Vitamins No Benefit to Heart Disease - Study

Tue Nov 19, 2002

CHICAGO (Reuters) - Post-menopausal women suffering from heart disease get no benefit from taking vitamin supplements and may be increasing their risk of developing artery blockages, researchers said on Tuesday.

In the 4-1/2-year study of 423 women, those who took supplements containing the anti-oxidant vitamins E and C to help fend off post-menopausal symptoms ended up with greater artery constriction than those taking inert placebos.

The same tendency toward artery constriction was found among study participants receiving hormone replacement therapy (HRT), and among those who took both HRT and vitamin supplements. HRT is designed to alleviate post-menopausal ailments from osteoporosis to hot flashes and vaginal dryness.

A much-publicized study in July showed long-term use of the most popular form of HRT, which is made using horse urine, raises the risk of heart disease as well as cancer and stroke. Hormone therapy was previously thought to have protective properties against coronary disease.

"The results of this trial add to the accumulating evidence that neither HRT nor antioxidant vitamin supplements improve the clinical course of coronary disease in post-menopausal women," Dr. David Waters, of San Francisco General Hospital, wrote in this week's Journal of the American Medical Association.

The vitamin dosage in the study was 400 units of Vitamin E and 500 milligrams of Vitamin C. Both vitamins are considered to have anti-oxidant properties that can boost the immune system and offset free radicals associated with the development of various diseases, including cancer.

Twenty-six of the patients taking the vitamin supplements either died, suffered a nonfatal heart attack or stroke, the same number as those taking HRT and outnumbering those taking placebos.

Waters called the finding about mortality related to vitamin intake "unexpected." Though it could be a "chance finding," he discouraged women from using both HRT and high doses of vitamins E and C.

Yeast Experiments Challenge Scientists' Notions About Aging

July 17, 2002

Source: ***Nature***

(AP) PORTLAND, Oregon - **An entire diet and supplement industry has sprung up around the notion that one of the keys to a long life is removing oxygen molecules called free radicals from the body. But now experiments with yeast have called that theory into question.**

The experiments challenge the notion that free radicals play a central role in aging and longevity.

Sales of "antioxidant" vitamins and supplements have grown since earlier studies suggested that free radicals damage cells and DNA.

Another way to reduce free radicals is a severely restricted diet. Scientists have known for more than 60 years that limiting food intake to about two-thirds of normal can extend the lives of rats and keep them healthier, a finding that has been duplicated in yeast, fish, worms and other creatures.

But in a study in Thursday's issue of the journal ***Nature***, yeast cells lived 20 percent longer after scientists made genetic changes that speeded up their metabolism, or the rate at which cells turn food into energy. Metabolism produces free radicals.

"The old idea was there was simply less production of oxygen radicals and less oxidative damage to the cell with calorie restriction," said Leonard Guarente of the Massachusetts Institute of Technology, who led the study. "But I think the results of this study really challenge that idea."

In an accompanying commentary, Siu Sylvia Lee and Gary Ruvkun of Harvard Medical School warned that what applies in yeast does not necessarily apply in animals.

But they agreed that the findings "contradict the theory that a decrease in free radicals is an essential feature of increased longevity."

Lee and Ruvkun said it is still not clear whether limiting free radicals by severely restricting calorie intake has any benefit or is just a gimmick promoted by "a variety of optimists, hucksters and fanatics."

Dr. Richard Weindruch, who is studying the effects of calorie restriction on monkeys at the University of Wisconsin, said there is no reason for people to stop taking antioxidants such as vitamin C to try to reduce cell damage.

"I don't think the results of this yeast study should influence public health recommendations," Weindruch said.

Antioxidants Don't Help, Again

NEJM Volume 345:1583-1592 Number 22 November 29, 2001

In a study of cholesterol-lowering drugs with or without antioxidants, the drugs simvastatin (brand name Zocor) plus niacin reduced serum lipids and heart disease but an antioxidant mixture did not. In a surprise finding, when antioxidants were combined with the cholesterol-lowering drugs, the beneficial effect was greatly decreased.

Groups of 33 to 40 patients who had low HDL cholesterol (the protective variety) and evidence of heart disease were treated for three years. **The antioxidant mix included 800 IU of vitamin E, 1000 mg of vitamin C, 25 mg of beta-carotene, and 100 micrograms of selenium.** In addition to serum lipids, arteriography was performed to determine blockages of coronary arteries, and cardiovascular events (heart attack, stroke, vascular surgery, death) were counted. The study was published in the November 29, 2001 edition of the New England Journal of Medicine.

Although this was a small study, its results are consistent with most other trials of antioxidants for heart disease. There was no benefit on arterial lesions judged to be early or late in formation. Not only are excess intakes not beneficial, they may be harmful if taken with cholesterol-lowering drugs known as statins.

JAMA. 2002;288:2432-2440

Effects of Hormone Replacement Therapy and Antioxidant Vitamin Supplements on Coronary Atherosclerosis in Postmenopausal Women

A Randomized Controlled Trial

David D. Waters, MD; Edwin L. Alderman, MD; Judith Hsia, MD; Barbara V. Howard, PhD; Frederick R. Cobb, MD; William J. Rogers, MD; Pamela Ouyang, MD; Paul Thompson, MD; Jean Claude Tardif, MD; Lyall Higginson, MD; Vera Bittner, MD; Michael Steffes, MD, PhD; David J. Gordon, MD, PhD; Michael Proschan, PhD; Naji Younes, PhD; Joel I. Verter, PhD

Context Hormone replacement therapy (HRT) and antioxidant vitamins are widely used for secondary prevention in postmenopausal women with coronary disease, but no clinical trials have demonstrated benefit to support their use.

Objective To determine whether HRT or antioxidant vitamin supplements, alone or in combination, influence the progression of coronary artery disease in postmenopausal women, as measured by serial quantitative coronary angiography.

Design, Setting, and Patients The Women's Angiographic Vitamin and Estrogen (WAVE) Trial, a randomized, double-blind trial of 423 postmenopausal women with at least one 15% to 75% coronary stenosis at baseline coronary angiography. The trial was conducted from July 1997 to January 2002 in 7 clinical centers in the United States and Canada.

Interventions Patients were randomly assigned in a 2 ✖2 factorial design to receive either 0.625 mg/d of conjugated equine estrogen (plus 2.5 mg/d of medroxyprogesterone acetate for women who had not had a hysterectomy), or matching placebo, and 400 IU of vitamin E twice daily plus 500 mg of vitamin C twice daily, or placebo.

Main Outcome Measure Annualized mean (SD) change in minimum lumen diameter (MLD) from baseline to concluding angiogram of all qualifying coronary lesions averaged for each patient. Patients with intercurrent death or myocardial infarction (MI) were imputed the worst rank of angiographic outcome.

Results The mean (SD) interval between angiograms was 2.8 (0.9) years. Coronary progression, measured in mean (SD) change, worsened with HRT by 0.047 (0.15) mm/y and by 0.024 (0.15) mm/y with HRT placebo (*P* = .17); and for antioxidant vitamins by 0.044 (0.15) mm/y and with vitamin placebo by 0.028 (0.15) mm/y (*P* = .32). When patients with intercurrent death or MI were included, the primary outcome showed an increased risk for women in the active HRT group (*P* = .045), and suggested an increased risk in the active vitamin group (*P* = .09). Fourteen patients died in the HRT group and 8 in the HRT placebo group (hazard ratio [HR], 1.8; 95% confidence interval [CI], 0.75-4.3), and 16 in the vitamin group and 6 in the vitamin placebo group (HR, 2.8; 95% CI, 1.1-7.2). Death, nonfatal MI, or stroke occurred in 26 HRT patients vs 15 HRT controls (HR, 1.9; 95% CI, 0.97-3.6) and in 26 vitamin patients and 18 vitamin controls (HR, 1.5; 95% CI, 0.80-2.9). There was no interaction between the 2 treatment interventions.

Conclusion In postmenopausal women with coronary disease, neither HRT nor antioxidant vitamin supplements provide cardiovascular benefit. Instead, a potential for harm was suggested with each treatment.

Antioxidant Vitamins Not Good for Heart

In yet another study of antioxidant vitamins, no benefit was found in a group of over 400 postmenopausal women. Each woman had narrowing of the coronary arteries demonstrated by angiography and was given 800 IU of vitamin E and 1000 mg of vitamin C for almost three years.

There actually was a trend to more arterial blockage with the vitamin treatment, but it was not statistically meaningful. **Deaths and heart attacks were also somewhat increased in the group taking vitamins. The report appeared in the November 20, 2002 edition of the Journal of the American Medical Association.** < http://jama.ama-assn.org/issues/v288n19/abs/joc21018.html >

HERE'S WHAT YOU NEED TO KNOW: Although this is not a terribly large study, it suggests that not only is there no benefit from very high doses of antioxidant vitamins, there may be harm. No one knows what the optimal intakes of these vitamins are yet, but the more evidence that accumulates, the more it seems clear that very high doses cannot be justified.

Are Antioxidant Vitamins all They are Cracked up to Be?

The Lancet **2003;361:2017-2023**
14 June 2003 Issue

Antioxidant vitamins such as vitamin E and beta carotene do not ward of heart problems and beta carotene, a vitamin A source, may be harmful, according to an analysis of 15 key studies.

Antioxidants have been widely recommended for heart health, however recent studies have suggested that the pills may not be effective and may even be damaging. Some experts argue that while the pills don't seem to prevent heart attacks and premature death, they might be useful if started early and may delay the progression of heart disease or other blood vessel problems.

In the current study, researchers analyzed 15 studies involving nearly 220,000 people, most of whom had either had heart or blood vessel disease or were at an

increased risk of such problems.

Eight of the studies involved beta carotene alone or in combination with other antioxidants, while seven of the studies involved vitamin E, either alone or with other antioxidants. Follow-up periods ranged from one to 12 years.

Researchers found that beta carotene was associated with a 0.3 percent increased risk of cardiovascular death and a 0.4 percent increased risk of death from any cause. They noted, however, that the harmful effect was largely due to two studies that included a lot of smokers.

Vitamin E did not reduce death from cardiovascular or any other cause and did not lower the incidence of strokes.

It was thought that antioxidant vitamins protect the heart by blocking the damaging effects of oxygen. Animal studies show favorable results with this approach and studies have found that people who eat vitamin-rich foods have less heart disease.

Experts suggest that antioxidants may work when they are in food but not necessarily when they are in pills. Additionally, they say that people who eat vitamin-rich food generally take better care of themselves, which may explain their lower heart disease risk.

However, some experts say that the role of antioxidants in delaying death or potentially benefiting other heart problems, such as cardiac arrhythmias, needs to be explored.

Are We Certain that Vitamin Therapy is Not Pro-Neoplastic?

by
Jonathan Collin M.D.
Editor-in-Chief, The Townsend Letter for Doctors

In an editorial last month (Issue #154 May 1996), I expressed a fairly controversial viewpoint that beta carotene might be contributing to pro-neoplasia formation, meaning favoring malignant cell growth, in the high-risk smoking population. I fully expect that a letter will appear soon shooting down that hypothesis. Nevertheless, it raises the issue that appears to underlie the unconventional medical communities championing of vitamins and stoning of drugs. The pithy reason given for bad-mouthing medical physicians prescription(s) is that drugs are dangerous, ultimately toxic and potentially carcinogenic, whereas mega-vitamin supplementation is safe, nontoxic and noncarcinogenic. Broadly speaking, vitamin supplementation has rarely created significant poisoning or toxicity, except in the fiasco several years ago when an unscrupulous Japanese manufacturer of amino acids unloaded a tainted batch of tryptophan on the American wholesale market. However, long-term megavitamin therapy has never undergone methodical outcome research for morbidity, and the question of it playing a pro-neoplastic role remains essentially unknown. When a long-time follower of natural healing ultimately dies of cancer, heart disease, or infection, did the use of supplementation stave off the disease that would have presented even earlier in the individuals life, or did it possibly contribute to the disease formation? It seems that mega-vitamin use in quenching free radical pathology, would argue that vitamins prevent degenerative disease formation, but this theory remains a belief system rather than a documented observation.

Mostly what we do in alternative medical therapy is experimental. We assume that long-term use of mega-vitamin supplementation will benefit the patient, because short-term use obviously improves his or her symptoms. The sticky question remains did we really prevent the major disease from happening? One cannot set the clock back and take the patient who has succumbed to a malignancy and check out a different course of action, using no megavitamin therapy, or no alternative treatment. Preventing disease in an individual is not a measurable event.

Given the fact that we cannot measure prevention, might it not be prudent to reassess yearly, what we are doing with our patients megavitamin supplementation? Are there any signs that we might be off course, actually encouraging new degeneration occurrence? If so, should we shift gears and radically change the patients supplementation protocol? It would appear that the only rational approach to this difficulty would be to give the protocol a testing. Eliminating supplement use for a time period allows some observation as to supplement need, dependency, and adverse effect versus benefit. Changing supplements offers a glimpse at how one group of nutrients may be affecting our system quite differently from a second grouping. The soft sciences of electrical field diagnosis by devices capable of measuring subtle energies appears to diagnose supplement compatibility. Such techniques, including muscle testing of supplements, may be quite

irrational scientifically, but may offer clues that some supplement(s) just aren't right for us and may need avoidance or elimination.

As difficult as these questions may be, we must consider that a supplement is not being used just today, last week, last month, next week, or next month. For many of our patients, the supplement has been used the last several years, even the last several decades. When a patient follows our advice and then falls away from our practice, the vitamin prescription is still acting on their system. If they develop cancer or cardiovascular disease, we cannot just ignore it as an anomaly. Just like the accountant's statement of assets and debits, we have those who really did benefit preventive-wise and others who did not. Aware of that uncertainty, we should always question if our supplement prescriptions are really on track or might be contributing to pro-neoplasia.

Jonathan Collin, M.D.

Vitamin E (*tocopherols*) vs. Wheat Germ Oil

The literature reporting the advantages of wheat germ oil, or vitamin E, in the treatment of various disorders can be very confusing with respect to the exact material used. The following is from *American Journal of Digestive Diseases*, Vol. 12, no.1, Jan,1945. pages 20-21.
In a symposium held in London 1939 Vogt-Moeller stated, "Finally, let it be kept in mind that wheat germ oil, which so far has been the preparation most commonly employed for therapeutic trials, may contain many biologically active substances other than Vitamin E, and one must consider the possibility that some of these may have contributed to the observed effects. Even though this appears to me rather unlikely, the question can soon be settled with certainty by repeating the experiments with pure tocopherols. (commonly referred to as vitamin E)
In the work referred to above, Vogt-Moeller gives the results of just such an experiment. He points out that the various reports on the influence of vitamin E on neuromuscular disorders are confusing because vitamin E was used in some experiments while wheat germ oil was used in others. It has been shown previously that wheat germ oil contains factors other than vitamin E (Martin, G. J. : J. Nutrition, 13:679 (1937)).
Vogt-Moeller planned an experiment involving 90 dogs affected by distemper. All dogs, including the controls, were placed on a balanced diet with a supplementary vitamin B-complex preparation. Before instituting treatment, he waited until all dogs had developed the initial symptoms of distemper. These usually preceded the development of neuromuscular disturbances.
Thirty dogs were the control group.
Thirty dogs were injected daily with 10mg of alpha tocopherol (vitamin E).
Thirty dogs were injected daily with 5cc of wheat germ oil, which contained 10mg of alpha tocopherol.
The results were as follows:

	Control	Tocopherol	Wheat Germ Oil
# of dogs	30	30	30
Died	14	16	12
Dogs developing neuro-muscular symptoms--- Died	10	11	3
Dogs developing neuro-muscular symptoms & survived	11	12	2
Total developing neuro-muscular symptoms	21	23	5

It appears that, for the first time, evidence has been presented of the presence in wheat germ oil of a factor that exerts a beneficial effect other than vitamin E (tocopherols). For many years it has been suggested that research workers in reporting their work make a sharp distinction between Vitamin E (tocopherols) and wheat germ oil. Vogt-Moeller's work makes such a distinction imperative.
Also the method of extraction of the oils determines their effectiveness.
I hope that this sheds a little light on the difference between the extracted tocopherols (also commonly called vitamin E) and the **Vitamin E-complex** that occurs in its natural form in wheat germ oil.

Harvard Medical School
Harvard Health Publications

Harvard Health Letter

(Vol 27, No 4, 2/02)

Taking Stock of Antioxidants

- “. . . the results of recent studies have begun to sow some doubts about antioxidants, particularly in pill form. Indeed, in some circumstances, high doses of antioxidants may do more harm than good."
- " . . . the list of compounds that have antioxidant properties seems to grow daily . . . "
- “. . . some of these compounds may interact . . . They may have other functions, too, that overshadow their role as antioxidants."
- "The idea that antioxidants are good for you wasn't invented out of whole cloth. It rests on credible research. But most of the positive results have come from foods rich in antioxidants rather than large doses in pill form."
- "The next generation of nutrition research may clear away some of the confusion."

Harvard Health Letter (Vol 27, No 4, 2/02) in its Nutrition feature cover article, "Taking Stock of Antioxidants," adds credence to our contention of the superiority of synergism over synthesis:

" . . . the results of recent studies have begun to sow some doubts about antioxidants, particularly in pill form. Indeed, in some circumstances, high doses of antioxidants may do more harm than good."

" . . . the list of compounds that have antioxidant properties seems to grow daily . . . "

" . . . some of these compounds may interact . . . They may have other functions, too, that overshadow their role as antioxidants."

"The idea that antioxidants are good for you wasn't invented out of whole cloth. It rests on credible research. But most of the positive results have come from foods rich in antioxidants rather than large doses in pill form."

"The next generation of nutrition research may clear away some of the confusion."

The New York Times

Heart Study Bolsters Doubt on Hormones

By THE ASSOCIATED PRESS

November 19, 2002

CHICAGO, Nov. 19 (AP) — Casting still more doubt on long-held assumptions, a study suggests that **hormone supplements and antioxidant vitamins hold no heart benefits for older women who already have heart disease.**

In fact, heart disease appeared to progress more quickly in women who took hormones, high doses of vitamins E and C, or both, than in those on placebos. That finding was not statistically significant, but the researchers said the trend was worrisome.

"It's a little bit surprising that the outcomes for both treatments were so bad," said the lead author, Dr. David Waters, chief of cardiology at San Francisco General Hospital. "When the study was designed in the early 1990's, both of these treatments were thought to be highly promising."

Hormone supplements were once thought to benefit the heart because naturally occurring estrogen helps keep cholesterol at healthy levels. But a landmark study that was reported last summer found that the pills might actually increase the risk of heart attacks and strokes**. Similarly, antioxidant vitamins were thought to block the effects of oxygen molecules that could damage heart cells. But more recent studies have questioned the heart benefits and suggested that the vitamins might interfere with cholesterol-lowering drugs.**

The new study, to appear on Wednesday in *The Journal of the American Medical Association*, involved 423 postmenopausal heart patients over three years. By its end, 2 women on placebos had died, compared with 4 who took hormones, 6 who took high doses of vitamins C and E, and 10 who took both vitamins and hormones.

John Hathcock, vice president for nutritional and regulatory science at the Council for Responsible Nutrition, a trade group for makers of vitamins and other dietary supplements, argued that the study did not disprove earlier research implying a benefit from vitamins. Mr. Hathcock called the results "a chance finding" and said the statistics were too weak to support the researchers' conclusions.

Vitamins No Benefit to Heart Disease - Study

Tue Nov 19, 2002

CHICAGO (Reuters) - Post-menopausal women suffering from heart disease get no benefit from taking vitamin supplements and may be increasing their risk of developing artery blockages, researchers said on Tuesday.

In the 4-1/2-year study of 423 women, those who took supplements containing the anti-oxidant vitamins E and C to help fend off post-menopausal symptoms ended up with greater artery constriction than those taking inert placebos.

The same tendency toward artery constriction was found among study participants receiving hormone replacement therapy (HRT), and among those who took both HRT and vitamin supplements. HRT is designed to alleviate post-menopausal ailments from osteoporosis to hot flashes and vaginal dryness.

A much-publicized study in July showed long-term use of the most popular form of HRT, which is made using horse urine, raises the risk of heart disease as well as cancer and stroke. Hormone therapy was previously thought to have protective properties against coronary disease.

"The results of this trial add to the accumulating evidence that neither HRT nor antioxidant vitamin supplements improve the clinical course of coronary disease in post-menopausal women," Dr. David Waters, of San Francisco General Hospital, wrote in this week's Journal of the American Medical Association.

The vitamin dosage in the study was 400 units of Vitamin E and 500 milligrams of Vitamin C. Both vitamins are considered to have anti-oxidant properties that can boost the immune system and offset free radicals associated with the development of various diseases, including cancer.

Twenty-six of the patients taking the vitamin supplements either died, suffered a nonfatal heart attack or stroke, the same number as those taking HRT and outnumbering those taking placebos.

Waters called the finding about mortality related to vitamin intake "unexpected." Though it could be a "chance finding," he discouraged women from using both HRT and high doses of vitamins E and C.

MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20 536 high-risk individuals: a randomised placebo-controlled trial

THE LANCET
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Correspondence to: *Heart Protection Study, Clinical Trial Service Unit and Epidemiological Studies Unit, Radcliffe Infirmary, Oxford OX2 6HE, UK (e-mail:hps@ctsu.ox.ac.uk)*

Summary

Background It has been suggested that increased intake of various antioxidant vitamins reduces the incidence rates of vascular disease, cancer, and other adverse outcomes.

Methods 20 536 UK adults (aged 40-80) with coronary disease, other occlusive arterial disease, or diabetes were randomly allocated to receive antioxidant vitamin supplementation (600 mg vitamin E, 250 mg vitamin C, and 20 mg ß-carotene daily) or matching placebo. Intention-to-treat comparisons of outcome were conducted between all vitamin-allocated and all placebo-allocated participants. An average of 83% of participants in each treatment group remained compliant during the scheduled 5-year treatment period. Allocation to this vitamin regimen approximately doubled the plasma concentration of α-tocopherol, increased that of vitamin C by one-third, and quadrupled that of ß-carotene. Primary outcomes were major coronary events (for overall analyses) and fatal or non-fatal vascular events (for subcategory analyses), with subsidiary assessments of cancer and of other major morbidity.

Findings There were no significant differences in all-cause mortality (1446 [14·1%] vitamin-allocated *vs* 1389 [13·5%] placebo-allocated), or in deaths due to vascular (878 [8·6%] *vs* 840 [8·2%]) or non-vascular (568 [5·5%] *vs* 549 [5·3%]) causes. Nor were there any significant differences in the numbers of participants having non-fatal myocardial infarction or coronary death (1063 [10·4%] *vs* 1047 [10·2%]), non-fatal or fatal stroke (511 [5·0%] *vs* 518 [5·0%]), or coronary or non-coronary revascularisation (1058 [10·3%] *vs* 1086 [10·6%]). For the first occurrence of any of these "major vascular events", there were no material differences either overall (2306 [22·5%] *vs* 2312 [22·5%]; event rate ratio 1·00 [95% CI 0·94-1·06]) or in any of the various subcategories considered. There were no significant effects on cancer incidence or on hospitalisation for any other non-vascular cause.

Interpretation Among the high-risk individuals that were studied, these antioxidant vitamins appeared to be safe. But, although this regimen increased blood vitamin concentrations substantially, it did not produce any significant reductions in the 5-year mortality from, or incidence of, any type of vascular disease, cancer, or other major outcome.

Lancet 2002; **360:** 23-33

Introduction

LDL-cholesterol may be rendered more atherogenic by oxidative modification that allows it to accumulate in the artery walls, and antioxidants have been shown to slow the progression of atherosclerosis in animal studies.[1-4] Vitamin E is a major antioxidant in LDL particles, and supplementation with vitamin E substantially prolongs the in-vitro resistance of LDL particles to oxidative damage, and has other potentially protective effects.[3-8] ß-carotene, which can also function as a fat-soluble antioxidant in certain physiological circumstances, is carried with vitamin E in the fatty core of LDL particles.[3,4] Vitamin C is a major water-soluble antioxidant in the plasma, and it can help to regenerate oxidised vitamin E.[4,9-11] In several non-randomised observational studies in different populations, dietary intake or plasma concentrations of these antioxidant vitamins were inversely associated with vascular disease incidence and mortality,[12-17] and blood concentrations of autoantibodies to oxidised LDL and the degree of LDL susceptibility to oxidative damage have been associated with atherosclerosis.[18,19] Dietary intake of antioxidant vitamins has also been reported in observational studies to be inversely associated with the incidence of various types of cancer.[16,17,20-23] But, without large-scale randomised evidence, the possibility that these associations merely reflect the effects of other aspects of the diet or lifestyle on disease rates cannot be ruled out.[20,24]

Promising results on the progression of atherosclerosis[25,26] and on the incidence of vascular disease[27,28] have been reported from some small randomised trials of a few years of vitamin E in people with pre-existing vascular disease. But, the available results from much larger randomised trials of several years of vitamin E have been unpromising.[29-34] Similarly, the results thus far available from large long-term randomised trials of ß-carotene and of vitamin C have not provided good evidence of benefit.[29,30,34-37] Indeed, the results of some trials have even suggested that these vitamins have adverse effects (in particular on the incidence of haemorrhagic stroke and particular cancers[30,35]), although this observation has not been confirmed by other trials.

The Heart Protection Study provides further evidence about the effects of these three antioxidant vitamins on vascular and non-vascular mortality and major morbidity by assessing 5 years of their supplementation in a large number of high-risk individuals.

Patients and methods

Details of the study objectives, design, and methods are reported elsewhere[38,39] (including the protocol on the study website: www.hpsinfo.org) and are summarised below. As well as comparing antioxidant vitamins versus matching placebo in 20 536 randomised participants (which is the subject of the present report), a "2x2 factorial" design was used to allow the separate assessment of cholesterol-lowering therapy (see accompanying report[39]).

Eligibility and recruitment

Medical collaborators from 69 UK hospitals appointed senior nurses to run special clinics for the study (see Acknowledgments section in accompanying report[39]), and obtained local ethics committee approval. Men and women aged about 40 years to 80 years with non-fasting blood total cholesterol concentrations of at least 3·5 mmol/L were eligible provided they were considered to be at substantial 5-year risk of death from coronary heart disease because of a past medical history of coronary heart disease, of other occlusive arterial disease, of diabetes mellitus, or of treated hypertension alone.[38,39] People were ineligible if they had other life-threatening conditions, such as chronic liver disease, severe renal disease, severe heart failure, severe chronic airways disease, or diagnosed cancer (other than non-melanoma skin cancer). In addition, anyone already taking high-dose vitamin E supplements, or in whom such supplements were considered indicated, was not to be randomised. Those individuals who appeared eligible for the study were given detailed information about it, and asked for their written agreement to participate.

Potentially eligible people entered a prerandomisation "run-in" phase, which involved about 2 months of active vitamins. Compliant individuals who did not have a major vascular event or other serious problem during the run-in, and agreed to participate in the study for several years, were then randomly allocated to receive the antioxidant vitamins (600 mg synthetic vitamin E, 250 mg vitamin C, and 20 mg ß-carotene daily) or matching placebo capsules in specially prepared calendar packs. The central telephone randomisation system used a minimisation algorithm[40] to balance the treatment groups with respect to eligibility criteria and other major prognostic factors.

Follow-up

Following randomisation between July, 1994, and May, 1997, participants were to be seen in the study clinics for routine follow-up checks at 4, 8, and 12 months, and then 6-monthly until the final follow-up visits between May, and October, 2001. Those who became unable or unwilling to attend the clinics were to be contacted by telephone at the time of their scheduled follow-up (or, alternatively, follow-up was to be maintained via their general practitioner), and could continue to be supplied with their allocated study vitamins or matching placebo capsules by mail.

Compliance with study treatment was assessed at each follow-up by reviewing the calendar-packed capsules remaining and, for those who had stopped, the reasons for doing so were sought.

To assess the effects of the treatment allocation on blood concentrations of the vitamins being studied, assays were performed in non-fasting samples collected from about 5% of participants at the initial screening visit and at an average of about 3 years of follow-up (ie, the approximate mid-point of the study). Blood lipids were assessed in a selected sample of about 5% of participants due for follow-up at about the same time each year, and in all participants attending follow-up between August, 2000, and February, 2001. Differences in blood vitamin and lipid concentrations were based on comparisons between all those allocated the study vitamins and all those allocated placebo, irrespective of whether or not they were still compliant (with any missing data imputed from the screening values, assuming non-compliance).

Information was recorded at each follow-up of any suspected myocardial infarction, stroke, vascular procedure, cancer, or other serious adverse experience, and of the main reasons for all other hospital admissions (including day cases). Further details were sought from the participant's general practitioner (plus, if considered necessary, from any relevant hospital records) about all reports that might relate to major vascular events, cancers, or deaths, and from the UK national registries about the sites of any registered cancers and the certified causes of any deaths. All such information was reviewed by coordinating centre clinical staff who were kept unaware of the study treatment allocation, and events were coded according to prespecified criteria.[39]

Statistical analysis

The data analysis plan was prespecified either in the original protocol[38] or in amendments (see study website) made before any analyses of the effects of treatment on clinical outcomes were available to the Steering Committee. All comparisons involved logrank analyses of the first occurrence of particular events during the scheduled treatment period after randomisation among all

those allocated the vitamins versus all those allocated matching placebo capsules (ie, they were "intention-to-treat" analyses).[41] The logrank analysis yielded the average event or death rate ratio (with the proportional reduction in this ratio expressed as a percentage), and the test of statistical significance (two-sided p value). The primary comparisons were of the effects of allocation to the vitamins on "major coronary events" (defined as non-fatal myocardial infarction or death from coronary disease) and on fatal coronary heart disease. Secondary comparisons were of the effects: (i) on major coronary events, and on "major vascular events" (defined as major coronary events, strokes of any type, and coronary or non-coronary revascularisations), during the first 2 years and during the later years of scheduled treatment; and (ii) on non-fatal or fatal strokes of any type. Other secondary comparisons included the effects on major coronary events, and on major vascular events, in various subcategories of participants determined at study entry. Tests for heterogeneity or, if more appropriate, trend were to be used to assess whether the proportional effects observed in specific subcategories differed clearly from the overall effects (after due allowance for multiple comparisons). In addition, several tertiary outcomes were prespecified (including site-specific cancer, cerebral haemorrhage, vascular procedures, and hospitalisation for various causes), again with due allowance in interpretation to be made for the exploratory and, perhaps, data-dependent nature of these, and the many other, analyses that might be performed.[41]

Based on previous studies in similar populations, it was estimated that there would be about 3000 major coronary events and 5000 major vascular events among 20 000 such high-risk patients followed for an average of 5 years.[38] If so, and if the antioxidant vitamins reduced these event rates by at least 10%, then the study had an excellent chance of demonstrating such effects at convincing levels of statistical significance. There were also expected to be more than 1000 deaths from causes other than coronary disease and more than 1000 new cancers during the scheduled follow-up. Such numbers would allow reasonably reliable assessment of the 5-year effects of the vitamin supplementation not just on all-cause mortality but also on the main non-coronary causes of death and on the main types of cancer. Interim analyses of mortality and of other major events were reviewed at least annually by the independent Data Monitoring Committee, but the investigators remained unaware of the results until completion of the scheduled treatment period.

Role of the funding source

The study was designed, conducted, analysed, and interpreted by the investigators entirely independently of all funding sources.

Results

Patient enrolment

A total of 20 536 individuals (15 454 men and 5082 women) were randomised (figure 1), with 5806 aged at least 70 years at study entry.[39] Previous myocardial infarction was reported by 8510 (41% of those randomised), some other history of coronary disease by 4876 (24%), and no history of coronary disease by 7150 (35%). Among the 7150 participants without diagnosed coronary disease, 1820 had cerebrovascular disease, 2701 had peripheral arterial disease, and 3982 had diabetes mellitus (with some having more than one of these three conditions), whereas among the 13 386 with coronary disease, 1460, 4047, and 1981, respectively, had these conditions (again, with some "non-additivity" of these groups). Although treated hypertension was recorded in 8457 (41%) participants, only 237 (1%) were included on the basis of hypertension alone. The large size of the study (and the use of minimisation) produced good balance between the treatment groups (see subcategory figures below).

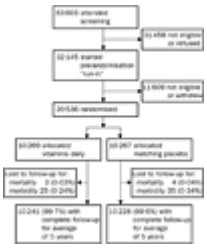

Figure 1: **Trial profile**

Numbers lost to follow-up relate to those without information to the end of the scheduled treatment period for mortality (as well as morbidity) and for morbidity alone.

Compliance and effects on blood assays

The mean duration of follow-up was 5 years for all randomised patients: 5·3 years for those who survived to the scheduled end of study treatment and about half that for those who did not (yielding 50 837 person-years among all those allocated the study vitamins and 50 948 among all those allocated matching placebo). Compliance at each follow-up was defined as at least 80% of the scheduled vitamin or placebo capsules having been taken since the previous follow-up. Similar percentages of participants remained compliant in each treatment group, with the average during the study being 83% (table 1). Compared with placebo, allocation to the study vitamins approximately doubled the average plasma concentration of α-tocopherol, increased that of vitamin C by about one-third, and quadrupled that of ß-carotene (table 2). There were also small, but highly significant, increases in the measured values of plasma total cholesterol, LDL cholesterol, and triglycerides among those allocated the study vitamins (table 2).

Follow-up (years)	**Vitamin-allocated**	**Placebo-allocated**
1	9003/10 113 (89%)	8971/10 082 (89%)
2	8369/9859 (85%)	8419/9876 (85%)
3	7918/9585 (83%)	7978/9642 (83%)
4	7427/9296 (80%)	7436/9333 (80%)
5	5640/7278 (77%)	5632/7317 (77%)
Study average (SE)	83% (0·1)	83% (0·1)

For missing follow-up, non-compliance is assumed.

Table 1: **Compliance with study vitamins (≥80% taken) during follow-up**

	Mean (SE) plasma concentrations*		
	Vitamin-allocated	Placebo-allocated	Difference (vitamin-placebo)
Vitamins (μmol/L)			
α-tocopherol	**49·5 (0·6)**	**27·0 (0·2)**	**22·5 (0·6)**
Ascorbic acid	**58·9 (1·0)**	**43·2 (1·0)**	**15·7 (1·4)**
ß-carotene	**1·22 (0·03)**	**0·32 (0·01)**	**0·89 (0·03)**
Lipids and lipoproteins			
Total cholesterol	4·89 (0·017)	4·74 (0·017)	0·15 (0·024)
LDL cholesterol	2·82 (0·014)	2·74 (0·014)	0·08 (0·019)
HDL cholesterol	1·10 (0·005)	1·13 (0·005)	-0·03 (0·007)
Triglycerides	2·13 (0·020)	1·92 (0·018)	0·21 (0·027)
Apolipoprotein A_1	1·083 (0·004)	1·063 (0·005)	0·021 (0·007)
Apolipoprotein B	1·022 (0·007)	0·970 (0·007)	0·051 (0·010)

*Intention-to-treat comparisons, with missing data inputed from initial pretreatment screening values; mmol/L for total, LDL, HDL, and triglycerides, and g/L for apolipoproteins.

Table 2: **Average plasma concentrations of vitamins and lipids during follow-up**

Effects on mortality

During the scheduled treatment period, allocation to the study vitamins was associated with a non-significant excess in all-cause mortality (1446 [14·1%] vitamin *vs* 1389 [13·5%] placebo deaths; death rate ratio [RR] 1·04; 95% CI 0·97-1·12: figure 2). This excess involved slight, and non-significant, adverse trends in the mortality attributed to coronary heart disease (664 [6·5%] *vs* 630 [6·1%]; RR 1·06; 95% CI 0·95-1·18), other vascular causes (214 [2·1%] *vs* 210 [2·0%]; RR 1·02; 95% CI 0·84-1·24), and non-vascular causes (568 [5·5%] *vs* 549 [5·3%]; RR 1·04; 95% CI 0·92-1·17). No significant differences were observed between the treatment groups in any of the prespecified categories of non-vascular mortality.

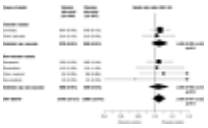

Figure 2: **Effects of vitamin allocation on cause-specific mortality**
Rate ratios (RRs) are plotted (black squares with area proportional to the amount of statistical information in each subdivision) comparing outcome among participants allocated vitamins to that among those allocated placebo, along with their 95% CIs (horizontal lines; ending with arrowhead when CI extends beyond scale). For particular subtotals and totals, the result and its 95% CI are represented by a diamond, with the RR (95% CI) and its statistical significance given alongside. Squares or diamonds to the left of the solid vertical line indicate benefit, and to the right of the line indicate harm, with the vitamins (but this would be conventionally significant [p<0·05] only if the horizontal line or diamond did not overlap the solid vertical line).

Effects on major vascular events

The non-significant excess of vascular mortality was not supported by any excess of non-fatal vascular events, so it may well have been largely or wholly due to chance. Taking non-fatal and fatal events together, no significant differences were observed between the treatment groups in the numbers of participants who had non-fatal myocardial infarction or coronary death (1063 [10·4%] vitamin-allocated *vs* 1047 [10·2%] placebo-allocated; RR 1·02; 95% CI 0·93-1·11), or had any coronary or non-coronary revascularisation procedure (1058 [10·3%] *vs* 1086 [10·6%]; RR 0·98; 95% CI 0·90-1·06: figure 3). Nor were there significant differences in the numbers who had a non-fatal or fatal stroke (511 [5·0%] *vs* 518 [5·0%]; RR 0·99; 95% CI 0·87-1·12: figure 3), or strokes of any particular type or severity (figure 4). In particular, there was no significant effect of the study vitamins on the numbers having a haemorrhagic stroke (51 [0·5%] *vs* 53 [0·5%]).

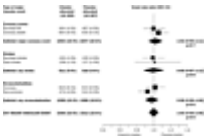

Figure 3: **Effects of vitamin allocation on first major coronary event, stroke, and revascularisation (defined prospectively as "major vascular events")**
Symbols and conventions as in figure 2. Analyses are of the numbers of participants with a first event of each type during follow-up (with non-fatal and fatal events also considered separately), so there is some non-additivity between different types of event. MI=myocardial infarction.

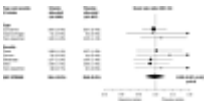

Figure 4: **Effects of vitamin allocation on first stroke**
Symbols and conventions as in figure 2. For stroke type, analyses are of the numbers of participants having a first ischaemic or a first haemorrhagic stroke (with 11 having both stroke types), whereas those reporting only strokes that could not be classified are given in the final row. (Haemorrhagic stroke includes subarachnoid haemorrhage: 13 vitamin-allocated versus 7 placebo-allocated.) For stroke severity, black squares relate to the most severe stroke that could be classified (so these categories are mutually exclusive). Open squares are used to indicate rate ratios for participants who had only strokes of unknown type or severity.

A more stringent test of whether there was any net effect of the study vitamins on vascular disease is provided by analyses of all major coronary events, strokes, and revascularisations considered together. Allocation to the study vitamins did not significantly affect the numbers of participants who had any of these "major vascular events" (2306 [22·5%] vitamin *vs* 2312 [22·5%] placebo; RR 1·00; 95% CI 0·94-1·06: figure 3). The large numbers of events on which this comparison is based allows reliable assessment of the effects of the study vitamins in different circumstances. No significant difference was observed between the treatment groups in the numbers of participants who had a first major vascular event either during the first 2 years of scheduled treatment or, after more prolonged treatment, during subsequent years (figures 5 and 6). Nor were significant differences found in any of the various prior disease categories included, or in any other subcategory of participants examined (figures 7 and 8).

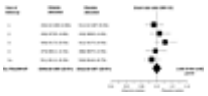

Figure 5: **Effects of vitamin allocation on first major vascular event during follow-up**
Symbols and conventions as in figure 2. Analyses are of numbers of participants having a first event during each year of follow-up and of those still at risk of a first event at the start of each year.

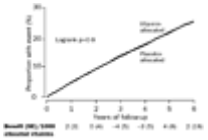

Figure 6: **Life-table plot of effects of vitamin allocation on percentages having major vascular events**
See figure 5 for numbers of participants having a first event during each year of follow-up.

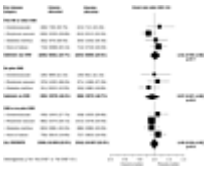

Figure 7: **Effects of vitamin allocation on first major vascular event in different prior disease categories**
Symbols and conventions as in figure 2. There is no overlap between participants in "Any CHD" and "No CHD" baseline disease categories, but within each of these categories there is some overlap (and, hence, some non-additivity). χ^2 test on one degree of freedom is given for heterogeneity between rate ratios in participants with any prior coronary heart disease (CHD) versus those with no prior CHD.

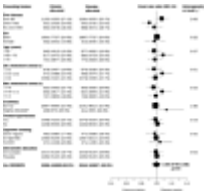

Figure 8: **Effects of vitamin allocation on first major vascular event in different categories of participant**

Symbols and conventions as in figure 2. χ^2 tests on one degree of freedom are given for heterogeneity between rate ratios within dichotomous categories and for trend within other categories (with value >3·84 equivalent to p<0·05 before making allowance for multiple comparisons). Lipid categories relate to measured values at the initial screening visit prior to starting any statin treatment.[39] *Slightly elevated creatinine defined as $\geq$110 µmol/L for women and $\geq$130 µmol/L for men, but <200 µmol/L for both.

Effects on cancers

New primary cancers (excluding non-melanoma skin cancer) were diagnosed in 800 (7·8%) of the participants allocated vitamins compared with 817 (8·0%) of those allocated placebo (RR 0·98; 95% CI 0·89-1·08: figure 9), and were associated with death in 359 (3·5%) versus 345 (3·4%) participants (RR 1·04; 95% CI 0·90-1·21: figure 2). These differences were not significant, and nor were there significant differences between the treatment groups in the incidence of cancers in any particular body system (figure 9), or in non-melanoma skin cancer (only one of which was fatal). When cancer sites were more finely divided to investigate hypotheses raised in previous studies, there were still no clearly significant differences between the treatment groups (for example, lung: 160 [1·6%] vitamin *vs* 141 [1·4%] placebo: p=0·3; stomach: 66 [0·6%] *vs* 50 [0·5%]: p=0·1; prostate: 138 [1·8%] *vs* 152 [2·0%] men: p=0·4).

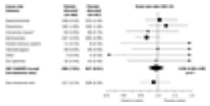

Figure 9: **Effects of vitamin allocation on site-specific cancer incidence**
Symbols and conventions as in figure 2. Analyses are of the numbers of participants developing cancer at each site (excluding recurrences or new cancers at the same site), so there is some non-additivity between cancers at different sites. *Not including non-melanoma skin cancer, which is given separately.

Effects on other outcomes

Neuropsychiatric disorders--It had been suggested that antioxidant vitamins (in particular, vitamin E) might slow cognitive decline,[42] so the modified Telephone Interview for Cognitive Status (TICS-m) questionnaire[43] was administered to participants during their final follow-up. A TICS-m score below 22 out of 39 was prespecified to be indicative of some cognitive impairment, and (as described in the accompanying paper[39]) this well validated test appeared to have good discriminatory ability. However, no significant difference was observed between the treatment groups in the percentages of participants classified as cognitively impaired (23·4% vitamin-allocated *vs* 24·4% placebo-allocated) or in mean TICS-m score (24·11 *vs* 24·02; difference 0·09 [SE 0·07]). Similar numbers of participants in each treatment group were reported to have developed dementia during follow-up (31 [0·3%] *vs* 31 [0·3%]) or to have some other psychiatric disorder (62 [0·6%] *vs* 65 [0·6%]).

Respiratory disease--In non-randomised observational studies, higher intake of antioxidant vitamins has been associated with lower rates of asthma and chronic obstructive pulmonary disease,[44-46] so respiratory function was assessed by spirometry in all those attending the final follow-up visit. No significant differences were observed between the treatment groups in forced expiratory volume during one second (FEV_1: 2·06 L vitamin-allocated *vs* 2·06 L placebo-allocated; difference 0·00 L [SE 0·01]) or in forced vital capacity (FVC: 2·83 L *vs* 2·82 L; difference 0·01 L [SE 0·01]). Nor were significant differences observed in the numbers of participants hospitalised for chronic obstructive pulmonary disease or asthma (149 [1·5%] *vs* 133 [1·3%]) or for any other non-neoplastic respiratory cause (641 [6·2%] *vs* 642 [6·3%]).

Fractures--Higher dietary intake and blood concentrations of vitamin C have been associated in observational studies with greater bone density and lower prevalence of fractures.[47] Tertiary comparisons were, therefore, prespecified of the effects of the allocated vitamins on fractures (excluding the few related to road-traffic accidents). No significant differences were observed in the numbers of participants having any such fractures (234 [2·3%] vitamin *vs* 237 [2·3%] placebo) or those that are particularly related to osteoporosis (ie, hip, wrist, or spine: 101 [1·0%] *vs* 99 [1·0%]).

Other outcomes--There did not appear to be any significant difference between the treatment groups in the numbers hospitalised for any other particular reason (even before making allowance for the exploratory nature of such analyses). In particular, there was no significant support for the suggestion from observational studies that antioxidant vitamin supplementation might prevent cataracts,[48,49] with 379 (3·7%) vitamin-allocated versus 418 (4·1%) placebo-allocated participants reporting cataract (p=0·2). That result is consistent with the lack of clear effects on cataract in the large randomised Age-Related Eye Disease (ARED) trial of a similar antioxidant regimen,[34] and in other randomised trials of antioxidant vitamins that have assessed this outcome.[50-54] No significant differences were observed between the treatment groups in blood pressure or bodyweight recorded at the final follow-up visit.

Discussion

No clear evidence of benefit or harm

The results of the Heart Protection Study indicate that 5 years of daily supplementation with 600 mg vitamin E, 250 mg vitamin C, and 20 mg ß-carotene is safe. But, although this regimen substantially increased the plasma concentrations of these vitamins, no significant benefits were observed among the high-risk individuals that were studied. These results effectively rule out any substantial reductions--or, indeed, increases--in heart attacks, strokes, cancers, or other major adverse events during 5 years of use of these vitamins. For example, proportional decreases or increases of as little as 10% in the rate of major vascular events are both excluded by even a 99% CI (0·93-1·08). Factors to consider in interpreting these findings include the population studied, the vitamin dosages (and combination) tested, and the duration of treatment and follow-up.

Relevance of populations studied

The non-randomised observational studies that found a lower incidence of cardiovascular events to be associated with higher intakes of different antioxidant vitamins were chiefly of people without known coronary or other vascular disease, and it has been suggested that these vitamins might be protective only before occlusive disease has developed.[55,56] But, more than 7000 of the participants in the Heart Protection Study had no evidence of coronary disease prior to randomisation, and among them there was no evidence of benefit. Likewise, about 4500 older American adults who had not had a recent vascular event were randomised in the ARED placebo-controlled trial of a similar combination regimen of 400 IU synthetic vitamin E, 500 mg vitamin C, and 15 mg ß-carotene daily. But, despite nearly 500 deaths during the scheduled treatment period in that study, it too did not find any difference in mortality between the treatment groups.[34] Oxidative stress is increased in some types of people, such as those with diabetes, and it has been suggested that antioxidant vitamins might be particularly effective in them.[55,57] There was, however, no evidence of benefit either among all 6000 people with diabetes in the present study or among the 3000 with diabetes who had no occlusive arterial disease at entry--or, indeed, in any other category of participant considered.

The same is true for trials of the primary prevention of vascular disease with particular components of this antioxidant regimen. Among about 4500 randomised people without diagnosed vascular disease in the Primary Prevention Project (PPP), 300 mg of synthetic vitamin E daily did not appear to produce any improvement in cardiovascular outcomes.[33] Similarly, about 22 000 of the 29 000 randomised participants in the Alpha-Tocopherol Beta-Carotene (ATBC) trial were free of coronary disease at entry, but no significant improvements in cardiovascular mortality were observed either with 50 mg of synthetic vitamin E daily (albeit a relatively low dose) or with 20 mg of ß-carotene daily.[30] Several other large-scale randomised trials of between 15 mg and 30 mg daily of ß-carotene (either alone[36,37] or in combination with 30 mg vitamin E[29] or 25 000 IU vitamin A[35]) have been done in people without known vascular disease, but none has provided any good evidence of benefit. One of those trials, which was done in 30 000 people from Linxian in China,[29] also involved the separate assessment of 120 mg vitamin C daily (combined with 30 µg molybdenum). It had been thought that supplementation with antioxidant vitamins might be particularly effective in Linxian because of subclinical deficiencies of such micronutrients in this population,[58] and because of the high rates of strokes and certain types of cancers.[58] But, although plasma concentrations of ß-carotene and of ascorbic acid were increased substantially in that trial, there were no clearly significant reductions in cancer incidence or in mortality from vascular or other causes. Hence, the available evidence from large-scale randomised trials of different antioxidant regimens in various populations does not suggest that the lack of any clear benefits has been due to the types of people studied.

Choice of antioxidant regimen

The daily dose of 600 mg of vitamin E tested in the Heart Protection Study is greater than the amounts that have been associated, in non-randomised observational studies, with 20-40% proportional reductions in the incidence of coronary events.[4,12,14,15] The synthetic form of vitamin E (all-rac-α-tocopherol: 1·1 IU/mg) used in this trial is considered to be somewhat less bioavailable than the natural form (RRR [2R, 4'R, 8'R], or *d*-α-tocopherol: 1·5 IU/mg).[7,59,60] Despite this, the study regimen doubled plasma concentrations of α-tocopherol, and the synthetic formulation has been shown to prolong substantially the in vitro resistance of LDL to oxidative modification[6,8] (with no evidence that concomitant simvastatin influences these effects[61]). Moreover, the randomised Heart Outcome Prevention Evaluation (HOPE) trial used 400 IU daily of natural vitamin E in over 9000 similar high-risk patients, and it too found no evidence of any beneficial effects on vascular or other outcomes.[31] The daily doses of 20 mg ß-carotene and of 250 mg vitamin C tested in the present trial are also well above the levels of dietary consumption that have been associated with lower rates of vascular disease and cancer in observational studies.[4,12-17,20-23] The ß-carotene dose produced a highly significant four-fold increase in plasma concentrations, and although vitamin C concentrations increased by only about one third, doses of vitamin C above 200 mg daily do not appear to produce much further increase in either blood concentrations or inhibition of lipid peroxidation.[62] It has been suggested that such antioxidant vitamins may be more effective when, as typically occurs in the diet, they are taken together.[2,11,56] But, despite the combination of dosages that were within the ranges considered likely to be effective,[2,23,56] and good compliance with the allocated treatment producing substantial increases in blood concentrations, there was no evidence of benefit in the Heart Protection Study.

Duration of treatment and follow-up

It has also been suggested that antioxidants may chiefly prevent the development of new atherosclerotic plaques (although, presumably, slowing the uptake of modified LDL cholesterol should also slow the growth of existing plaques) and, as a consequence, that any benefits might take many years to emerge.[55,56] Most large randomised trials of these vitamins have involved an average of only about 4-6 years of treatment, but no benefits emerged among the 22 000 randomised participants in the Physicians' Health Study even after 12 years of ß-carotene supplementation.[36] Several randomised trials, including the present one, have shown that a substantial reduction in vascular events emerges within just 1-2 years of lowering LDL cholesterol.[39,63,64] Hence, if long-term treatment with antioxidant vitamins can eventually produce substantial protection against vascular disease by rendering LDL particles less atherogenic, then significant benefits would have been expected during the 5-year duration of the Heart Protection Study. But, there was no suggestion that beneficial effects were beginning to emerge even during the later years of treatment with these vitamins (figure 5). Participants will, however, continue to be followed for several more years to determine whether, after an average of 5 years of vitamin supplementation, any delayed effects on subsequent vascular events, cancers, or other major outcomes do eventually emerge.

Conclusions

Based on the presumption that the likelihood of benefit outweighs any low probability of harm, daily supplementation with a few hundred mg of vitamin E (and with other vitamins) has been recommended for middle-aged and older people.[7,56] But, despite assessing the combined effects of several years of substantial daily doses of different antioxidant vitamins (including 600 mg of vitamin E) in a large number of high-risk people, the Heart Protection Study has not been able to demonstrate any benefits from such supplementation. Moreover, this antioxidant regimen produced small, but definite, increases in the measured values of plasma triglycerides and LDL cholesterol (table 2), with a 3% higher mean LDL cholesterol concentration corroborated by a 5% higher mean apolipoprotein B concentration. (Although very high concentrations of vitamin C can interfere with lipid measurements, they have been found to produce artefactually low, rather than high, values for cholesterol and triglycerides.[65]) Blood lipid concentrations during treatment were not measured routinely in most previous large-scale trials of antioxidant vitamins, but trends similar to those in table 2 have been observed for triglycerides,[32,66] though not for total or LDL cholesterol,[30,32,34,66] in those trials that did.

Other large-scale randomised trials of different antioxidant regimens in different populations are in progress,[4,12,23] and long-term follow-up continues in several completed trials (including the present one). But, in light of the unpromising results during at least 5 years of treatment in several large randomised trials, the lower risks of vascular disease and cancer found in observational studies among people with higher intake of these antioxidant vitamins must have been largely or wholly artefactual (ie, due to other differences in lifestyle that were actually responsible for the lower risks). Hence, continued recommendation of supplementation with such vitamins is difficult to justify. Instead, the main emphasis should be on those treatments (eg, aspirin, statins, angiotensin-converting-enzyme inhibitors, ß-blockers, and antihypertensive therapy) and those behavioural changes (eg, increasing physical activity and, particularly, stopping smoking) that are definitely known to prevent heart attacks, strokes, and other adverse outcomes.

Acknowledgments

The collaborators and committees involved in the conduct of the MRC/BHF Heart Protection Study are listed in the accompanying article[39] (which also provides a conflict of interest statement). The study was funded by the UK Medical Research Council, the British Heart Foundation, Merck & Co (manufacturers of simvastatin) and Roche Vitamins (manufacturers of the vitamins).

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Many vitamins useless, study says

C, E and beta-carotene: 'I'm going to have to change my story,' says vitamin advocate

Friday, July 05, 2002

One of the largest studies ever conducted on vitamins found no evidence the pills lessen heart attacks and strokes, cancers, diabetes or other diseases.

The British Heart Protection study, which tracked 20,500 adults for five years, adds to a growing consensus that people who take vitamins are healthier because of their lifestyle, not because they take vitamins.

The researchers conclude that supplementation with "anti-oxidants" -- vitamins E, C and beta-carotene -- is probably a waste of time.

"It did not produce any significant reductions in the five-year mortality from, or incidence of, any type of vascular disease, cancer or other major outcome," says the study published tomorrow in The Lancet, a British medical journal.

Anti-oxidants are among the biggest-selling vitamins.

The findings are deeply disappointing to academics who have called for more research into vitamins.

"You might have hoped that you'd see some benefit with such a huge study, so that's kind of sad, but if that's the way the research is, I'm going to have to change my story, too," says Dr. John Hoffer, a professor of medicine at McGill University and a leading proponent of vitamins.

Although five years is not enough time to properly assess the effects of vitamins on cancer, says Dr. Hoffer, it is adequate to measure their effects on cardiovascular disease.

However, some scientists believe such vitamins and minerals as selenium, vitamins B-6, B-12 and folic acid might still have potent health benefits, especially over longer times.

Vitamins are believed to improve heart health by preventing the oxidation of fat particles in the blood, which leads to hardening of the arteries. Lab tests, animal studies and a few small human studies seem to confirm this result, especially in the case of vitamin E.

"But the available results from much larger randomized trials of several years of vitamin E have been unpromising," the Lancet study says.

In fact, the British researchers instead found a small but worrying effect in this study: The vitamin regimen caused a 3% mean increase in LDL cholesterol, usually known as "bad" cholesterol.

Rather than take vitamins, the researchers suggest, people at risk of heart disease and stroke should take proven medications such as Aspirin, statins, ACE inhibitors, beta blockers and blood pressure drugs, as well as increase exercise and quit smoking.

The study followed 20,536 adults living in the United Kingdom who suffered from coronary disease, hardened arteries or diabetes. Half received a daily dose of 600 milligrams of vitamin E, 250 mg of vitamin C and 20 mg of beta-carotene. The rest took placebo pills.

The results show no difference in rates of heart attack, stroke, cancer, diabetes, osteoporosis, asthma or memory loss.

However, vitamin advocates have argued such studies use dosages too low to offer any benefits. Some doctors believe taking doses of vitamin C as high as 10 grams a day -- 40 times as much as given in the U.K. study -- can prevent cancer and strengthen blood vessels.

The late Nobel Prize winner Linus Pauling was a leading proponent of this theory. He said primitive humans lost the ability, held by most animals, to produce their own vitamin C, resulting in a chronic shortage. In speeches, Dr. Pauling would show audiences a vial containing the vitamin C a goat produces every day, which he said showed why the animals suffer less disease than humans.

"I would trust the biochemistry of a goat over the advice of a doctor," he would say.

Yet, while a few small studies have shown promising results for supplements, most have not. For example, after 12 years of taking beta-carotene supplements, no health benefits have emerged for the 22,000 participants in the Boston-based Physicians' Health Study.

"In the cardiovascular community, we've been pretty convinced by previous studies that the vitamins mentioned in this study are probably not of very much value to the prevention of vascular disease," says Dr. Lyall Higginson, chief of cardiology at the University of Ottawa Heart Institute.

Dr. Higginson said the situation mirrors that of hormone replacement therapy. Estrogen pills, first introduced in 1942, were believed to protect the heart because women who took them tended to have fewer heart attacks. But now doctors believe women who took estrogen pills really owed their health to a tendency to exercise more, smoke less and eat a balanced diet.

A comprehensive study published this week in the Journal of the American Medical Association confirms this belief.

"Not only was there no cardiovascular benefit, there were adverse affects, including blood clots and gallbladder disease," said Deborah Grady, a professor of epidemiology and medicine at the University of California in San Francisco.

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The effect of ascorbate and alpha-tocopherol supplementation in vitro on DNA integrity and hydrogen peroxide-induced DNA damage in human spermatozoa.

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The aim of this study was to determine the effects of supplementation with ascorbate and alpha-tocopherol, both singly and in combination, during sperm preparation on subsequent sperm DNA integrity, induced DNA damage and reactive oxygen species (ROS) generation. Semen samples with normozoospermic and asthenozoospermic profiles (n = 15 for each control and antioxidant group) were prepared by Percoll density centrifugation (95.0-47.5%) where the medium had been supplemented with these antioxidants to a number of different concentrations, all within physiological levels. Controls were included which had no ascorbate or alpha-tocopherol added. DNA damage was induced using hydrogen peroxide (H(2)O(2)) and DNA integrity was determined using a modified alkaline single cell gel electrophoresis (Comet) assay, while ROS generation was measured using chemiluminescence. Addition of ascorbate to sperm preparation medium did not affect baseline DNA integrity but did provide sperm with complete protection against H(2)O(2)-induced DNA damage. Generation of H(2)O(2)-induced ROS was also significantly reduced after treatment with ascorbate, although baseline levels were unaffected by this antioxidant. Supplementation of sperm preparation medium with alpha-tocopherol did not influence baseline DNA integrity but provided sperm with dose-dependent protection against H(2)O(2)-induced DNA damage. Generation of H(2)O(2)-induced ROS was significantly reduced after treatment with alpha-tocopherol, although baseline ROS levels were unaffected by this antioxidant. **Addition of both ascorbate and alpha-tocopherol in combination to sperm preparation medium actually induced DNA damage and intensified the damage induced by H(2)O(2), however, H(2)O(2)-induced ROS production was significantly reduced in a dose-dependent manner by supplementation with both vitamins.**

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The New York Times

TUESDAY, APRIL 11, 2000

Report Disputes Benefits of Taking Large Doses of Vitamins

By DENISE GRADY

Even though millions of Americans take vitamins C and E and other antioxidants in the hope of warding off illness and aging, a report being issued today by nutrition experts says there is no evidence that the large doses that have become popular can prevent chronic disease or that most Americans need to take supplements at all.

In fact, large doses of vitamins C and E and selenium can be harmful, according to the new report by the Institute of Medicine, a branch of the National Academy of Sciences. Because of concerns about toxicity, for the first time, the institute set upper limits for the nutrients and emphasized that most Americans already get enough of the nutrients from the food they eat.

There has been great interest in antioxidants in recent years because studies have hinted that they might play a role in disease prevention. Antioxidants counteract the adverse effects in the body of highly reactive forms of oxygen and nitrogen, known as free radicals, which accumulate from normal metabolism. Free radicals can damage cells, and are thought by some scientists to contribute to aging, cancer, cardiovascular disease, eye problems like cataracts and macular degeneration, Alzheimer's disease and Parkinson's disease and some complications of diabetes.

But the authors of the institute report, directed by Dr. Norman Krinsky of the department of biochemistry at Tufts University in Boston, could not find convincing evidence that taking vitamins or selenium would help prevent any of those diseases.

Although many studies have shown that people who eat diets rich in fruits and vegetables have a lower risk of many types of cancer, the studies could not pinpoint particular nutrients as providing the benefit, and many researchers believe that fruits and vegetables contain other substances, as yet unidentified, that may have important effects on health.

The findings were similar for heart disease. Although one study did find a benefit from vitamin E supplements, three others found it made no difference.

For cataracts, studies did show a lower risk in people who had higher blood levels of antioxidants. But the studies did not convince the panel that supplements could prevent cataracts.

For macular degeneration, studies have shown a lower risk in people who eat a lot of fruits and vegetables, but cause and effect have not been proved, the study said.

Dr. Kenneth Ayoob, a pediatric nutritionist at Einstein Medical Center in New York and a spokesman for the American Dietetic Association, said the report "seems to suggest that there's a lot of power in food, and that we have a lot more data on food than we do on supplements."

Nonetheless, the panel recommended small increases in the recommended daily intake of vitamins C and E, which can be obtained through a diet rich in fruits and vegetables.

For vitamin C, the group recommended that women consume 75 milligrams per day, and men 90 milligrams. Smokers need 35 milligrams more than nonsmokers. Vitamin C is plentiful in citrus fruit, potatoes, strawberries, broccoli and leafy green vegetables. But for those who take supplements, no

one should take more than 2,000 milligrams of vitamin C a day, the report said, because it can cause diarrhea.

For vitamin E, the recommended intake for men and women is 15 milligrams, or 22 International Units, or I.U., of alpha tocopherol. Vitamin E is in nuts, seeds, liver, whole grains and leafy vegetables. The upper limit for vitamin E, which a person could achieve only by taking supplements, is 1,500 I.U. if the product is "d-alpha tocopherol," or 1,100 I.U. if the product is "dl-alpha-tocopherol," a synthetic version of the vitamin. Higher amounts could cause hemorrhaging, the report said.

For selenium, the recommended intake for both men and women is 55 micrograms per day. Selenium is found in brazil nuts, seafood, garlic, liver, meat and grains.

More than 400 micrograms a day can cause selenosis, which causes loss of hair and fingernails.

The report also considered the antioxidants known as carotenoids, including beta carotene, which is converted into vitamin A in the body. But the panel said there was not enough evidence to recommend a daily intake or set upper limits. The only people in need of supplements would be those with vitamin A deficiencies, which are uncommon.

More Vitamins Should Come From Food

April 11, 2000

WASHINGTON (AP) - While Americans should have more vitamins C and E in their diets than currently recommended, huge doses of these vitamins and other antioxidants have no proven benefit and may even be harmful, government researchers said Monday.

Antioxidants scavenge the body for roaming oxygen molecules known as "free radicals" suspected of triggering cancer and other disease. Many people routinely take high doses of vitamin C and other antioxidants in the belief that they will prevent or cure illnesses.

But not enough evidence exists to support claims that massive doses of antioxidants can improve health, said researchers from the Institute of Medicine. The institute, a private organization that advises the federal government, is reviewing the nation's Recommended Daily Allowances, or RDAs, for nutrients.

"Much more research is needed to determine whether dietary antioxidants can actually stave off chronic disease, " said Norman I. Krinsky, chair of the study's antioxidant panel.

For the first time the institute has set upper limits on the daily consumption of vitamins C and E to reduce the risk of harmful side effects.

Adults should keep their daily vitamin C intake from both food and supplements below 2,000 milligrams because anything higher may cause diarrhea.

The upper level for vitamin E, based only on vitamin supplements, is 1,000 milligrams. That's roughly equivalent to 1,500 International Units, or I.U., of "d-alpha-tocopherol," sometimes labeled as "natural source" vitamin E. Since the nutrient can act as a blood anticoagulant, people consuming more than the upper limit face a greater risk of uncontrolled bleeding.

Although most American and Canadian adults already get enough of their vitamins C and E in their food, the researchers decided to increase the current overall intake recommendations.

Under the new recommendations, women should consume 75 milligrams of vitamin C each day, and men should consume 90 milligrams. Smokers, who are more likely to suffer from damaged cells and depleted vitamin C levels, need an additional 35 milligrams daily.

People can get vitamin C by eating citrus fruits, potatoes, strawberries, broccoli, and leafy green vegetables.

For vitamin E, both women and men should consume 15 milligrams or 22 I.U. each day from food sources including nuts, seeds and liver. The vitamin E consumed should be "alpha-tocopherol," the only type that human blood can maintain and transfer to cells when needed.

Women and men should also get 55 micrograms of the nutrient selenium each day from foods including seafood, liver, meat, and grains, according to the recommendation.

The maximum intake level for selenium from both food and supplements is 400 micrograms per day. More than this amount could cause selenosis, a toxic reaction marked by hair loss and brittle nails.