prefer to take over-the-counter pills of proven benefit, including vitamin E. All these considerations underscore the crucial importance of avoiding harmful lifestyles and drugs proved nonbeneficial, as well as taking prescribed drugs of proven benefit as adjuncts, not alternatives, to the avoidance of harmful lifestyles.

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REFERENCES