Vitamin E did not reduce myocardial infarction, death, or stroke in adults at high risk for cardiovascular events

The Heart Outcomes Prevention Evaluation Study Investigators. **Vitamin E supplementation and cardiovascular events in high-risk patients.** N Engl J Med. 2000 Jan 20;342:154-60.

QUESTION

In adults who have a high risk for cardiovascular events, do vitamin E supplements improve cardiovascular outcomes?

DESIGN

Randomized {allocation concealed*}†, blinded {patients, clinicians, and outcome assessors}‡,* placebo-controlled trial with a 2 × 2 factorial design and a mean follow-up of 4.5 years (Heart Outcomes Prevention Evaluation [HOPE] study).

SETTING

{161 centers in North America, 76 in 14 western European countries, and 30 in Argentina and Brazil.}‡

PATIENTS

9541 patients (mean age 66 y, 73% men) who were {≥ 55 years of age and had a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes and ≥ 1 other cardiovascular disease risk factor. Exclusion criteria were heart failure, ejection fraction < 0.4, use of an angiotensin-converting enzyme inhibitor or vitamin E, uncontrolled hypertension, nephropathy, or myocardial infarction (MI) or stroke in the previous 4 weeks. Follow-up was 99.9%.}‡

INTERVENTION

Patients were allocated to 1 of 4 groups: ramipril and vitamin E; ramipril and placebo; vitamin E and placebo; or placebo alone. 4761 adults were assigned to vitamin E and 4780 to placebo. Doses were 10 mg/d of ramipril and 400 IU/d of vitamin E .

MAIN OUTCOME MEASURES

Combined outcome of MI, stroke, or death from cardiovascular causes. Secondary outcomes included all-cause mortality.

MAIN RESULTS

Vitamin E and placebo groups did not differ for any outcome (Table).

CONCLUSION

In adults at high risk for cardiovascular events, vitamin E, 400 IU/d, did not reduce myocardial infarction, stroke, or death.

Sources of funding: Medical Research Council of Canada; Natural Source Vitamin E Association; Negma; Hoechst-Marion Roussel; AstraZeneca; King Pharmaceuticals; Heart and Stroke Foundation of Ontario.

For correspondence: Dr. S. Yusuf, Canadian Cardiovascular Collaboration Project Office, Hamilton General Hospital, 237 Barton Street East, Hamilton, Ontario L8L 2X2, Canada. FAX 905-521-1166. ■

*See Glossary.

†**The HOPE Study Investigators.** Can J Cardiol.1996;12:127-37.

‡**The Heart Outcomes Prevention Evaluation Study Investigators.** N Engl J Med. 2000;342:145-53.

Vitamin E vs placebo for adults at high risk for cardiovascular events§

Outcomes at mean 4.5 y	Vitamin E	Placebo	RRI (95% CI)	NNH
Myocardial infarction, stroke, or cardiovascular mortality	16%	15%	5% (–4 to 15)	Not significant
Cardiovascular mortality	7.1%	6.9%	5% (–10 to 21)	Not significant
Myocardial infarction	11.2%	11.0%	2% (–9 to 14)	Not significant
Stroke	4.4%	3.8%	17% (–4 to 42)	Not significant
All-cause mortality	11%	11%	0% (–11 to 12)	Not significant

§Abbreviations defined in Glossary; RRI, NNH, and CI calculated from data in article.

COMMENTARY

Research linking low-density lipoprotein (LDL) oxidation with atherogenesis led to expectations that antioxidant supplements would reduce cardiovascular disease. The HOPE study is yet another large, randomized, controlled trial that fails to show any cardiovascular benefit from antioxidants (1, 2). Although a single tertiary prevention trial found that vitamin E reduced the risk for nonfatal MIs, results were challenged because supplements were taken for a relatively short time, treatment groups were not comparable at baseline, and cardiovascular mortality risk was unaffected (3).

Why was vitamin E not effective for the high-risk patients in the HOPE study? Healthy adults receiving 400 IUs of vitamin E can substantially increase plasma antioxidant levels and inhibit LDL oxidation. However, patients with existing disease may need higher doses because of increased oxidative stress. Another possibility is that longer-term antioxidant treatment is required, although an observational study found that 2 years of supplemental intake was sufficient to lower the risk for coronary disease (1). Ongoing trials are also looking at combinations of antioxidants, which may be more effective than a single supplement (1). Furthermore, several of these trials address potential sex differences in outcomes by enrolling only women; women made up just 27% of the HOPE study participants.

How should antioxidants be used in practice? Vitamin E is clearly safe, but no conclusive evidence exists to show that supplements reduce cardiovascular disease. While awaiting results from ongoing trials, providers should encourage patients to eat fruits and vegetables and to continue with proven strategies to prevent cardiovascular disease.

Richard M. Hoffman, MD, MPH
Albuquerque Veterans Affairs Medical Center
Albuquerque, New Mexico, USA

References

1. **Jha P, Flather M, Lonn E, Farakouh M, Yusuf S.** The antioxidant vitamins and cardiovascular disease. A critical review of epidemiologic and clinical trial data. Ann Intern Med. 1995;123:860-72.
2. **GISSI-Prevenzione Investigators.** Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet. 1999;354:447-55.
3. **Stephens NG, Parsons A, Schofield PM, et al.** Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). Lancet. 1996;347:781-6.

