Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials

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CRD summary
This review assessed the effects of antioxidant vitamins on long-term cardiovascular outcomes. The authors concluded that the routine use of vitamin E cannot be recommended, and that the use of vitamin supplements containing beta-carotene should be actively discouraged. The authors’ conclusions appear to be reliable, but the limited search means that some relevant studies might have been missed.

Authors' objectives
To assess the effects of antioxidant vitamins on long-term all-cause mortality and cardiovascular death.

Searching
MEDLINE was searched; the search terms were given. In addition, reviews and bibliographies of identified studies were screened.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with at least 1,000 patients were eligible for inclusion.

Specific interventions included in the review
Studies of vitamin E, beta-carotene, or both combined, for the primary or secondary prevention of cardiovascular disease were eligible for inclusion. Studies in the review were classified as secondary prevention if they included patients with known or documented vascular disease, active tobacco use or asbestos exposure, or documented previous malignant disease. The included studies used vitamin E (50 to 300 mg, or 400 to 800 IU) or beta-carotene (15 to 50 mg, four times daily), either alone or in combination with other vitamins such as retinol and vitamin C.

Participants included in the review
Studies of participants from developed countries with no evidence of vitamin deficiency were eligible for inclusion. Studies of secondary prevention included smokers, survivors of recent myocardial infarction (MI), patients with previous asbestos exposure, known vascular disease, previous non-melanoma skin cancer or diabetes, and patients at risk of vascular disease. The primary prevention studies included people at risk of cataract or vision loss, basal-cell or squamous-cell cancer, people with no history of cancer or vascular disease, and patients with at least one risk factor.

Outcomes assessed in the review
Studies that reported all-cause mortality, cardiovascular death, all-cause cerebrovascular accident, and the combined end point of cardiovascular death or nonfatal MI were eligible for inclusion. The included studies followed participants for 1.4 to 12 years.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies.

Assessment of study quality
Study inclusion was based on the quality of the study methods, i.e. sample size, method of randomisation and use of intention-to-treat (ITT) analysis. However, it was unclear how methods of randomisation or use of ITT was assessed. Two reviewers independently assessed validity.
Data extraction
Two reviewers independently extracted the data on an ITT basis. For each study, the number of events per treatment group was extracted and the absolute events rates and odds ratios (ORs) were calculated, along with 95% confidence intervals (CIs). Authors of reports with missing data were contacted for additional information.

Methods of synthesis
How were the studies combined?
Studies of vitamin E and beta-carotene were combined in separate meta-analyses. Pooled ORs and 95% CIs were calculated.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Breslow-Day test; a P-value of less than 0.05 was considered statistically significant. Vitamin E studies were classified according to the risk status of the population (primary or secondary prevention) and a separate meta-analysis was conducted for each of these subgroups. The analysis was repeated after including 2 RCTs that failed to meet the inclusion criterion for sample size; there were no details of how these 2 studies were selected. Some potential causes of differences among the studies were discussed.

Results of the review
Twelve RCTs were included. Seven RCTs (n=81,788) examined vitamin E and 8 RCTs (n=138,113) examined beta-carotene.

Vitamin E.
Over all studies, there was no statistically significant difference between vitamin E and control for all-cause mortality (OR 1.02, 95% CI: 0.98, 1.06, P=0.42), cardiovascular mortality (OR 1.0, 95% CI: 0.94, 1.06, P=0.94), or cerebrovascular accident (OR 1.02, 95% CI: 0.92, 1.12, P=0.71). No statistically significant heterogeneity was detected.

A subgroup analysis found no statistically significant difference between vitamin E and control for all-cause mortality among secondary or primary prevention studies. The results were similar after including 2 RCTs that did not meet the inclusion criterion for size.

No statistically significant difference was found between vitamin E and control for the combined outcome of cardiovascular death or nonfatal MI, but statistical heterogeneity was found (P=0.053).

Beta-carotene.
Beta-carotene was associated with a slight statistically significantly increase in all-cause mortality (OR 1.07, 95% CI: 1.02, 1.11, P=0.003) and cardiovascular death (OR 1.1, 95% CI: 1.03, 1.17, P=0.003) when compared with control. Based on 3 RCTs, there was no statistically significant difference between treatments for all-cause cerebrovascular accident (OR 1.0, 95% CI: 0.91, 1.09, P=0.92). No statistically significant heterogeneity was detected.

Authors' conclusions
The studies consistently showed no reduction in cardiovascular disease among diverse populations with vitamin E, thus the routine use of vitamin E cannot be recommended. The use of vitamin supplements containing beta-carotene should be actively discouraged.

CRD commentary
The review question was clear in terms of the study design, intervention, participants and outcomes. Only one database was searched, which might have resulted in the omission of other relevant studies. The search strategy was not reported in full and it was unclear whether any language limitations were applied. Some limited attempts to minimise small study bias were made. Two reviewers independently selected the studies and extracted the data, which reduces the potential for bias and errors. The validity of the included studies was assessed systematically and used to select studies for...
Adequate details of each included study were given. The studies were combined in a meta-analysis and statistical heterogeneity was assessed. However, limitations in the reporting of validity means it is not possible to assess whether it was appropriate. Potential causes of the significant heterogeneity found in the meta-analysis of vitamin E using the combined outcome were not explored. The evidence presented appears to support the authors’ conclusions, although the limited search means it is likely that some relevant studies might have been overlooked.

**Implications of the review for practice and research**

*Practice:* The authors stated that the use of vitamin supplements containing beta-carotene and vitamin A should be actively discouraged, and that vitamin E should not be included in future studies of primary or secondary prevention in patients at high risk of coronary artery disease.

*Research:* The authors stated that further research, to determine the reason for the increased risk of death with beta-carotene and the lack of improvement in cardiovascular outcomes with vitamin E, is required.

**Bibliographic details**


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**Other publications of related interest**

This additional published commentary may also be of interest. Gundling K. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. FACT 2004;9:27-8.

**Indexing Status**

Subject indexing assigned by NLM

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.