Review: Antioxidant supplements for primary and secondary prevention do not decrease mortality

Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. **Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis.** JAMA. 2007;297:842-57.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Cardiology ★★★★★★☆ Endocrinology ★★★★★★☆ Gastroenterology ★★★★★★☆ Geriatrics ★★★★★☆☆ Nephrology ★★★★★★☆ Neurology ★★★★★☆☆ Oncology ★★★★★★☆ Rheumatology ★★★★★★☆ Dermatology ★★★★★★☆

QUESTION

In healthy people or patients with chronic diseases, do antioxidant supplements (ASs) decrease mortality?

METHODS

Data sources: MEDLINE (1966 to October 2005), EMBASE/Excerpta Medica (1985 to October 2005), Cochrane Central Register of Controlled Trials (Issue 3, 2005), Science Citation Index Expanded (1945 to October 2005), and bibliographies of relevant studies.

Study selection and assessment: Randomized controlled trials (RCTs) that compared ASs (β-carotene; vitamin A, C, or E; or selenium, separately or in combination) with placebo or no intervention in healthy adults or patients with chronic diseases. Trials on acute, infectious, or malignant diseases except for nonmelanoma skin cancer were excluded. 68 RCTs (n = 232 606, mean age 62 y, mean 45% women in 63 RCTs, follow-up range 28 d to 14 y [median 2 y]) met the selection criteria. Among them, 47 (n = 68 167) were secondary prevention trials and included patients with gastrointestinal, cardiovascular, neurologic, ocular, dermatologic, rheumatoid, renal, cardiovascular, endocrinologic, or unspecified diseases. All ASs were administered orally: β-carotene 1.2 to 50 mg (mean 18 mg), vitamin A 1333 to 200 000 IU (mean 20 219 IU), vitamin C 60 to 2000 mg (mean 488 mg), vitamin E 10 to 5000 IU (mean 569 IU), and selenium 20 to 200 µg (mean 99 µg) daily or on alternate days for a period of 28 days to 12 years (mean 2.7 y). 47 RCTs (n = 180 938) had high methodological quality that was defined as adequate randomization, allocation concealment, blinding, and follow-up.

Outcomes: Mortality.

MAIN RESULTS

Meta-analysis of 68 RCTs showed that groups did not differ for mortality (Table). Meta-analysis of 47 high-quality RCTs showed that ASs increased mortality, while meta-analysis of 21 low-quality RCTs showed that ASs decreased mortality (borderline significance) (Table). Subgroup analysis of high-quality RCTs (excluding selenium trials) showed that β-carotene (RR 1.07, CI 1.02 to 1.11), vitamin A (RR 1.16, CI 1.10 to 1.24), or vitamin E (RR 1.04, CI 1.01 to 1.07), alone or combined, increased mortality. Subgroup analysis also showed that vitamin C or selenium had no significant effect on mortality.

CONCLUSION

In healthy people or patients with chronic diseases, antioxidant supplements do not decrease mortality.

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Antioxidant supplements (β-carotene; vitamin A, C, or E; or selenium, separately or in combination) vs placebo or no intervention in healthy adults or patients with chronic diseases*

Outcomes at median 2 years	Number of trials (n)	Weighted event rates		RRI (95% CI)	NNH (CI)
		Antioxidant supplements	Placebo or no intervention		
Mortality in all included RCTs	68 (232 606)	11%	11%	2% (–2 to 6)	Not significant
Mortality in high-quality RCTs	47 (180 938)	12%	11%	5% (2 to 8)	180 (112 to 449)
				RRR (CI)	NNT (CI)
Mortality in low-quality RCTs	21 (51 668)	6.4%	7.0%	9% (0 to 17)	160 (85 to ∞)

*Abbreviations defined in Glossary. Weighted event rates, RRI, RRR, NNT, NNH, and CI calculated from data in article using a random-effects model.

COMMENTARY

ASs are used by a large segment of the population. Hence, the review by Bjelakovic and colleagues has major implications for public health. More relevant than the overall analysis that combined chemically diverse antioxidants (including combinations) in diverse settings, the agent-specific analyses suggest that β-carotene, vitamin A, or vitamin E, alone or combined, increase mortality, whereas vitamin C or selenium has no effect. The results are believable because of the careful, prespecified protocol, comprehensive sensitivity analyses, and precise confidence limits.

2 other features of the review lend further support to the findings. First, signals of increased mortality were even more prominent in methodologically strong trials characterized as being at low risk for bias. Second, causality was strengthened by significant dose-response gradients for several of the antioxidants.

Given the number of persons exposed to these agents, this review suggests that several thousand deaths each year may result from use of ASs, which have hitherto been considered by many physicians to be benign or even beneficial compounds. The public perception that vitamins and other antioxidants have favorable health effects because they are "natural" rather than pharmacologic is clearly wrong and in light of this review must be corrected by clinicians and other health advocates.

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