Vitamin E: As in *E*ffective?

EVIDENCE MATTERS

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A not-uncommon conversation with a patient:

Doctor: Are you taking any medications?

Patient: No.

Doctor: Do you take any herbs, supplements, or vitamins?

Patient: Well, I take St. John's wort. And of course, 800 units of vitamin E every day.

Vitamin E seems to have practically become a standard among my patients. This week I heard Dr. Zorba Paster endorse its use during his popular call-in public radio talk show, Zorba Paster on Your Health. A wellness newsletter from the University of California at Berkeley and academic cardiologists at continuing medical education presentations have encouraged its use. The *New England Journal of Medicine* has published correspondence encouraging widespread use.[1] But does it work?

In this Evidence Matters, I review the three randomized trials of high-dose vitamin E for secondary prevention of coronary heart disease: CHAOS (Cambridge Heart Antioxidant Study, GISSI (Gruppo Italiano per lo Studio della Spravivenza nell'Infarto Miocardio), and HOPE (Heart Outcomes Prevention Evaluation). The enthusiasm for vitamin E use was fueled by the publication of the CHAOS results 4 years ago. After a rather short follow-up period, nonfatal myocardial infarction (MI) was reduced in patients assigned to vitamin E. Of patients receiving vitamin E, 1.4% had an MI compared with 4.2% of those receiving placebo. These results seem phenomenal if reported as a reduction in relative risk (RR) (77% lower risk with vitamin E use). However, it has been shown that focusing on RR reduction promotes acceptance of therapies more than when absolute risk benefits are reported.[2, 3] So, note carefully that fewer than 3% of patients seemed to have been spared an infarction. Finally, one of the tenets of evidence-based medicine is that all relevant outcomes must be examined. In this regard, CHAOS falls short of confirming vitamin E's benefit: It failed to positively impact mortality. For these reasons, the CHAOS results were actually inconclusive. Nonetheless, the impressive RR reduction for MI associated with vitamin E use in CHAOS was, I believe, a factor in the increasing popularity of vitamin E supplementation.

Thanks to the GISSI and the HOPE investigators, in the past year we have been given data that are more conclusive. These trials included more patients, lasted longer, and reported a larger number of events. Unfortunately, the magic bullet—a vitamin supplement that would provide a simple, easy way to improve heart disease outcomes—has remained elusive. The GISSI investigators, in contrast to the CHAOS investigators, found no effect whatsoever on nonfatal cardiovascular events. Furthermore, despite including twice as many patients as the CHAOS investigators, they found no mortality benefit from vitamin E. The HOPE study used the more rigorous placebo-controlled, double-blind trial design, and again, vitamin E conferred no benefit.

These results are important for two reasons. First, with more and more effective secondary prevention strategies for atherosclerotic disease, it is becoming increasingly important for patients not to be distracted by useless strategies. Some

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patients may be more motivated to adopt healthier lifestyles, for example, if they understand that vitamin E is not a shield that can protect them from cardiac disease. For others, having one less medication can only help them adhere to the several drugs from which they can benefit.

Second, the results provide another reminder that more treatment is not necessarily better. Even though vitamin E supplementation may be appealing because it is "natural" and simple, it is simply ineffective.

References

1 O'Keefe JH Jr, Lavie CJ. Vitamin E and the risk of coronary disease. N Engl J Med. 1993;329:1425.

2 Bucher HC, Weinbacher M, Gyr K. Influence of method of reporting study results on decision of physicians to prescribe drugs to lower cholesterol concentration. BMJ. 1994;309:761-4.

3. Naylor CD, Chen E, Strauss B. Measured enthusiasm: does the method of reporting trial results alter perceptions of therapeutic effectiveness? Ann Intern Med. 1992;117:916-21.

CHAOS

Stephens NG, Parsons A, Schoffield PM, et al. Randomized controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). Lancet. 1996;347:781-86.

OBJECTIVE. To determine whether treatment with high-dose vitamin E reduces the risk for MI and cardiovascular death in patients with established ischemic heart disease.

DESIGN. Double-blind, placebo-controlled, single-center, randomized trial.

PATIENTS. Patients were included if they had angiographically proven coronary atherosclerosis and had not used vitamin E supplements.

INTERVENTION. Patients were assigned to receive either 800 IU or 400 IU of vitamin E or placebo.

RESULTS. Median follow-up was 1.4 years. It should be noted that the treatment and the placebo groups differed significantly at baseline in five characteristics. This suggests that the randomization process failed to produce equivalent groups. Treatment with vitamin E was associated with a reduced risk for nonfatal MI, and because of the reduction in MI, a reduced risk for nonfatal MI or cardiovascular death. Cardiovascular death was slightly higher in the vitamin E group. Use of vitamin E was associated with a nonsignificant increase in risk for death from any cause. **Table 1** shows the key results.

CONCLUSIONS. In this study of patients with documented coronary artery disease, treatment with vitamin E was associated with fewer nonfatal MIs. However, neither cardiovascular deaths nor deaths from any cause were reduced in patients assigned to vitamin E. The number of patients who had an event was small, the duration of follow-up was short, and there were significant baseline differences between the groups. This trial provides only suggestive evidence of benefit from vitamin E and does not support an association between vitamin E and a reduced risk for cardiovascular death.

GISSI

GISSI Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Lancet. 1999;354:447-55.

OBJECTIVE. To determine the effects of vitamin E and n-3 polyunsaturated fatty acids on morbidity and mortality after an MI. (Only the effects of vitamin E are reviewed here.)

DESIGN. Multicenter, open-label, randomized, controlled trial.

PATIENTS. Patients who had had an MI within 3 months, had no contraindications to study medications, and did not have a poor short-term prognosis (e.g., overt heart failure).

INTERVENTION. There were 5660 patients randomly assigned to receive 300 mg/day of vitamin E, and 5664 controls did not.

RESULTS. Dietary intake of fish, fruit, vegetables, and olive oil as well as use of cardiovascular medications, including aspirin, β-blockers, angiotensive-converting enzyme inhibitors, and cholesterol-lowering drugs, were equivalent among the groups throughout the study. Vitamin E supplementation was not associated with a significant reduction in fatal events, nonfatal cardiovascular events, or the combination of fatal and nonfatal events. The most important results are shown in **Table 2**.

CONCLUSIONS. Vitamin E, 300 mg daily, used as secondary prevention after an MI was not beneficial. Patients can safely be advised to avoid vitamin E supplementation.

HOPE

The Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Vitamin E supplementation and cardiovascular events in high-risk patients. N Engl J Med. 2000; 342:154-60.

OBJECTIVE. To evaluate whether a high dose of vitamin E would reduce adverse cardiovascular outcomes in patients at high risk for such events.

DESIGN. Multicenter, placebo-controlled, double-blind, randomized trial.

PATIENTS. Patients were included if they were at least 55 years of age; had a history of coronary artery disease, stroke, or peripheral vascular disease; or had diabetes and at least one other risk factor (hypertension, elevated total cholesterol levels, low high-density lipoprotein cholesterol levels, a smoking habit, or microalbuminuria).

INTERVENTION. Patients were assigned to receive either 400 IU of vitamin E from natural sources or placebo each day for 4 to 6 years.

RESULTS. Mean follow-up was 4.5 years. Patients taking vitamin E had no reduction in any primary outcome (stroke, MI, death from a cardiovascular cause, or the composite of these outcomes). All-cause mortality was not reduced in patients taking vitamin E. See **Table 3** for the key results.

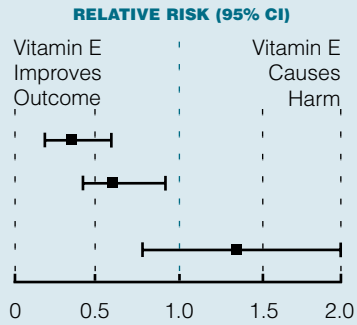
Furthermore, vitamin E did not reduce the incidence of secondary outcomes: hospitalizations for unstable angina, hospitalization for heart failure, revascularizations or limb amputations, new-onset angina, and microvascular diabetic complications. No outcome showed any trend toward benefit from vitamin E.

CONCLUSIONS. In a population at increased risk for adverse cardiovascular outcomes, daily intake of highly bioavailable vitamin E, 400 IU/day, conferred no benefit. Patients can be advised that vitamin E intake does not reduce cardiovascular events and can safely be avoided.

TABLE 1

CHAOS Data*

OUTCOME	VITAMIN E GROUP (*n* = 1035)	PLACEBO GROUP (*n* = 967)
Nonfatal myocardial infarction	1.4%	4.2%
Cardiovascular death or myocardial infarction	4.0%	6.6%
Any death	3.5%	2.7%

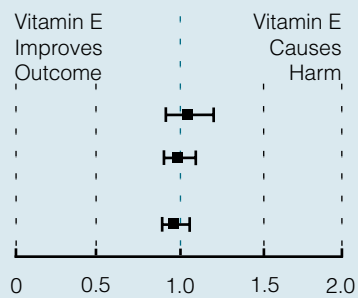


**CHAOS = Cambridge Heart Antioxidant Study.*

TABLE 2

GISSI Data*

OUTCOME	VITAMIN E GROUP (*n* = 5660)	CONTROL GROUP (*n* = 5664)
Nonfatal cardiovascular event	5.2%	5.0%
Cardiovascular death, myocardial infarction, or stroke	10.1%	10.3%
Any death	8.6%	9.3%

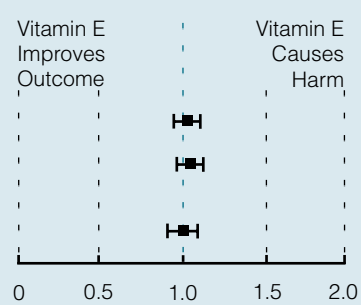


**GISSI = Gruppo Italiano per lo Studio della Spravivenza nell'Infarto Miocardio*

TABLE 3

HOPE Data*

OUTCOME	VITAMIN E GROUP (*n* = 4761)	PLACEBO GROUP (*n* = 4780)
Myocardial infarction	11.2%	11.0%
Cardiovascular death, myocardial infarction, or stroke	16.2%	15.5%
Any death	11.2%	11.2%



**HOPE = Heart Outcomes Prevention Evaluation.*