Effects of α tocopherol and β carotene supplements on symptoms, progression, and prognosis of angina pectoris

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Abstract

***Objective*—To evaluate the effects of α tocopherol and β carotene supplements on recurrence and progression of angina symptoms, and incidence of major coronary events in men with angina pectoris.**

***Design*—Placebo controlled clinical trial.**

***Setting*—The Finnish α tocopherol β carotene cancer prevention study primarily undertaken to examine the effects of α tocopherol and β carotene on cancer.**

***Subjects*—Male smokers aged 50–69 years who had angina pectoris in the Rose chest pain questionnaire at baseline (n = 1795).**

***Interventions*—α tocopherol (vitamin E) 50 mg/day, β carotene 20 mg/day or both, or placebo in 2 × 2 factorial design.**

***Main outcome measures*—Recurrence of angina pectoris at annual follow up visits when the questionnaire was readministered; progression from mild to severe angina; incidence of major coronary events (non-fatal myocardial infarction and fatal coronary heart disease).**

***Results*—There were 2513 recurrences of angina pectoris during follow up (median 4 years). Compared to placebo, the odds ratios for recurrence in the active treatment groups were: α tocopherol only 1.06 (95% confidence interval (CI) 0.85 to 1.33), α tocopherol and β carotene 1.02 (0.82 to 1.27), β carotene only 1.06 (0.84 to 1.33). There were no significant differences in progression to severe angina among the groups given supplements or placebo. Altogether 314 major coronary events were observed during follow up (median 5.5 years) and the risk for them did not differ significantly among the groups given supplements or placebo.**

***Conclusions*—There was no evidence of beneficial effects for α tocopherol or β carotene supplements in male smokers with angina pectoris, indicating no basis for therapeutic or preventive use of these agents in such patients.**

(*Heart* 1998;**79**:454–458)

Keywords: antioxidants; angina pectoris; prevention; vitamin supplements

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Accepted for publication 17 November 1997

Epidemiological studies show that dietary intake,[1–4] serum,[5 6] and adipose tissue[7] concentrations of antioxidants are inversely related to coronary heart disease, but results from clinical trials of antioxidant supplements are inconsistent. Efficacy of vitamin E supplements in angina pectoris was suggested over 50 years ago by Vogelsang and Shute,[8] but their contemporaries failed to confirm the findings. Emergence of the oxidation hypothesis of atherosclerosis has reawakened interest in the role of antioxidants in patients with coronary heart disease. One study found a decrease in the risk of non-fatal myocardial infarction with α tocopherol,[9] however, we reported recently increased coronary mortality with antioxidants in men with a history of a myocardial infarction.[10] Results from the physician's health study suggested that β carotene treatment was beneficial in patients with angina pectoris,[11] but with prolonged follow up, these effects diminished.[12] Current concepts of the role of antioxidants in atherosclerotic heart disease have been reviewed recently.[13]

We report the effects of long term α tocopherol and β carotene supplement use on recurrence, progression, and prognosis of angina pectoris in male smokers.

Methods

Study participants were recruited from the α tocopherol β carotene cancer prevention (ATBC) study—a controlled clinical trial done primarily to examine effects of antioxidant supplements on cancer. The final number of participants in the ATBC study was 29 133 (fig 1). Study design, methods, participant characteristics, and compliance have previously been reported in detail.[14]

SUBJECTS

Male smokers (five or more cigarettes daily) aged 50–69 years living in south western Finland were eligible for the trial. Exclusion criteria were malignancy, severe angina pectoris (angina when walking at normal pace on the level), renal insufficiency, cirrhosis of the liver, other medical problems limiting participation, and use of anticoagulants or vitamin E, vitamin A, or β carotene supplements.

The subjects were randomised in blocks of eight to receive 50 mg/day α tocopherol (as synthetic DL α tocopheryl acetate), 20 mg/day of (synthetic) β carotene, both α tocopherol 50 mg/day and β carotene 20 mg/day, or placebo in a 2 × 2 design. Intervention allocation was double blinded throughout the study. Enrollment took place from 1985 to 1988 and the intervention continued until 30 April 1993.

Angina pectoris at baseline and during follow up was assessed with the WHO (Rose)[15]

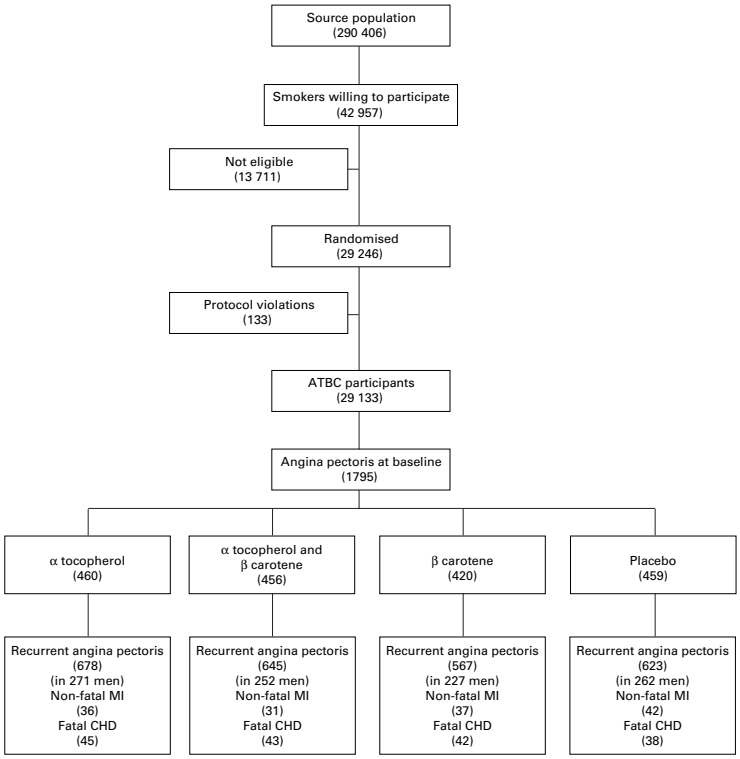

Figure 1 Recruitment, randomisation, and follow up of participants. ATBC, α tocopherol β carotene cancer prevention study; MI, myocardial infarction; CHD, coronary heart disease.

chest pain questionnaire. At baseline there were 1795 men who experienced mild angina pectoris (symptoms only when walking uphill or hurrying).

All participants gave written informed consent. The study was approved by the review boards of both the National Public Health Institute, Helsinki, Finland, and the National Cancer Institute, Bethesda, Maryland, USA.

BASELINE ASSESSMENTS AND OUTCOME MEASURES

At baseline the men completed questionnaires on medical and smoking history. Previous diseases (such as myocardial infarction and diabetes) had to have been diagnosed by a physician. Height and weight were measured and body mass index calculated. Blood pressure was measured with a mercury sphygmomanometer. Total cholesterol and high density lipoprotein cholesterol were determined enzymatically. Alcohol use was determined as part of the dietary history.

Table 1 Baseline characteristics (medians) of men with angina pectoris at baseline in the ATBC study

Characteristic	*α tocopherol (n = 460)*	*α tocopherol and β carotene (n = 456)*	*β carotene (n = 420)*	*Placebo (n = 459)*
Age (years)	58.8	58.4	58.7	58.9
Serum cholesterol (mmol/l)	6.29	6.31	6.26	6.33
HDL cholesterol (mmol/l)	1.03	1.05	1.07	1.06
Systolic blood pressure (mm Hg)	140	139	140	140
Diastolic blood pressure (mm Hg)	87	86	88	88
Body mass index (kg/m^2)	26.6	26.7	26.3	26.9
Number of cigarettes/day	20	20	20	20
Smoking years	40	40	40	40
Alcohol use (g/day)	9.7	10.0	9.6	11.0
History of diabetes (%)	8	8	5	6
History of myocardial infarction (%)*	35	31	29	26

*p = 0.03 between groups.

Table 2 Multivariate adjusted odds ratios (OR) and 95% confidence intervals (CI) of recurrent angina pectoris in men with angina pectoris at baseline in the ATBC study

Supplement	*Recurrences*	*OR* (95% CI)*
α tocopherol	678	1.06 (0.85 to 1.33)
α tocopherol and β carotene	645	1.02 (0.82 to 1.27)
β carotene	567	1.06 (0.84 to 1.33)
Placebo	623	1.00

*Adjusted for the following variables at baseline: age, body mass index, serum total cholesterol, HDL cholesterol, systolic blood pressure, number of cigarettes daily, daily alcohol use, history of diabetes, and history of myocardial infarction. Continuous variables are in tertiles except daily alcohol use, which is categorised as non-users, up to 30 g/day, and over 30 g/day.

Follow up consisted of three visits each year to the local study centre. Once a year a more comprehensive evaluation was made, including readministration of the chest pain questionnaire to assess recurrence and worsening of symptoms of angina pectoris.

Outcome measures were recurrent angina pectoris, progression to severe angina, and major coronary events (non-fatal myocardial infarction and fatal coronary heart disease), which were identified from national registers as described previously.[10]

STATISTICAL ANALYSIS

Each recurrence of angina pectoris in the annual questionnaire readministrations was registered. The recurrences for each group were analysed with logistic regression using generalised estimating equations,[16] which take into account dependence of serial measurements within individuals and thus give more correct standard errors and confidence intervals (CI) for the estimates of the odds ratio (OR). The models were adjusted for age, body mass index, serum total and high density lipoprotein cholesterol, systolic blood pressure, number of cigarettes smoked each day, daily alcohol use, history of diabetes, and history of myocardial infarction. Continuous variables were divided into tertiles, except for alcohol, which was categorised as non-users, up to 30 g/day, and more than 30 g/day. Follow up for recurrence of angina consisted of 6810 person years.

Angina pectoris could only be registered if the study subject was an active participant, therefore dropout is a potential problem. We found no indication that dropping out from the trial was dependent on angina pectoris at previous visit or treatment group.

Progression to more severe symptoms of angina was defined as the first occurrence of severe symptoms (angina when walking at normal pace on level ground) at interview. Follow up consisted of 5741 person years. An incident case of major coronary event was the first occurrence of non-fatal myocardial infarction or fatal coronary heart disease, with 9543 person years of follow up. Supplementation specific cumulative rates of these events were calculated with the Kaplan-Meier method, using the log-rank test to calculate statistical differences among the groups. Cox's proportional hazards regression was used to calculate relative risks of the events using the treatment groups as explanatory variables. These analyses

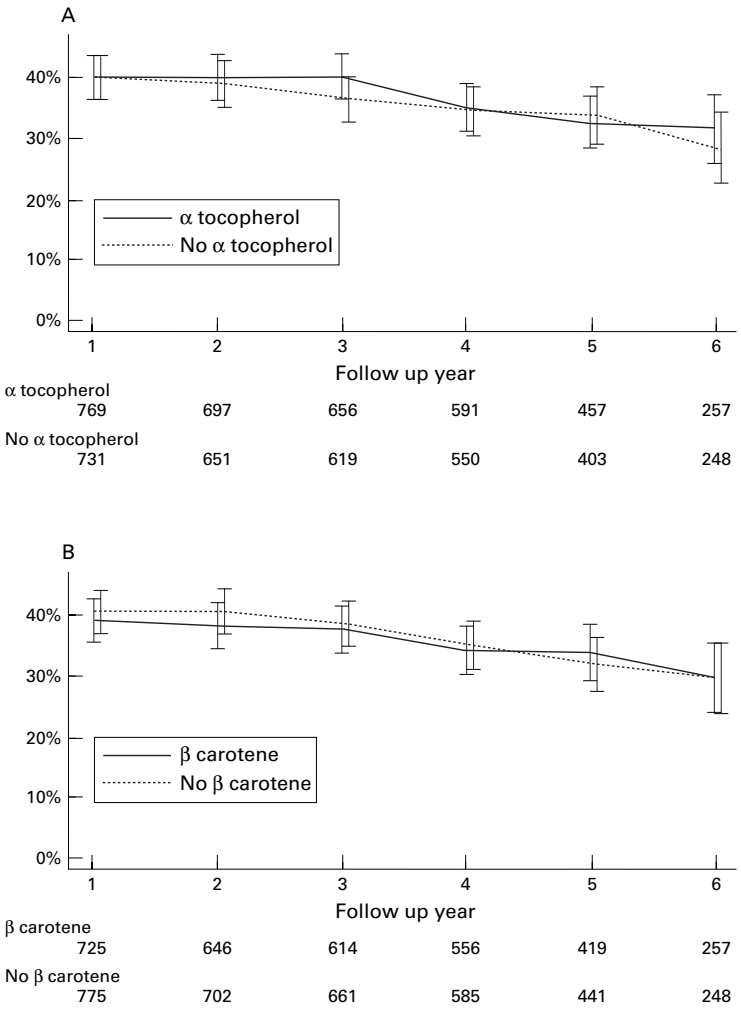

Figure 2 Percentage of subjects reporting typical angina symptoms at annual interview. Number of participants attending interview are given under the figure.

were adjusted for the same baseline variables as the analyses of recurrent angina.

Interactions between the supplements in recurrence of angina pectoris were tested by comparing nested logistic regression generalised estimating equations models, and in progression to severe angina and in major coronary events by comparing nested Cox regression models. No interactions between α tocopherol and β carotene were observed. Interactions between the supplements and background variables were also tested, with an additional test for a trend in the interaction at different levels of the baseline variables.

Table 3 Relative risk (RR) and 95% confidence intervals (CI) of severe angina pectoris in men with angina pectoris at baseline in the ATBC study

Supplement	*Number of cases*	*RR* (95% CI)*
α tocopherol	103	1.14 (0.84 to 1.53)
α tocopherol and β carotene	85	0.98 (0.72 to 1.34)
β carotene	89	1.15 (0.85 to 1.57)
Placebo	86	1.00

*Adjusted for the following variables at baseline: age, body mass index, serum total cholesterol, HDL cholesterol, systolic blood pressure, number of cigarettes daily, daily alcohol use, history of diabetes, and history of myocardial infarction. Continuous variables are in tertiles, except daily alcohol use, which is categorised as non-users, up to 30 g/day, and over 30 g/day.

Results

At baseline the subjects were 58.8 years old, smoked 20 cigarettes a day, had a total cholesterol concentration of 6.29 mmol/l, and a systolic blood pressure of 140 mm Hg (median values). Table 1 summarises baseline data by group. There was a significant difference among the study groups in the history of myocardial infarction. All other background variables were similar among the groups. Dropout rates were highest during the first and second years of follow up (14–17% and 8–11%, respectively), levelling off to about 6% annually thereafter, with no significant differences among the groups.

The 1795 men reported 2513 recurrences of angina pectoris during follow up (median 4 years). Table 2 shows the multivariate adjusted odds ratios of angina pectoris in the three active supplement groups compared with placebo. There was no evidence of any effect of the supplements on recurrence of anginal symptoms. Analyses comparing α tocopherol to no α tocopherol (OR 1.01, 95% CI 0.87 to 1.19) and β carotene to no β carotene (OR 1.00, 95% CI 0.86 to 1.18) similarly showed no effect on recurrence of angina. Figure 2 shows that the proportion of subjects having angina pectoris did not differ among the supplement groups with time. No significant interactions between supplements and background variables were observed.

Table 3 shows that 363 men progressed to severe angina pectoris during a median follow up of three years, with no significant differences among the supplement groups.

There were 314 major coronary events (146 non-fatal myocardial infarctions and 168 fatal coronary heart disease) during a median follow up time of 5.5 years (table 4), with no difference among the groups. There were no significant differences in the risk of major coronary events between α tocopherol supplemented and non-supplemented groups (OR 0.87, 95% CI 0.69 to 1.10), and β carotene supplemented and non-supplemented groups (OR 0.99, 95% CI 0.78 to 1.25). For non-fatal myocardial infarction the relative risk for α tocopherol *v* no α tocopherol was 0.78 (95% CI 0.56 to 1.11) and for β carotene *v* no β carotene it was 0.92 (95% CI 0.65 to 1.30). For fatal coronary heart disease the corresponding figures were 0.96 (0.70 to 1.33) and 1.04 (0.76 to 1.44). In non-fatal myocardial infarction there was an interaction between α tocopherol and serum total cholesterol. In the highest cholesterol tertile α tocopherol seemed to protect against non-fatal myocardial infarction, whereas at lower cholesterol concentrations there was no such effect. Subjects with a history of myocardial infarction who received β carotene had an increased risk for fatal coronary heart disease, there was no such effect in subjects without previous myocardial infarction.

To account for the possible effect of previous myocardial infarction we performed all analyses excluding subjects with a history of myocardial infarction; there were no significant

Table 4 Relative risks and 95% confidence intervals (CI) of major coronary events in men with angina pectoris at baseline in the ATBC study

Coronary event	*α tocopherol*	*α tocopherol and β carotene*	*β carotene*	*Placebo*
Major coronary events				
Number of cases	81	74	79	80
Relative risk (95% CI)	0.95 (0.68 to 1.33)	0.86 (0.61 to 1.20)	1.08 (0.78 to 1.50)	1.00
Non-fatal myocardial infarction				
Number of cases	36	31	37	42
Relative risk (95% CI)	0.83 (0.52 to 1.34)	0.73 (0.45 to 1.18)	0.98 (0.61 to 1.57)	1.00
Fatal coronary heart disease				
Number of cases	45	43	42	38
Relative risk (95% CI)	1.08 (0.68 to 1.72)	1.01 (0.63 to 1.60)	1.18 (0.74 to 1.87)	1.00

Relative risks adjusted for the following variables at baseline: age, body mass index, serum total cholesterol, HDL cholesterol, systolic blood pressure, number of cigarettes daily, daily alcohol use, history of diabetes, and history of myocardial infarction. Continuous variables are in tertiles, except daily alcohol use, which is categorised as non-users, up to 30 g/day, and over 30 g/day.

effects of the supplements on any outcome measure (data not shown).

Discussion

Antioxidant supplements had no effect on recurrence or progression of symptoms or on major coronary events in patients with angina pectoris.

There were no differences in classic risk factors of coronary heart disease at baseline among the groups except for history of myocardial infarction, which was accounted for in the regression models. It is plausible to assume that worsening symptoms of angina would lead to discontinuation of active participation, which could be a source of error. Dropout rates, however, were similar across the groups. We also found dropout to be independent of angina pectoris at the previous visit. However, it cannot be totally ruled out that dropout affected the angina pectoris results. As major coronary events were followed up through registers, cases could be identified regardless of whether the subject was actively participating. The validity of the register diagnoses has been evaluated and reported to be good.[17]

Current medication, another potential source of error, was not accounted for. It is unlikely that pre-randomisation medications among the groups differed. Medication during follow up might differ among the groups, assuming that the supplements affected angina pectoris symptoms. Accounting for anti-anginal medication in the analyses is problematic, as many anti-anginal drugs, such as β blockers and calcium antagonists, can be prescribed for other conditions. We do not believe that differences in medication during the trial would be large enough to obscure a true beneficial effect of the vitamin supplements.

Angina pectoris symptoms were assessed by the WHO chest pain questionnaire, designed by Geoffrey Rose in 1962.[15] It is the most widely used questionnaire of chest pain symptoms in epidemiological studies and large trials. Its findings correlate well with clinical diagnoses and ECG findings (sensitivity 56–83%, specificity 77–100%).[18 19] Comparisons with angiography and thallium scintigraphy are not as good (sensitivity 18% and 44%, specificity 81% and 77%, respectively).[20 21] Angina pectoris, however, is a clinical diagnosis of exertional chest pain and it is understandable that correlations with more exact methods, especially those assessing coronary anatomy, are not very high. However, angina pectoris determined with the questionnaire effectively predicts future coronary heart disease mortality and total mortality.[22]

At the first follow up visit about 40% of the participants reported angina pectoris, and the proportion slightly decreased thereafter. Angina symptoms assessed by the questionnaire are known to vary substantially, which probably reflects a combination of true physiological variation of the symptoms and variability in answering the questionnaire. Repeatability is correlated with severity of the symptoms[23] and decreases with time.[19] Several studies have reported similar percentages (35–40%) of repeatability at annual interviews.[19 23–25] Rose observed that repeated examinations gave a better picture of disease severity than a single examination, and increased the ability to observe differences among groups.[23] We see no reason why repeatability would be dependent on the vitamin supplements. Despite known limitations, we consider it unlikely that the shortcomings of the questionnaire could explain the observed lack of effect.

Two randomised placebo controlled trials in the 1970s showed no functional improvement in angina pectoris patients with α tocopherol.[26 27] A trial with serial coronary angiography assessments showed less lesion progression among vitamin E supplement users (100 IU/day or more),[28] but the fact that antioxidant use in that study was not randomised seriously limits the conclusions that can be drawn. Risk of non-fatal myocardial infarction decreased with α tocopherol supplement use (400–800 IU/day) in patients with coronary heart disease in the Cambridge heart antioxidant study (CHAOS), but mortality was unaffected.[9] We observed a non-significant increase in fatal coronary heart disease in ATBC participants with previous myocardial infarction taking α tocopherol.[10]

The dose of α tocopherol in this study was quite low. Jialal *et al* suggested that at least 400 IU/day of α tocopherol are needed to decrease the susceptibility of low density lipoprotein cholesterol to oxidation,[29] but there is evidence that smaller doses may also have some effect.[30] The physiological relevance of doses able to inhibit in vitro oxidation is unknown.

Studies with β carotene in angina pectoris are even more limited. A subgroup analysis in subjects with coronary heart disease (n = 333) in the physician's health study initially showed substantial prognostic improvement,[11] but there was attenuation of benefits with prolonged follow up.[12] We observed a slight tendency towards increased risk of fatal coronary heart disease with β carotene use, but the risk was raised only among participants with a history of myocardial infarction, as we have reported previously.[10]

Angina pectoris is a clinical diagnosis of chest pain and it may be argued that it is not a relevant outcome measure for a prevention or treatment trial. Angina pectoris results, however, are in harmony with the "harder" outcome measures in this study—myocardial infarction and fatal coronary heart disease. Although confidence intervals of these major coronary events are rather wide and cannot totally exclude clinically relevant beneficial (or harmful) effects, the current results are in line with previous results from the ATBC study,[10 25 31 32] which did not show any usefulness of the supplements in prevention or treatment of coronary heart disease. Other large controlled trials, with the exception of CHAOS,[9] have also failed to demonstrate beneficial effects of antioxidant supplements on coronary heart disease.[33 34]

In conclusion, we observed no effect of α tocopherol and β carotene supplements on recurrence or progression of angina symptoms, or subsequent major coronary events in subjects with angina pectoris at baseline examination. While there are limitations to this study, these are unlikely to nullify any favourable effect. We see no therapeutic or prophylactic use for these agents at these doses for patients with angina pectoris.

This study was supported by the Finnish Foundation for Cardiovascular Research and the Academy of Finland. The ATBC study was supported by a contract with the United States National Cancer Institute (N01-CN-45165).

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