Beyond cholesterol reduction in coronary heart disease: is vitamin E the answer?

To date both primary and secondary prevention of coronary heart disease (CHD) have focused almost exclusively on the modification of conventional risk factors such as smoking, hyperlipidaemia, and hypertension. The exciting new concept is emerging that a common factor may mediate atherogenesis across what at first sight appears to be a wide spectrum of risk. This factor is oxidised low density lipoprotein (Ox-LDL). Ox-LDL damages the endothelium and has potent proatherogenic actions including enhanced uptake by macrophages leading to cholesterol ester enrichment and monocyte chemotaxis and cytotoxicity. Vitamin E inhibits oxidation of LDL and supplementation with vitamin E therefore seems to be a logical interventional strategy to prevent CHD.

Ox-LDL
Atheromatous disease has long been viewed as essentially a degenerative process. However, recent evidence demonstrates that it is a chronic inflammatory condition. Ox-LDL injures the endothelium and activates the expression of genes leading to the production of inflammatory molecules and subsequent formation of the fatty streak, the precursor of the mature atheromatous lesion. Because endothelial damage precedes the onset of clinically evident atheroma much interest has focused on the finding that impaired endothelium-dependent relaxation is seen in subjects at high risk of CHD. Endothelium-dependent relaxation is mediated by nitric oxide (NO), which has potential anti-atherogenic actions. There has, however, been some dispute as to whether “endothelial dysfunction” initiates the atheromatous process or is simply a marker for other aspects of endothelial damage. Improved understanding of the molecular mechanisms underlying endothelial dysfunction and atherogenesis suggest that oxidative stress mediates both processes. This is supported by in vitro studies which clearly show that Ox-LDL is far more potent at inhibiting endothelial function than is native LDL. The susceptibility to lipid oxidation, the ability to inactivate biologically important oxidised lipids, and the degree of response to oxidised lipids seems to be genetically determined. This may explain in part the differing susceptibility of individuals to coronary atherosclerosis despite equivalent conventional risk factors. Lowering LDL cholesterol or inhibiting its oxidation therefore offers the prospect for reducing CHD in such high risk individuals.

Vitamin E
Vitamin E is incorporated into the lipoprotein particle rendering the LDL less susceptible to oxidation. This is conventionally assessed by the lag time for the formation of conjugated dienes. In normal subjects the lag time to oxidation can be increased by about 50% by supplementation with vitamin E. As the molecular aspects of free radical chemistry are unravelled it is seeming more likely that vitamin E is involved in complex interactions. For example, vitamin E acts synergistically with NO to scavenge free radicals such as superoxide anion. In hypercholesterolaemic rabbits vitamin E supplementation both inhibits LDL oxidation and reverses endothelial dysfunction.

Epidemiological studies have shown an inverse correlation between vitamin E intake and both CHD and carotid atheroma. Despite this there have been few controlled interventional trials designed to test beneficial effects of vitamin E in CHD. The Alpha-Tocopherol Beta Carotene Cancer Prevention Study was designed primarily to investigate the effects of antioxidant vitamins on the incidence of lung cancer in Finnish male smokers but it also reported on mortality from CHD. There was no difference in the rate of coronary disease between subjects on supplementation with vitamin E and the control group. However, this study used a low dose of vitamin E (75 IU) which was considerably lower than that at which greatest benefit had been demonstrated in large epidemiological studies. These studies showed a dose response relation between vitamin E consumption and CHD, with greatest benefit apparent in those whose median consumption was in excess of 400 IU. Such high doses (400 and 800 IU) were used in the recently reported CHAOS (Cambridge Heart Anti-Oxidant Study). This was a secondary prevention trial designed to study the effect of dietary supplementation with vitamin E on cardiovascular events in patients with known ischaemic heart disease. 2002 patients with angiographically confirmed coronary artery disease were randomly assigned double blind to placebo or vitamin E at a dose of either 400 or 800 IU for a median follow up period of 510 days. Vitamin E reduced non-fatal myocardial infarction by 77% but cardiovascular death was not reduced. The mechanisms underlying this reduction in myocardial infarction remain unclear: the authors suggest that vitamin E may be acting by multiple mechanisms such as reduction in platelet adhesion and aggregation, inhibition of vitamin K dependent clotting factors, and Ox-LDL mediated stimulation of endothelin production or inhibition of NO production in addition to plaque stabilisation. The authors also emphasised the need to identify the patient groups most likely to benefit from vitamin E supplementation. A study by Hodis et al suggests that antioxidant supplementation may enhance the benefits of cholesterol reduction. A subgroup analysis was performed in 156 men aged 40–59 who were enrolled in the CLAS (Cholesterol Lowering Atherosclerosis Study) trial. Subjects had total cholesterol concentrations between 4.79 and 9.07 mmol/l at entry and all had undergone previous coronary artery bypass grafting. After baseline coronary angiography they were randomised to colestipol-niacin plus a cholesterol lowering diet v placebo.
plus a cholesterol lowering diet. After two years’ treatment the subjects had repeat coronary angiography to assess the extent of atheromatous coronary artery lesion progression. Overall, subjects with supplementary vitamin E intake of 100 IU per day demonstrated less coronary artery lesion progression than subjects with an intake of less than 100 IU per day. Within the placebo group vitamin E had no effect on lesion progression. Mean LDL cholesterol during the trial was 2.6 mmol/l for the treatment group and 4.2 mmol/l in the placebo group, suggesting that concomitant reduction in LDL cholesterol may be important. No benefit was demonstrated in subjects taking supplementary vitamin C either alone or in combination with vitamin E. As with previous retrospective studies, results from this study need to be interpreted with caution because vitamin E intake was non-randomised and self reported. The effect of antioxidants in other patient groups remains to be evaluated. Diabetic patients at high risk of CHD and subject to increased oxidative stress seem an obvious group to target.4

Endothelial function
The CHAOS study and the recent primary and secondary cholesterol lowering studies16–17 have all demonstrated a rapid onset in reduction of coronary events. In contrast such interventions produce only modest effects on regression of atheromatous lesions.15,18 This disparity suggests that the benefits may relate to an improvement in endothelial function. Indeed such improvements have been demonstrated to occur rapidly after cholesterol reduction.19 In a recent small study of hypercholesterolaemic patients at risk of CHD vitamin E failed to improve endothelial function.20 A possible explanation for this could be the need for concomitant lipid lowering treatment for improvements in endothelial function to become apparent. This is supported by a study in the human coronary circulation where the antioxidant probucol used in combination with intensive lipid lowering treatment improved endothelial function to a greater extent than cholesterol lowering treatment alone.21 These studies on endothelial function support the assertion that beneficial effects of vitamin E should be examined in association with intensive cholesterol reduction or in patient groups with relatively normal LDL but increased oxidative stress such as diabetes and hypertension.4

Conclusions
The CHAOS study now provides evidence to recommend high dose pharmacological vitamin E supplementation for the secondary prevention of CHD. Many questions, however, remain unanswered: dose, the combination with lipid lowering treatment, and the groups most likely to benefit. Subjects with normal LDL cholesterol but evidence of increased susceptibility to LDL oxidation such as those with hypertension or diabetes and individuals with insulin resistance are obvious target groups. These questions may be answered by relatively small ongoing studies in which endothelial function is used as a surrogate end point. This will allow for the optimum design of large scale randomised trials to examine the effect of pharmacological vitamin E supplementation for the primary prevention of CHD. There is no direct evidence for the primary prevention of CHD with vitamin E. If the protective effects of vitamin E act synergistically with cholesterol reduction16,17 then such evidence is likely to follow. Meanwhile the benefits of a healthy diet rich in vitamin E have already been promoted by Oliver.22

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