# Vitamin E reduced secondary cardiovascular disease events in patients receiving long-term hemodialysis

Boaz M, Smetana S, Weinstein T, et al. **Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): randomised placebo-controlled trial.** Lancet. 2000 Oct 7; 356:1213-8.

### QUESTION

In patients receiving long-term hemodialysis, does vitamin E reduce secondary cardiovascular disease (CVD) events?

### DESIGN

Randomized (allocation concealed*), blinded (patients and outcome assessors),* controlled trial with median follow-up of 519 days (range 10 to 763 d).

### SETTING

5 dialysis centers in Israel.

### PATIENTS

196 patients (mean age 65 y, 69% men) with CVD (myocardial infarction [MI], ischemic stroke [IS], angina pectoris, transient cerebral ischemia, or peripheral vascular disease [excluding arteriovenous fistulas]) who were stable on hemodialysis. Exclusion criteria included anticoagulant therapy with warfarin, malignant disease, pregnancy, or treatment with a hypolipemic agent ≤ 8 weeks before study inception. Follow-up was 100%.

### INTERVENTION

After stratification by sex and age, patients at each center were allocated to 800 IU of vitamin E to be taken at night ($n$ = 97) or to placebo ($n$ = 99).

### MAIN OUTCOME MEASURES

Composite outcome of MI (fatal and nonfatal), unstable angina, IS, or peripheral vascular disease in a previously unaffected limb (excluding arteriovenous fistulas). Secondary outcome measures were individual composite outcomes, CVD mortality (fatal MI, fatal IS, or sudden death), and all-cause mortality.

### MAIN RESULTS

All-cause mortality was 31% in the vitamin E group and 29% in the placebo group ($P$ = 0.7). CVD mortality (including sudden death) was 9% in the vitamin E group and 15% in the placebo group ($P$ = 0.25). Fewer total CVD events and MIs occurred in the vitamin E group than in the placebo group (Table).

### CONCLUSION

Vitamin E reduced the composite end point of fatal and nonfatal myocardial infarction, fatal and nonfatal ischemic stroke, unstable angina, or peripheral vascular disease in previously unaffected limbs (excluding arteriovenous fistulas) in patients with cardiovascular disease who were receiving long-term hemodialysis.

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*See Glossary.

**Vitamin E vs placebo for total cardiovascular disease (CVD) events† and myocardial infarction (MI) in patients receiving long-term hemodialysis‡**

| Outcomes at 700 d | Vitamin E | Placebo | RRR (95% CI) | NNT (CI) |
|---|---|---|---|---|
| CVD events | 19% | 34% | 46% (12 to 67) | 6 (4 to 29) |
| MI | 8% | 18% | 55% (3 to 79) | 10 (5 to 230) |

†CVD events = the composite end point of MI, ischemic stroke, unstable angina, or peripheral vascular disease in previously unaffected limbs (excluding arteriovenous fistulas).
‡Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

## COMMENTARY

In their study, Boaz and colleagues note that their findings were consistent with the results of the Cambridge Heart Antioxidant Study (CHAOS) (1) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio (GISSI) (2) trials. The CHAOS study randomly allocated 2002 patients with angiographically proven coronary atherosclerosis to receive vitamin E (400 or 800 IU/d) or placebo. Although nonfatal MI was reduced by 73%, overall CVD mortality was not significantly decreased in the vitamin E group. The GISSI study randomized 11 324 patients after MI using a 2 × 2 factorial design with vitamin E (300 mg/d) and n-3 polyunsaturated fatty acids. Vitamin E was associated with a significant risk reduction for CVD deaths but only in a 4-way analysis. The authors concluded that vitamin E was not beneficial for their primary end point of death, nonfatal MI, or stroke. Similarly, the HOPE study (3), which enrolled nearly 10 000 patients with CVD risk factors, found that vitamin E supplements (400 IU/d) had no effect on the combined end point of CVD death, stroke, or myocardial infarction. No conclusive evidence exists from these 3 studies to show that vitamin E supplements reduce the risk for secondary CVD events.

However, patients with prevalent CVD who need long-term hemodialysis may be more likely to benefit from antioxidant supplements because they have increased oxidative stress and excess CVD mortality. The Secondary Prevention with Antioxidants of Cardiovascular Disease in Endstage Renal Disease (SPACE) study results are encouraging, but the trial had a follow-up of < 2 years and was small: The 46% relative risk reduction with vitamin E supplements represented only 16 fewer CVD events. The authors appropriately recommend a larger trial with sufficient power to evaluate risk reduction for CVD death and fatal and nonfatal MIs.

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***References***

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