

## Antioxidant Vitamin Supplements and Cardiovascular Disease

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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<sup>1</sup>) 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 diets rich in 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.

As reviewed in the first AHA Science Advisory<sup>2</sup> 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  $\beta$ -carotene). Recent epidemiological evidence<sup>3</sup> is consistent with the earlier epidemiological and population studies (reviewed in the first Science Advisory).<sup>2</sup> 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<sup>2</sup> recommended that the general population consume a balanced diet with emphasis on antioxidant-rich fruits, vegetables, and whole grains, advice that was consistent with the AHA Dietary Guidelines at the time. In the absence of data from randomized, controlled clinical trials, no recommendations were made with regard to the use of antioxidant supplements.

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).<sup>4–21</sup> These studies have been the subject of several recent reviews<sup>22–26</sup> 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  $\beta$ -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  $\beta$ -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.<sup>27</sup> 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  $\alpha$ -tocopherol (Cambridge Heart AntiOxidant Study,<sup>13</sup> Secondary Prevention with Antioxidants of Cardiovascular disease in End-stage renal disease study),<sup>15</sup>  $\alpha$ -tocopherol and slow-release vitamin C (Antioxidant Supplementation in Atherosclerosis Prevention study),<sup>16</sup> and vitamin C plus vitamin E (Intravascular Ultrasonography Study)<sup>17</sup> on cardio-

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

Study	Subjects				Treatment			Study Outcome	RR/Statistics
	No.	Sex	Age, y	Characteristics	Dose	Duration, y	Prevention Goal		
<b>Vitamin E</b>									
GISSI (1999) <sup>4</sup>	11 324	M, F	No age limits	Post-MI adults	300 mg (synthetic)	3.5	Secondary	No effect on MI + CVD death + stroke	0.98 (0.87–1.10)
HOPE (2000) <sup>5</sup>	9541	M, F	≥55	High CVD risk	400 IU (natural)	4.5	Primary and secondary	No effect on MI + CVD death + stroke	1.05 (0.95–1.16)
PPP (2001) <sup>6</sup>	4495	M, F	64	At risk of CVD	300 mg (synthetic)	3.6	Primary	No effect on MI + CVD death + stroke	1.07 (0.74–1.56)
MICRO-HOPE (2002) <sup>7</sup>	3654	M, F	65	Diabetes	400 IU (natural)	4.5	Secondary	No effect on MI + CVD death + stroke	1.03 (0.88–1.21)
VEAPS (2002) <sup>8</sup>	353	M, F	≥40	Elevated LDL-C	400 IU dl- $\alpha$ -tocopherol	3	Primary	No effect on intima-media thickness + clinical events	<i>P</i> =0.81 for CVD events (14 placebo and 11 vitamin E)
<b><math>\beta</math>-Carotene</b>									
ATBC (1998) <sup>9</sup>	27 271	M	50–69	Smokers with no history of MI	20 mg	6.1	Primary	No effect on: All coronary cases Nonfatal MI Fatal CHD	1.03 (0.91–1.16) 1.06 (0.90–1.24) 0.99 (0.83–1.19)
SCPS (1996) <sup>10</sup>	1805	M, F	<85	Skin cancer patients	50 mg	8.2	Primary	No effect on CVD mortality	1.16 (0.82–1.64)
PHS (1996) <sup>11</sup>	22 071	M	40–84	Healthy	50 mg on alternate days	12	Primary	No effect on: MI CVD CVD mortality	0.96 (0.84–1.09) 1.00 (0.91–1.09) 1.09 (0.93–1.27)
<b>Antioxidant cocktails</b>									
ATBC (1998) <sup>9</sup>	27 271	M	50–69	Smokers with no history of MI	50 mg vitamin E and 20 mg $\beta$ -carotene	6.1	Primary	No effect on: All coronary cases Nonfatal MI Fatal MI	0.97 (0.86–1.09) 0.99 (0.84–1.16) 0.94 (0.79–1.13)
HPS (2002) <sup>12</sup>	20 536	M, F	40–80	High CVD risk	600 mg vitamin E, 250 mg vitamin C, 20 mg $\beta$ -carotene		Secondary	No effect on CVD mortality	1.05 (0.95–1.15)

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.

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,<sup>21</sup> 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,<sup>20</sup> subjects with angiographically demonstrated coronary artery disease on simvastatin/niacin and an antioxidant cocktail (vitamin E,  $\beta$ -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.<sup>25–28,29</sup> This conclusion is consistent with the American College of Cardiology/American Heart Associa-

**TABLE 2. Selected Controlled Clinical Trials of Antioxidant Supplements on CVD Events (Studies Showing Beneficial Effects)**

Study	Subjects				Treatment			Study Outcome	RR/Statistics
	No.	Sex	Age, y	Characteristics	Dose	Duration, y	Prevention Goal		
Vitamin E									
CHAOS (1996) <sup>13</sup>	2002	M, F	62	Coronary disease	800 or 400 IU	1.4	Secondary	Decreased nonfatal acute MI	0.23 (0.11–0.47)
ATBC (1997) <sup>14</sup>	1862	M	50–69	Smokers who had an MI	50 IU vitamin E	5.3	Secondary	38% reduction in nonfatal MI Fatal coronary end points not reduced	0.62 (0.41–0.96) 1.83 (0.85–3.95)
SPACE (2000) <sup>15</sup>	196	M, F	40–75	Hemodialysis patients	800 IU	2	Secondary	Decreases acute MI + stroke + peripheral vascular disease + unstable angina	0.46 (0.27–0.78)
Vitamins E and C									
ASAP (2000) <sup>16</sup>	520	M, F	45–69	Elevated cholesterol levels	182 mg d- $\alpha$ -tocopherol + 500 mg vitamin C	3	Secondary	Progression of intima-media thickness reduced from placebo (odds ratio) for men but not women	0.26 (0.11–0.64)
IVUS (2002) <sup>17</sup>	40	M, F	$\geq 18$	After cardiac transplantation	500 mg vitamin C + 400 IU vitamin E	1	Secondary	No increase in intimal index in treatment group vs the placebo group (which increased 8%)	$P=0.008$

MI indicates myocardial infarction; CHAOS, Cambridge Heart AntiOxidant Study; SPACE, Secondary Prevention with Antioxidants of Cardiovascular disease in End-stage renal disease; ATBC, Alpha-Tocopherol-Beta-Carotene Cancer Prevention study; ASAP, Antioxidant Supplementation in Atherosclerosis Prevention study; and IVUS, Intravascular Ultrasonography Study.

tion 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).<sup>30</sup> In addition, “Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women”<sup>31</sup> 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,<sup>15</sup> 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. It will be important to clarify the discrepancy between the randomized clinical trials and the population studies. The positive findings from observational studies with regard to vitamin E supplementation and lower rates of CVD may be a reflection of the generally healthy lifestyles and dietary intakes of supplement users. At this time, the scientific evidence supports recommending consumption of a diet

high in food sources of antioxidants and other cardioprotective nutrients, such as fruits, vegetables, whole grains, and nuts, instead of antioxidant supplements to reduce risk of CVD.<sup>32,33</sup> It does not support the use of antioxidant vitamin supplements.

The failure of these particular trials does not necessarily rule out a role for oxidative mechanisms in the pathogenesis of 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.

**TABLE 3. Selected Controlled Clinical Trials of Antioxidant Supplements on CVD Events (Studies Showing Adverse Effects)**

Study	Subjects				Treatment			Study Outcome	RR/Statistics
	No.	Sex	Age, y	Characteristics	Dose	Duration, y	Prevention Goal		
<b>Vitamin E</b>									
ATBC (1994) <sup>18</sup>	29 133	M	50–69	Smokers with no medical problems	50 mg vitamin E	6.1	Primary	Increase in hemorrhagic stroke	66 cases vs 44 in control ( <i>P</i> not reported)
<b>β-Carotene</b>									
ATBC (1994) <sup>18</sup>	29 133	M	50–69	Smokers with no medical problems	20 mg β-carotene	6.1	Primary	Increase in overall mortality	1.08 (1.01–1.06)
								More deaths due to:	
								Ischemic heart disease	653 cases vs 586 in control
								Hemorrhagic stroke	59 cases vs 51 in control
								Ischemic stroke	68 cases vs 55 in control ( <i>P</i> not reported)
<b>Antioxidant cocktails</b>									
CARET (1996) <sup>19</sup>	4060	M	45–74	Asbestos workers	30 mg β-carotene and 2500 IU retinol	5.5	Primary	Increase in all-cause mortality	1.17 (1.03–1.33)
	14 254	M, F	50–69	Current/former smokers				No effect on CVD mortality	1.26 (0.99–1.61)
HATS (2001) <sup>20</sup>	160	M F	<63 <70	With CVD	800 IU vitamin E (as d-α-tocopherol); 1000 mg vitamin C; 25 mg natural β-carotene; 100 μg selenium; and simvastatin + niacin	3.5	Secondary	Simvastatin/niacin alone induced 0.4% atheroregression, whereas adding antioxidant cocktail resulted in a stenosis progression of 0.7%	<i>P</i> <0.001 <i>P</i> =0.004
								CVD death or nonfatal infarct (cerebral or myocardial) or revascularization	1.38 (not reported)
WAVE (2002) <sup>21</sup>	423	F		Postmenopausal women with CVD	800 IU of vitamin E and 1000 mg of vitamin C plus HRT	2.8	Secondary	All-cause mortality was higher in the antioxidant group + HRT vs (hazard ratio) vitamin placebo group	2.8 (1.1–7.2)

ATBC indicates Alpha-Tocopherol-Beta-Carotene Cancer Prevention study; CARET, Carotene and Retinol Efficacy Trial; HATS, HDL-Atherosclerosis Treatment Study; WAVE, Women's Angiographic Vitamin and Estrogen Study; and HRT, hormone replacement therapy.

This position is consistent with recommendations that have been made by the AHA in 2004<sup>31</sup> for the prevention of CVD in women as well as by the American College of Cardiology and AHA in 2002<sup>30</sup> 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;<sup>1</sup> 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.

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