



# evidence based or wishful thinking?

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**T**he use of vitamin E and other antioxidant preparations as cardioprotective agents seems to be substantial. However, current evidence supporting their use seems to be somewhat conflicting. In this review, the evidence favouring the use of vitamin E is examined. Criteria by which the relationship between vitamin E and atherosclerotic cardiovascular disease may be judged are used to provide the framework for this examination (Table). In addition, the issue of study design in the examination of the evidence is addressed as some designs are clearly more appropriate than others in establishing the veracity of any relationship. Finally, conclusions are drawn from the evidence with regard to therapy.

## Lipids and oxygen free radicals

Before examining the evidence for and against the use of vitamin E, it is valuable to briefly revise Steinberg's hypothetical, but widely accepted, oxidation theory of atherosclerosis. Cross-cultural epidemiological associations indicated the role of serum cholesterol in the pathogenesis of atherosclerotic cardiovascular disease many years ago. Subsequently, the role of low density lipoprotein (LDL) was elucidated with further basic scientific research. More recent data from a number of lipid-lowering, randomised, controlled trials has put this issue beyond reasonable doubt.

LDL entry to cells is regulated by receptors on the cell surface and, when cell saturation occurs, receptor down-regulation follows. Atherosclerosis is characterised by excess accumulation of intracellular lipid, and endothelial macrophages are the principle site for this accumulation. Steinberg's hypothesis holds that a "scavenger receptor" not subject to the usual regulatory mechanisms of the LDL receptor is involved in recognising, and avidly taking up, oxidised LDL. Monocytes, later to become tissue macrophages, become engorged with lipid and form foam cells, the embryonic lipid plaque.

LDL oxidation occurs when it reacts with oxygen-derived free radicals. Free radicals are found in all tissues and only when the cells own antioxidant defence mechanisms are overwhelmed are they capable of reacting with LDL and other molecules. Based on this hypothesis, preventing the oxidation of LDL would mitigate the adverse effects of the scavenger pathway and prevent atherogenesis at an early stage.

## Epidemiological studies

### The strength of the relationship

Strong relationships are less likely to be explained away by chance or other unforeseen factors not accounted for in a study. Many epidemiological studies support a relationship between vitamin E and cardiovascular disease. These include prospective studies such as the Health Professionals and Nurses Health Studies involving large numbers of individuals followed for many years.

The strength of the relationship on the basis of these studies is, however, variable, and is consistent with either a very strong relationship or, alternatively, with only a weak relationship. The reduction in risk of coronary artery disease (CAD) for subjects with high intake of vitamin E in foods ranged from 5% to 65%. For those who took vitamin E supplements, the change in risk ranged from a reduction of approximately 50% to an increase of 10%. On this basis, the most optimistic view indicates that vitamin E may reduce the risk of CAD by between one-half and two-thirds.

### Dose-response relationship

As in the case of serum cholesterol levels, a graded response between risk factor and disease outcome indicates support for a causal relationship. Of four prospective studies involving dietary intake of vitamin E, two are consistent with a dose-response relationship. For subjects with vitamin E intake in the highest one-third of the intake distribution, the chance of developing CAD was approximately 65%



lower, while those with intakes in the middle one-third had a 30% lower risk of CAD. Those in the lowest one-third acted as the comparison group. For those in other studies who took vitamin E supplements, no evidence of a dose-response relationship was found.

### Consistency

The consistency of a relationship from one study to another and from one population to another argues strongly in favour of its significance. In the Nurses Health study, vitamin E sourced from supplements was inversely related to risk of CAD, while that from foods was not. Conversely, in the Iowa Womens Health study, dietary vitamin E was inversely related to risk. Therefore, all studies indicated an inverse relationship between vitamin E levels and risk of CAD, but the source of vitamin E differed among the studies.

### Specificity

The issue of specificity is of little importance in multifactorial diseases. The established cardiovascular risk factors such as smoking are also risk factors for other diseases, while it is clear that non-smokers may also develop atherosclerosis. This is a particularly difficult area in nutritional epidemiology, as diets are not pure entities and foods rich in vitamin E such as soybean, nuts and wheatgerm may also be replete with other important factors.

### Biological plausibility

The biological basis for the use of antioxidant vitamins as preventive therapy for atherosclerosis has already been alluded to. Many species of vitamin E exist including alpha, beta, gamma and delta tocopherol with alpha being the most common and active form. Vitamin E is lipid soluble and may act to inhibit the oxidation of LDL. However, while the biological plausibility of this hypothesis seems secure on the basis of *in vitro* experiments, unexpected adverse findings from randomised controlled trials suggest that this criterion alone cannot be relied upon to determine causality.

### Temporal relationship

Are low levels of vitamin E a cause or a consequence of cardiovascular disease? A high incidence of cardiovascular disease has certainly been related to low vitamin E levels in cross-sectional epidemiological studies such as the WHO Monica study of 16 European countries. Case-control studies also yield data, but these are prone to bias brought about by the likely effect of lifestyle and dietary changes made following a cardiovascular event.

Prospective studies where subjects' samples are taken and stored years before the vascular event are therefore more appropriate to a consideration of the relationship between vitamin E and CAD. Yet, subjects who, for exam-

ple, take vitamin supplements in a prospective cohort study may engage in other more healthy behaviour than non-users and thus lead to confounding. It is against this background that randomised controlled trials have been devised to further examine the relationship.

### Randomised, controlled trials

To date, three randomised, controlled trials have been reported. In the first of these, the Cambridge Heart Antioxidant Study (CHAOS), 2,002 patients with angiographic evidence of CAD were randomised to receive a daily dose of 400-800IU of alpha-tocopherol or placebo. The risk of suffering the primary trial endpoint [combined non-fatal myocardial infarction (MI) and cardiovascular death] was almost halved (47%). A significant reduction in risk of non-fatal MI by 77% was also found. However, a non-significant increase (18%) in fatal MI was noted.

In the alpha-tocopherol and beta-carotene trial (ATBC), 29,000 Finnish high-risk male smokers were randomised to receive either vitamin E 50mg daily, beta-carotene 20mg daily, both or placebo. The primary objective was to examine the risk reduction for lung cancer over five to eight years.

This trial included 1,862 subjects with a previous history of MI. There was no effect on the total number of cardiovascular events in any treatment group. A reduced risk of non-fatal MI of approximately 38% was noted in subjects randomised to receive vitamin E, compared to those who received placebo. As in the CHAOS trial, an excess of fatal MI and other fatal cardiovascular events, including haemorrhagic stroke, was recorded in all treatment groups except placebo and the ATBC trial was terminated early. In those randomised to receive beta-carotene alone or in combination with alpha-tocopherol, a significant excess number of fatalities was observed.

The GISSI-Prevenzione trial, recently reported, fails to provide support for the routine use of synthetic vitamin E

Table 1: Hills criteria for causality 1964

- **Strength of the relationship:** robust relationships are less likely due to chance.
- **Consistency:** how many studies indicate the same relationship?
- **Specificity:** single unique relation between risk factor and disease?
- **Temporal relationship:** risk factor precedes disease?
- **Dose-response relationship:** the more risk factor, the more disease.
- **Biological plausibility:** what is the biological mechanism?
- **Reversibility:** reducing the risk factor reduces disease - tested by randomised controlled trials.



in patients who have survived MI. In addition, there was no evidence of synergism between vitamin E and n-3 polyunsaturated fatty acids. It had been suggested that vitamin E might prevent the oxidation of these polyunsaturated fatty acids.

### **Drawing conclusions from the evidence**

Do the data available provide support for a relationship between cardiovascular disease and vitamin E? The evidence clearly does not meet the criteria for causality set out more than 30 years ago by Hill (Table). The strength varies from study to study and inconsistencies abound. Evidence for a dose-response relationship is scant. The biological plausibility for the use of antioxidants seems secure on the basis of the lipid peroxidation hypothesis of atherosclerosis, but this has recently been called into question. The study design is, in general, appropriate to an examination of the relationship.

If the biological basis for using antioxidants is correct, it raises some questions regarding the suitability of subjects enrolled in some of the randomised controlled trials for testing the hypothesis. If antioxidants are effective in the primary prevention of atherosclerosis, it may be unreasonable to anticipate beneficial effects in subjects with established and symptomatic CAD. This seems especially illogical since the adverse events that occur in such patients may relate more to myocardial complications of the disease than to early manifestations of endothelial dysfunction.

Secondly, one would not anticipate the findings of CHAOS on the basis of Steinberg's hypothesis since, as originally stated, the beneficial effect of antioxidants should occur in the long term and should not influence the stability of the more advanced atherosclerotic plaque, a key factor in fatal and non-fatal MI. The beneficial effects of CHAOS were evident at 200 days.

The worrying finding of an increase in haemorrhagic stroke in those randomised to receive high dose vitamin E raises the possibility of adverse effects on the coagulation cascade. In particular, it has been suggested that those who take the vitamin K antagonist warfarin or who have coagulation defects due to vitamin K deficiency should not take high dose supplemental vitamin E as the combination may predispose to haemorrhage.

The extraordinary results from the CHAOS trial have been the subject of criticism for a number of reasons. These include the alteration of dose of alpha-tocopherol from 800 to 400IU during the trial. No information was provided on baseline evidence of previous MI, angina, or previous arrhythmias. Randomised controlled trials are undertaken in the expectation that the only factor differing between the two groups is that of the random exposure to the experimental treatment. The active treatment and placebo groups in CHAOS were not comparable in terms

of gender, diabetes, current smoking or beta-blocker use.

Finally, all subjects exposed to vitamin E were analysed as a homogeneous group irrespective of the dose used. The data derived from such a study cannot be considered sufficiently reliable to alter clinical practice.

Alternative explanations for the findings from CHAOS have recently been proposed. The high frequency of a genetic polymorphism conferring reduced endothelial function on the subjects affected has been reported. Subjects with this trait, it is suggested, are particularly susceptible to the beneficial effects of vitamin E.

A number of other discrepancies exist in the evidence base. These include the relationship between relatively low exposure to vitamin E and benefit seen in the observational studies (<100mg/day) compared to the lower dose in the ATBC trial (50mg/day) and high exposure in the CHAOS trial (400-800mg/day). The dose used in GISSI-Prevenzione (300mg/day) is more than 10 times the current recommended daily allowance. Equally important may be a disequilibrium brought about by providing vitamin E as alpha-tocopherol only in the trials. Such a disequilibrium has been suggested to explain the adverse effects attributed to beta-carotene.

Gamma rather than alpha-tocopherol may be the more potent antioxidant and lower levels of gamma-tocopherol have been found in dyslipidaemic patients with CAD, perhaps because of differential biliary excretion. Finally, pro-oxidant effects of alpha-tocopherol have been reported and proposed as explanations for the higher total mortality among those receiving it in trials.

At present, there are no firm data to suggest that we should change our practice and prescribe vitamin E for our patients with CAD. The data that exist require confirmation, and further basic scientific research is needed to clarify the appropriateness of using alpha-tocopherol over other species of vitamin E. The optimal dose, duration and source (diet or tablet) of vitamin E are also unknown.

For patients with CAD, a diet low in saturated, high in mono- and polyunsaturated fats, as well as high in fruit and vegetable consumption is still recommended. In terms of public health, for a Northern European population not traditionally exposed to high intakes of fruit and vegetables, current recommendations for the prevention of cardiovascular disease favour a varied diet rich in such food items. It may be useful to note that the Mediterranean diet, low in saturated fats, rich in monounsaturated fats, fruit, vegetables and legumes is replete with natural antioxidants such as polyphenols but is low in vitamin E.

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**References on request.**