Is there a vitamin E paradox?

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In addition to epidemiologic studies that suggest a benefit for high intakes of α-tocopherol, studies of supplementation in humans have clearly shown that α-tocopherol decreases lipid peroxidation, platelet aggregation, and functions as a potent anti-inflammatory agent. In the five large prospective clinical trials with α-tocopherol therapy, four have shown a beneficial effect on cardiovascular end-points (two studies on a primary end-point and two studies on other cardiovascular end-points). Thus, the totality of evidence based on the epidemiologic data, in-vitro studies and animal models, and the clinical trials appears to support a benefit for α-tocopherol supplementation in patients with pre-existing cardiovascular disease. However, definitive recommendations must await ongoing clinical trials. Curr Opin Lipidol 12:49–53.

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Abbreviations

AT	α-tocopherol
ATBC	Alpha-Tocopherol Beta-Carotene
CAD	coronary artery disease
CHAOS	Cambridge Heart Antioxidant Study
CI	confidence interval
GISSI	Gruppo Italiano per lo Studio della Supravivenza nell'Infarto miocardico
HOPE	Heart Outcomes Prevention Evaluation
MI	myocardial infarction
PUFA	polyunsaturated fatty acids

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Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in the Western world. Several lines of evidence support a role for oxidative stress in the pathogenesis of atherosclerosis. Furthermore, epidemiologic studies [1••] appear to suggest that low levels of α-tocopherol (AT) are associated with increased risk for cardiovascular disease, and increased intakes appear to be protective. In-vitro studies [1••,2] have shown that AT, in addition to functioning as an antioxidant, inhibits smooth muscle cell proliferation, platelet adhesion and aggregation, and monocyte endothelial adhesion. Also, some studies in animal models have shown a decrease in lesion progression with supplementation. Supplementation with AT in humans has been shown by numerous groups to result in the following effects [1••]: decreased lipid peroxidation (decreased LDL oxidative susceptibility and decreased F_2-isoprostanes, a measure of in-vivo oxidative stress), decreased platelet adhesion and aggregation, and an anti-inflammatory effect.

Clinical trials

The present review focuses on the larger prospective clinical trials that have tested the effect of AT supplementation on cardiovascular events in different populations. The five clinical trials that will be discussed include (1) the Alpha-Tocopherol Beta-Carotene (ATBC) Study, (2) the Cambridge Heart Antioxidant Study (CHAOS), (3) the Gruppo Italiano per lo Studio della Supravivenza nell'Infarto miocardico (GISSI) Study, (4) the Heart Outcomes Prevention Evaluation (HOPE) Study and (5) the SPACE study.

The Alpha-Tocopherol Beta-Carotene cancer prevention study

The ATBC cancer prevention study [3] was designed to determine whether vitamin E [synthetic, *all rac* AT acetate, 50 mg/day (50 IU/day)] and β-carotene (20 mg/day), either alone or in combination, would decrease the incidence of lung cancer. A total of 29 133 male smokers aged 50–69 years from southwestern Finland were randomly assigned to one of the three regimens or placebo and followed for 5–8 years. At entry, on average the men were 57.2 years old, smoked 20.4 cigarettes/day, and had smoked for 35.9 years. Although AT supplementation had no effect on the primary end-point (lung cancer), an 18% increase in lung cancer incidence was observed in the β-carotene supplemented group ($P = 0.01$).

Serum AT and β-carotene concentrations were measured before and after supplementation. The median value of

serum AT at baseline was 26.7 μmol/l and increased to 40.2 μmol/l after 3 years of AT supplementation. A similar dose of 50 mg synthetic α-tocopheryl acetate supplements was administered to nonsmoking men and women (aged 21–31 years) by Princen *et al.* [4]. Those investigators reported that plasma AT concentrations were 24 ± 3.6 μmol/l at baseline and increased 4 μmol/l with supplementation to 28.7 ± 5.1 μmol/l, which is in sharp contrast to the 14 μmol/l increase observed in the ATBC Study. It is likely the greater increase in serum AT observed in the ATBC Study results from higher lipid levels in the older individuals because plasma vitamin E is confined to the lipoprotein fraction [5]. The impact on delivery of AT to tissues when plasma AT concentrations are elevated as a result of lipid levels, as compared with elevations resulting from higher intakes of AT, is unknown. Certainly, reporting of measurements of the plasma ratios of AT : cholesterol could aid in the interpretation of vitamin E status [6].

In a study in smokers without pre-existing cardiovascular disease [7], AT therapy had no significant effect on the first major coronary event (fatal or nonfatal). In a further analysis of the ATBC Study in male smokers with previous myocardial infarction (MI) [8], although there were no significant effects on the number of major coronary events or fatal coronary artery disease (CAD), there was a significant reduction in the multivariate-adjusted relative risk for nonfatal CAD [0.62, 95% confidence interval (CI) 0.41–0.96] in the AT group. In a subsequent report of the ATBC Study, Rapola *et al.* [9] also showed that AT supplementation was associated with a minor decrease in the incidence of angina pectoris (relative risk 0.91, 95% CI 0.83–0.99; $P = 0.04$).

The incidence and mortality from stroke in the ATBC trial has been examined in detail [10,11]. Because AT is carried in lipoproteins, its relationship with serum lipids confounds interpretation. For example, the risk of cerebral infarction was increased in those with serum total cholesterol concentrations greater than 7.0 mmol/l. However, pretrial high serum AT, which is dependent on serum lipid levels, decreased the risk of intracerebral hemorrhage by half and cerebral infarction by one-third [10]. AT supplementation appeared to increase the risk of subarachnoid hemorrhage by 50% (95% CI −3% to 132%; $P = 0.07$), but decreased the risk of cerebral infarction by 14% (95% CI −25% to −1%; $P = 0.03$). The increase in mortality caused by subarachnoid hemorrhage with AT supplements was 181% (95% CI 37–479%; $P = 0.01$). The overall net effects of supplementation on the incidence and mortality from total stroke were nonsignificant.

The interpretation that AT supplements increase the incidence of hemorrhagic stroke is not uniformly accepted, because this adverse effect has not been observed in the other intervention trials with vitamin E (see below). Steiner *et al.* [12] in fact have shown in a double-blind randomized study of 100 patients with transient ischemic attacks, minor strokes, or residual neurologic deficits that the patients who received AT and the antiplatelet agent, aspirin (400 and 325 IU/day respectively) had a significant reduction in ischemic strokes and recurrent transient ischemia attacks compared with patients taking aspirin alone. Moreover, no increase in hemorrhagic strokes was observed in a study that was designed to evaluate neurologic function in patients with Alzheimer's disease consuming 2000 IU/day of supplemental *all rac* AT for 2 years [13]. However, the number of individuals and the duration of the trial may have been insufficient to detect an effect. Nevertheless, because AT has antiplatelet effects [14] that may promote bleeding, the observation that AT supplementation increases hemorrhagic stroke incidence in smokers should be considered with caution.

The Cambridge Heart Antioxidant Study

The CHAOS trial [15] was a prospective, randomized, placebo-controlled, double-blind, single-center trial in the East Anglia region of England, which examined the effects of AT therapy on CAD. A total of 2002 individuals with overt clinical and angiographic evidence of CAD were randomized to receive natural or *RRR*-AT ($n = 1035$) or placebo ($n = 967$). The first 546 individuals in the AT group were given 800 IU/day for a median of 731 days (range 3–981 days) and the remainder were given 400 IU/day for 366 days (range 8–961 days), but the two groups were combined for statistical analysis (the trial was not designed to determine dose–response effects of AT on the primary end-points).

Participants requested 73.2% of all prescribed AT or placebo as follow-up medications. Treatment with AT was well tolerated, with only 11 out of the 2002 patients (0.55%) discontinuing therapy due to diarrhea, dyspepsia or rash. There was no significant difference between the treatment groups with regard to these side effects. Both 400 and 800 IU/day of AT significantly increased serum AT levels at least twofold over baseline, as reported previously in the literature [16]. Importantly, in the placebo group there was no significant increase in serum AT levels during follow up. The primary outcome variables were a combined end-point of cardiovascular death and nonfatal MI, and nonfatal MI alone [15]. After a median follow up of 510 days (range 3–981 days), those on AT experienced a significant 47% reduction (95% CI −66 to −17%; $P = 0.005$) in CAD death and nonfatal MI, which was the primary trial end-point [15]. This effect was due to a significant 77% reduction (95% CI −89 to −53%; $P = 0.005$) in the risk for nonfatal MI.

There was a nonsignificant effect on CAD death alone ($P = 0.78$) or total mortality ($P = 0.31$).

The nonsignificant increase in deaths due to CAD in this trial has been subjected to a subsequent analysis [17]. With regard to total mortality, this analysis revealed that there were 120 deaths from all causes, 68 in the AT group ($n = 1035$) and 52 in the placebo group ($n = 967$; cardiovascular deaths 53 versus 44; $P = 0.48$). It was also revealed that the majority of deaths (78%) occurred in those patients who were noncompliant with AT therapy. This subsequent analysis lessens concern about possible dangers of the use of AT in patients with established CAD.

The salient characteristics of the CHAOS trial [15] are as follows. The effect was examined in a homogeneous and stable population with established CAD, on an English diet. A dose of natural AT ($\geqslant$400 IU/day) was used that has been shown to decrease LDL oxidizability and platelet aggregation. Compliance was assessed by both drug accounts and serum levels of AT that rose 2- to 2.5-fold in the AT group, but were essentially unchanged in the placebo group. Although a larger dose was used than in the ATBC Study [3], AT supplementation in CHAOS [15] was not associated with an increased risk for hemorrhagic stroke, despite these patients also being on antiplatelet therapy.

Gruppo Italiano per lo Studio della Supravivenza nell'Infarto miocardico

The Italian GISSI trial [18••] investigated, in patients who had suffered an MI within the past 3 months, whether a number of treatments (all over 3.5 years) had an effect on the primary combined efficacy end-point of death, myocardial infarction, and stroke. These treatments were as follows: n-3 polyunsaturated fatty acids (PUFA; 1 g/day, $n = 2836$); *all rac* AT (300 mg/day or 330 IU/day, $n = 2830$); a combination of n-3 PUFA and AT ($n = 2830$); or control ($n = 2828$). This was a multicenter study with an open-label design. The patients received, in addition to the supplements, the usual preventive measures, including aspirin, β-blockers and angiotensin-converting enzyme inhibitors. A major strength of this study, in contrast to other clinical trials, was that dietary information was detailed with regard to fish, fruit, vegetable, and olive oil intake. The primary combined efficacy end-points were the cumulative rate of all-cause death, nonfatal MI and nonfatal stroke; and the cumulative rate of cardiovascular death, nonfatal MI and nonfatal stroke.

In this study, it was shown that n-3 PUFA resulted in a significant 10% decrease in the combined primary end-point of death, nonfatal MI and nonfatal stroke in a two-way factorial analysis ($P = 0.048$). However, the decrease in the risk of other combined end-points of cardiovascular death, nonfatal MI and non-fatal stroke was only borderline significant ($P = 0.053$). The four-way analysis, which compared the n-3 PUFA group with the control group (i.e. those receiving no supplements), provided a clearer profile of the effects of n-3 PUFA. That analysis indicated a relative decrease in the risk of the combined end-point of 15% ($P = 0.023$), and of 20% for cardiovascular death, nonfatal MI and nonfatal stroke ($P = 0.008$). With regard to the primary end-points, patients receiving AT did not differ significantly from control individuals according to the two-way factorial analysis. In addition, the combination of AT and n-3 PUFA did not confer greater benefit over n-3 PUFA alone. However, when the more appropriate four-way analysis was conducted, there was a significant 20% reduction in cardiovascular death in the AT group compared with the control group (95% CI 0.65–0.99) [19].

A weakness of this study was that it was an open-label trial with an approximately 25% dropout rate at the end of the study. Additionally, no objective assessment of compliance such as measurement of n-3 PUFA or AT was provided, even in a subgroup of participants. Furthermore, because these patients were on a healthy Mediterranean diet, which is clearly rich in antioxidants, this could also have attenuated the benefits of AT. However, it should be emphasized that the GISSI Prevenzione trial demonstrated a significant 20% reduction in cardiovascular death: relative risks for cardiac death 0.77 (95% CI 0.61–0.97), coronary death 0.75 (95% CI 0.59–0.96) and sudden death 0.65 (95% CI 0.48–0.89) after AT supplementation.

The Heart Outcomes Prevention Evaluation Study

The HOPE Study [20••] included 2545 women and 6996 men, who were aged 55 years or older and who were at high risk for cardiovascular events because they had cardiovascular disease or diabetes, in addition to one other risk factor. These patients were randomly assigned according to a two-by-two factorial design to receive either 400 IU/day vitamin E from natural sources or matching placebo, and either an angiotensin-converting enzyme inhibitor (ramipril) or matching placebo. They were followed up for a period of 4–6 years (mean 4.5 years). The primary outcome was a composite end-point of MI, stroke, and death from cardiovascular disease. Secondary outcomes included unstable angina, congestive heart failure, revascularization or amputation, death from any cause, complications of diabetes, and cancer.

There was no significant difference between the patients who received vitamin E ($n = 4761$) and those receiving placebo ($n = 4780$) with respect to the primary end-point. There was no significant difference in number of deaths from cardiovascular causes. Furthermore, there was no

significant difference in incidence of secondary cardiovascular outcomes or in death from any cause. Also, there was no increase in incidence of hemorrhagic stroke associated with vitamin E use, despite 77% of the patients receiving an antiplatelet agent. Finally, there were no significant adverse effects of vitamin E supplementation. It was concluded, in patients who are at high risk for cardiovascular events, that treatment with vitamin E for a mean of 4.5 years had no apparent effect on cardiovascular outcomes. It should be emphasized that, because of the overwhelming positive findings with regard to the angiotensin-converting inhibitor ramipril, the study was stopped by the Data and Safety Monitoring Board prior to their revised recommendation of a 5-year follow up instead of 3.5 years as originally decided.

This is an important study that arrives at the negative conclusion: that vitamin E is without effect in patients who are at high risk for cardiovascular disease. However, the study suffers from certain deficiencies [21]. Although it was undertaken in many geographic areas (USA, Canada, Western Europe and South America) with clearly different dietary intakes, data on the dietary intakes, especially antioxidants, were not reported. In addition, for no subgroup were plasma levels of vitamin E provided, as in the CHAOS Study, in order to confirm supplementation. Furthermore, the HOPE investigators appear to have used natural vitamin E, which comprises tocopherols and tocotrienols. Because AT is the most potent member of the vitamin E family, this could also have a bearing on the findings because of the scant information on the other forms of vitamin E.

Secondary Prevention with Antioxidants of Cardiovascular disease in end-stage renal disease (SPACE)

The SPACE study was a double-blind, placebo-controlled, randomized, secondary prevention trial performed at 6 hemodialysis units in Israel that examined the effect of high dose AT supplementation on cardiovascular disease outcomes in hemodialysis patients with pre-existing cardiovascular disease [22]. The patients ($n = 196$) aged 40–75 years at baseline from six dialysis centres were enrolled and randomized to receive 800 IU/day *RRR*-AT ($n = 97$) or matching placebo ($n = 99$). Patients were followed for a median 519 days. The primary endpoint was a composite variable consisting of myocardial infarction (fatal and non-fatal), ischaemic stroke, peripheral vascular disease (excluding the arteriovenous fistula), and unstable angina. Secondary outcomes included each of the component outcomes, total mortality, and cardiovascular-disease mortality. Lipid-adjusted AT levels were monitored and rose significantly in the AT group compared to the placebo group 23.3 ± 10.7 μM at baseline and 20.2 ± 6.9 μM on-treatment. Treatment with AT significantly decreased the primary endpoints (54% reduction in primary endpoint risk in the AT group, $P = 0.014$). There was a 39% non-significant reduction in CAD mortality (RR0.61, 95%CI 0.28–1.3, $P = 0.25$). Also, AT supplementation was associated with a 70% reduction in total myocardial infarction rate ($P = 0.016$). There were no significant differences between number of side effects reported for the placebo and AT groups. Thus, like CHAOS, the SPACE study also reported a significant reduction in composite cardiovascular disease endpoints and myocardial infarction with AT supplementation in patients with preexisting cardiovascular disease. Also, they measured plasma AT levels in this study. Thus, it appears that higher doses of AT (800 IU/day) would be beneficial with regards to secondary prevention of coronary artery disease.

Conclusion

In the present review, the five major prospective clinical trials that investigated the effect of AT supplementation on cardiovascular end-points are critically appraised. Whilst two studies (CHAOS and SPACE) clearly show a reduction in both cardiovascular death and nonfatal MI (the defined primary end-point), as shown in Table 1 the GISSI and ATBC studies also demonstrated benefit on certain end-points, despite the primary end-point not being significant. It should be emphasized that the primary end-point in the ATBC Study was cancer and not cardiovascular disease. The only study that was negative for all end-points was the HOPE Study. The increase in mortality from subarachnoid hemorrhage in male smokers in the ATBC Study does not concur with the results of the other studies, which in fact used higher doses, coupled with antiplatelet agents. This unex-

Table 1. Summary of prospective vitamin E clinical trials

Study	Dose	Primary Endpoint	Other Endpoints	Adverse Effect
ATBC (Primary and Secondary Prevention)	50 IU/DAY	– (Cancer)	+[3]	+[6]
CHAOS (Secondary prevention)	400&800 IU/day	+[1]	–	–
GISSI (Secondary prevention)	330 IU/day	–	+[4]	–
HOPE (Primary and Secondary Prevention)	400 IU/day	–	–	–
SPACE (Secondary Prevention, ESRD)	800 IU/day	+[2]	+[5]	–

+ denotes positive finding; – denotes negative finding; 1 = cardiovascular death and nonfatal myocardial infarction; 2 = composite of myocardial infarction, ischemic stroke, peripheral vascular disease and unstable angina; 3 = decrease in the incidence of angina, nonfatal CAD in patients with previous MI and reduction in cerebral infarction; 4 = reduction in cardiovascular death; 5 = total myocardial infarction rate; and 6 = increase in subarachnoid hemorrhage mortality.

pected finding will be settled in the ongoing trials [23••]. Thus, although the data thus far from the prospective clinical trials are not overwhelming, the majority of studies appear to suggest a benefit of AT supplementation.

Studies of this nature would be more informative if they included data on dietary intakes of antioxidants, measurements of AT levels and antioxidant status, and measurements of biomarkers of oxidative stress such as F_2-isoprostanes, nitrotyrosine, and LDL oxidizability, among others. It is quite possible that individuals who are vitamin E replete might not gain additional benefit from supplements. It should also be emphasized that the trials used different doses of AT, ranging from 50 to 400 IU/day in different study populations (primary and secondary prevention). Despite these deficiencies, these studies concur with the general body of evidence (epidemiologic, in-vitro and animal models), and the totality of evidence suggest that AT supplementation is beneficial in patients with pre-existing cardiovascular disease. However, definitive recommendations must await completion of the ongoing clinical trials [23••].

Acknowledgements

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