Antioxidant vitamins in the prevention of cardiovascular disease

The epidemiological evidence

Introduction

Recent evidence suggests that in vivo oxidation, primarily by oxygen free radicals, may be involved in atherogenesis. In particular, the atherogenicity of low density lipoprotein appears to be increased by oxidative modification\(^1\). Oxidation of polyunsaturated fatty acids in low density lipoprotein is believed to occur locally within atherosclerotic lesions. Following oxidation, the low density lipoprotein is taken up by macrophages more rapidly than normal to form cholesterol-laden foam cells\(^2\) (Fig. 1).

Antioxidant molecules may influence atherogenesis by interfering with this oxidation process. Vitamin E is the major lipid-soluble antioxidant preventing the formation of lipid hydroperoxides from polyunsaturated fatty acids. It occurs in low density lipoprotein where its concentration increases by 2-4-fold when vitamin E is taken by mouth\(^3\). There is biochemical evidence that vitamin C can scavenge free radicals in the cytoplasm and may also participate in the regeneration of vitamin E\(^4\). Vitamin A (retinol) and certain carotenoids (notably beta-carotene, a vitamin A precursor, and the non-vitamin A precursor lutein and lycopene) have substantial singlet oxygen scavenging ability\(^5\) and beta-carotene is contained within low density lipoprotein\(^6\).

The antioxidant vitamins required by humans are derived from fresh fruit and vegetables, and from vegetable oils and polyunsaturated fatty acid margarines in the case of vitamin E, but cannot be synthesized from simple precursors. Thus, concentrations of vitamins in plasma and body tissues are determined by dietary intake, absorption, metabolism and storage. Evidence from vitamin supplementation studies and comparison of of food frequency questionnaires with circulating vitamin levels generally correlate well with dietary intake\(^5-8\), although dietary beta-carotene may not determine plasma levels as accurately in smokers who have lower circulating levels of the pro-vitamin than non-smokers\(^7,8\). However, increases in dietary vitamin A do not result in long-term increases in the level of circulating retinol as surplus vitamin is stored in the liver\(^9\).

The influence of antioxidant vitamin levels in the diet on plasma concentrations, together with their biochemical properties, raises the possibility that increased consumption of these vitamins could prevent or decelerate the atherogenic process. We review the epidemiological evidence for such an effect in the context of coronary heart disease and subsequently, in peripheral arterial disease.

Vitamin E

Dietary intake

There is fairly good evidence from two large-scale, prospective studies that a high intake of vitamin E is associated with a reduced risk of coronary artery disease\(^9,10\). In the Nurses Health Survey, a 31% reduction in non-fatal myocardial infarction and cardiovascular death was evident in women taking at least 100 mg daily of supplementary vitamin E for over 2 years\(^9\). This effect persisted after adjustment for age, smoking, obesity, exercise, blood pressure, cholesterol and use of postmenopausal oestrogen replacement, aspirin, vitamin C and beta-carotene. Men in the Health Professionals Follow-up Study had a 40% reduction in non-fatal myocardial infarction, cardiovascular death and coronary revascularization with increased dietary vitamin E intake, even after adjustment for age, coronary risk factors and intake of vitamin C and beta-carotene\(^10\). The main effect was again due to supplement use. An inverse relationship between dietary vitamin E and subsequent coronary mortality in 5000 Finnish men and women was not altered by adjustment for vitamin supplement use, although coronary mortality was again lower among supplement users (3% of the population) than among non-users\(^11\). In a case-control study, the risk of newly diagnosed coronary heart disease was...
lower in the highest quintiles of dietary vitamin E for men but not for women[12]. Although the opposite effect was observed for men who were already aware of their condition, this may have been due to changes in diet following diagnosis.

Whilst dietary studies are highly suggestive of an association between vitamin E and coronary heart disease, in some cases, extra vitamin E in the form of supplements appears to be required to produce protective in vivo levels. Alternatively, individuals who choose to take vitamin supplements may have other characteristics which make them less prone to developing heart disease. Furthermore, it cannot be excluded that nutrient(s) other than vitamin E in vitamin E-rich foods could be responsible for many of the effects observed in studies relying on dietary questionnaires. This problem is partially addressed by measuring vitamin levels in plasma and other body fluids directly.

**Plasma levels**

In a recent cross-cultural survey, plasma levels of vitamin E in men aged 40–49 years correlated strongly, and inversely, with the age-specific mortality from ischaemic heart disease in 16 European regions[13], although plasma levels did not reflect coronary mortality rates among a smaller group of four European populations[14]. There was no association between plasma vitamin E and prevalence of ischaemic heart disease in a cross-sectional survey of 1132 Finnish men, but dietary changes secondary to the diagnosis of heart disease were not evaluated[15].

Similarly, most case-control studies found no relationship between plasma vitamin E levels and subsequent coronary mortality[16,17], or risk of myocardial infarction[18,19]. Adipose tissue concentrations were also found not to influence the risk of heart attack[20]. On the other hand, plasma vitamin E was found to be independently and inversely related to the risk of newly diagnosed angina pectoris after adjustment for age, smoking, blood pressure, lipids and weight[21]. All but this latter study analysed vitamin levels from frozen blood samples which had been stored for several years. This raises the possibility that degeneration of vitamin E in storage was responsible for the negative results, although a recent review indicated that concentrations of vitamin E were fairly stable for at least 15 years if stored at −70 °C or colder[22].

A single prospective study on 2975 healthy males, followed-up for 7 years, failed to show a relationship between plasma vitamin E and mortality from ischaemic heart disease[23]. This lack of association has been blamed on exceptionally high vitamin E levels in the population under study; all vitamin quintiles may have been above a presumed critical level for improving coronary artery disease risk[24]. However, the study also lacked power because the mortality rate was less than 3%.

In summary, prospective data suggest that high dietary and/or supplemental intake of vitamin E is associated with a reduced risk of coronary heart disease, but support from blood- and tissue-based case control studies is scanty. Reasons for these disparate results are unknown but may include changes in diet following disease diagnosis, poor classification of controls and lack of variability in plasma levels within...
populations not using supplements. Ultimately, definitive conclusions must be sought from clinical trials.

**Clinical trials (Table 1)**

In an early clinical trial, 52 patients with angina pectoris demonstrated no symptomatic benefit following 6 months of vitamin E treatment compared with placebo[23]. However, both patient numbers and the period of follow-up in this study were limited. In the Alpha-Tocopherol and Beta-Carotene (ATBC) Study, vitamin E supplementation for 5–8 years had no effect on coronary mortality in 29,000 male smokers[26] and reduced the incidence of new angina pectoris by only a minor amount in 22,269 men free of coronary artery disease at baseline (relative risk 0.91, P = 0.04)[27]. However, the dose of vitamin E used was low (50 mg per day) and the synthetic preparation of alpha-tocopherol used has a low bioavailability so that mean blood levels were increased by only 50%, less than that produced by many dietary supplements of vitamin E. In the recent Cambridge Heart Antioxidant Study (CHAOS), higher doses of vitamin E (400 and 800 mg per day) were tested in 2002 patients with angiographically confirmed coronary artery disease. After an average of 17 months follow-up, patients taking vitamin E had 75% fewer non-fatal myocardial infarctions and 50% fewer non-fatal myocardial infarctions and cardiovascular deaths combined that those given placebo. Although there was a non-significant excess of cardiovascular deaths in the vitamin E group, the number of such events in each group was small (27 vs 23)[28].

Several other randomized controlled trials which include vitamin E are currently in progress. The Woman’s Health Study (WHS) is a primary prevention trial investigating the effects of vitamin E, beta-carotene and aspirin on cardiovascular disease and cancer in 40,000 women aged 50 years and over[29]. In France, the Supplementation Vitamins, Minerals, and Antioxidant (SU.VI.MAX) Trial is testing a combination of antioxidant vitamins including vitamin E, vitamin C, and beta-carotene in 18,000 subjects with above average risk of future coronary artery disease. After an average of 4 years, the number of such events in each group was small (27 vs 23)[28].

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In Gey’s cross-cultural survey, neither plasma vitamin A nor beta-carotene correlated consistently with ischaemic heart disease mortality in 16 European populations; neither was there an association with the major subset of 12 populations with normal cholesterol[13]. The only significant association was a weak inverse correlation between lipid-standardized levels of vitamin A and coronary mortality in all populations.

Five case control studies found variable results (Table 2). In Finland, mean retinol levels were higher in female cases of coronary death, but the same effect was not found for men[16]. In the Netherlands, there was no association between vitamin A and coronary mortality in either sex[17]. An initial inverse relationship between angina and low plasma carotene in Scottish males disappeared after adjustment for smoking; no relationship was found for vitamin A[21]. More recently, an increased risk of myocardial infarction was demonstrated for smokers with reduced levels of beta-carotene[19] although the same effect was not found in non-smokers. Similarly, an increased risk of myocardial infarction in the lowest quintile of adipose tissue beta-carotene was confined mainly to smokers[30].

In the Basle prospective study, there was an increased risk of mortality from ischaemic heart disease at initially low plasma levels of beta-carotene, independent of vitamin E and other cardiovascular risk factors[23]. In 1899 middle-aged hyperlipidaemic men, carotenoid levels were independently and inversely correlated with the subsequent risk of myocardial infarction.
Table 1  Randomized controlled trials of antioxidant vitamins in coronary artery disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>n</th>
<th>Duration</th>
<th>Vitamins (dose)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gillilan et al. 1977 [27]</td>
<td>Men with angina</td>
<td>52</td>
<td>6 months</td>
<td>Vitamin E (1600 mg. day⁻¹)</td>
<td>No symptomatic improvement</td>
</tr>
<tr>
<td>Physicians Health Study 1990 [30]</td>
<td>Men with stable angina or coronary surgery</td>
<td>333</td>
<td>6 years</td>
<td>Beta-carotene (50 mg. altday⁻¹)</td>
<td>44% reduction in major coronary events</td>
</tr>
<tr>
<td>ATBC Study 1994 [26]</td>
<td>Male smokers 50-69 years</td>
<td>29000</td>
<td>5-8 years</td>
<td>Vitamin E (50 mg. day⁻¹)</td>
<td>No effect on coronary mortality (increased incidence of lung cancer with beta-carotene)</td>
</tr>
<tr>
<td>CARET Study 1994 [41]</td>
<td>Men and women Heavy smokers and asbestos workers</td>
<td>18000</td>
<td>2-3 years</td>
<td>Vitamin A (25 000 IU. day⁻¹)</td>
<td>Terminated 1996, cardiovascular results awaited, 28% increase in lung cancer, 17% increase in deaths</td>
</tr>
<tr>
<td>CHAOS Study 1996 [28]</td>
<td>Men and women with coronary atheroma</td>
<td>2002</td>
<td>3-981 days (median 510)</td>
<td>Vitamin E (400 mg or 800 mg. day⁻¹)</td>
<td>75% reduction in non-fatal MI, non-significant increase in cardiovascular death</td>
</tr>
<tr>
<td>Physicians Health Study [34]</td>
<td>Healthy males 40-84 years</td>
<td>22071</td>
<td>10 years</td>
<td>Beta-carotene (50 mg. altday⁻¹)</td>
<td>Cancer and cardiovascular results awaited</td>
</tr>
<tr>
<td>SU.VI.MAX Trial [35]</td>
<td>Healthy men and women</td>
<td>15000</td>
<td>Ongoing</td>
<td>Vitamin E</td>
<td>Cardiovascular endpoints</td>
</tr>
<tr>
<td>Womans Health Study [29]</td>
<td>Healthy females 40-84 years</td>
<td>40000</td>
<td>Ongoing (Began 1992)</td>
<td>Vitamin E (600 mg. altday⁻¹)</td>
<td>Cancer and cardiovascular endpoints (Beta-carotene terminated 1996)</td>
</tr>
<tr>
<td>Heart Protection Study [33]</td>
<td>Men and women at increased risk of future MI</td>
<td>18000</td>
<td>Ongoing (Began 1994)</td>
<td>Vitamin E (600 mg. day⁻¹)</td>
<td>Incidence of coronary and all-cause mortality</td>
</tr>
<tr>
<td>WACDT [36]</td>
<td>Women with coronary artery disease</td>
<td>80000</td>
<td>Ongoing (Began 1995)</td>
<td>Vitamin C (250 mg. day⁻¹)</td>
<td>Cardiovascular endpoints</td>
</tr>
<tr>
<td>HOPE Study [32]</td>
<td>Men and women at increased risk of future MI</td>
<td>90000</td>
<td>Ongoing (Began 1995)</td>
<td>Vitamin C (1 g. day⁻¹)</td>
<td>Cardiovascular endpoints</td>
</tr>
<tr>
<td>Study</td>
<td>Definition of disease</td>
<td>Vitamin</td>
<td>Sex</td>
<td>Mean vitamin levels**</td>
<td>P</td>
</tr>
<tr>
<td>------------------------</td>
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</tr>
<tr>
<td>Salonen et al. 1985</td>
<td>Death from coronary artery disease</td>
<td>Vitamin A</td>
<td>M</td>
<td>653 g \cdot l^{-1}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F</td>
<td>647 g \cdot l^{-1}</td>
<td></td>
</tr>
<tr>
<td>Kok et al. 1987</td>
<td>Death from coronary artery disease</td>
<td>Vitamin A</td>
<td>M</td>
<td>56.3 \mu g \cdot dl^{-1}</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Riemersma 1991 et al.</td>
<td>Angina pectoris</td>
<td>Beta-carotene</td>
<td>M</td>
<td>17.2 \mu g \cdot dl^{-1}</td>
<td>0.03</td>
</tr>
<tr>
<td>Kardinaal 1993 et al.</td>
<td>Acute myocardial infarction</td>
<td>Beta-carotene</td>
<td>M</td>
<td>0.35 \mu g \cdot g^{-1} fatty acid</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Street et al. 1994</td>
<td>First diagnosis of myocardial infarction</td>
<td>Beta-carotene</td>
<td>M+F</td>
<td>120 g \cdot l^{-1}</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Vitamin concentrations in plasma except for Kardinaal et al. where concentration measured in adipose tissue.
ns=not significant; M= male, F= female.

*Standardized for level of serum cholesterol.
or coronary death\textsuperscript{37}. Mean carotenoid levels were lower in the events group in both smokers and non-smokers, although the difference was greater in non-smokers\textsuperscript{37}.

Thus, there is some indication that increased dietary intake of beta-carotene is associated with a reduced risk of coronary artery disease, although the evidence is less convincing than that for vitamin E. Results of three case control and two prospective studies also suggest that plasma beta-carotene levels are associated with a reduced risk of disease. Several studies indicate that dietary and circulating levels of the pro-vitamin affect smokers more than non-smokers\textsuperscript{10,19,20}, although the opposite effect was observed in hyper-lipidaemic men\textsuperscript{35}. It may be that a high dietary intake of beta-carotene is especially important in smokers who have both an increased demand for antioxidants (to combat smoking-induced free radicals) and a correspondingly lower circulating level of the pro-vitamin for a given dietary intake\textsuperscript{38}. Studies on vitamin A are scarce but in general do not indicate an independent role for this vitamin in coronary artery disease, perhaps unsurprisingly in view of the resistance of plasma vitamin A levels to changes in dietary intake. Definitive conclusions on the effects of these vitamins on the risk of coronary artery disease await the final analysis of ongoing randomized controlled trials.

Clinical trials (Table 1)

In the ATBC Study, beta-carotene had no significant effect on coronary mortality\textsuperscript{26} or on the incidence of new angina pectoris\textsuperscript{27} in male smokers, but did result in an 8% increase in total mortality and an 18% increase in lung cancer. A second large randomized controlled trial of beta-carotene in the primary prevention of cancer and cardiovascular disease, the Harvard Physicians Health Study\textsuperscript{29}, ended in December 1995. Early results from a subset of 333 men with chronic stable angina or coronary revascularization at the time of randomization, indicated a 44% reduction in all major coronary events in those receiving beta-carotene\textsuperscript{39}. Detailed results from the full trial on 22,071 healthy men are awaited, although a preliminary report suggested that beta-carotene had no effect on disease or death\textsuperscript{40}. The Beta-Carotene and Retinol Efficacy Trial (CARET), a trial of beta-carotene and vitamin A against lung cancer in 18,000 smokers and asbestos workers\textsuperscript{41} was terminated almost 2 years early due to a 28% increase in lung cancer and a 17% increase in deaths\textsuperscript{40}. Results for the effect of treatment on cardiovascular disease are awaited. In view of the adverse findings of the ATBC and CARET studies, the Woman’s Health Study, which began in 1992\textsuperscript{42}, has also terminated the beta-carotene arm of its trial, but results to date have not been reported\textsuperscript{40}. The three other trials which involve beta-carotene, factored with vitamins E and C are continuing\textsuperscript{28,31}.

Vitamin C

Dietary intake

In the Harvard Physicians Follow-Up Study, a high intake of vitamin C was not associated with a lower risk of coronary heart disease in men\textsuperscript{10}, whilst in women from the Nurses Health Survey, an initial effect was attenuated after adjustment for multivitamin use\textsuperscript{42}. There was no association between vitamin C intake and subsequent cardiovascular events in 1462 Swedish women followed up for 5 years, but a total of only 23 myocardial infarctions was recorded\textsuperscript{43}. Vitamin C intake was associated with a reduced risk of coronary mortality among 2385 women in Finland, but not among a similarly sized group of men and no adjustment was made for intake of vitamin E and beta-carotene\textsuperscript{11}. Indeed, only one prospective study involving 11,348 adults demonstrated an inverse relationship between vitamin C intake and cardiovascular mortality\textsuperscript{44}. This effect was due largely to the use of vitamin C in supplements and again may have been due to antioxidant vitamins other than vitamin C in multivitamins, the supplement most widely used by study participants. In a single case-control study, men with previously undiagnosed ischaemic heart disease had lower vitamin C intake than healthy controls\textsuperscript{12}. No association between vitamin C levels and risk of coronary artery disease was found in women, or in men who were already aware of their diagnosis.

Plasma and leucocyte levels

In Gey’s cross-cultural study, plasma vitamin C correlated weakly with coronary mortality in the major subgroup of 12 populations with normal cholesterol levels, but this association disappeared on inclusion of all 16 populations\textsuperscript{13}. Plasma levels were not correlated with coronary mortality rates among four European populations\textsuperscript{14}, or with prevalent coronary disease in Finland\textsuperscript{15}. Decreased leucocyte ascorbic acid levels were found in cases of angiographically proven coronary artery disease compared with controls referred for cardiac catheterization\textsuperscript{45}. However, an initial relationship between newly diagnosed angina and low vitamin C was non-significant after controlling for cigarette smoking\textsuperscript{21}. In the Basle prospective study, low levels of vitamin C alone did not increase the risk of ischaemic heart disease, although the risk of disease at low levels of both vitamin C and beta-carotene was greater than that for beta-carotene alone\textsuperscript{23}.

In conclusion, there is very little evidence in support of a role for vitamin C in the aetiology of coronary artery disease. Further information should be forthcoming from the two ongoing secondary prevention trials\textsuperscript{28,31} and one primary prevention trial\textsuperscript{39} in which vitamin C is factored with vitamin E and beta-carotene (Table 1).
Peripheral arterial disease

In comparison with coronary artery disease, relatively few studies have investigated the relationship between antioxidant vitamins and peripheral arterial disease. In a recent case control study, dietary vitamin C intake was significantly lower in cases of lower limb atherosclerosis than controls, but there were no significant differences in the intake of vitamins A and E. Reduced levels of vitamin E were found in the skeletal muscle of elderly claudicants and serum and leucocyte vitamin C levels were lower in seven patients with intermittent claudication than in 13 controls. Finally, baseline plasma beta-carotene and vitamin E levels were inversely related to the 12 month progression of carotid artery wall thickness in hypercholesterolaemic men.

There have been at least six clinical trials of vitamin E in lower limb atherosclerosis (Table 3). Although these early trials have been small and of variable quality, all but one indicated an improvement in peripheral arterial disease with vitamin E supplementation in the range of 300 mg to 1.6 g per day. Of all the studies, that finding no benefit was among the shortest performed and used a dose of 300 mg vitamin E which may have been much lower than the 400 mg per day estimated by the authors. A systematic review of vitamin E treatment in peripheral arterial disease is currently in progress (J. Kleijnen, personal communication). In addition, a randomized controlled trial of fatty acids and an antioxidant combination including vitamin C, beta-carotene, selenium, zinc and pyridoxine is currently underway in claudicants. The results should be available in 1997, although it will not be possible to examine the effects of individual antioxidant vitamins in this combined preparation.

Despite limited data, there is some indication that the effects of antioxidant vitamins in peripheral arterial disease may be similar to those in coronary artery disease. However, further prospective studies and clinical trials will be required before firm conclusions can be drawn.

Table 3 Randomized controlled trials of vitamin E in the treatment of peripheral arterial disease

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of subjects</th>
<th>Definition of disease</th>
<th>Dose and duration of vitamin E</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamilton et al. 1953</td>
<td>41</td>
<td>Intermittent claudication</td>
<td>&lt;450 mg. day⁻¹ 12 weeks</td>
<td>No change in symptoms</td>
</tr>
<tr>
<td>Livingston and Jones 1958</td>
<td>40</td>
<td>Intermittent claudication</td>
<td>600 mg. day⁻¹ 40 weeks</td>
<td>No change in exercise tolerance</td>
</tr>
<tr>
<td>Williams et al. 1962</td>
<td>33</td>
<td>Intermittent claudication</td>
<td>1.6 g. day⁻¹ 3-43 months</td>
<td>Improvement in walking distance*</td>
</tr>
<tr>
<td>Boyd and Marks 1963</td>
<td>33</td>
<td>Intermittent claudication</td>
<td>400 mg. day⁻¹ 13 weeks</td>
<td>Improvement in walking distance</td>
</tr>
<tr>
<td>Haeger 1966</td>
<td>227</td>
<td>Intermittent claudication &gt;75% stenosis at angiography</td>
<td>300 mg. day⁻¹ 3-4 years</td>
<td>Improvement in symptoms</td>
</tr>
<tr>
<td>Williams et al. 1971</td>
<td>74</td>
<td>Intermittent claudication Positive arteriogram</td>
<td>1.6 g. day⁻¹ 9 months</td>
<td>Improvement in walking distance*</td>
</tr>
<tr>
<td>Haeger 1974</td>
<td>46</td>
<td>Intermittent claudication Femoropopliteal occlusion</td>
<td>300 mg. day⁻¹ 3 months</td>
<td>Improvement in walking distance</td>
</tr>
</tbody>
</table>

*Improvement only for patients with femoropopliteal occlusion and poor distal arterial bed.

**Vitamin E compared to alternative treatment regimes (vasodilators, anticoagulants or multivitamins without vitamin E).

Conclusions

Available epidemiological evidence is consistent with the possibility that antioxidant vitamins have a protective role in cardiovascular disease. Evidence with respect to vitamins C and A is weak, that for beta-carotene somewhat stronger and evidence for a role for vitamin E highly suggestive. Most investigators and reviewers have concentrated on the effect of antioxidant vitamins in coronary artery disease and, as yet, there is very little information on the role of antioxidant vitamins in peripheral arterial disease. However, clinical trials of vitamin E in claudicants have been encouraging and further work is required, especially in view of the possible link between beta-carotene and smoking (a particularly strong risk factor for peripheral arterial disease).

Whilst there may be specific requirements for all the antioxidant vitamins, their proposed common effect on atherosclerotic disease via inhibition of low density lipoprotein oxidation raises the possibility of additive or even synergistic effects. Synergistic interactions between antioxidants have been described in many experimental studies and in the Basle prospective study there was an over-multiplicative increase in cardiovascular risk at low concentrations of vitamin C and beta-carotene. Although plasma levels of vitamin E can be increased only approximately twofold by dietary supplementation,

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there is evidence that vitamin C may regenerate and spare vitamin E\(^{[58]}\), such that the protection afforded by the two given together should be additive. Although detailed epidemiological evidence on possible interactions between the antioxidant vitamins is lacking, it is generally felt that antioxidant vitamins in ischaemic heart disease prevention should be tested by an antioxidant mixture aimed at optimizing the total antioxidant effect\(^{[59]}\). Several ongoing large-scale trials are therefore using a factorial design in which it should be possible to test the effects of all the antioxidant vitamins combined as well as their individual effects\(^{[30,31]}\).

It is tempting to suggest that as these antioxidant vitamins are potentially beneficial and do not appear to be harmful, then their consumption should be encouraged. However, current evidence does not support the routine use of antioxidant vitamins against cardiovascular disease, and dietary guidelines should await the outcome of clinical trials presently in progress.

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[28] The HOPE (Heart Outcomes Prevention Evaluation) Study. The design of a large, simple randomised trial of an angiotensin converting enzyme inhibitor (ramipril) and vitamin E in...


