

Comment on the *Lancet* Article “Use of Vitamins for the Prevention of Cardiovascular Disease”

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The June 14, 2003 issue of the *Lancet* medical journal contained an article (pages 2017-2023), authored by members of the Department of Cardiovascular Medicine at the Cleveland Clinic, that reviewed seven randomized, prospective trials of vitamin E treatment and eight of beta-carotene.¹ All of the selected trials included a minimum of 1000 patients. The vitamin E dosage ranged from 50 IU to 800 IU and the beta-carotene dosage ranged from 15 mg to 50 mg. Only one of the selected trials evaluated the use of vitamin E in primary prevention of cardiovascular disease, while the rest assessed secondary prevention or patients not at risk. This review concluded that “...the lack of a salutary effect was seen consistently for various doses of vitamins in diverse populations. Our results, combined with the lack of mechanistic data for efficacy of vitamin E, do not support the routine use of vitamin E.”

Was the meta-analysis biased toward secondary prevention studies, which tend to have different outcomes?

The timing of vitamin E administration is a very important factor to take into consideration. It is becoming increasingly accepted among experts in the field that antioxidant vitamins are more effective in inhibiting the early stages of atherosclerosis, such as fatty streak formation, rather than the later stages of the disease.² Given that only one of the randomized trials was a primary prevention trial with vitamin E alone and that this study had a modestly positive outcome, it may be that the conclusions were heavily biased toward the null results of the secondary prevention studies in which subjects had already been diagnosed with serious disease.

As was pointed out in the article, “...in all animal studies in which a significant antiatherosclerotic effect of vitamin E has been reported, the vitamin E was started at the time of high-fat diet or before any histological evidence of neointimal or fatty-streak formation.”

Was the breadth of research on antioxidants evaluated?

The majority of the clinical trials chosen for review on the role of vitamin E in cardiovascular disease prevention indicated that vitamin E was not harmful, only it did not have a statistically significant positive impact. This observation seems to contradict the previously published epidemiological studies on the relationship between antioxidant vitamin consumption and cardiovascular disease, as well as animal studies in which vitamin E has been shown to be antiatherogenic and prevent fatty streak formation. For example, Stampfer et al. reported a nearly 50% lower incidence of heart disease in men and women who consumed the highest level of vitamin E in their diet versus those who consumed the lowest.³ Losonczy et al. reported that individuals who supplemented with

vitamin E and C had more than a 35% lower incidence of cardiovascular disease than those who did not supplement their diet with these antioxidant vitamins.⁴ A number of other studies suggest that vitamin E protects against increased risk of cardiovascular disease, perhaps through its ability to suppress oxidative action and reduce pulmonary endothelial dysfunction.⁵⁻⁷

Were the subjects in the studies stratified for baseline levels of oxidative stress?

Another important feature of these studies was that they did not stratify the patients for any known risk factors for potential oxidative stress, including C-reactive protein levels, homocysteine, serum lipid peroxides, apo E4 genotype, serum isoprostane levels, or 8-hydroxy-deoxyguanosine levels. There is evidence accumulating that the people who might benefit most from antioxidant supplementation are those people who have the highest baseline oxidative stress.⁸

What about beta-carotene?

The conclusion of the beta-carotene trials are more clear cut in that it appears that supplementing with beta-carotene alone does not offer protection against cardiovascular disease and cancer, and may actually increase these risks in some people. This seems to be a result of the fact that when beta-carotene supplements are taken alone, they can be easily damaged through oxidative enzymes. The “injured” beta-carotene results in abnormal signal transduction and the up-regulation of growth factors associated with altered cellular proliferation.⁹

Many studies done in the 1980's and 1990's used synthetic all-trans beta-carotene alone—rather than a naturally derived form—including the Finnish study in 1994 which reported a slight increase in lung cancer mortality with supplementation. Another important point from this study is that a cohort given vitamin E in combination with synthetic beta-carotene did not demonstrate an increase in cancer incidence.¹⁰ Research suggests that balanced intake of antioxidants and other protective nutrients, such as alpha-carotene and vitamin E, helps to reduce cancer and cardiovascular disease risk.¹¹⁻¹³ Thus, as I have stated before in other articles, it is suggested from all the intervention trials done with beta-carotene that it should be part of a complex antioxidant mixture, rather than a stand-alone synthetic supplement, to protect it from oxidative injury and enhance cellular oxidative defenses.^{11,14,15}

Was this summary justified from the data reviewed?

Another point of concern is the suggestion in the conclusion that “the lack of a salutary effect was seen consistently for various doses of vitamins....” It is important to point out that the meta-analysis done for this paper was only for selected intervention trials with vitamin E and beta-carotene. It does not cover all vitamins or minerals in its analysis. For instance, the ongoing research that suggests folate, vitamin B12, vitamin B6, and betaine help prevent heart disease in people with hyperhomocysteinemia was not included in this meta-analysis.

Should a person supplement their diet with vitamin E given the results of the intervention trials?

According to authorities in the field, such as William Pryor, PhD of Louisiana State University, Balz Frei, PhD of the Linus Pauling Institute of Science and Medicine, and Walter Willett, MD of Harvard University School of Medicine, the evidence still indicates that vitamin E is an important fat-soluble antioxidant, and there is suggestive evidence that when supplementation is started early it can help in cardiovascular disease prevention.^{2,16,17} There may be other potential benefits to antioxidant supplementation, such as cancer prevention, that might tip the balance toward advantages with vitamin E supplementation even further.¹¹ It is also emerging that specific individuals might have a much greater response to antioxidant supplementation than others, depending upon their oxidant stress status. Lastly, it is becoming more apparent that a balanced mixture of antioxidant nutrients might be more useful than taking a single antioxidant supplement.

Given this analysis and opinions of experts in the field, the conclusion in the *Lancet* article which states, "...we do not support the continued use of vitamin E treatment and discourage the inclusion of vitamin E in future primary and secondary prevention trials..." seems unduly strong and unwarranted. This conclusion seems out of perspective due to the fact that: 1) reports of safety concerns are lacking; 2) there is published clinical information suggesting that vitamin E does provide health benefits, and may be particularly beneficial in individuals with increased oxidative stress and when supplementation is started early; and 3) the meta-analysis was based on a select group of studies.

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