

Review: Prophylactic use of β -carotene may increase the risk for all-cause mortality and cardiovascular death

Vivekananthan DP, Penn MS, Sapp SK, Hsu A, Topol EJ. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. *Lancet*. 2003;361:2017-23.

QUESTION

In persons at risk, is prophylactic use of antioxidant vitamins (vitamin E and β -carotene) effective for primary and secondary prevention of all-cause mortality and cardiovascular (CDV) events?

DATA SOURCES

Studies were identified by searching MEDLINE, searching for known randomized controlled trial (RCT) acronyms cited in review articles, and reviewing bibliographies of relevant articles.

STUDY SELECTION AND ASSESSMENT

Studies were selected if they were RCTs that compared antioxidant vitamins (vitamin E or β -carotene) with a control treatment for primary and secondary prevention of all-cause mortality and CDV events in ≥ 1000 participants from developed countries without overt evidence of vitamin deficiencies. RCTs that did not report all-cause mortality were excluded from the review.

OUTCOMES

All-cause mortality, CDV death, all-cause cerebrovascular accident, nonfatal myocardial infarction, and a composite endpoint

of CDV death or nonfatal myocardial infarction.

MAIN RESULTS

12 RCTs met the selection criteria. 8 RCTs ($n = 138\ 113$) evaluated β -carotene alone or in combination with other antioxidants, and 7 RCTs ($n = 81\ 788$) evaluated vitamin E alone or in combination with other antioxidants. β -carotene: The rates of all-cause mortality and CDV death were greater in the β -carotene group than in the control treatment group (Table). The groups did not differ for all-cause cerebrovascular accident. Vitamin E: The groups did not differ for all-cause mortality, CDV mortality, and cere-

brovascular accidents (Table), and the composite endpoint of CDV death or nonfatal myocardial infarction (9.4% vs 9.7%, $P > 0.05$).

CONCLUSION

In persons at risk, β -carotene may increase the risk for all-cause mortality and cardiovascular death, whereas vitamin E does not have any effect on these outcomes.

Source of funding: No external funding.

For correspondence: Dr. M.S. Penn, Cleveland Clinic Foundation, Cleveland, OH, USA. E-mail pennm@ccf.org. ■

β -carotene or vitamin E vs control treatment for primary and secondary prevention of all-cause mortality and cardiovascular events at 1.4 to 12 years*

Outcomes	Comparisons	Weighted event rates	RRI (95% CI)	NNH (CI)
All-cause mortality	β -carotene vs control	7.3% vs 7.0%	6% (1 to 11)	326 (140 to ∞)†
	Vitamin E vs control	11.5% vs 11.1%	4% (-2 to 10)	Not significant†
Cardiovascular death	β -carotene vs control	3.3% vs 3.1%	11% (1 to 22)	409 (176 to ∞)†
	Vitamin E vs control	6.0% vs 6.0%	0% (-5 to 6)	Not significant
All-cause stroke	β -carotene vs control	2.4% vs 2.3%	0% (-9 to 9)	Not significant
	Vitamin E vs control	3.6% vs 3.5%	3% (-7 to 13)	Not significant

*Abbreviations defined in Glossary; RRI, NNH, and CI calculated from data in article using a fixed-effects model.

†Meta-analyses were done using a random-effects model.

COMMENTARY

The physiologic basis for using antioxidant therapy to modify development of atherosclerosis and thereby prevent CDV events appears logical and has much appeal to the public and health care providers. This is particularly so when observational studies have suggested that treatment with antioxidant vitamins, mainly vitamin E and β -carotene, may be beneficial in reducing all-cause mortality and CDV events. Subsequent RCTs, however, have not confirmed the promising results of the early nonrandomized studies.

The meta-analysis of large RCTs by Vivekananthan and colleagues showed that despite the enhanced statistical power offered by the overall data, use of vitamin E did not have any beneficial effects and that β -carotene was associated with a slight but significant increase in risk for all-cause and CDV mortality. It is important to note that, individually, the RCTs consistently did not show treatment benefits in the vitamin E trials and most β -carotene trials showed trends toward excess harm with active treatment.

Several reasons have been given to explain why the RCT results did not substantiate the promise of benefit found in the earlier studies. First, it is possible that the hypothesis evaluation process did not actually test the antioxidant hypothesis. The drug preparations may differ from the ingredients in antioxidant-rich food; they may not have the necessary

antioxidant potency or they may even be pro-oxidants. Second, the lifestyle followed by the patients can affect study outcomes and may have a major confounding effect on the results, particularly in the uncontrolled studies. Third, it is possible that the extent of illness or baseline comorbid conditions could influence the responsiveness to the treatment. In the Heart Outcomes Prevention Evaluation study (1), it was speculated that a longer duration of treatment and follow-up would be necessary for the effects of the treatment to become evident. However, the results from additional 2.6-year follow-up beyond the initial 4.5-year follow-up did not show benefits of vitamin E treatment.

Thus, the potential benefits suggested by the "antioxidant hypothesis" are not realized with antioxidant supplements. At present, one can conclude that routine use of antioxidant vitamin therapy does not confer a clinical benefit, and in the case of β -carotene, the effect may be harmful.

Koon K. Teo, MB, PhD
McMaster University
Hamilton, Ontario, Canada

Reference

1. The Heart Outcomes Prevention Evaluation Study Investigators. Vitamin E supplementation and cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342:154-60.