Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS)

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Summary

Background Vitamin E (α-tocopherol) is thought to have a role in prevention of atherosclerosis, through inhibition of oxidation of low-density lipoprotein. Some epidemiological studies have shown an association between high dietary intake or high serum concentrations of α-tocopherol and lower rates of ischaemic heart disease. We tested the hypothesis that treatment with a high dose of α-tocopherol would reduce subsequent risk of myocardial infarction (MI) and cardiovascular death in patients with established ischaemic heart disease.

Methods In this double-blind, placebo-controlled study with stratified randomisation, 2002 patients with angiographically proven coronary atherosclerosis were enrolled and followed up for a median of 510 days (range 3-981). 1035 patients were assigned α-tocopherol (capsules containing 800 IU daily for first 546 patients; 400 IU daily for remainder); 967 received identical placebo capsules. The primary endpoints were a combination of cardiovascular death and non-fatal MI as well as non-fatal MI alone.

Findings Plasma α-tocopherol concentrations (measured in subsets of patients) rose in the actively treated group (from baseline mean 34.2 μmol/L to 51.1 μmol/L with 400 IU daily and 64.5 μmol/L with 800 IU daily) but did not change in the placebo group. α-tocopherol treatment significantly reduced the risk of the primary trial endpoint of cardiovascular death and non-fatal MI (41 vs 64 events; relative risk 0.53 [95% CI 0.34–0.83; p=0.005]). The beneficial effects on this composite endpoint were due to a significant reduction in the risk of non-fatal MI (14 vs 41; 0.23 [0.11–0.47]; p=0.005); however, there was a non-significant excess of cardiovascular deaths in the α-tocopherol group (27 vs 23; 1.18 [0.62–2.27]; p=0.61). All-cause mortality was 36 of 1035 α-tocopherol-treated patients and 27 of 967 placebo recipients.

Interpretation We conclude that in patients with angiographically proven symptomatic coronary atherosclerosis, α-tocopherol treatment substantially reduces the rate of non-fatal MI, with beneficial effects apparent after 1 year of treatment. The effect of α-tocopherol treatment on cardiovascular deaths requires further study.

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See Commentary page 776

Introduction

The Cambridge Heart Antioxidant Study (CHAOS) was designed to test the hypothesis that treatment with a high dose of α-tocopherol (vitamin E) would reduce the risk of myocardial infarction (MI) in patients with angiographic evidence of coronary atherosclerosis. This hypothesis developed from the idea that macrophage-mediated oxidation of low-density lipoprotein (LDL) has a central role in atherogenesis and the extensive experimental and epidemiological evidence to support this view.1

Epidemiological studies of dietary intake and serum concentrations of α-tocopherol in relation to risk of coronary atherosclerosis have had mixed results. Three large, prospective, nested case-control studies found no correlation between serum α-tocopherol concentrations and subsequent myocardial infarction or cardiovascular death.2–4 However, two studies in the USA found significant risk ratios of 0.64 in men and 0.66 in women between quintiles with the highest and lowest intake.5,6

The single published randomised controlled trial of α-tocopherol (in the prevention of lung cancer)7 found no effect on cardiovascular mortality, with a low dose of α-tocopherol (50 mg daily). An overview of epidemiological data suggested that a trial of α-tocopherol in ischaemic heart disease would need to use large doses of α-tocopherol to demonstrate any treatment effect.

In CHAOS, we studied the effects of α-tocopherol at doses of 400 IU or 800 IU daily on the risk of cardiovascular death and non-fatal MI in patients with overt clinical and angiographic coronary atherosclerosis at recruitment. These individuals are at higher risk of subsequent MI than an unselected group; the higher risk allows an adequately powered trial with a smaller sample than a primary prevention trial.

Chemical evidence of lipid oxidation is evident at all stages of atherosclerosis, especially in macrophage-rich and early atherosclerotic lesions.8 Steinberg9 therefore suggested that antioxidants might exert their greatest effect in early lesions, with a long lag time before impact on clinical events in healthy subjects. However, patients with advanced coronary atherosclerosis are at much greater risk of MI (which generally occurs as a result of rupture of mature atheromatous plaques10), and are therefore the most appropriate subjects for investigation of the clinical value of antioxidant treatment on prevention of MI. An effect of α-tocopherol in this setting would be

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support for the antioxidant hypothesis of atherogenesis and would have clinical implications for prevention of MI in high-risk individuals.

The regional structure of cardiac services in our part of the UK allowed us to design a low-cost, prospective study of \( \alpha \)-tocopherol. Papworth Hospital is a tertiary referral centre that undertakes the majority of invasive cardiac procedures for a population of 2-2 million, with accurate follow-up in the seven referring hospitals that have coronary-care units.

**Methods**

CHAOs was a prospective, double-blind, placebo-controlled, randomised, single-centre trial in the East Anglian region of the UK. Patients were recruited at one centre (Papworth Hospital) The study compared two parallel groups of patients with angiographically proven coronary atherosclerosis. One group received \( \alpha \)-tocopherol and the other placebo. The primary outcome variables were a combined endpoint of cardiovascular death and non-fatal MI, and non-fatal MI alone. Enrolment began on Oct 10, 1992, and ended on Dec 15, 1994. The analysis included all endpoints between Oct 10, 1992, and June 18, 1995. The CHAOs trial was designed to have 80% power (with \( 2p=0.05 \)) to detect a relative risk of the combined endpoint (non-fatal MI and cardiovascular death) of less than 0.75 between the treatment groups after median follow-up of 1-5 years. This calculation assumed an accrual rate of 1000 individuals per year for 2 years, and an event rate of 5% per year, which were estimated from past referral and event rates at Papworth Hospital. Blinded interim analysis was planned for safety reasons, with trial termination if the relative risk between the treatment groups was below 0.70 with 2\( p \leq 0.001 \) in either of the primary endpoints. The prospectively defined stopping criteria were not met in the interim analysis in June, 1994.\(^{16}\)

When the trial was designed, there were few data to guide the choice of vitamin E dose. The first 546 patients on active therapy took 800 IU daily to double the Cox proportional hazards model, and 150 IU daily to increase the Cox model estimates for all MI analyses. When we had adequate evidence from measurements of \( \alpha \)-tocopherol concentrations on therapy that a lower dose would exceed physiological values, newly recruited subjects were allocated 400 IU daily. The dose was constrained by the need to exceed a physiological concentration of \( \alpha \)-tocopherol and to avoid interruption of recruitment through the limited supplies of study drugs available to use. There was no attempt at randomisation between the two vitamin E dosage groups, and the study was not planned to examine dose-effect responses on the primary endpoints. These two groups are therefore not distinguished in this analysis.

The inclusion criterion was angiographically proven coronary atherosclerosis. More than 90% of patients had angina, evidence of reversible cardiac ischaemia or both features, although these characteristics were not required. Almost all the subjects were recruited on the day of their admission immediately after elective coronary angiography. There were no exclusion criteria except prior use of vitamin supplements containing vitamin E. Patients were prestratified by seven variables—sex, blood pressure (cutoff for systolic 160 mm Hg, diastolic 90 mm Hg), age (55 years), body-mass index (25 kg/m\(^2\)), total cholesterol (6.5 mmol/L), smoking habit, and planned therapy (medical therapy, percutaneous transluminal coronary angioplasty [PTCA], or coronary artery bypass grafting [CABG]). Randomisation was done by means of a computer programme, which used a random-number database to allocate treatment by blocks of two after clinical data had been entered. Active treatment was capsules of \( \alpha \)-tocopherol (free 254 gum \( \alpha \)-tocopherol from natural sources in soya oil), 400 or 800 IU daily (268 or 537 mg) in one daily dose. The identical placebo capsules (oil only) contained a maximum of 0-4 mg \( \alpha \)-tocopherol. 546 patients took 800 IU daily for a median of 731 days (range 3-981); 489 took 400 IU daily for 366 days (8-961); 967 took placebo for 494 days (9-965).

An initial supply of 2 months' \( \alpha \)-tocopherol or placebo was dispensed at recruitment. Patients were asked to request all

<table>
<thead>
<tr>
<th>Age (years)*</th>
<th>( \alpha )-tocopherol (n=1035)</th>
<th>Placebo (n=967)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td>61.8 (9-3)</td>
<td>61.8 (8-9)</td>
</tr>
<tr>
<td>Vessels with &gt;75% stenosis</td>
<td>848/187</td>
<td>842/125</td>
</tr>
<tr>
<td>0 or 1</td>
<td>372</td>
<td>370</td>
</tr>
<tr>
<td>2</td>
<td>253</td>
<td>216</td>
</tr>
<tr>
<td>3 or left main stem</td>
<td>393</td>
<td>359</td>
</tr>
<tr>
<td>Intended therapy+CABG</td>
<td>402</td>
<td>356</td>
</tr>
<tr>
<td>Medical</td>
<td>355</td>
<td>324</td>
</tr>
<tr>
<td>PTCA</td>
<td>257</td>
<td>265</td>
</tr>
</tbody>
</table>

**Left ventricular impairment (n=706)**

- None: 208
- Mild: 59
- Moderate: 60
- Severe: 34

**Serum concentrations**

- Fasting total cholesterol (mmol/L): 5.96 (1-19) vs 5.81 (1-11)
- \( \alpha \)-tocopherol (\( \mu \)mol/L) (mean\pm SD): 33.8 (11-0) vs 33.2 (10-2)
- Lipid-corrected \( \alpha \)-tocopherol: 1.00 (0.28) vs 1.00 (0.28)

**Blood pressure (mm Hg)**

- Systolic: 135 (21) vs 133 (30)
- Diastolic: 79 (13) vs 78 (12)

**Diabetic**

- 102 (9-9%) vs 68 (7-0%)

**Smoking status**

- Current smoker: 149 vs 121
- Ex-smoker (>2 years): 300 vs 269
- Non-smoker: 586 vs 577

**Family history in first-degree relative**

- <60 years old (n=521): 90 (36-6%) vs 105 (40-2%)

**Body-mass index (kg/m\(^2\))**

- 26-5 (3-5) vs 26-4 (3-4)

**Alcohol intake (units per week) (n=1390)**

- 6-97 (10-3) vs 6-96 (10-5)

**Drug treatment**

- Calcium antagonist: 718 (69-4%) vs 666 (68-9%)
- \( \beta \)-blocker: 410 (39-6%) vs 325 (33-7%)
- Nitrate: 557 (53-8%) vs 556 (57-5%)
- \( \alpha \)-Adrenergic agonist: 82-9 (53-3) vs 82-8 (55-5)

*Mean (SD). Some totals do not reach 1035 and 967 because of missing data.

**Table 1: Baseline characteristics of patients**

follow-up study medication, which was posted to them. The time of request provided a simple index of compliance. Other management and medication were at the discretion of the physician responsible for the patient's usual care.

All patients gave informed, written consent to participation in the study, which was approved by the Huntingdon District Local Research Ethics Committee.

Two endpoints were examined—non-fatal MI alone and a combination of non-fatal MI and cardiovascular death (major cardiovascular events). Non-fatal MI and death were distinguished in the trial design, with a separate analysis of treatment effects on non-fatal MI. This distinction was made because of greater diagnostic precision in non-fatal MI allowed by examination of electrocardiography, cardiac enzyme measurements, and case notes over the hospital admission. For these cases, definite or probable MI was defined by a modified modification of the MONICA criteria.\(^{12}\) The certified cause of death was judged to be cardiovascular if the cause was classified according to the International Classification of Diseases, 9th revision, as codes 410, 427, 428, 434, or 441. Necropsy data were available in 21 (34%) of 62 cases. There was no information about cause of death in one case; this patient was censored in the survival analysis at the reported date of death and was not included in the analysis as a cardiovascular death. All events were classified by a member of the study team independently of the main analysis.

There was no planned clinic follow-up as part of the trial, because of the large geographical area served by the study centre (up to 120 km radius). A dedicated database was installed in seven coronary-care units serving the region's population, to allow tracking of admissions of study patients. In addition, we sent a questionnaire to patients and their family physicians to
Figure 1: Serum α-tocopherol concentrations during follow-up

find out about the occurrence of study endpoints and other events. Compliance was measured as the ratio of days that study medication was requested to per-protocol days prescribed.

Serum α-tocopherol concentrations were measured by high-performance liquid chromatography \(^{(13)}\) at baseline in 1763 individuals and in 482 who reattended after 15–836 days (in 307 cases these patients returned for planned CABG).

Baseline continuous variables were compared by Student’s \( t \) test and categorical variables by Pearson’s \( \chi^2 \) test. Bivariate correlation was with Pearson’s correlation coefficient. ANOVA was used to compare the effect of treatment on follow-up serum cholesterol and α-tocopherol. A lipid-standardised serum α-tocopherol concentration was calculated as the ratio of the measured serum α-tocopherol to the concentration predicted by a linear regression equation based on serum total cholesterol. The main analysis was by intention to treat. Primary-endpoint-free survival curves were calculated by the Kaplan-Meier technique and treatment groups were compared by the log-rank test. A Cox proportional hazards regression model was used to assess the influence of all potential explanatory baseline variables on relative hazards of the primary endpoints. Ordinal variables (New York Heart Association class, number of vessels diseased, and planned management) were treated as continuous in the model. Eighteen variables were entered stepwise into a model, with significance levels for backwards removal and 0-4 and 0-2. A separate per-protocol analysis was done by treating compliance with active therapy as a time-dependent variable in a Cox regression model. The difference between treatment groups in all-cause mortality was tested with \( \chi^2 \). The difference in side-effects between groups was tested by Pearson’s \( \chi^2 \) test, with odds ratios calculated by the approximation of Woolf.

Results

Of the 2002 patients recruited, 1035 were assigned α-tocopherol and 967 placebo (table 1). Median follow-

up was 510 days (range 3–981). There were small differences between active treatment and placebo groups in sex ratio, serum total cholesterol, systolic blood pressure, presence of diabetes, and the proportion taking β-blockers. These differences arose because there were fewer women than men and so some of the rarer stratification blocks were unbalanced when recruitment stopped. All these differences weighted risk in favour of the placebo group. Overall, the study patients were at high risk of further cardiovascular events—37-6% had triple-vessel or left-main-stem coronary disease and 24-6% had moderate or severe left ventricular dysfunction.

73-2% of all prescribed α-tocopherol or placebo were requested as follow-up medications. There was no difference between treatment groups in the proportion who were 100% compliant with the trial medication (48% placebo, 49% α-tocopherol; \( p=0.76 \)). Complete follow-up data were available in 98% of participants. There were no differences between the groups in completeness of follow-up (98-0% placebo, 97-8% active treatment; \( p=0.80 \)).

Baseline serum α-tocopherol concentration was 34.2 μmol/L (95% CI 33.1–35.3; \( n=226 \)). Mean serum α-tocopherol did not change on placebo therapy 32.4 (30.9–33.9; \( n=224 \)) μmol/L but increased to 51.1 μmol/L (46.5–55.9; \( n=114 \)) on therapy with 400 IU daily and 64.5 μmol/L (59.6–69.5; \( n=142 \)) with 800 IU daily. Follow-up measurements were made at 6–836 (median 266) days. There was no trend in serum α-tocopherol concentrations with time (figure 1).

Treatment did not affect serum cholesterol: the mean follow-up concentration was 5.77 mmol/L (5.51–6.04) on placebo, 5.55 mmol/L (5.29–5.81) on 400 IU daily, and 5.93 mmol/L (5.60–6.24) on 800 IU daily (\( p=0.24 \)). The strong correlation between serum total cholesterol and α-tocopherol reported previously \(^{(14,15)}\) was seen for baseline concentrations in this study (\( r=0.39; p<0.0001 \)). The regression equation used to predict serum α-tocopherol (\( p=0.150; p<0.0001 \)) was:

\[
\text{α-tocopherol (μmol/L) = 12.5} + 3.61 \times (\text{cholesterol (mmol/L)})
\]

There was no significant association between baseline measured or corrected α-tocopherol concentration and risk of cardiovascular death or MI.

There were 50 cardiovascular deaths and 55 non-fatal MIs during the study period (table 2). 14 recipients of α-tocopherol (3/489 on 400 IU, 11/546 on 800 IU daily) and 41 placebo recipients had non-fatal MIs. Of the 50 cardiovascular deaths, 27 were in the α-tocopherol group (10/489 on 400 IU, 17/546 on 800 IU daily) and 23 in

<table>
<thead>
<tr>
<th>ICD-9 code</th>
<th>α-tocopherol group (n=1035)</th>
<th>Placebo group (n=967)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal MI</td>
<td>410</td>
<td>14</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>410</td>
<td>15</td>
</tr>
<tr>
<td>Fatal MI</td>
<td>428</td>
<td>5</td>
</tr>
<tr>
<td>Left ventricular failure</td>
<td>434</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>441-3</td>
<td>2</td>
</tr>
<tr>
<td>Ruptured AAA</td>
<td>427</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>Total cardiovascular deaths</td>
<td>36</td>
<td>26</td>
</tr>
</tbody>
</table>

Other causes of death

| Pulmonary embolism | 415 | 3 | 1 |
| Septicaemia | 38 | 2 | 0 |
| Bovine carcinoma | 150-159 | 4 | 1 |
| Unknown | 0 | 1 |
| Total deaths | 36 | 26 |

AAA—abdominal aortic aneurysm.

Table 2: Distribution of non-fatal MI and deaths by certified cause in each treatment group.
Figure 2: Kaplan-Meier survival analysis for major cardiovascular events, non-fatal-MI, and cardiovascular deaths

the placebo group. Total mortality was slightly but not significantly greater in the \( \alpha \)-tocopherol group than in the placebo group (36 [3-5%] vs 26 [2-7%], \( p = 0.31 \)).

Kaplan-Meier survival curves for the combined primary endpoint and separately for non-fatal MI and cardiovascular death are shown in figure 2. Treatment with \( \alpha \)-tocopherol significantly reduced the rates of major cardiovascular events (log-rank \( p = 0.015 \)), and of non-fatal MI (\( p = 0.0001 \)) but had no effect on cardiovascular deaths (\( p = 0.78 \)). There was a delay in the onset of treatment benefit, with divergence of the Kaplan-Meier curves after about 200 days.

In the Cox model, treatment with \( \alpha \)-tocopherol reduced the risks of a major cardiovascular event (relative risk 0.53 [95% CI 0.34–0.83], \( p = 0.005 \)) and of a non-fatal MI (0.23 [0.11–0.47], \( p = 0.001 \)).

Table 3: Risk of cardiovascular death or non-fatal MI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative risk (95% CI)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha )-tocopherol vs placebo</td>
<td>0.53 (0.34–0.83)</td>
<td>0.005</td>
</tr>
<tr>
<td>NYHA class</td>
<td>1.71 (1.17–2.49)</td>
<td>0.005</td>
</tr>
<tr>
<td>Age</td>
<td>1.04 (1.01–1.07)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.93 (1.04–3.60)</td>
<td>0.04</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.94 (1.02–3.69)</td>
<td>0.04</td>
</tr>
<tr>
<td>Atenolol vs no ( \beta )-blocker</td>
<td>2.14 (0.86–5.34)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

NYHA=New York Heart Association.

Discussion

The idea that lipid oxidation within the atherosclerotic lesion might contribute to atherogenesis was raised during the 1980s.\textsuperscript{16,18} Support for this idea has come from laboratory studies\textsuperscript{19} that showed oxidation of LDL particles (particularly their polyunsaturated cholesterol esters\textsuperscript{20}) by macrophages\textsuperscript{4} in atheromatous plaques. The oxidation products of these reactions have various effects that may promote plaque progression and instability.\textsuperscript{16,19}

The CHAOS trial design took advantage of the unitary cardiac service of a large health region to examine the effects of \( \alpha \)-tocopherol on the rate of major cardiac events in a homogeneous and stable population with established coronary disease. We found that \( \alpha \)-tocopherol, in a higher dose than in previous studies, reduced the risk of the primary trial endpoint (a combination of death and non-fatal MI) by 47%. This benefit was due to a reduction in the risk of a non-fatal myocardial infarction of 77% and this treatment effect was apparent after about 200 days. The effects on the combined endpoint were not due to a reduction in cardiovascular death; indeed, there were more cardiovascular deaths among \( \alpha \)-tocopherol recipients than among placebo recipients. By contrast with the delayed effects of non-fatal MI, this increased risk was due to an excess of early events (before 200 days).

Because of the study design, this trial did not have sufficient power for us to form conclusions about the reason for the disparity in treatment effects on cardiovascular death and non-fatal MI. The discrepancy may be due to chance alone or it may reflect a difference in antioxidant effects on the biological processes leading to death and those leading to non-fatal MI. Most of the deaths occurred in the early part of the follow-up period, perhaps before any putative beneficial effects on
atheromatous plaques could have occurred. Furthermore, the deaths certified (most without necropsy evidence) as due to ischaemic heart disease will include deaths due to causes less likely to be responsive to α-tocopherol treatment (eg, arrhythmias, progression of heart failure, or perioperative complications). Whether there is a true adverse effect on early mortality cannot be ascertained from these data and must await the results of longer-term multicentre trials designed with mortality as a primary endpoint.

We did not plan to study treatment effects on endpoints such as unplanned CABG, hospital admission with angina, or restenosis after PTCA. These endpoints are appropriate in prospective studies in healthy populations that seek to find out the subsequent incidence of ischaemic heart disease,9 but lack precision in a population who already have severe atherosclerosis and symptomatic cardiac ischaemia at baseline.

Despite the randomisation process, there were small but significant differences in the distribution of five conventional coronary risk factors between the active treatment and placebo groups. However, all these differences weighted risk in favour of the placebo group and so posed a more rigorous test for α-tocopherol treatment. This trial was not designed to examine dose-response relations in terms of the primary endpoints. The use of two doses of α-tocopherol does not obscure interpretation of the effects on primary endpoints; a similar approach in randomised controlled trials of drug treatment for hypertension allowed analysis of effects on definable cardiovascular endpoints.22 The lipid oxidation hypothesis might predict a greater benefit for α-tocopherol in patients who smoke, who are diabetic, or who have vascular hypertrophy due to hypertension. This study does not have sufficient power to allow us to draw firm conclusions about these patients, but we hoped that stratification before randomisation would reveal any trends towards greater benefit in these subgroups. Direct comparisons of this type were, however, precluded by the small number of women recruited and the consequent imbalance in stratification subgroups.

This study could not directly address the mechanism by which α-tocopherol reduces the risk of myocardial infarction. The extent of the risk reduction suggests that the benefit may be due to more than one mechanism, such as α-tocopherol-mediated reductions in platelet adhesion and aggregation,23,24 inhibition of vitamin-K-dependent clotting factors by the oxidised moiety vitamin-E-2-quinone,25 and oxidised-LDL-mediated stimulation of endothelin production and inhibition of nitric oxide production.26 However, we believe that inhibition of oxidation is likely to exert its main effects by modification of plaque enlargement or plaque rupture.

We carried out this study because of evidence that even advanced atherosclerotic lesions may be influenced by antioxidants.27 The presence of large numbers of macrophage foam cells in advanced lesions may be an index of progression.28 Although their numbers are variable, macrophages are found mainly at the periphery of advanced lesions, which suggests continuous peripheral recruitment of monocytes and enlargement of the lesion.29 Macrophage-rich intermediate and advanced lesions and the peripheral part of ulcerated advanced lesions show chemical evidence of enhanced lipid oxidation.30 The enhancement of lipid oxidation may bring about further macrophage recruitment4 and progressive death of macrophage foam cells, enlarging the lipid core. Occulsive thrombosis, leading to MI, probably results from rupture of the plaque at the soft, macrophage-rich periphery.29

There is a striking contrast between the clinical benefit on non-fatal MI in our study and the modest effects of α-tocopherol intake on the severity of carotid and coronary atherosclerosis as assessed by ultrasonography and angiography.30,31 This disparity suggests that the beneficial effects of antioxidant therapy are on the lipid composition of atheromatous plaques rather than their volume.

Our findings are the first from a prospective clinical trial to be consistent with the lipid oxidation theory of human coronary artery disease. Our findings support the use of a high dose of α-tocopherol to prevent non-fatal MI in patients with angina and coronary atherosclerosis, although there was no benefit in terms of cardiovascular death or total mortality. Further studies will be required to show the patient groups for whom these findings are applicable.

This study was supported by the East Anglia Region locally organised research scheme. We thank the Henkel Corporation (La Grange, Illinois, USA) for supply of d-α-tocopherol and placebo capsules; the Council for Responsible Nutrition, Thames Ditton, UK; Janine Kelleher for recruitment of patients; Michael Petch, Leonard Shapiro, and David Stone for permission to recruit patients in their care; Linda Sharples (MRC Biostatistics Unit, Cambridge) and Bianca de Stavola (London School of Hygiene and Tropical Medicine) for statistical advice and critical comments on the manuscript.

References
9 Steinberg D. Clinical trials of antioxidants in atherosclerosis: are we doing the right thing? Lancet 1995; 346: 36–38.
15 Horwitt MK, Harvey CC, Dahm CH Jr, Seary MT. Relationship


Cyclical variation in paroxysmal supraventricular tachycardia in women

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**Summary**

**Background** Paroxysmal supraventricular tachycardia (SVT) in premenopausal women is often judged to be related to anxiety, and may be associated with the menstrual cycle. The aim of this study was to determine whether a cyclical variation of episodes of SVT exists and to correlate such variation with cyclical variation in plasma ovarian hormones.

**Methods** 26 women (mean age 36 [SD 8]) years; with paroxysmal SVT were screened; those with regular menses who experienced at least three episodes of paroxysmal SVT in two consecutive 48-hour ambulatory ECG recordings were included. 13 patients (aged 32 [6] years) met these criteria. Patients underwent 48-hour ambulatory ECG monitoring and determination of plasma concentrations of oestradiol-17β and progesterone on day 7, 14, 21, and 28 of their menstrual cycle.

**Findings** An increase in the number and duration of episodes of paroxysmal SVT was observed on day 28 as compared to day 7 of the menstrual cycle. A significant positive correlation was found between plasma progesterone and number of episodes and duration of SVT (5·6 [2·2] ng/mL; r=0·83, p<0·0004; and r=0·82, p=0·0005), while a significant inverse correlation was found between plasma oestradiol-17β and number of episodes and duration of SVT (155 [22] ng/mL; r=0·89, p<0·0001; and r=0·81, p=0·0007).

**Interpretation** Women with paroxysmal SVT and normal menses exhibit a cyclical variation in the occurrence of the arrhythmia with their menstrual cycle. There is a close correlation between the episodes of paroxysmal SVT and the plasma concentrations of ovarian hormones. These data suggest that changes in plasma levels of ovarian hormones (and their interaction) may be of importance in determining episodes of arrhythmia in such patients. The mechanisms of these effects are unknown.

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**Introduction** Paroxysmal supraventricular tachycardia (SVT) can occur in the absence of cardiac disease. Ovarian hormones exhibit a cyclical variation in their plasma concentration during the menstrual cycle. These changes appear to be associated with changes in plasma catecholamine levels and adrenergic activity. Oestrogens play a role in neurotransmitter synthesis, uptake, and degradation involving receptors at both presynaptic as well as postsynaptic sites. Decreased or progesterin-opposed oestrogen production is associated with increased adrenergic activity and vasomotor instability. An increase in plasma catecholamines may contribute to facilitate the occurrence of episodes of paroxysmal SVT.

In addition, ovarian hormones may have direct effects on the cardiovascular system. Hyperpolarisation of vascular smooth muscle in dog coronary arteries after treatment with oestradiol-17β has led to the suggestion that the hormone acts by increasing potassium conductance, while recent studies on isolated cardiac...