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

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Summary

Introduction Oxidised LDL is thought to play an important part in the pathogenesis of atherosclerosis. Observational studies have associated α tocopherol (vitamin E), β carotene, or both, with reductions in cardiovascular events, but not clinical trials. We did a meta-analysis to assess the effect of these compounds on long-term cardiovascular mortality and morbidity.

Methods We analysed seven randomised trials of vitamin E treatment and, separately, eight of β carotene treatment; all trials included 1000 or more patients. The dose range for vitamin E was 50–800 IU, and for β carotene was 15–50 mg. Follow-up ranged from 1·4 to 12·0 years.

Findings The vitamin E trials involved a total of 81 788 patients and the β carotene trials 138 113 in the all-cause mortality analyses. Vitamin E did not provide benefit in mortality compared with control treatment (11·3 *vs* 11·1%, odds ratio 1·02 [95% CI 0·98–1·06] p=0·42) or significantly decrease risk of cardiovascular death (6·0 *vs* 6·0%, p=0·86) or cerebrovascular accident (3·6 *vs* 3·5%, p=0·31). β carotene led to a small but significant increase in all-cause mortality (7·4 *vs* 7·0%, 1·07 [1·02–1·11] p=0·003) and with a slight increase in cardiovascular death (3·4 *vs* 3·1%, 1·1 [1·03–1·17] p=0·003). No significant heterogeneity was noted for any analysis.

Interpretation The lack of a salutary effect was seen consistently for various doses of vitamins in diverse populations. Our results, combined with the lack of mechanistic data for efficacy of vitamin E, do not support the routine use of vitamin E.

Lancet 2003; **361:** 2017–23

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Introduction

The oxidative-modification hypothesis of atherosclerosis[1–4] has prompted the study of antioxidant vitamins in the prevention of the initiation and progression of cardiovascular disease. Preclinical studies suggested that supplementation of the diet with various compounds that have antioxidant properties before the development of vascular disease inhibited the atherogenic process.[5–9] These findings led to several large, prospective, cohort studies in human beings, in which significant reductions in mortality[10] and cardiovascular events[11,12] were identified in men and women taking antioxidant vitamins. However, sizeable randomised trials of antioxidant vitamins[13–17] have shown no such mortality reduction, although in one study non-fatal myocardial infarction (MI) was significantly reduced.[18] More importantly, in two randomised trials of β carotene[16,19] no benefit, and possibly an increased risk of cardiovascular events, was seen. Findings from small randomised studies of antioxidant vitamins have also suggested a potential harmful effect of antioxidant vitamins in patients with known or suspected coronary disease.[20,21]

Despite the absence of efficacy of antioxidant vitamins reported in larger randomised trials, two important opinion articles have favoured the universal use of multivitamins by consumers.[22,23] The multivitamins recommended, however, contain β carotene and α tocopherol (vitamin E), two compounds that have not been proven to reduce cardiovascular morbidity or mortality, and may adversely affect lipid concentrations when used at higher doses.[13,20] Since the use of antioxidant vitamins continues to grow, partly encouraged by physicians advocating their use,[24] we did a meta-analysis of randomised trials to find out what effect antioxidant vitamins have on all-cause mortality and cardiovascular death.

Methods

Study population

We did a MEDLINE search to identify all randomised controlled trials of antioxidant vitamins in primary and secondary prevention. We used the search terms: "randomized controlled trials", "vitamin E", and "beta carotene". We did additional searches for known trial acronyms cited in review articles, and searched by hand the bibliographies of primary studies identified through the initial search. To limit the effects of publication bias of smaller trials we included only studies of 1000 or more patients. To reduce the possibility of confounding from inclusion of nutritionally deficient populations, our analysis was limited to studies in populations from developed countries without overt evidence of vitamin deficiencies.

Two investigators (DPV and SKS) independently reviewed the primary studies to assess the appropriateness for inclusion in our analysis and data abstraction. Trial

	Patients' characteristics	Location of study population	Number in Treatment group		Dose	Length of follow-up (years)
			β carotene	Control		
Trial						
Secondary prevention						
ATBC[16]*	Age range 50–69 years; 100% male smokers (n=29 133)	Southwestern Finland, multicentre	14 560	14 573	20 mg four times daily	6·1
CARET[19]	Age range 45–69 years; former/active smokers or asbestos exposure; 66% male (n=18 314)	USA, multicentre	9420	8894	15–30 mg four times daily + 25 000 IU retinol	4·0
HPS[13]*	Age range 40–80 years; known vascular disease or at-risk of vascular disease; 75% male (n=20 536)	UK, multicentre	10 269	10 267	20 mg four times daily	5·0
SCP[25]	Age <85 years (most <65 years); previous non-melanoma skin cancer; 69% male (n=1805)	USA, multicentre	913	892	50 mg four times daily	5·0
Primary prevention						
AREDS[26]*	Age range 55–80 years; at-risk of cataract or vision loss; 44% male (n=4757)	USA, multicentre	2370	2387	15 mg four times daily	6·3
NSCP[27]	Age range 20–69 years; at-risk of basal-cell or squamous-cell cancer; 44% male (n=1621)	Queensland, Australia multicentre	820	801	30 mg four times daily	4·5
PHS[28]	Age range 40–84 years; no history of cancer or vascular disease; 100% male physicians (n=22 071)	USA, multicentre	11 036	1035	50 mg four times daily	12·0
WHS[29]*	Age range >45 years; no history of cancer or vascular disease; 100% female health professionals (n=39 876)	USA, multicentre	19 939	19 937	50 mg four times daily	2·1

*β carotene taken as part of antioxidant cocktail or factorial randomisation including vitamin E.

Table 1: **Summary of randomised trials of β carotene treatment**

inclusion was based on the quality of the study's methods, including trial size, randomisation scheme, and use of an intention-to-treat analysis. The prospectively identified outcomes of interest included all-cause mortality, cardiovascular death, all-cause cerebrovascular accident, and non-fatal MI. Many trials did not report the individual rates of non-fatal MI and, therefore, we chose to use the more widely reported combined endpoint of cardiovascular death or non-fatal MI. We excluded trials without all-cause mortality data.

We identified 12 trials for analysis (tables 1 and 2). Eight trials involving β carotene alone or in combination with other antioxidants were analysed (table 1). We further classified the studies in our analysis by cardiovascular risk of the study population. Four studies were secondary prevention studies, defined as including patients with known or documented vascular disease, active tobacco use or asbestos exposure, or documented history of previous malignant disease. The Alpha-Tocopherol Beta Carotene Cancer Prevention Study (ATBC)[16] investigated the effects of β carotene, vitamin E, or both, on the frequency of major cardiac events and rate of lung cancer in a population of middle-aged male smokers. The Beta Carotene and Retinol Efficacy Trial (CARET)[19] assessed efficacy and safety of β carotene in men and women at high risk of lung cancer because of previous asbestos exposure or extensive cigarette smoking. The Heart Protection Study (HPS)[13] assessed the impact of an antioxidant vitamin combination (600 mg vitamin E, 250 mg vitamin C, and 20 mg β carotene) on vascular and non-vascular mortality and morbidity among patients at high risk because of history of coronary disease, diabetes, or peripheral vascular disease. The Skin Cancer Prevention Study (SCP)[25] assessed the efficacy of β carotene in the secondary prevention of non-melanoma skin cancer among elderly patients who had a history of biopsy-proven basal-cell or squamous-cell carcinoma.

Four β-carotene trials were primary prevention studies or were among low-risk patients. The Age-Related Eye Disease Study (AREDS)[26] assessed the safety and efficacy of an antioxidant combination (15 mg β carotene, 400 IU vitamin E, and 500 mg vitamin C) in the prevention of

	Patients' characteristics	Location of study population	Number in treatment group		Dose	Length of follow-up (years)
			Vitamin E	Control		
Trial						
Secondary prevention						
ATBC[16]*	Mean age 57 years; male smokers without known lung cancer (n=29 133)	Southwestern Finland, multicentre	14 564	14 569	50 mg	6·1
CHAOS[18]†	Median age 62 years; angiographically proven CAD; 84% male (n=2002)	UK, single centre	1035	967	400–800 IU	1·4
GISSI[17]	Survivors of recent MI (<3 months); 85% male (n=11 324)	Italy, multicentre	5660	5664	300 mg	3·5
HOPE[15]†	Mean age 66 years; known cardiovascular disease or diabetes; 73% male (n=9541)	Multinational: Canada, USA, Europe, South America	4761	4780	400 IU	4·5
HPS[13]*	Age range 40–80 years; known vascular disease or at-risk of vascular disease; 75% male (n=20 536)	UK, multicentre	10 269	10 267	600 mg	5·0
Primary prevention						
AREDS[26]*	Age range 55–80 years; at-risk of cataract of vision loss; 44% male (n=4757)	USA, multicentre	2370	2387	400 IU	6·3
PPP[14]	Mean age 64·4 years; primary prevention in patients with at least one risk factor; 57% male (n=4495)	Italy, multicentre	2231	2264	300 mg	3·6

*Vitamin E as part of antioxidant cocktail or factorial randomisation including β carotene. †Vitamin E from natural sources.

Table 2: **Summary of randomised trials of vitamin E treatment**