The American Heart Association (AHA) has had a long-standing commitment to provide information about the role of nutrition in cardiovascular disease (CVD) risk reduction. Many activities have been and are currently directed toward this objective, including issuing AHA Dietary Guidelines periodically (most recently in 2000) and Science Advisories and Statements on an ongoing basis to review emerging nutrition-related issues. The objective of the AHA Dietary Guidelines is to promote healthful dietary patterns. A consistent focus since the inception of the AHA Dietary Guidelines has been to reduce saturated fat (and trans fat) and cholesterol intake, as well as to increase dietary fiber consumption. Collectively, all the AHA Dietary Guidelines have supported a dietary pattern that promotes the consumption of dairy products, fish, legumes, poultry, and lean meats. This dietary pattern has a low energy density to promote weight control and a high nutrient density to meet all nutrient needs.

As reviewed in the first AHA Science Advisory on antioxidant vitamins, epidemiological and population studies reported that some micronutrients may beneficially affect CVD risk (ie, antioxidant vitamins such as vitamin E, vitamin C, and β-carotene). Recent epidemiological evidence is consistent with the earlier epidemiological and population studies (reviewed in the first Science Advisory). These findings have been supported by in vitro studies that have established a role of oxidative processes in the development of the atherosclerotic plaque. Underlying the atherosclerotic process are proatherogenic and prothrombotic oxidative events in the artery wall that may be inhibited by antioxidants. The 1999 AHA Science Advisory recommended that the general population consume a balanced diet with emphasis on antioxidant-rich fruits, vegetables, whole grains, low-fat or nonfat dairy products, fish, legumes, poultry, and lean meats. This dietary pattern has a low energy density to promote weight control and a high nutrient density to meet all nutrient needs.

In the past 5 years, a number of controlled clinical studies have reported the effects of antioxidant vitamin and mineral supplements on CVD risk (see Tables 1 through 3). These studies have been the subject of several recent reviews and formed the database for the present article. In general, the studies presented in the tables differ with regard to subject populations studied, type and dose of antioxidant/cocktail administered, length of study, and study end points. Overall, the studies have been conducted on post–myocardial infarction subjects or subjects at high risk for CVD, although some studied healthy subjects. In addition to dosage differences in vitamin E studies, some trials used the synthetic form, whereas others used the natural form of the vitamin. With regard to the other antioxidants, different doses were administered (eg, for β-carotene and vitamin C). The antioxidant cocktail formulations used also varied. Moreover, subjects were followed up for at least 1 year and for as long as 12 years. In addition, a meta-analysis of 15 studies (7 studies of vitamin E, 50 to 800 IU; 8 studies of β-carotene, 15 to 50 mg) with 1000 or more subjects per trial has been conducted to ascertain the effects of antioxidant vitamins on cardiovascular morbidity and mortality. Collectively, for the most part, clinical trials have failed to demonstrate a beneficial effect of antioxidant supplements on CVD morbidity and mortality. With regard to the meta-analysis, the lack of efficacy was demonstrated consistently for different doses of various antioxidants in diverse population groups.

Although the preponderance of clinical trial evidence has not shown beneficial effects of antioxidant supplements, evidence from some smaller studies documents a benefit of α-tocopherol (Cambridge Heart AntiOxidant Study, Secondary Prevention with Antioxidants of Cardiovascular disease in End-stage renal disease study), α-tocopherol and slow-release vitamin C (Antioxidant Supplementation in Atherosclerosis Prevention study), and vitamin C plus vitamin E (Intravascular Ultrasonography Study) on cardio-
vascular end points. To complicate matters, there is some evidence of potentially adverse effects of antioxidant supplements on CVD as assessed by angiographic end points. In the Women’s Angiographic Vitamin and Estrogen Study,21 postmenopausal women with coronary disease on hormone replacement therapy given vitamin E plus vitamin C had an unexpected significantly higher all-cause mortality rate and a trend for an increased cardiovascular mortality rate compared with the vitamin placebo women. Likewise, in the HDL-Atherosclerosis Treatment Study,20 subjects with angiographically demonstrated coronary artery disease on simvastatin/niacin and an antioxidant cocktail (vitamin E, β-carotene, vitamin C, and selenium) had a 0.7% progression in stenosis after 3 years, compared with 0.4% regression in the group on only simvastatin/niacin. Thus, antioxidant supplements may have interfered with the efficacy of statin-plus-niacin therapy. Further evaluation showed that the addition of the antioxidant vitamins blunted the expected rise in the protective HDL-2 cholesterol and apolipoprotein A1 subfractions of HDL. In general, the studies showing either positive or adverse effects (especially for vitamins E, vitamins E and C, and the antioxidant cocktails) are much smaller studies than the larger clinical trials that consistently have not shown any beneficial effects of antioxidant supplements on several CVD end points.

Thus, in agreement with many in the field, we conclude that the existing scientific database does not justify routine use of antioxidant supplements for the prevention and treatment of CVD.

### TABLE 1. Selected Controlled Clinical Trials of Antioxidant Supplements on CVD Events (Studies Showing No Effects)

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Sex</th>
<th>Age, y</th>
<th>Characteristics</th>
<th>Dose</th>
<th>Duration, y</th>
<th>Prevention Goal</th>
<th>Study Outcome</th>
<th>RR/Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GISSI (1999)</td>
<td>11324</td>
<td>M, F</td>
<td>No age limits</td>
<td>Post-MI adults</td>
<td>300 mg (synthetic)</td>
<td>3.5</td>
<td>Secondary</td>
<td>No effect on MI + CVD death + stroke</td>
<td>0.98 (0.87–1.10)</td>
</tr>
<tr>
<td>HOPE (2000)</td>
<td>9541</td>
<td>M, F</td>
<td>≥55</td>
<td>High CVD risk</td>
<td>400 IU (natural)</td>
<td>4.5</td>
<td>Primary and secondary</td>
<td>No effect on MI + CVD death + stroke</td>
<td>1.05 (0.95–1.16)</td>
</tr>
<tr>
<td>PPP (2001)</td>
<td>4495</td>
<td>M, F</td>
<td>64</td>
<td>At risk of CVD</td>
<td>300 mg (synthetic)</td>
<td>3.6</td>
<td>Primary</td>
<td>No effect on MI + CVD death + stroke</td>
<td>1.07 (0.74–1.56)</td>
</tr>
<tr>
<td>MICRO-HOPE (2002)</td>
<td>3654</td>
<td>M, F</td>
<td>65</td>
<td>Diabetes</td>
<td>400 IU (natural)</td>
<td>4.5</td>
<td>Secondary</td>
<td>No effect on MI + CVD death + stroke</td>
<td>1.03 (0.88–1.21)</td>
</tr>
<tr>
<td>VEAPS (2002)</td>
<td>353</td>
<td>M, F</td>
<td>≥40</td>
<td>Elevated LDL-C</td>
<td>400 IU dl-α-tocopherol</td>
<td>3</td>
<td>Primary</td>
<td>No effect on intima-media thickness + clinical events</td>
<td>P=0.81 for CVD events</td>
</tr>
<tr>
<td>β-Carotene</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATBC (1998)</td>
<td>27271</td>
<td>M</td>
<td>50–69</td>
<td>Smokers with no history of MI</td>
<td>20 mg</td>
<td>6.1</td>
<td>Primary</td>
<td>No effect on: All coronary cases 0.93 (0.91–1.16)</td>
<td>1.03 (0.91–1.16)</td>
</tr>
<tr>
<td>SCPS (1996)</td>
<td>1805</td>
<td>M, F</td>
<td>&lt;85</td>
<td>Skin cancer patients</td>
<td>50 mg</td>
<td>8.2</td>
<td>Primary</td>
<td>No effect on CVD mortality 1.16 (0.82–1.64)</td>
<td>1.16 (0.82–1.64)</td>
</tr>
<tr>
<td>PHS (1996)</td>
<td>22071</td>
<td>M</td>
<td>40–84</td>
<td>Healthy</td>
<td>50 mg on alternate days</td>
<td>12</td>
<td>Primary</td>
<td>No effect on: MI 0.96 (0.84–1.09)</td>
<td>1.00 (0.91–1.09)</td>
</tr>
<tr>
<td>Antioxidant cocktails</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATBC (1998)</td>
<td>27271</td>
<td>M</td>
<td>50–69</td>
<td>Smokers with no history of MI</td>
<td>50 mg vitamin E and 20 mg β-carotene</td>
<td>6.1</td>
<td>Primary</td>
<td>No effect on: All coronary cases 0.97 (0.86–1.09)</td>
<td>0.97 (0.86–1.09)</td>
</tr>
<tr>
<td>HPS (2002)</td>
<td>20536</td>
<td>M, F</td>
<td>40–80</td>
<td>High CVD risk</td>
<td>600 mg vitamin E, 250 mg vitamin C, 20 mg β-carotene</td>
<td>Secondary</td>
<td>No effect on CVD mortality 1.05 (0.95–1.15)</td>
<td>1.05 (0.95–1.15)</td>
<td></td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico-prevenzione study; HOPE, Heart Outcomes Protection Evaluation trial; PPP, Primary Prevention Project; MICRO-HOPE, Microalbuminuria Cardiovascular Renal Outcomes–Heart Outcomes Prevention Evaluation trial; ATBC, Alpha-Tocopherol-Beta-Carotene Cancer Prevention study; SCPS, Skin Cancer Prevention Study; PHS, Physicians’ Health Study; HPS, Heart Protection Study; and VEAPS, Vitamin E Atherosclerosis Prevention Study.
placement 2002 Guideline Update for the management of patients with chronic stable angina, which states that there is no basis for recommending that patients take vitamin C or E supplements or other antioxidants for the express purpose of preventing or treating coronary artery disease (Class III, Level A Evidence).30 In addition, "Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women"31 concludes that antioxidant vitamin supplements should not be used to prevent CVD, pending the results of ongoing trials (Class III, Level A Evidence). Whether or not to use vitamin E in highly specialized situations, such as in subjects on hemodialysis,15 also remains unsettled until further studies in this setting are conducted. Moreover, although there is some evidence of beneficial effects of antioxidant supplements, it also is apparent that some studies suggest adverse effects of antioxidant supplement use. An important question is: What should we be doing in clinical practice? At this time, there is little reason to advise that individuals take antioxidant supplements to reduce risk of CVD. Nonetheless, we recommend that antioxidant research continue in order to resolve whether the oxidative modification hypothesis is relevant to human atherosclerosis. Antioxidant compounds cannot be indiscriminately lumped together; they differ quantitatively and even qualitatively from one another. We still know too little about the oxidative mechanisms in vivo and lack biochemical markers with which to evaluate candidate antioxidant compounds. Moreover, antioxidant treatment may need to begin earlier in life to be effective. The discrepancy between the impressive observational data and the clinical trials could reflect the difference between lifelong exposure to an antioxidant-rich diet and a limited, 5-year exposure to antioxidant supplements. However, several other factors (such as identity, type, and form of antioxidant; particular antioxidant combinations; trial design issues; outcome measures; length; populations under study; etc) could also be important in explaining the lack of agreement between the predicted positive benefits and the results of the clinical trials conducted to date. Clearly, further research is needed.

**Summary**

At this time, the scientific data do not justify the use of antioxidant vitamin supplements for CVD risk reduction.
This position is consistent with recommendations that have been made by the AHA in 2004 for the prevention of CVD in women as well as by the American College of Cardiology and AHA in 2002 for patients with chronic stable angina. CVD risk reduction can be achieved by the long-term consumption of diets consistent with the AHA Dietary Guidelines; the long-term maintenance of a healthy body weight through balancing energy intake with regular physical activity; and the attainment of desirable blood cholesterol and lipoprotein profiles and blood pressure levels. No consistent data suggest that consuming micronutrients at levels exceeding those provided by a dietary pattern consistent with AHA Dietary Guidelines will confer additional benefit with regard to CVD risk reduction.

**Acknowledgment**

Members of the Nutrition Committee thank Dr Neil Stone for his careful and thoughtful review of this scientific statement.

**References**


29. Steinberg D, Witztum JL. Is the oxidative modification hypothesis relevant to human atherosclerosis? Do the antioxidant trials conducted to date refute the hypothesis? Circulation. 2002;105:2107–2111.


KEY WORDS: AHA Science Advisory • antioxidants • nutrition • coronary disease • cardiovascular diseases
Antioxidant Vitamin Supplements and Cardiovascular Disease
Penny M. Kris-Etherton, Alice H. Lichtenstein, Barbara V. Howard, Daniel Steinberg and Joseph L. Witztum
for the Nutrition Committee of the American Heart Association Council on Nutrition, Physical Activity, and Metabolism

Circulation. 2004;110:637-641
doi: 10.1161/01.CIR.0000137822.39831.F1
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/110/5/637

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/