

# Randomised trial of $\alpha$ -tocopherol and $\beta$ -carotene supplements on incidence of major coronary events in men with previous myocardial infarction

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## Summary

**Background** Epidemiological data suggest that the intake of antioxidants such as  $\alpha$ -tocopherol (vitamin E) and  $\beta$ -carotene has an inverse correlation with the incidence of coronary heart disease. The results from clinical trials of antioxidant supplementation in people with known coronary heart disease are inconclusive.

**Methods** We studied the frequency of major coronary events in 1862 men enrolled in the Alpha-tocopherol Beta-carotene Cancer Prevention Study (smokers aged between 50 and 69 years) who had a previous myocardial infarction. In this randomised, double-blind, placebo-controlled study, men had received dietary supplements of  $\alpha$ -tocopherol (50 mg/day),  $\beta$ -carotene (20 mg/day), both, or placebo. The median follow-up was 5.3 years. The endpoint of this substudy was the first major coronary event after randomisation. Analyses were by intention to treat.

**Findings** 424 major coronary events (non-fatal myocardial infarction and fatal coronary heart disease) occurred during follow-up. There were no significant differences in the number of major coronary events between any supplementation group and the placebo group ( $\alpha$ -tocopherol 94/466;  $\beta$ -carotene 113/461;  $\alpha$ -tocopherol and  $\beta$ -carotene 123/497; placebo 94/438 [log-rank test,  $p=0.25$ ]). There were significantly more deaths from fatal coronary heart disease in the  $\beta$ -carotene (74/461, multivariate-adjusted relative risk 1.75 [95% CI 1.16–2.64],  $p=0.007$ ) and combined  $\alpha$ -tocopherol and  $\beta$ -carotene groups (67/497, relative risk 1.58 [1.05–2.40],  $p=0.03$ ) than in the placebo group (39/438), but there was no significant increase in the  $\alpha$ -tocopherol supplementation group (54/466, relative risk 1.33 [0.86–2.05],  $p=0.20$ ).

**Interpretation** The proportion of major coronary events in men with a previous myocardial infarction who smoke was not decreased with either  $\alpha$ -tocopherol or  $\beta$ -carotene supplements. In fact, the risk of fatal coronary heart disease increased in the groups that received either  $\beta$ -carotene or the combination of  $\alpha$ -tocopherol and  $\beta$ -carotene; there was a non-significant trend of increased deaths in the

$\alpha$ -tocopherol group. We do not recommend the use of  $\alpha$ -tocopherol or  $\beta$ -carotene supplements in this group of patients.

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## Introduction

Oxidative modification of low-density lipoprotein may be a key event in the initiation and progression of atherosclerosis. Dietary  $\alpha$ -tocopherol (vitamin E) supplements protect low-density-lipoprotein cholesterol from oxidation *in vitro*, but  $\beta$ -carotene supplements have not always shown this effect.<sup>1–3</sup> Data from prospective cohort studies suggest that dietary intakes of vitamin E and  $\beta$ -carotene are inversely associated with coronary heart disease.<sup>4–7</sup> However, data from controlled clinical trials do not support these findings.

Large studies of antioxidant supplementation for chronic disease prevention have found either no effect on cardiovascular disease<sup>8</sup> or a slight increase in cardiovascular mortality.<sup>9–11</sup> Only two studies have investigated the use of antioxidant supplements for secondary prevention of coronary heart disease. The Cambridge Heart Antioxidant Study<sup>12</sup> found that among patients with pre-existing coronary heart disease, supplementation with  $\alpha$ -tocopherol decreased the incidence of non-fatal myocardial infarction, but not the risk of cardiovascular death. In the Physicians' Health Study,<sup>13</sup> a subgroup of men with pre-existing coronary heart disease initially seemed to benefit from  $\beta$ -carotene supplementation, but further analysis showed a non-significant increase in cardiovascular deaths.<sup>14</sup> Thus, the safety and efficacy of antioxidants in these patients is not proven.

The primary aim of the Alpha-tocopherol Beta-carotene Cancer Prevention (ATBC) Study was to investigate the effects of  $\alpha$ -tocopherol and  $\beta$ -carotene supplements on the incidence of lung cancer. An evaluation of the effects of the supplements on cardiovascular diseases, however, was also a part of the study protocol. We report here the effects of  $\alpha$ -tocopherol and  $\beta$ -carotene supplements on the frequency of major coronary events among men at high risk of a coronary event because of myocardial infarction before entry to the ATBC Study.

## Methods

29 133 male smokers aged 50–69 years were recruited between 1985 and 1988 by a postal questionnaire from the male population living in southwestern Finland ( $n=290\,406$ ) (figure 1). The study design, methods, participants' characteristics, and compliance have been reported in detail.<sup>15</sup>

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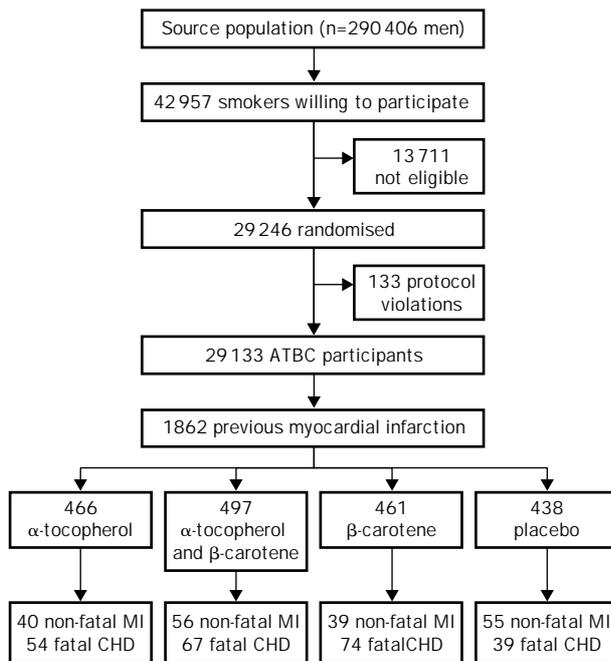


Figure 1: Trial profile

MI=myocardial infarction; CHD=coronary heart disease

The exclusion criteria were: proven malignant disease, severe angina pectoris (defined as angina on walking on level ground), chronic renal insufficiency, cirrhosis of the liver, alcoholism, other medical problems that might limit participation, anticoagulant therapy, and use of vitamin E, vitamin A, or  $\beta$ -carotene supplements in doses that exceeded prespecified limits. The men were randomly assigned to one of the following supplementation groups in a  $2 \times 2$  factorial design in blocks of eight. They received either  $\alpha$ -tocopherol (*d,l*- $\alpha$ -tocopheryl acetate) 50 mg daily,  $\beta$ -carotene 20 mg daily, both supplements, or placebo, on a double-blind basis. This design allows the investigation of two agents in a single trial provided there is no interaction between the effects.

1862 men had had a myocardial infarction before entry to the study. The flow of participants is shown in the trial profile (figure 1).

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

Participants completed a questionnaire about their general background, smoking and medical histories, including a question about a previous myocardial infarction diagnosed by a physician. The questionnaire also asked about the time and place of treatment for the myocardial infarction. At the first visit, a trained study nurse reviewed the questionnaire with the participant and made corrections if necessary. Alcohol intake was assessed in a detailed diet-history questionnaire. The frequency of leisure-time physical activity, slightly strenuous activity for a minimum of 30 min per episode, was categorised: less than once a week, once or twice a week, and three or more times a week. Height and weight were measured and body-mass index was calculated (weight in

kg/[height in m]<sup>2</sup>). Blood pressure was measured in the right arm with a mercury sphygmomanometer under standard conditions and the lower of two measurements at least 1 min apart was recorded. Serum total and high-density-lipoprotein cholesterol concentrations were measured by an enzymatic method (CHOD/PAP, Boehringer Mannheim, Mannheim, Germany), and serum  $\alpha$ -tocopherol and  $\beta$ -carotene concentrations by high-performance liquid chromatography.<sup>16</sup>

Participants were reviewed three times per year at a local study centre. At each visit they returned their previous capsule pack and received a new one. Smoking habits were assessed at each visit. A participant was deemed to have stopped smoking if he reported not smoking at two consecutive follow-up visits. A second blood sample was taken 3 years after entry. Follow-up continued until April 30, 1993. The median follow-up time was 5.3 years with a total of 9505 person-years.

The endpoint in this analysis was the first major coronary event after randomisation. The endpoints were identified from national morbidity and mortality registers. In Finland, all hospital treatments are recorded on the National Hospital Discharge register. All deaths are recorded on the National Register of Causes of Death. Both registers use the codes of the International Classification of Diseases (ICD). During the study, the 8th edition (ICD-8) was used up to the end of 1986, and the 9th edition (ICD-9) thereafter.

Record linkage of the study database and the registers was made by the unique Finnish personal identification number of each participant. We searched for the first myocardial infarction (codes 410.00–410.99 in ICD-8 and 4100–4109 in ICD-9) after randomisation in the hospital discharge register and the register of causes of death.

Major coronary events were classified into two groups. In the non-fatal myocardial infarction group were patients who survived the first 28 days after the event. The fatal coronary heart disease group included patients who died of any cause within 28 days of a myocardial infarction and other deaths where the underlying cause was listed under codes 411.00–414.99 and 4110–4149 in ICD-8 and ICD-9, respectively. The death certificates were also reviewed to find out whether the cause of death had been confirmed by necropsy, and to identify cases of sudden death—ie, those within 1 h of symptom onset. The validity of the diagnoses of major coronary events in the registers at the ATBC study has been previously reported.<sup>17</sup>

### Statistical methods

Supplementation-specific cumulative frequencies for  $\alpha$ -tocopherol and  $\beta$ -carotene were calculated by the Kaplan-Meier method, and the log-rank test was used to test for differences between the groups. Age and multivariate-adjusted relative risks and their 95% CI were estimated by Cox's proportional-hazards regression with the supplementation groups as explanatory variables. The proportional-hazards assumption was evaluated and tested. All analyses were by intention to treat.

Interaction between the supplements was tested by comparing nested-Cox models with the likelihood ratio test. An interaction was found in the non-fatal myocardial infarction group ( $p=0.024$ ), but not in the fatal coronary heart disease group ( $p=0.11$ ) or in both events together ( $p=0.72$ ). An interaction

Characteristic	$\alpha$ -tocopherol (n=466)	$\alpha$ -tocopherol and $\beta$ -carotene (n=497)	$\beta$ -carotene (n=461)	Placebo (n=438)
Age (years)*	59.0 (55.1–62.7)	60.0 (56.2–63.6)	60.2 (56.5–64.2)	59.3 (55.3–62.8)
Body-mass index (kg/m <sup>2</sup> )	26.4 (24.2–29.0)	26.5 (24.0–28.6)	26.2 (23.8–28.9)	26.6 (24.5–28.9)
Cigarettes (per day)	20 (15–24)	20 (12–25)	20 (15–20)	20 (15–25)
Smoking years	40 (34–44)	40 (35–45)	40 (35–45)	40 (34–44)
Alcohol intake (g/day)	8.2 (1.7–22.9)	8.0 (1.7–21.9)	10.7 (1.8–23.7)	8.5 (1.8–22.8)
Physical activity $\geq 3$ times/week (%)	27	28	24	24
History of diabetes (%)	9	9	8	6
Systolic blood pressure (mm Hg)	140 (128–154)	140 (128–154)	140 (128–154)	140 (128–152)
Diastolic blood pressure (mm Hg)	86 (80–94)	86 (80–92)	86 (80–92)	86 (78–92)
Serum cholesterol (mmol/L)	6.32 (5.49–7.12)	6.33 (5.65–7.06)	6.32 (5.56–7.11)	6.23 (5.61–7.04)
High-density-lipoprotein cholesterol (mmol/L)	1.03 (0.88–1.23)	1.03 (0.89–1.23)	1.04 (0.89–1.22)	1.04 (0.87–1.23)

Median (interquartile range). \* $p=0.0048$  for difference between the four groups.

Table 1: Baseline characteristics of participants by supplementation group

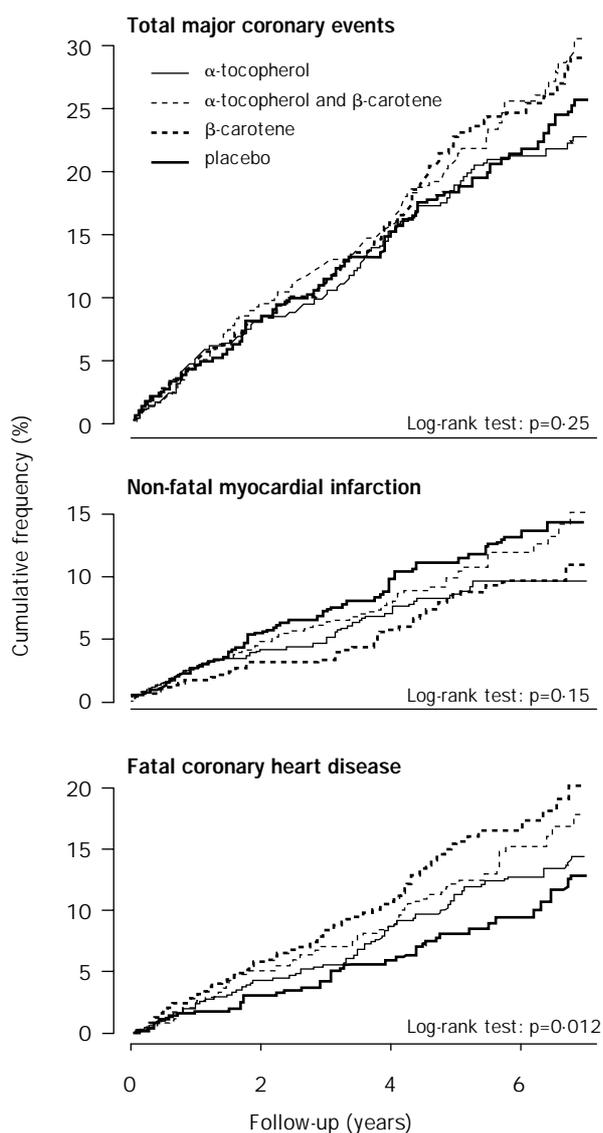


Figure 2: Kaplan-Meier estimates of frequencies of coronary events

between supplements and baseline variables was similarly tested with additional tests for a linear trend of interaction between the supplements and levels of baseline variables (continuous variables were divided into tertiles). No statistically significant interactions were found.

Multivariate analyses were adjusted for the following baseline characteristics: age, serum total and high-density-lipoprotein cholesterol, systolic blood pressure, body-mass index, number of cigarettes smoked daily, alcohol intake (g/day), frequency of leisure-time physical activity, and history of diabetes.

## Results

The numbers of participants and endpoints are summarised in figure 1. Baseline characteristics are given in table 1. The median age ranged from 59.0 to 60.2 years between the four groups ( $p=0.005$ ). There were no other significant differences between groups. 17% of all participants stopped smoking while taking part in the study; this percentage did not differ significantly between the supplementation groups. Of the men who had an endpoint event, 76% were active participants in the study at the time, and there were no significant differences in this percentage between the groups.

Serum concentrations of  $\alpha$ -tocopherol increased from a median of 28.5  $\mu\text{mol/L}$  at baseline to 42.5  $\mu\text{mol/L}$  at 3 years in the  $\alpha$ -tocopherol-supplemented group. Similarly,  $\beta$ -carotene supplementation increased serum  $\beta$ -carotene concentrations from a median of 0.298  $\mu\text{mol/L}$  at baseline to 5.54  $\mu\text{mol/L}$  at 3 years. In men who received supplements there were no differences in serum concentrations ( $\alpha$ -tocopherol 45.9  $\mu\text{mol/L}$  and 43.5  $\mu\text{mol/L}$ ,  $p=0.17$ ;  $\beta$ -carotene 6.16  $\mu\text{mol/L}$  and 5.16  $\mu\text{mol/L}$ ,  $p=0.25$ ) between those who had a non-fatal or total endpoint event, respectively.

A total of 424 major coronary events were observed; 190 (45%) were non-fatal myocardial infarctions and 234 (55%) fatal coronary heart disease events. The frequencies of all major coronary events, non-fatal myocardial infarctions and fatal coronary heart disease, are shown in figure 2. There were no differences between the supplementation groups in the total number of major coronary events. The risk of non-fatal myocardial infarction was lower in all supplemented groups than in the placebo group and this was significant in the  $\alpha$ -tocopherol group on multivariate adjustment (table 2).

There was a significant difference between groups in fatal coronary heart disease (log-rank test  $p=0.012$ ); the highest frequency was in the  $\beta$ -carotene-supplemented group and the lowest in the placebo group. The numbers of events, incidence rates, and age-adjusted and multivariate-adjusted relative risks of the three supplementation groups compared with placebo are given in table 2.

Coronary event	$\alpha$ -tocopherol	$\alpha$ -tocopherol and $\beta$ -carotene	$\beta$ -carotene	Placebo
<b>All events</b>				
Number	94	123	113	94
Incidence (per 1000 person-years)	38.9	48.9	48.7	41.7
Age-adjusted RR (95% CI)	0.94 (0.70-1.25)	1.16 (0.89-1.52)	1.16 (0.88-1.52)	1.00
Multivariate-adjusted RR (95% CI)*	0.90 (0.67-1.22)	1.14 (0.87-1.51)	1.11 (0.84-1.48)	1.00
<b>Non-fatal myocardial infarction</b>				
Number	40	56	39	55
Incidence (per 1000 person-years)	16.6	22.3	16.8	24.4
Age-adjusted RR (95% CI)	0.68 (0.45-1.02)	0.91 (0.63-1.32)	0.69 (0.46-1.04)	1.00
Multivariate-adjusted RR (95% CI)*	0.62 (0.41-0.96)	0.86 (0.58-1.26)	0.67 (0.44-1.02)	1.00
<b>Fatal coronary heart disease</b>				
Number	54	67	74	39
Incidence (per 1000 person-years)	22.4	26.7	31.9	17.3
Age-adjusted RR (95% CI)	1.30 (0.86-1.96)	1.51 (1.02-2.24)	1.81 (1.23-2.67)	1.00
Multivariate-adjusted RR (95% CI)*	1.33 (0.86-2.05)	1.58 (1.05-2.40)	1.75 (1.16-2.64)	1.00

\*Adjusted for age, number of daily cigarettes, serum total and high-density-lipoprotein cholesterol, systolic blood pressure, body-mass index, daily alcohol intake, frequency of leisure-time physical activity, and history of diabetes at baseline.

Table 2: Incidence and adjusted relative risks (RR) of coronary events by supplementation group

Coronary event	Number	Incidence (per 1000 person-years)	Relative risk (95% CI)
<b>All events</b>			
α-tocopherol	217	44.0	0.97 (0.80-1.19)
No α-tocopherol	207	45.2	1.00
β-carotene	236	48.8	1.19 (0.97-1.45)
No β-carotene	188	40.3	1.00
<b>Non-fatal myocardial infarction</b>			
α-tocopherol	96	19.5	0.89 (0.67-1.20)
No α-tocopherol	94	20.5	1.00
β-carotene	95	19.6	0.95 (0.71-1.28)
No β-carotene	95	20.3	1.00
<b>Fatal coronary heart disease</b>			
α-tocopherol	121	24.6	1.05 (0.80-1.37)
No α-tocopherol	113	24.7	1.00
β-carotene	141	29.2	1.43 (1.08-1.88)
No β-carotene	93	19.9	1.00

\*Adjusted for age, number of daily cigarettes, serum total and high-density-lipoprotein cholesterol, systolic blood pressure, body mass index, daily alcohol intake, frequency of leisure-time physical activity, and history of diabetes at baseline.

Table 3: Incidence and adjusted relative risk of coronary events by supplementation with either α-tocopherol or β-carotene

The risk of fatal coronary heart disease was significantly increased in the β-carotene group ( $p=0.007$ ) and combined β-carotene and α-tocopherol group ( $p=0.03$ ).

Analysis by the  $2 \times 2$  design, showed a 19% increase ( $p=0.093$ ) in the multivariate-adjusted risk of total major coronary events in β-carotene-supplemented men, whereas α-tocopherol supplementation had a neutral effect. Neither supplement had a significant effect on non-fatal myocardial infarction, but a 43% ( $p=0.011$ ) increase in the risk of fatal coronary heart disease was found with β-carotene supplementation compared with those not supplemented (table 3).

We also analysed the data with myocardial infarction as the only endpoint—ie, ICD-8 codes 410.00-410.99 and ICD-9 codes 410.0-410.9 (table 4). The multivariate-adjusted relative risks of all myocardial infarctions by supplementation group were similar to those of total major coronary events. There was an increased relative risk of fatal myocardial infarction in all supplementation groups, which was greatest in the β-carotene only group (3.44 [1.70-6.94]).

Total mortality is shown in figure 3. There was a significant difference between the groups (log-rank test  $p=0.049$ ); the highest mortality was in the β-carotene group and the lowest in the placebo group. There were similar numbers of deaths from causes other than ischaemic heart disease in all the supplementation groups. Sudden death occurred in one-third of the cases of fatal coronary heart disease. This proportion varied between 28% and 37% in the placebo and α-tocopherol groups, respectively, but no differences between groups were significant.

Coronary event	α-tocopherol	α-tocopherol and β-carotene	β-carotene	Placebo
<b>Total myocardial infarction</b>				
Number	64	86	79	66
Incidence (per 1000 person-years)	26.5	34.2	34.0	29.3
Relative risk	0.81 (0.56-1.17)	1.14 (0.82-1.59)	1.11 (0.79-1.56)	1.00
<b>Fatal myocardial infarction</b>				
Number	24	30	40	11
Incidence (per 1000 person-years)	9.9	11.9	17.2	4.9
Relative risk	1.83 (0.85-3.95)	2.67 (1.30-5.48)*	3.44 (1.70-6.94)†	1.00

\*Adjusted for age, number of daily cigarettes, serum total and high-density lipoprotein cholesterol, systolic blood pressure, body mass index, daily alcohol intake, frequency of leisure-time physical activity, and history of diabetes at baseline (95% CI). \* $p=0.007$ , † $p<0.001$  compared with placebo.

Table 4: Incidence and adjusted relative risk of total myocardial infarction and fatal myocardial infarction by supplementation group

## Discussion

Dietary supplementation with α-tocopherol, β-carotene, or their combination had little effect on the total number of major coronary events. However, both dietary supplements, especially β-carotene, increased the risk of fatal coronary heart disease. A non-significant decrease in non-fatal myocardial infarction was found with both supplements, and although a protective effect cannot be ruled out, the decrease is probably a reflection of the increased mortality. The excess mortality was greatest in the fatal myocardial infarction group, but because only 11 deaths were seen in the placebo group the relative-risk estimates should be interpreted with caution.

The ATBC Study was primarily a study of lung cancer. An investigation of cardiac events, however, was planned when the study was designed—which can be seen in the questions about previous cardiac diseases, an annually repeated chest-pain questionnaire, and continuous monitoring of the registers for cardiovascular events.

24% of the events occurred in men who were no longer active participants. The withdrawal rates did not differ by supplementation group. In intention-to-treat analyses, such as these, withdrawals tend to dilute the effect of the intervention, so it is possible that the true effects of the supplements may be even greater than we observed. There was a significant interaction between α-tocopherol and β-carotene supplementation in non-fatal myocardial infarction, which should be considered in the interpretation of the results in table 3. We do not know of any plausible explanation for this interaction, which may be a chance finding. Because of this interaction, however, we analysed and presented the results primarily for the four separate supplementation groups rather than by the original  $2 \times 2$  design.

Background variables at baseline were well balanced across the supplementation groups, except for age. To take account of this difference, all analyses were age adjusted. The specific risk factors for recurrent coronary events such as total cholesterol, high-density-lipoprotein cholesterol, and smoking were in good balance.<sup>18,19</sup> Multivariate adjustment for known risk factors did not change the results.

The endpoints were identified from national registries and thus event follow-up was not dependent on the men's active participation. Validation of the diagnoses of major coronary events in the registries has been done in a sample of ATBC participants.<sup>17</sup> The positive predictive value of the diagnoses of major coronary events in the registries was 94%, and there were no statistically significant differences between the supplementation groups. We conclude therefore that the register diagnoses are valid for endpoint assessment. Necropsy confirmation was available for similar proportions of the four groups (53% overall).

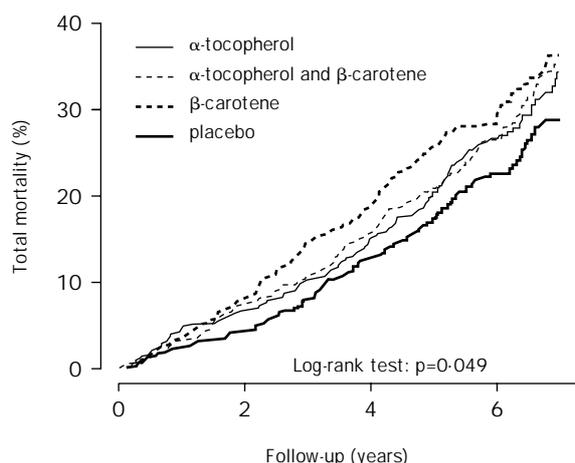


Figure 3: Kaplan-Meier estimates of mortality

Patients with previous myocardial infarctions are at high risk of another major coronary event. In our study, the first major coronary event during follow-up was a non-fatal myocardial infarction in 10% of the participants and death from coronary heart disease in 13%. These percentages are similar to those of other studies.<sup>18,20</sup>

There are few data from clinical trials of antioxidants in people with pre-existing coronary heart disease. The Physicians' Health Study<sup>13</sup> excluded people with a history of a myocardial infarction. However, there was a subgroup in this study (n=333) with pre-existing coronary heart disease other than myocardial infarction; they initially seemed to benefit from  $\beta$ -carotene supplementation.<sup>13</sup> Another report on this subgroup found there was a non-significant increase in cardiovascular deaths with  $\beta$ -carotene.<sup>14</sup> In the Cambridge Heart Antioxidant Study,<sup>12</sup>  $\alpha$ -tocopherol supplementation decreased the risk of non-fatal myocardial infarction by 77% in patients with angiographically documented coronary heart disease. There were, however, 29% more deaths, including fatal myocardial infarctions in the  $\alpha$ -tocopherol supplemented group than in the placebo group, although this difference, possibly because of small numbers, was not significant. In our study, serum concentrations of  $\alpha$ -tocopherol in the supplemented group (mean 44.7  $\mu\text{mol/L}$ ) were similar to concentrations achieved with 400 IU  $\alpha$ -tocopherol supplementation in the Cambridge Heart Antioxidant Study (mean 51.1  $\mu\text{mol/L}$ ).<sup>12</sup>

$\beta$ -carotene supplementation increased serum concentrations 19-fold—an increase similar to the concentrations in the full ATBC Study.<sup>9</sup> These concentrations are much higher than those found in people on normal diets. The possible toxic effects of these concentrations of  $\beta$ -carotene are not known. Serum  $\beta$ -carotene concentrations, however, did not significantly differ between men who had a non-fatal or fatal coronary event.

The mechanism of the increase in deaths with the supplements is unknown. But, since this finding was observed with both supplements, it may be associated with their antioxidant activity. One proposed mechanism is that the antioxidant effect of  $\alpha$ -tocopherol limits or abolishes preconditioning—ie, the protection of myocardium against ischaemia by short periods of ischaemia and reperfusion.<sup>21</sup> Preconditioning in animals is, at least partly, mediated by reactive oxygen species, and the protective effect of preconditioning can be inhibited with antioxidants.<sup>22,23</sup> Whether preconditioning occurs in human beings needs to be established, but there is some evidence that it does.<sup>24-26</sup>

There are other possible mechanisms.  $\beta$ -carotene is easily incorporated into the atherosclerotic plaque<sup>27,28</sup> and whether its presence may render the plaque more susceptible to rupture is not known. A decrease in spontaneous thrombolysis and electrical or mechanical instability of the injured myocardium are also possible mechanisms. Finally, the size of the study group and the number of endpoints cannot completely exclude the possibility of a chance finding.

In conclusion, both  $\alpha$ -tocopherol and  $\beta$ -carotene increased the risk of fatal coronary heart disease. Based on these findings we recommend that patients with a previous myocardial infarction who smoke should not use these agents. Further studies will provide information about the safety and efficacy of antioxidants in secondary prevention of coronary heart disease.<sup>29</sup>

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## Diastolic ventricular interaction in chronic heart failure

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### Summary

**Background** Diastolic ventricular interaction describes a situation in which the volume of one ventricle is directly influenced by the volume of the other ventricle. Such interaction is normally negligible, but it is accentuated in circumstances associated with pulmonary hypertension and volume overload. When this interaction occurs, acute volume unloading results in a reduction in right ventricular end-diastolic volume, as expected, but left ventricular end-diastolic volume paradoxically increases. Since chronic heart failure is a volume-overloaded state associated with pulmonary hypertension, we hypothesised that this interaction may be clinically important in patients with heart failure.

**Methods** A radionuclide technique incorporating cardiac scintigraphy was used to measure the effect of acute volume unloading, achieved by 30 mm Hg lower-body suction, on right and left ventricular end-diastolic volumes in 21 patients with chronic heart failure and 12 healthy individuals (controls).

**Findings** In nine heart-failure patients, there was a paradoxical increase in left ventricular end-diastolic volume in association with an expected decrease in right ventricular end-diastolic volume during lower-body suction. This response was not seen in the control group. The mean change in left ventricular end-diastolic volume differed significantly between the heart-failure patients and controls (6 [SD 19] vs -19 [12] mL,  $p=0.0003$ ). However, the change in right ventricular end-diastolic volume was similar in the two groups (-18 [11] vs -20 [8]%,  $p=0.70$ ). Patients who increased left ventricular end-diastolic volume during lower-body suction had higher resting pulmonary

arterial and pulmonary capillary wedge pressures than the remaining heart-failure patients.

**Interpretation** The response of nine patients in our study suggests diastolic ventricular interaction, which we believe could be common in patients with chronic heart failure. This finding is relevant to their management, since it emphasises the importance of venodilator therapy. The relation between stroke volume and left ventricular end-diastolic volume, by the Frank-Starling law of the heart, may explain why some patients with chronic heart failure paradoxically increase stroke volume when pulmonary capillary wedge pressure is lowered with vasodilators.

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### Introduction

Acute volume loading normally causes an increase in both left and right ventricular end-diastolic volumes until the pericardium becomes stretched to its limit, which then prevents further increases in total cardiac volume—pericardial constraint. When this occurs, pericardial pressure increases and contributes significantly to raised left ventricular end-diastolic pressure.<sup>1,2</sup> In the presence of pericardial constraint and secondary pulmonary hypertension (eg, pulmonary embolism, chronic obstructive pulmonary disease), any increase in right ventricular volume caused by volume loading can then occur only at the expense of left ventricular volume, so that total cardiac volume remains unchanged.<sup>2-5</sup> Volume unloading in this setting will reduce right ventricular end-diastolic volume and increase left ventricular end-diastolic volume; total cardiac volume will remain essentially unchanged.<sup>2,5</sup> These changes contrast with the healthy cardiovascular system, in which a reduction in both left and right ventricular end-diastolic volumes occurs during acute volume unloading (figure 1).<sup>6,7</sup> This phenomenon, by which the volume of one ventricle directly influences the volume of the other, is termed direct diastolic ventricular interaction and is important in settings of volume overload and pulmonary hypertension in human beings and in animal models.<sup>2-5</sup> Chronic heart failure has features in

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