Is there a role for antioxidant vitamins in the prevention of cardiovascular diseases: an update on epidemiological and clinical trials data

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Authors' objectives
To review prospective epidemiological studies and randomised clinical trials regarding the role of antioxidant vitamins (vitamins E and C and beta-carotene) in the prevention of cardiovascular diseases.

Searching
MEDLINE and the Science Citation Index were searched (dates and search terms were not stated). Manual searches on the role of antioxidant vitamins in cardiovascular disease management were also carried out (no further details were given).

Study selection
Study designs of evaluations included in the review
Prospective epidemiological studies and double-blind, randomised controlled trials (RCTs) with at least 100 participants were included in the review. Retrospective studies, geographical correlations and case series were excluded.

Specific interventions included in the review
The interventions included in the review were vitamin E, vitamin C and beta-carotene.

Participants included in the review
The participants were men and women aged from 16 to 75 years who had hyperlipidaemia, or were smokers or postmenopausal women. Their occupations included nurses, health professionals, pharmaceutical employees, and nursing home residents.

Outcomes assessed in the review
Mortality and cardiovascular outcomes were assessed including coronary heart disease, cerebrovascular disease, peripheral vascular disease and atherosclerosis.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors do not report the method used to assess quality, or how the quality assessment was performed.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Methods of synthesis
How were the studies combined?
The studies were grouped according to the type of antioxidant vitamin assessed and the type of study design (i.e. prospective observational study versus RCT). Relative risk values were calculated for all of the prospective epidemiological studies, and relative risk reductions were calculated for all of the RCTs. Where the relative risk reduction was not quoted in the original publication, it was estimated using the Mantel-Haenszel method. Quantitative
pooling of the results was precluded due to differences in the patient and study characteristics; consequently, the results were synthesised in a narrative form.

How were differences between studies investigated?

Very significant differences were identified between the studies in terms of the following: the study populations; type (supplemental versus dietary) and dosage of antioxidant vitamins; the duration of follow-up; and the overall study design. Specific differences were highlighted in the narrative comparison of studies.

Results of the review

Eighteen studies with 295,311 participants were included in the review: 12 prospective observational studies and 6 RCTs. Of these studies, 7 (227,493 participants) assessed vitamin E, 12 (246,488 participants) assessed beta-carotene, and 10 (186,985 participants) assessed vitamin C.

Vitamin E.

Large, prospective cohort studies of vitamin E suggested that, overall, there is a lower risk of cardiovascular disease for vitamin E users. However, there were several inconsistencies in the data. One study clearly identified that the use of vitamin E supplements (i.e. higher doses than generally provided by diet and multivitamins) for prolonged periods of time (100 IU for at least 2 years) was protective. In contrast, another study did not find a protective effect in women taking vitamin E supplements, although it identified vitamin E from food sources to be potentially protective. Similarly, the RCTs included in the review showed vitamin E to be a potentially promising intervention in preventing cardiovascular disease, although its benefit was not clearly and conclusively demonstrated. The authors identified a number of large ongoing randomised trials looking at the effect of vitamin E supplements in both primary and secondary prevention, which may help to clarify the situation.

Beta-carotene.

The evidence from large, prospective epidemiological studies of beta-carotene was somewhat inconsistent, but did suggest the possibility of lower adverse cardiovascular outcomes; in particular, for men who are current or former smokers, and who consume large amounts of dietary beta-carotene provided by nutritional sources or vitamin supplements. Some of the studies also suggested an association between high beta-carotene intake and a lower risk of cancer, particularly lung cancer. This association was strongest in current and former smokers. Evidence from RCTs failed to demonstrate any benefit for beta-carotene supplementation at adequate doses (leading to 4- to 5-fold rises in blood levels), even for prolonged periods of time (over a decade in one study). Certain studies also highlighted concern that an increased risk of cancer was evident; in particular, one large trial amongst smokers (Beta-Carotene and Retinol Efficacy Trial) was terminated earlier than planned due to an increase in lung cancer amongst individuals randomised to receive beta-carotene and vitamin A. There were no adequate trials to assess the role of beta-carotene in secondary prevention.

Vitamin C.

The evidence from epidemiological studies was inconclusive and did not clearly identify vitamin C intake as a significant protective factor against cardiovascular disease. In addition, few RCTs (not listed in the results tables) rigorously assessed the effects of vitamin C supplements. One small trial of 578 patients, which assessed the use of 200 mg vitamin C supplements in geriatric patients, found that mortality was not reduced after 6 months. A second larger trial, which examined the effect of a combination of vitamin C and molybdenum, failed to find a reduction in overall mortality or mortality from cardiovascular disease.

Authors' conclusions

Prospective epidemiological investigations suggested that there was a reduction in cardiovascular risk associated with an increased intake of antioxidant vitamins, particularly vitamin E. RCTs remain inconclusive with regard to the role of vitamin E in cardiovascular protection. The large RCT of beta-carotene in primary prevention showed no effect associated with the use of beta-carotene, and possibly a potential for harm. There were inconclusive and insufficient epidemiological and clinical trial data with regard to the role of vitamin C in cardiovascular protection.
CRD commentary
This was a clearly presented review that included well-defined inclusion criteria and study designs. The authors appear to have attempted a reasonable search of the available evidence, although they failed to provide details of the search terms used and the publication period covered by the search. Consequently, it is difficult for others to repeat the search strategy or to comment further on its effectiveness. The inclusion criteria for the participants were not clearly defined, resulting in diverse groups of participants from which it was difficult to compare studies. The review also includes four RCTs whose primary outcome was mortality from cancer, which seemed inappropriate. No information was given on how the studies were assessed for inclusion and quality, and how the data were extracted from the studies.

Considering the underlying differences between the studies, a narrative synthesis of the studies seems to have been appropriate and the authors' conclusions appear to be supported by the evidence presented.

Implications of the review for practice and research
The authors recommend that widespread use of antioxidant vitamins in cardiovascular protection should not be instituted, and should await the results of further ongoing trials.

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