	Vitamin E (μmol/L)	Cholesterol (mmol/L)	Vitamin E/ cholesterol
Patients with angina pectoris[3]	22·7 (0·6)	6·19 (0·11)	3·66
SPACE trial[4]	22·85 (4·64)	4·63 (1·13)	4·92
Patients with transplant-associated atherosclerosis[5]	24 (14)	5·49 (1·34)	4·37
Heart Protection Study[4]	27·0 (0·2)	4·74 (0·017)	5·69
Healthy individuals (n=50)	29 (5·1)	4·91 (0·81)	5·9

Mean (SD) concentrations of vitamin E and cholesterol, and vitamin E/cholesterol ratio in trials with vitamin E supplementation, patients with stable angina, and healthy individuals

vitamin E or other antioxidants might be of crucial relevance for defining the risk of cardiovascular disease. Therefore, an alternative explanation for the results of HPS is that this trial did not enrol patients who really needed antioxidant treatment. Identification of patients with increased oxidant stress and reduced concentrations of natural antioxidants in plasma could represent an alternative approach for testing the clinical efficacy of antioxidant vitamins in patients at high risk of cardiovascular disease.

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Authors' reply

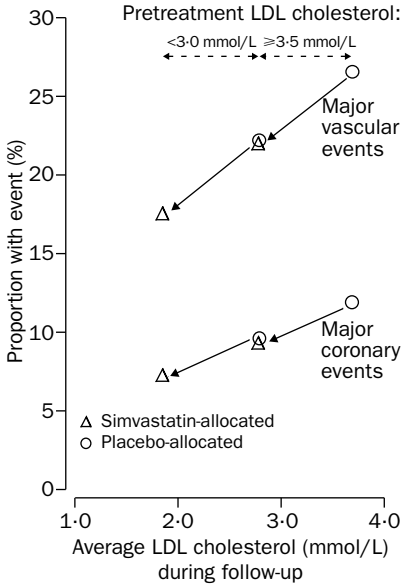
Sir—Observational studies indicate that the relationship between coronary disease risk and blood LDL cholesterol concentration is approximately linear when coronary disease risk is plotted on a logarithmic (or "doubling") scale, which implies that the proportional reduction in risk produced by a given absolute reduction in LDL cholesterol would be similar throughout the range studied. This hypothesis is strongly supported by the clear demonstration in HPS that a 1 mmol/L reduction in LDL cholesterol concentration from about 4 mmol/L to 3 mmol/L reduces the risk of "major vascular events" (defined as major coronary event, stroke, or revascularisation) by about one quarter, and that reducing LDL cholesterol from about 3 mmol/L to 2 mmol/L also reduces risk by about one quarter.[1] Sander Robins and Jean-Pierre Despres suggest that this finding might be due to the inclusion of revascularisation in the outcome measure, but the results are similar for "major coronary events" (defined as non-fatal myocardial infarction or coronary death): see figure and webfigure 2 in the original report.[1]

In their figure, Carl Vaughan and Brendan Buckley have mistakenly compared the rates of major coronary events in other statin trials with the rates of major vascular events in HPS, and the results for major coronary events do not support their argument. The highly significant risk reduction among the 6793 patients presenting with LDL cholesterol below 3·0 mmol/L in HPS, which is based on large numbers of major vascular events (598 [17·6%] simvastatin-allocated *vs* 756 [22·2%] placebo-allocated; p<0·0001), provides reliable refutation of any "threshold" at about this level below which lowering LDL cholesterol would not reduce risk.[1] Moreover, among the high-risk individuals studied, statin therapy produced substantial absolute benefits that were not much influenced by the initial concentrations of blood lipids (figure).

Nicholas Wald and Malcolm Law request the results for major coronary events by year of follow-up (http://image.thelancet.com/extras/02cor9176webfigure1.pdf), which resemble those for major vascular events (see figure 5 of the original report[1]).

In response to Paul Durrington, there was a highly significant 33% (SE 10; 95% CI 17–46) proportional reduction in major vascular events (135 [9·3%] simvastatin *vs* 196 [13·5%]; p=0·0003) among the 2912 diabetic patients who did not have any diagnosed occlusive vascular disease at entry; the mean triglycerides concentration during the study among placebo-allocated participants with baseline concentrations of at least 4·0 mmol/L was 4·4 mmol/L; similar proportional reductions in major vascular events were observed irrespective of pretreatment apolipoprotein concentrations (http://image.thelancet.com/extras/02cor9176webfigure2.pdf); and the average difference in apolipoprotein B concentrations during the study between the simvastatin and placebo groups was 0·28 g/L (see table 2 of the original report for further details[1]).

By contrast with the substantial reductions in vascular events that emerged within just a few years of lowering LDL cholesterol with simvastatin, HPS was not able to demonstrate any benefit with several years of substantial daily doses of antioxidant vitamins (600 mg vitamin E, 250 mg vitamin C, and 20 mg β carotene).[2] These doses are all greater than the amounts associated, in non-randomised observational studies, with lower rates of vascular disease and of cancer. Hence, it does seem likely that the apparent protective effects in those observational studies are largely or wholly artifactual (ie, due to other differences in diet or lifestyle). C J Bates attributes the lack of benefit in HPS either to use of these vitamins during the prerandomisation phase or to use of non-study vitamins during the randomised phase. But, whereas there was little change from the pretreatment plasma concentrations among participants allocated placebo, there were



Effects of simvastatin allocation on plasma LDL concentrations during follow-up, and on absolute risks of first major vascular event and first major coronary event, among participants with pretreatment LDL cholesterol concentrations <3·0 mmol/L or ≥3·5 mmol/L[1]

substantial increases among those allocated the vitamins. In particular, the plasma vitamin C concentration increased from 39 μmol/L to 59 μmol/L, which is entirely consistent with the meta-analysis he cites.[3] Moreover, no beneficial effects were beginning to emerge in HPS even during the later years of treatment, and only about 5% in each group were taking non-study vitamins by the end of the study.

Morris J Brown, who was principal investigator of the Cambridge Heart Antioxidant Study (CHAOS),[4] concludes that its promising result was most probably a "false positive" due to the play of chance in a relatively small study. No genetic subgroup analyses have yet been conducted in HPS to investigate his suggestion that antioxidant vitamins might be effective in people with particular genotypes, but there was no evidence of benefit in any of the subgroups that were studied (including the 8581 participants with total cholesterol concentrations of at least 6·0 mmol/L at entry, whose average cholesterol concentration of 5·3 mmol/L during the study was—despite the use of statin therapy—similar to that in CHAOS).

As was reviewed in detail,[2] large-scale randomised trials of different antioxidant regimens in various populations do not support the suggestion from Francesco Violi and colleagues that the lack of clear benefit reflects the types of people studied. Moreover, Violi and colleagues have mistakenly tabulated the plasma concentrations of vitamin E and cholesterol in HPS after the study vitamins and statin had started, and the pretreatment values (vitamin E: 30·4 μmol/L; total cholesterol: 5·9 mmol/L; ratio: 5·2 μmol/mmol) are actually quite similar to those in other populations with vascular disease (including CHAOS [33·5, 5·9, and 5·7, respectively], which was inadvertently omitted from their table).

In the absence of any good evidence of benefit for any identifiable category of patient, these antioxidant vitamins should not be routinely recommended for the avoidance of vascular or other major outcomes. By contrast, for many types of high-risk patient not currently being given cholesterol-lowering treatment, HPS shows that 40 mg simvastatin daily safely produces substantial benefits—irrespective of the person's age, underlying disease, or initial blood cholesterol concentrations.

R Collins, J Armitage, S Parish, and R Peto have had costs to participate in scientific meetings reimbursed by the pharmaceutical industry. P Sleight has received honoraria and costs for participating in such meetings.

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Tamoxifen for breast cancer in hysterectomised women

Sir—U Veronesi and colleagues' (March 30, p 1122)[1] report on chemoprevention in breast cancer reinforces earlier conclusions that tamoxifen does not significantly reduce the rate of breast cancer in hysterectomised women at normal or slightly reduced risk (premenopausal or oophorectomised) of disease. Their findings are at variance with the larger National Surgical Adjuvant Breast and Bowel Project (NSAB-P1) trial,[2] with decreases in cumulative incidence of invasive and non-invasive breast cancer decreased by 49% ($p<0·0001$) and 50% ($p<0·002$), respectively.

These differences in trial outcome have been attributed to several factors, including population size and intrinsic levels of risk among trial participants. There was a high rate of attrition in the Italian study, with more than 25% of patients withdrawing and treatment adherence estimated at no more than 70%. Moreover, at preliminary analysis, with a median follow up of 37 months, only 149 patients had completed 5 years of tamoxifen treatment, which may have contributed to the failure to show a chemoprotective effect.[3] In their latest report, with a median follow up of 55 months, 1217 patients have completed 5 years of tamoxifen treatment. Despite modest extended follow up, these results are based on a more robust trial process with greater statistical conviction.

Although no significant preventive effect has been noted for non-users of hormone-replacement therapy (HRT), patients who ever used HRT have an incidence of breast cancer similar to that for non-users. The investigators conclude that tamoxifen may compensate for the proliferative effects of HRT on breast tissue and partly negate the increased risk of breast cancer associated with HRT use.

This counter-protection provided by tamoxifen may be relevant to premenopausal women who have secondary oestrogen deprivation from chemotherapy, which is increasingly being used as adjuvant systemic therapy for node-negative women with moderate sized tumours (≥2 cm). In such patients, cardiovascular pathophysiology remains the most common cause of non-cancer deaths, irrespective of menopausal status.[4] The longer-term effects of premature menopause on the cardiovascular system and bone may yet translate into increased mortality, and treatments that induce oestrogen deprivation may have delayed adverse effects on overall survival. Although some chemotherapy regimens have less ovarian toxicity (eg, methotrexate, fluorouracil, and calcium folinate),[5] those with the greatest antitumour efficacy for breast cancer contain cyclophosphamide and an anthracycline, which carry significant risk of ovarian failure.

Administration of HRT to patients with iatrogenic menopause after chemotherapy may promote physiological health and prevent impaired survival from non-cancer causes. However, the proliferative effects of HRT on breast epithelium remain a cause for concern, although no clinical evidence supports activation of dormant tumour foci in breast-cancer patients. Veronesi and colleagues' results suggest that combined HRT and tamoxifen may keep to a minimum any increased breast-cancer risk while harnessing the long-term benefits of HRT on cardiovascular and osteoporotic events and avoiding any harmful effects on mortality in long-term (node-negative) breast-cancer survivors. Although no great changes in coagulation factors are reported with this combination, patients undergoing operative procedures should receive appropriate prophylaxis and temporarily discontinue hormonal therapy before elective surgery to minimise thromboembolic phenomena.

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