Antioxidant vitamins in the prevention of cardiovascular disease: a systematic review

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Authors' objectives
To assess whether antioxidant vitamins, in regular food or as food supplements, protect against myocardial infarction or stroke. In practice, the author assessed the effect of antioxidant vitamins for the primary prevention of myocardial infarction or stroke.

Searching
MEDLINE was searched from 1989 to November 2001 using all combinations of the following search terms: 'antioxidant(s)', 'carotene', 'ascorbic acid', 'tocopherols(s)', 'vitamin(s)', and 'cardiovascular', 'heart', 'cardiac', 'coronary', 'cerebrovascular', 'stroke', 'atherosclerosis'. Additional references were retrieved from the Science Citation Index by following 'landmark' articles, and by scrutinising the reference lists of published articles, reviews, editorials and textbook chapters.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), cohort and case-control studies were included in the review. Only the RCTs and some cohort studies were able to evaluate an intervention (food supplements). It was not possible to separate the results of the intervention (antioxidant food supplements) from the intake of antioxidants in regular food for the cohort studies. Therefore, the results presented here are limited to those from the RCTs.

Specific interventions included in the review
Food supplements of the antioxidant vitamins carotene, ascorbic acid and tocopherol were included. The actual supplements included: beta-carotene; beta-carotene in combination with retinol; beta-carotene plus alpha-tocopherol and selenium; alpha-tocopherol; ascorbic acid; ascorbic acid plus molybdenum; ascorbic acid plus alpha-tocopherol; aspirin plus alpha-tocopherol; some of the interventions were studied in factorial designs. No information on the doses was provided. The duration of treatment ranged from 3.6 to 12 years. Studies of other antioxidants, such as selenium and Q10, were excluded.

Participants included in the review
Healthy individuals, secondary prevention studies and studies among subgroups such as diabetic patients were excluded from the systematic review; some secondary prevention studies were discussed in a 'narrative' review. The age range and other demographic characteristics of the participants in the included studies were not provided. Two of the larger studies enrolled men only, while three enrolled high-risk individuals (smoking middle-aged men in Finland), smokers and asbestosis workers in the USA, and people with at least one cardiovascular risk factor or aged over 65 years in Italy. One study was conducted in low-risk health professionals from the USA, and another in a Chinese population where micronutrient deficiencies were common.

Outcomes assessed in the review
Cardiovascular disease, including ischaemic heart disease deaths or events, or stroke, was assessed. Adverse events were also reported. The outcomes were not clearly defined, and all-cause mortality was not considered.

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

Assessment of study quality
The author states that the validity of the studies was assessed against strict quality criteria and ranked into three categories: low, intermediate or high scientific quality. The quality criteria were not described, although a reference to a Database of Abstracts of Reviews of Effects (DARE)
non-English report was provided (see Other Publications of Related Interest). The results from the low-quality studies were excluded from the conclusions. The author does not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

**Data extraction**
The author does not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Data were extracted on the antioxidants given, the duration of treatment, the number and type of cardiovascular events reported, and the odds ratios (ORs) and 95% confidence intervals (CIs).

**Methods of synthesis**
How were the studies combined?
A narrative synthesis was undertaken. The ORs were pooled by a meta-analysis (Peto fixed-effect method).

How were differences between studies investigated?
No method of assessing heterogeneity between the studies was described.

**Results of the review**
Eight RCTS (104,512 participants, about 699,000 observation years) were included. Six RCTs (n=86,056) tested dietary supplements of beta-carotene, four (n=48,346) tested alpha-tocopherol, and two (n=16,700) ascorbic acid (in combination with molybdenum in one of these).

None of the RCTs showed any beneficial effect of antioxidant supplementation on cardiovascular disease. The pooled ORs were 1.02 (95% CI: 0.96, 1.08) for beta-carotene, 0.96 (95% CI: 0.88, 1.04) for alpha-tocopherol and 0.98 (95% CI: 0.75, 1.26) for ascorbic acid. In one study, there was a significantly increased risk for fatal or nonfatal intracerebral and subarachnoid haemorrhage in participants taking alpha-tocopherol (results not presented). Two trials found an association between the intake of carotene supplements and an increased risk of lung cancer in cigarette smokers (results not presented). These findings from the RCTs contradict the results of the observational (case-control and cohort) studies, which mostly identified reductions in the risk of cardiovascular events for participants with high plasma levels of these nutrients.

**Authors’ conclusions**
In the RCTs, antioxidant vitamins as food supplements had no beneficial effects in the primary prevention of myocardial infarction and stroke. The reported increased risks of intracerebral and subarachnoid haemorrhage during treatment with carotene and tocopherol may caution against the use of antioxidants in healthy people. Only two studies of ascorbic acid were identified, but the results were consistent with an earlier systematic review. The existing RCTs had limitations: most were not designed specifically to test the protective effect on cardiovascular disease outcomes; some of the largest trials included only smokers, and the relationship between smoking and oxidation is complex; the duration of treatment may have been too short, or the doses of vitamins too low; synthetic antioxidants may differ from natural ones in their effects on cardiovascular diseases; specific antioxidants have been used alone, or in combinations of two, when there may be advantages to a mixture.

**CRD commentary**
This review covered an important topic area, and reviewed observational and experimental evidence for antioxidant nutrients and cardiovascular disease. The author described some relevant ongoing studies (table 6), which was useful, although it is unclear how these were identified. Limitations of the primary studies were described in detail in the 'Discussion' section, although many methodological aspects were unclear. The search strategy was limited to MEDLINE and the Science Citation Index, and studies published after 1989. Other databases, such as EMBASE, should have been searched and earlier studies included. The author did not state whether any language restrictions were applied to the searches. The methods used to assess study eligibility, extract the data and assess quality were not described in sufficient detail. More details of the included RCTS are also required, such as the age ranges of the participants, doses.
of antioxidant supplements, and definitions of cardiac events. Heterogeneity between the studies was not considered.

The author reviewed many related topics, but most of these were not 'systematic' reviews. For example, the effects of antioxidants on intermediate variables such as blood lipids, blood-pressure or haemostatic variables, and antioxidant vitamins for the secondary prevention of cardiovascular disease.

Implications of the review for practice and research
Practice: The author states that antioxidant vitamins as food supplements cannot be recommended in the primary or secondary prevention of cardiovascular disease.

Reviewer's comment: A 'systematic' review was carried out for primary prevention only, therefore the author has no basis for commenting on the effectiveness of the intervention for secondary prevention.

Research: The author identified ongoing studies and the limitations of existing RCTs.

Bibliographic details

PubMedID
11982737

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Antioxidants /therapeutic use; Cardiovascular Diseases /physiopathology /prevention & control; Case-Control Studies; Dietary Supplements; Humans; Lipid Peroxidation; Randomized Controlled Trials as Topic; Vitamins /therapeutic use

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Record Status
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.