The role of vitamin E in the prevention of coronary events and stroke: meta-analysis of randomized controlled trials

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CRD summary
This review evaluated vitamin E supplements for the prevention of heart attacks and stroke. No effects were seen for most of the outcomes investigated, except for a small reduction in nonfatal heart attacks when vitamin E supplements were given to people with pre-existing heart disease. The authors' conclusions that vitamin E supplements are cost-effective and safe may be overstated.

Authors' objectives
To evaluate the role of vitamin E supplements in the prevention of coronary events and stroke in adults.

Searching
MEDLINE, EMBASE and the Cochrane Controlled Trials Register were searched from inception to March 2004; the search terms were reported. SciSearch was also searched for additional articles, as were the reference lists of review articles and identified trials. No language restrictions were applied.

Study selection

Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies that investigated oral vitamin E (tablet or capsule form), alone or with other supplements, compared with a placebo or other control group, were eligible for inclusion. The included studies administered vitamin E at doses ranging from 50 to 600 mg/day, or 400 to 800 IU/day. The comparators in the included studies were beta-carotene, placebo, polyunsaturated fatty acids and aspirin. Vitamin E was combined with beta-carotene, vitamin C, polyunsaturated fatty acids, multiple vitamins and minerals, or aspirin. The duration of the studies ranged from 510 days to 6.1 years.

Participants included in the review
Studies of adult (18 years or older) males or females, with or without risk factors for or existing cardiovascular disease (CVD), were eligible for inclusion. Most of the included studies enrolled patients with existing CVD or at high risk of CVD. About 18% of the participants in the included studies were women.

Outcomes assessed in the review
Studies were included in the review if they assessed one of the primary or secondary outcomes: total myocardial infarction (MI), fatal or nonfatal MI (primary outcomes), total stroke, ischaemic or haemorrhagic stroke, total cardiovascular mortality, or total mortality (secondary outcomes).

How were decisions on the relevance of primary studies made?
Two reviewers assessed studies independently for inclusion. Any disagreements were resolved by consensus, with a third reviewer providing arbitration.

Assessment of study quality
The validity of each trial was rated according to the following: adequacy of allocation concealment; randomisation method; rate of follow-up; whether all patients were accounted for in the final analysis; whether the patients were analysed in the groups to which they had been assigned; and whether the outcome assessment was blinded. Two
reviewers assessed the validity of each trial independently. Any disagreements were resolved by consensus, with a third reviewer providing arbitration.

**Data extraction**
Two reviewers extracted the data independently. Any disagreements were resolved by consensus, with a third reviewer providing arbitration. The numbers of events in each group were used to calculate the relative risk (RR) and risk difference (RD) for the outcomes assessed in each primary study.

**Methods of synthesis**
How were the studies combined?
The studies were combined in a meta-analysis using a fixed-effect model. The pooled RR and RD were calculated, with 95% confidence intervals (CIs). If there was significant between-study heterogeneity (see below), a random-effects model was used to pool study effects. If the RD was statistically significant, the number-needed-to-treat (NNT) or number-needed-to-harm were also calculated.

How were differences between studies investigated?
The chi-squared test was used to identify between-study heterogeneity, with a P-value of less than 0.10 indicating statistically significant heterogeneity. Subgroup analyses were performed for vitamin E alone, vitamin E in combination with other supplements, and for primary and secondary prevention trials.

**Results of the review**
Nine RCTs (n=80,645) were included.

Seven of the nine included RCTs were rated ‘A’ for quality, with the other two rated ‘B’. Blinding and intention-to-treat analysis were considered adequate in all studies.

Vitamin E alone versus control.
No statistically significant effect was seen on any of the included outcomes.

Vitamin E combined with other supplements versus control.
No statistically significant effect was seen on any of the included outcomes.

Subgroup analyses.
No statistically significant effect of vitamin E was seen in primary prevention studies. In secondary prevention studies, no statistically significant reduction was seen in any outcome except nonfatal MI (3 studies, n=3,102): pooled RR 0.51 (95% CI: 0.38, 0.70), RD -0.03, NNT 33. There was significant heterogeneity in this outcome (P=0.085). However, the effect was still significant when a random-effects model was used: RR 0.46 (95% CI: 0.25, 0.84).

Post-hoc analyses identified significant effects of high-dose (300 IU/day or more) and natural vitamin E on the risk of nonfatal MI. There was no statistically significant difference between groups in haemorrhagic events or gastrointestinal bleeding in the studies which reported these outcomes.

**Authors' conclusions**
Vitamin E supplementation resulted in a 3% absolute reduction in nonfatal MI in patients with pre-existing coronary artery disease, but was not associated with a decrease in total cardiovascular or all-cause mortality. Prophylactic use of vitamin E was not associated with serious adverse effects. The use of vitamin E for the secondary prevention of nonfatal MI was shown to be cost-effective and safe.
CRD commentary
This review had clearly stated inclusion criteria relating to the review question, and a comprehensive literature search was conducted with no language restrictions. Unpublished studies were eligible for inclusion and were sought, although only published studies were included. Publication bias was not assessed, so it was unclear whether any studies might have been missed. The review was carried out in such a way as to minimise bias and errors, with two reviewers independently selecting studies for inclusion, assessing validity and extracting the data. The meta-analysis seems appropriate. However, the authors’ conclusions that vitamin E was not associated with serious adverse effects and that its use was cost-effective were not supported by the evidence presented in the review: cost-effectiveness was not assessed and, as the review authors stated themselves, adverse events were often not reported. Therefore, while the results of the review may be sound, these conclusions should be viewed with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that future RCTs testing the efficacy of vitamin E supplements should use high-dose vitamin E from natural sources.

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