

## Further Insight into the Vitamin E Debate

Hayden KM, Welsh-Bohmer KA, Wengreen HJ, et al. Risk of mortality with vitamin E supplements: The Cache County Study. *Am J Med* 2007;120:180–4.

### Study Overview

**Objective.** To determine whether increased mortality risks seen in a recent meta-analysis [1] with use of vitamin E are associated with the presence of cardiovascular disease (CVD).

**Design.** Prospective, population-based cohort study.

**Setting and participants.** 4416 persons aged  $\geq 65$  years residing in Cache County, UT, who completed interviews at baseline and at 3 years regarding history of illness, including hypertension, hypercholesterolemia, diabetes, stroke, coronary artery bypass graft (CABG) surgery, or myocardial infarction (MI), and current use of medications and nutritional supplements. Use of vitamin E was noted if the participant reported using at least 4 doses of  $\geq 400$  IU vitamin E per week. The patient population was as follows: patients with no CVD and not taking vitamin E,  $n = 2318$ ; patients with no CVD and taking vitamin E,  $n = 254$ ; patients with any CVD and taking vitamin E,  $n = 172$ ; patients with any CVD and not taking vitamin E,  $n = 1672$ .

**Main outcome measures.** Relationship between vitamin E use, history of CVD, and all-cause mortality.

**Main results.** After adjusting for age and sex, there was no relationship between vitamin E use and mortality (adjusted hazard ratio [HR], 0.93 [95% confidence interval {CI}, 0.74–1.15]). Overall predictors of death included a history of diabetes, stroke, CABG surgery, or MI and use of warfarin, nitrates, or diuretics. Statistical models with and without adjustments for these clinical factors did not alter the overall relationship between vitamin E use and mortality. However, mortality rates were higher among vitamin E users who had a history of stroke (adjusted HR, 3.64 [95% CI, 1.73–7.68]), CABG surgery (adjusted HR, 4.40 [95% CI, 2.83–6.83]), or MI (adjusted HR, 1.95 [95% CI, 1.29–2.95]) and, independently, in those taking nitrates (adjusted HR, 3.95 [95% CI, 2.04–7.65]), warfarin (adjusted HR, 3.71 [95% CI, 2.22–6.21]), or diuretics (adjusted HR, 1.83 [95% CI, 1.35–2.49]). Patients with no comorbidities who used vitamin E had slightly lower mortality rates compared with healthy patients who did not use vitamin E, although these differences were not statistically significant.

**Conclusion.** Across the study population, vitamin E was not directly related to mortality risk. However, this may have been the result of a slightly increased mortality risk in vitamin E users with CVD and a slightly reduced mortality risk in vitamin E users without CVD.

### Commentary

The role of vitamin supplementation in preventing disease has been of interest for decades. Clinicians have hypothesized that higher doses of vitamins, especially “antioxidants,” may potentially prevent certain conditions such as heart disease. Unfortunately, most clinical trials have found little benefit from the use of antioxidant vitamins, such as vitamin E. A recent meta-analysis of randomized trials suggested that patients who took vitamin E at doses of 400 IU or more each day were at increased risk of death [1]. Despite these results, the attraction to vitamins remains.

The latest debate is whether vitamin E supplementation is helpful in patients who are at high risk for heart disease or cancer or who already have these conditions. Some argue that vitamin E is unlikely to benefit healthy patients if it is not helpful in high-risk patients, while others argue that because vitamins are most helpful in preventing disease, patients who already have conditions such as heart disease are unlikely to benefit from vitamin supplementation. The cohort study by Hayden and colleagues offers some insight into this debate. This study clearly demonstrated that among those with established CVD, especially in patients with a history of stroke, CABG surgery, or MI, vitamin E is harmful. However, the study also suggested that vitamin E may prevent death among healthy patients. A major limitation of the study is in its design. Because this was a cohort study, use of vitamin E was selected by the individual patient. Data from previous studies suggest that health-conscious patients are more likely to use vitamins, and this may account for the slightly lower mortality rates among healthy vitamin E users in this study.

### Applications for Clinical Practice

This study adds to the existing data that vitamin E is harmful in patients with established heart disease or those at high risk for developing this condition. There may be some benefits of vitamin E supplementation in healthy patients, but the limitations of the data make this finding less reliable.

Before vitamin E is recommended to healthy individuals, a large randomized trial of vitamin E supplementation limited only to healthy subjects is needed.

—Review by Ashish K. Jha, MD, MPH

### Reference

1. Miller ER 3rd, Pastor-Barriuso R, Dalal D, et al. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 2005;142:37–46.

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