

Vitamin Supplements: Do They Help?

According to one study, over 40% of American cardiologists have routinely taken antioxidants, and have prescribed them to their patients. Over 30% of the U.S. population currently uses supplements.



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The oxidative-modification hypothesis of atherosclerosis has been well-established with experimental studies over the last 15 years.^{1,2} Oxidative modification of low-density lipoprotein (LDL) is a key step in the initiation and progression of atherosclerosis (Figure 1).³

It was hypothesized that antioxidant vitamins could play a central role in preventing oxidative damage and, thus, decrease cardiovascular morbidity and mortality.

The antioxidant vitamins that have been studied the most extensively are vitamin E (d-alpha-tocopherol), vitamin C, and beta carotene (provitamin A). Vitamin E is a major antioxi-

In this article:

1. What have trials with antioxidant vitamins established?
2. Is there any potential harm in supplementing with vitamin E?
3. What about homocysteine and folic acid?

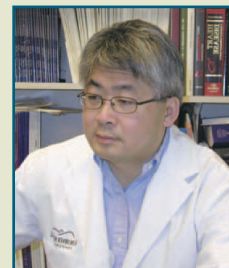
dant in LDL particles. Vitamin C is a water-soluble antioxidant that can regenerate oxidized vitamin E. Beta-carotene is a fat-soluble antioxidant with provitamin A activity that is found in the fatty core of LDL particles.

About the authors ...

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Promising laboratory studies have led to several large, prospective cohort studies that showed 20% to 40% reductions in the risk of coronary disease in both men and women taking antioxidant vitamins.^{4,5}

These results had a profound impact on physicians and their patients. A survey of 181 American cardiologists in 1997 demonstrated that over 40% routinely took antioxidants themselves, and prescribed them to their patients.⁶ Over 30% of the U.S.

population currently uses supplements.⁷ In addition to these staggering numbers, two recent opinion articles in the *New England Journal of Medicine* and the *Journal of the American Medical Association*, published in 2001 and 2002 respectively, have recommended the routine use of multivitamins in almost all patient populations.^{8,9} These preparations include vitamins E and C, and beta carotene. Physicians have been misled by observational studies in the past and, thus, a closer look at the randomized clinical trials in this area is warranted.

What have trials with antioxidant vitamins established?

Most physicians are aware that the Health Outcomes PrEvention (HOPE) trial examined the effects of an angiotensin-converting enzyme, and the Heart Protection Study (HPS) assessed the ability of a statin to reduce cardiovascular disease.^{10,11} It is less well-known, however, that these were also

landmark antioxidant vitamin studies. By using a 2x2 factorial design, the HOPE study looked at over 9,500 men and women, 55 or over, who were at high risk for cardiovascular events. Patients had a history of cardiovascular disease or diabetes in addition to one other risk factor. The trial demonstrated that treatment with 400 IU of vitamin E for 4.5 years had no effect on cardiovascular outcomes. HPS randomized 20,536 men and women at high risk for

Many researchers and clinicians feel we will have to undergo a substantial paradigm shift in our recommendations.

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cardiovascular disease to a combination of 600 mg of vitamin E, 250 mg of vitamin C, and 20 mg of beta carotene, or matching placebo, daily. Eligible patients were between 40 and 80, and had a history of either coronary artery disease, occlusive arterial disease, diabetes mellitus, or treated hypertension alone. Patients were followed for five years, and although this regimen substantially increased blood vitamin concentrations, there was no reduction in mortality, vascular disease, cancer, or any major outcome.¹¹

A large meta-analysis was recently published in *The Lancet* that examined 220,000 people involved in randomized controlled trials (RCTs) with antioxidant vitamins.¹² Both HOPE and HPS were included in the analysis. It has generated a lot of coverage in the general media, as many researchers and clinicians feel we will have to undergo a substantial paradigm shift in our recommendations regarding antioxidant vitamins.

Eight RCTs with over 138,000 people using beta carotene alone, or in combination with other antioxidants, were analysed. Four studies were classified as primary prevention (no known or documented vascular disease), while the remaining four were secondary prevention trials. Beta carotene led to a small but significant increase in all-cause mortality (7.4% versus 7%, $p=0.003$), and a slight increase in cardiovascular death. This harmful effect was consistent across all of the major trials but was most striking in patients who smoked and were at high risk for lung cancer.

Seven RCTs with over 81,000 patients using vitamin E alone or in combination with

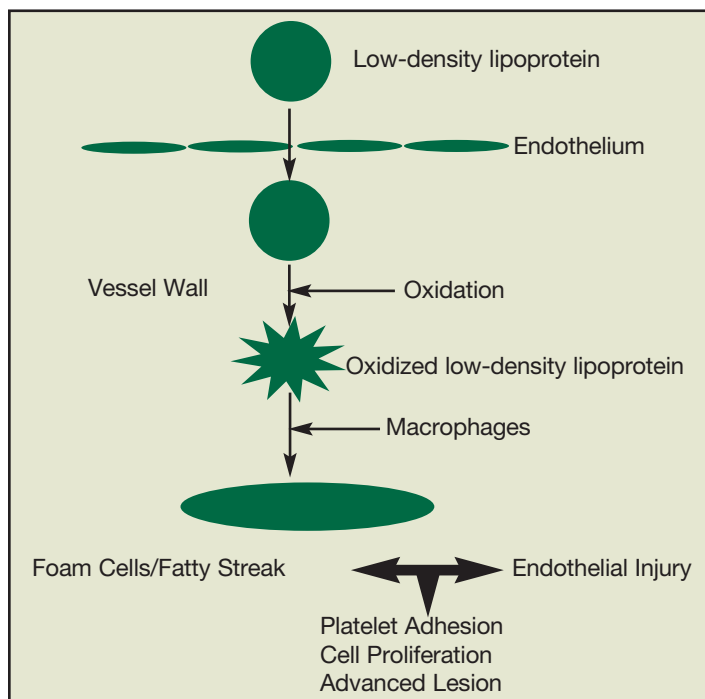


Figure 1. The role of oxidized LDL in the initiation and progression of atherosclerosis.

other antioxidants were analysed. Five studies were classified as secondary prevention, and two as primary prevention. Vitamin E did not provide a mortality benefit, and did not decrease the risk of cardiovascular death or stroke.

What are the controversies?

It has been suggested that the long-term benefits of vitamin E supplementation are still unclear, as most studies have focused on secondary prevention and have been of relatively short duration.⁸ Although the positive results found in observational studies were primarily seen in patients without cardiovascular disease, a substantial and diverse group of primary prevention patients have been studied in

Take-home message

- A balanced diet, including at least five servings of fruit and vegetables per day, is associated with a decreased incidence of cardiovascular disease in epidemiologic studies.
- There is no evidence to support the routine use of antioxidant vitamins for primary or secondary prevention of cardiovascular disease.
- Vitamin E has no impact on cardiovascular morbidity and mortality, but may adversely affect lipid concentrations when used at higher doses. Whether this is clinically significant remains to be elucidated.
- Beta carotene is associated with an increased risk of all-cause mortality and cardiovascular death in both primary and secondary prevention studies and, thus, its use should be actively discouraged.
- It remains unclear whether supplementation with folic acid and vitamins B6 and B12 to lower serum homocysteine levels will decrease cardiovascular morbidity and mortality. Further study is needed.

RCTs.¹² HPS, formally classified as a secondary prevention trial, looked at over 7,000 patients with no evidence of coronary disease prior to randomization, and found no evidence of benefit over five years.¹¹ We have outcome data with antioxidant regimens as long as 12 years and, thus, we likely do not need any further primary prevention studies.¹²

Is there any potential harm in supplementing with vitamin E?

It takes extremely high doses of vitamin E (1200 mg a day) to produce adverse effects, including nausea, diarrhea, headache, and gonadal dysfunction.¹³ More importantly for patients at risk for cardiovascular disease, HPS showed a small, but definite increase in triglyceride and LDL cholesterol (LDL-C) levels in patients receiving antioxidants.¹¹ In a study looking at the effect of a statin and niacin combination on cholesterol levels,

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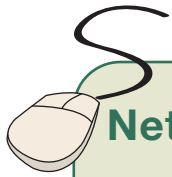
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the addition of antioxidant vitamins significantly blunted the ability of these agents to raise the beneficial high density lipoprotein cholesterol (HDL-C) subfraction (25% versus 18% increase in HDL-1-C at 1 year, $p=0.057$, 42% versus 0% increase in HDL-2-C at 1 year, $p=0.007$).¹⁴ Although this relationship needs to be better elucidated, it appears that routine antioxidant supplementation may have a detrimental effect on the serum cholesterol profile.

Have we looked at the correct type and dose of an antioxidant regimen?

Most experts agree that although vitamins obtained through a balanced diet are important, to adequately assess the effect of a nutrient in a study, it needs to be taken in a purified supplement form. There has been considerable controversy about what doses of antioxidant vitamins are optimal. HPS dealt with this by actually measuring the serum concentrations of the various vitamins.¹¹ They showed a fourfold increase over placebo in beta carotene, a twofold increase in vitamin E, and a one-third increase in vitamin C. Despite these high serum concentrations, there was still no impact on mortality


What about homocysteine and folic acid?

Homocysteine is an amino acid, and serum levels above 10 $\mu\text{mol/L}$ have been associated with an increased risk of cardiovascular disease.¹⁵ Supplementation with folic acid, in combination with vitamin B12, has been shown to decrease serum homocysteine levels.¹⁵ The Swiss Heart Study looked at 553 patients with predominantly normal baseline homocysteine levels (only 29% had mild elevations $> 12 \mu\text{mol/L}$) that had successful angioplasty of at least one significant ($\geq 50\%$) coronary stenosis, and were randomized to either a combination of folate and vitamins B6 and B12 or placebo.¹⁶ At one year, there was a significant 7.4% absolute risk reduction ($p=0.03$) in the composite end point of death, nonfatal myocardial infarction, and the need for repeat revascularization. This was primarily due to a reduced rate of target lesion revascularization (9.9% versus 16.0%, $p=0.03$). In contrast, the results of the Folate After Coronary Intervention Trial (FACIT) are dramatically different, and were recently presented at the American College of Cardiology's Annual Scientific Sessions. A total of 626 patients treated with folate and vitamins B6 and B12, after successful coronary stenting, were found to have higher rates of restenosis, and target vessel revascularization at their six-month followup than those randomized to placebo.

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At present, we only have observational trials looking at folic acid and vitamins B6, and B12. With conflicting results, caution is warranted until appropriately powered RCTs are completed. The HOPE study–2, looking at folate and vitamins B6 and B12 in the 9,500 high-risk HOPE trial patients, will be presented this November at the American Heart Association Scientific Sessions, and should provide us with some much needed answers. 

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For cases on vitamin supplements, please see page 15.

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