Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): randomised placebo-controlled trial


Summary

Background Excess cardiovascular mortality has been documented in chronic haemodialysis patients. Oxidative stress is greater in haemodialysis patients with prevalent cardiovascular disease than in those without, suggesting a role for oxidative stress in excess cardiovascular disease in haemodialysis. We investigated the effect of high-dose vitamin E supplementation on cardiovascular disease outcomes in haemodialysis patients with pre-existing cardiovascular disease.

Methods Haemodialysis patients with pre-existing cardiovascular disease (n=196) aged 40–75 years at baseline from six dialysis centres were enrolled and randomised to receive 800 IU/day vitamin E or matching placebo. Patients were followed for a median 519 days. The primary endpoint was a composite variable consisting of: myocardial infarction (fatal and non-fatal), ischaemic stroke, peripheral vascular disease (excluding the arteriovenous fistula), and unstable angina. Secondary outcomes included each of the component outcomes, total mortality, and cardiovascular-disease mortality.

Findings A total of 15 (16%) of the 97 patients assigned to vitamin E and 33 (33%) of the 99 patients assigned to placebo had a primary endpoint (relative risk 0·46 [95% CI 0·27–0·78], p=0·014). Five (5·1%) patients assigned to vitamin E and 17 (17·2%) patients assigned to placebo had myocardial infarction (0·3 [0·11–0·78], p=0·016). No significant differences in other secondary endpoints, cardiovascular disease, or total mortality were detected.

Interpretation In haemodialysis patients with prevalent cardiovascular disease, supplementation with 800 IU/day vitamin E reduces composite cardiovascular disease endpoints and myocardial infarction.

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Introduction Chronic haemodialysis patients have an age-adjusted mortality rate 3·5–4·0 times that of the general population, more than 40% of which is attributable to cardiovascular disease. The cardiovascular-disease mortality rate in this patient group is estimated to be five to 20 times that of the general population. These high mortality rates may be partly explained by this population’s enhanced oxidative stress compared with non-haemodialysis reference groups. Oxidative stress is greater in haemodialysis patients with cardiovascular disease compared with those without. These observations support a role for oxidative stress in the pathogenesis of cardiovascular disease in haemodialysis patients.

Panzetta and colleagues found that oral supplementation of haemodialysis patients for 30 days with 50 IU/day vitamin E significantly decreased LDL susceptibility to copper-induced oxidation in vitro measured by increased lag time. In a similar study of copper-catalysed LDL oxidation kinetics, oral supplementation of haemodialysis patients for 12 weeks with 800 IU/day vitamin E increased LDL α-tocopherol content by 94% and prolonged the lag phase for conjugated diene formation. Further, it has been shown that malondialdehyde-rich LDL from haemodialysis patients is removed more slowly from circulation than LDL from healthy controls. Oral supplementation for 2 weeks with 600 IU/day vitamin E improved LDL clearance from the circulation and reduced the malondialdehyde content of LDL.

Although few vitamin E intervention studies in end-stage renal disease patients with clinical endpoints have been reported, findings are consistent with a protective effect of vitamin E in haemodialysis patients. The effect of cellulose-membrane dialysers modified by vitamin E on lipid metabolism and atherosclerosis was assessed in a 2-year intervention study. Compared with dialysis with traditional cellulose membranes, dialysis with the membrane modified by vitamin E was associated with reduced LDL-malondialdehyde and oxidised LDL. Additionally, the increase in percentage of aortic calcification index as measured by computed tomography was significantly reduced, indicating a slowing of atherosclerosis progression.

The secondary prevention with antioxidants of cardiovascular disease in endstage renal disease, or SPACE study, was designed to test the effects of high-dose (800 IU/day), oral, vitamin E supplementation in...
the prevention of secondary cardiovascular disease events in haemodialysis patients with history of cardiovascular disease. Reduction of cardiovascular-disease endpoint rate in individuals treated with vitamin E would support a role for antioxidant therapy in the secondary prevention of cardiovascular disease in this especially high-risk group.

Methods

Study design

SPACE is a double blind, placebo-controlled, randomised, secondary prevention intervention trial done at six haemodialysis centres in greater Tel Aviv, Israel. Two groups of haemodialysis patients with documented cardiovascular disease were compared: one group received 800 IU/day vitamin E (n=97) and the other a matching placebo (n=99). Recruitment began on Nov 1, 1997, and continued until Jan 1, 1998. Analysis includes all endpoints occurring between Nov 1, 1997, and Dec 31, 1999. The study had 80% power (p=0·05) to detect a relative risk of less than 0·6 in the occurrence of the primary outcome variable during a 2 year follow-up, assuming an event rate of 30% per 2 years.

After the collection of baseline data, patients were stratified for sex, age (in 5 year categories), and randomly assigned to receive 800 IU vitamin E as natural α-tocopherol. Assignment was done by means of a computer-generated coin toss within each stratum by an individual not directly involved in the study. Each participating centre was randomised separately. Vitamin E was provided as two capsules of 400 IU each (Solgar, Inc, New York, USA, during the first year and Henkel Corp, La Grange, IL, USA, during the second year) or placebo capsules identical in appearance. Patients were instructed to take two capsules nightly. A subgroup (n=15) was randomly selected from each treatment group for the purpose of monitoring serum vitamin E concentrations at 6 month intervals throughout the study.

Study population

Five dialysis centres affiliated with Sackler Medical Faculty, Tel Aviv University, participated in the study: E Wolfson Medical Centre, Ichilov Hospital Medical Centre, Rabin Medical Centre-Golda Campus, Asaf Harofeh Medical Centre, and Chaim Sheba Medical Centre. Additionally, Nephromor, Givatayim, a dialysis centre associated with one of the national health-care organisations, participated. At all centres, the medical records of all patients receiving a minimum of 12 h haemodialysis weekly for a minimum of 3 months (n=598) were reviewed to identify haemodialysis patients with pre-existing cardiovascular disease. Eligible participants were stable haemodialysis patients between the ages of 40 and 75 years inclusive at baseline with a documented medical history of cardiovascular disease (including hospital records, appropriate electrocardiographic and biochemical supporting indices). Cardiographic disease was defined as one or more of the following: myocardial infarction; ischaemic stroke; angina pectoris; transient cerebral ischaemia; or peripheral vascular disease that did not include occlusion of the arterio-venous fistula. Exclusion criteria included: anticoagulant therapy with warfarin sodium; known history of malignant disease (except non-melanoma skin cancer); active liver disease; treatment with hypolipaemic agents for less than 8 weeks before the study started; pregnant or planning to become pregnant during duration of the study; any condition the treating physician deemed to preclude the patient on grounds of safety or study evaluation. 243 patients were identified as eligible. Of these, 196 haemodialysis patients were recruited. Recruited patients did not differ from eligible patients in terms of age, sex, diabetes, underlying cardiovascular disease diagnosis, primary renal diagnosis, or years of haemodialysis treatment (figure 1).

All individuals gave informed, written consent to participate in the study, which was approved by the Helsinki Committee at each participating centre, as well as by the ethics committee of the Israeli Ministry of Health.

Outcomes

The primary endpoint was a composite variable consisting of: acute myocardial infarction (fatal and non-fatal); ischaemic stroke; peripheral vascular disease (excluding the arterio-venous fistula) in a limb not previously affected; and unstable angina. Non-fatal myocardial infarction was defined as the presence of at least two of the following criteria: chest pain of typical duration and intensity, increased cardiac enzyme concentrations (at least twice the upper limit of normal), and diagnostic electrocardiographical changes. Because no necropsy data were available (necropsy is not routinely done in Israel because of religious sensitivities), fatal myocardial infarction was defined as a death occurring within 24 h of entering hospital for myocardial infarction. Death occurring outside hospital for which no other cause was assigned was regarded as sudden death and was included in the definition of cardiovascular-disease death together with fatal myocardial infarction and fatal ischaemic stroke. Deaths were classified by the treating physician and reviewed by a member of the medical monitoring committee independently of the endpoint analysis. Incident peripheral vascular disease was defined as the onset of progressive and limiting intermittent claudication or rest pain in a previously unaffected limb leading to reduced mobility, confirmed by doppler or duplex ultrasonography.

Secondary outcomes included each of the individual component endpoints: fatal and non-fatal myocardial infarction, cardiovascular-disease mortality (fatal myocardial infarction, ischaemic stroke or sudden death), total mortality, ischaemic stroke, peripheral vascular disease, and unstable angina.

Baseline data collection

Blood pressure was recorded and blood samples drawn before the patients' usual midweek dialysis session. Routine blood chemistry and complete blood count were done according to standard protocol at the biochemistry laboratory at E Wolfson Medical Centre by means of Boehringer-Mannheim products. Serum malondialdehyde was measured spectrophotometrically with 2-thiobarbituric acid solution, as described by Bird and Draper. Serum vitamin E concentrations were measured spectrophotometrically. Serum-intact parathyroid hormone was measured in the hospital's endocrinology laboratory by the Nichol's method. The delivered dose of haemodialysis was described as the fractional clearance of urea as a function of its distribution volume (Kt/V) and was determined by the Kt/V natural logarithm formula. We used the slow-flow sampling technique whereby the blood pump was slowed to 50 mL/min and, after 50 s had elapsed, blood was...
drawn from the arterial sampling port closest to the patient.

Statistical analysis

Data were stored on spreadsheet with Microsoft Excel 1997 software and Hebrew language support (Microsoft Corporation, Seattle, WA, USA, 1985–97). Analysis of data was done with SYSTAT statistical analysis software (Version 8.0, SPSS Inc, Chicago, IL, USA, 1997) and Statistix (Version 4.0, Statistics Analytic Software, La Jolla, CA, USA, 1992).

Continuous data such as biochemical data, age, and years of haemodialysis treatment, are reported as mean (SD). The t-test for independent samples was used to detect differences in these variables between treatment groups. Frequency counts including medians and range were calculated for categorical data such as treatment group, sex, specific medications, and diagnostic classifications. Differences in these variables were assessed by Pearson’s χ² with Yates’ correction when expected values were lower than necessary to accurately use χ². Relative risk with 95% CI was calculated for the primary and the secondary endpoints.

Survival curves comparing treatment effect on the primary composite endpoint were calculated by the Kaplan-Meier method and the log-rank test (Mantel-Cox method). Analysis was repeated by Cox proportional-hazards regression. In this model, treatment effects were adjusted for present smoking, hypertension or lipid-lowering therapy, blood chemistry, pressure, primary renal renal diagnosis, underlying cardiovascular-disease diagnosis, aspirin, anti-hypertensive or lipid-lowering therapy, blood chemistry, lipids, haemostatic factors, serum malondialdehyde, serum vitamin E, or Kt/V. Throughout the study, patients continued to receive regular monthly follow-up since it was reported 40% more frequently in the vitamin E group than in the placebo group (24 [24·7%] vs [14·1%], p=0·12). Additionally, an interaction term for vitamin E and smoking was added to the model.

Results

Characteristics of the 196 patients are described in table 1. Median follow-up time was 519 (range 10–763) days. Treatment conditions did not differ significantly at baseline by age, sex, smoking status, diabetes, blood pressure, primary renal renal diagnosis, underlying cardiovascular-disease diagnosis, aspirin, anti-hypertensive or lipid-lowering therapy, blood chemistry, lipids, haemostatic factors, serum malondialdehyde, serum vitamin E, or Kt/V. Throughout the study, patients continued to receive regular monthly follow-up by their unit dietitians, who instructed them to comply with dietary recommendations for maintenance haemodialysis patients. Vitamin supplementation was similar in the two treatment conditions. We prescribed folate (5–10 mg per day), vitamin B6 (10–250 mg/day), and vitamin B12 (250 μg/day) to 75 (57·5%) of the patients in the placebo group and 55 (36·7%) of patients in the vitamin E group. Only one patient (in the vitamin E group) received vitamin B12 as a monthly intramuscular injection. Vitamin C (100–500 mg/day) was prescribed to 42 (42·5%) of the placebo group and 42 (43·3%) of the vitamin E group.

A significant correlation between serum vitamin E and total cholesterol was detected by linear-regression analysis (r=0·53, p=0·01). Therefore, vitamin E was lipid standardised by dividing serum vitamin E by the concentrations predicted by the regression equation. At baseline, lipid-adjusted serum vitamin E concentrations were 22·04 (SD 7·7) μmol/L in the vitamin E group and 23·3 (10·7) μmol/L in the placebo group (p=0·97). The mean on-treatment lipid-adjusted serum vitamin E concentrations were 27·8 (9·3) μmol/L in the vitamin E group and 20·2 (6·9) μmol/L in the placebo group (p=0·03).

Primary outcomes

Distribution of endpoints by treatment condition is shown in table 2, together with relative risk and 95% CIs. As can be seen, treatment with vitamin E was
associated with significantly fewer primary cardiovascular disease endpoints and acute myocardial infarction. 48 primary endpoints occurred during follow-up, 33 in the placebo group and 15 in the vitamin E group (54% reduction in primary endpoint risk in the vitamin E group, p=0·014). When sudden death was included as a primary cardiovascular disease endpoint, 52 endpoints occurred, 34 in the placebo group and 18 in the vitamin E group (relative risk=0·54 [95% CI 0·33–0·89], p=0·016).

Individuals who had a primary cardiovascular disease endpoint had lower baseline haemoglobin concentrations (0·11 [0·01] vs 0·12 [0·02] g/L, p=0·03) than individuals who did not have an endpoint. Of individuals with cardiovascular disease endpoint, four (8·3%) reported present smoking compared with 33 (22·3%) of individuals without cardiovascular disease endpoint (p=0·06). Also, individuals with cardiovascular-disease endpoint were marginally older than those without (66·7 [7·1] vs 63·9 [9] years, p=0·07). Individuals with cardiovascular-disease endpoint did not differ from those free of cardiovascular-disease endpoint by any other variable. The smoking-adjusted Cox regression model showed that survival from the composite cardiovascular disease endpoint was greater in patients who received vitamin E treatment (adjusted relative risk 0·44 [0·2–0·99], p=0·02). No interaction between smoking and vitamin E treatment was detected (p=0·03). The Kaplan-Meier survival curves for the combined primary endpoint are shown in figure 2.

**Secondary outcomes**

A total of 60 deaths occurred during follow-up (table 3), 29 in the placebo group and 31 in the vitamin E group (1·09 [0·7–1·7], p=0·7). 23 cardiovascular-disease deaths (including fatal myocardial infarction, fatal ischaemic stroke, and sudden death) occurred during follow-up—15 in the placebo group and nine in the vitamin E group. This 39% relative reduction in cardiovascular disease mortality was not significant (0·61 [0·28–1·3], p=0·25). The Kaplan-Meier survival curves for cardiovascular disease mortality by treatment group did not differ significantly (p=0·06), nor did they differ with the Cox smoking-adjusted model (p=0·1).

**Myocardial infarction**

A total of 22 myocardial infarctions occurred during follow-up: 17 in the placebo and five in the vitamin E group (representing a 70% reduction in total myocardial-infarction rate, p=0·016). If all sudden deaths were regarded as fatal myocardial infarction, then a total of 26 myocardial infarctions occurred, 18 in the placebo and eight in the vitamin E group (0·45 [0·2–0·99], p=0·04). 12 non-fatal myocardial infarctions occurred, nine in the placebo and three in the vitamin E group. Although this is a 66% reduction in non-fatal myocardial infarction frequency, the difference is not significant (p=0·08). Not including the sudden deaths, of the ten fatal myocardial infarctions that occurred, eight were in the placebo group and two in the vitamin E group. This 74% reduction in fatal myocardial infarctions in the vitamin E group was not significant (p=0·06). Together with sudden deaths, 14 fatal myocardial infarctions occurred, nine in the placebo group and five in the vitamin E group (0·57 [0·1–1·6], p=0·3).

Individuals who had myocardial infarction during follow-up had lower haemoglobin (0·11 [0·01] vs 0·12 [0·02], p=0·04) than those who did not. Patients with a history of myocardial infarction were not more likely than others to have it during follow-up.

Compared with patients with non-fatal myocardial infarction, patients with fatal myocardial infarction did not differ in any variable. Patients who had a non-fatal myocardial infarction during follow-up were less likely than others to have had a previous myocardial infarction; however, this difference was not significant. Patients who died from fatal myocardial infarction were more likely to have had a previous myocardial infarction than others, but this difference was not significant. Among patients with myocardial infarction during follow-up, patients with fatal myocardial infarction were more likely to have had a myocardial infarction before.

The Kaplan-Meier survival curves for myocardial infarction by treatment group differed significantly.
were randomised to receive vitamin E (400 or 800 IU/day) angiographically documented coronary artery disease. Antioxidant Study (CHAOS), in which patients with consistent with those of the Cambridge Heart contributed to largely by the reduction in total sudden death) was attained in the primary endpoint, haemodialysis patients treated with high-dose vitamin E composite cardiovascular-disease endpoints in Discussion

Adverse effects

The following adverse effects were reported: difficulty swallowing capsules (three patients), gastrointestinal distress (three), and itching (two). There was no difference by treatment group in the number of side-effects reported (five vs three, p=0.7).

Discussion

Our trial was designed to detect a 40% reduction in composite cardiovascular-disease endpoints in haemodialysis patients treated with high-dose vitamin E during 2 years’ follow-up. A 46% reduction (including sudden death) was attained in the primary endpoint, contributed to largely by the reduction in total myocardial infarction (70%). These findings are consistent with those of the Cambridge Heart Antioxidant Study (CHAOS), in which patients with angiographically documented coronary artery disease were randomised to receive vitamin E (400 or 800 IU/day) or placebo. Vitamin E treatment was associated with a 47% reduction in primary endpoint (cardiovascular death and non-fatal myocardial infarction) plus non-fatal myocardial infarction, and a 77% reduction in non-fatal myocardial infarction alone.

No significant reduction in fatal myocardial infarction was recorded in CHAOS; on the contrary, a non-significant increase in cardiovascular death was detected in patients receiving vitamin E. In a further analysis of mortality, however, it became clear that only six of 72 cardiovascular-disease deaths occurred in patients compliant with vitamin E treatment. In our study, although fatal myocardial infarction was reduced by 43% (including sudden deaths as fatal myocardial infarction) and non-fatal myocardial infarction was reduced by 66% in the vitamin E group, neither of these secondary endpoint reductions was significant. SPACE was not designed to detect reduction in fatal or non-fatal myocardial infarction as individual endpoints, and lacked the power to do so. Nevertheless, the findings show a trend toward both fatal and non-fatal myocardial infarction risk reduction with vitamin E treatment in haemodialysis patients with pre-existing cardiovascular disease. An intervention trial designed to examine the effects of vitamin E on these particular endpoints seems warranted.

In the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico Prevenzione (GISSI) study, post-myocardial-infarction patients were randomised to one of four treatment conditions: 300 mg/day vitamin E (n=2830); 1 g daily n-3 polyunsaturated fatty acids (n=2807); both (n=2830); placebo (n=2828). Vitamin E supplementation alone was associated with reduced total cardiovascular-disease deaths but not with non-fatal myocardial infarction in four-way (but not two-way) analysis. Although 300 mg/day vitamin E is clearly beyond the range recommended as a daily requirement for healthy adults, it is below the range in which clinical trials report positive results. Moreover, the supplement given was synthetic vitamin E, which is equivalent to about 150 mg natural vitamin E.

In the Heart Outcomes Prevention Evaluation (HOPE) study, 9541 patients defined as being at high risk for cardiovascular disease events were randomised to receive ramipril (10 mg per day), vitamin E (400 IU per day), both, or a placebo. Patients were followed for a mean of 4-6 years. Primary outcomes, defined as myocardial infarction, stroke, or cardiovascular disease death, did not differ by vitamin E treatment whether given alone or in combination with ramipril. The investigators believed that perhaps longer follow-up was needed to detect benefit of vitamin E, although their data do not suggest a trend in that direction.

Lack of concurrence among these three major secondary interventions trials (CHAOS, GISSI, and HOPE) requires examination. Mean annual fatal and non-fatal myocardial infarction rate in the placebo groups of these populations was 5·1%, 2·5%, and 3·8%, respectively, giving rates 50-9% (GISSI) and 25-5% (HOPE) lower than CHAOS. Disparity of this magnitude could indicate underlying differences in risk-factor distributions between the cohorts, and may suggest variations in cohort dose-effect curves. The mean annual fatal and non-fatal myocardial infarction rate in the placebo group of SPACE was 12·3%. Clearly, SPACE is dissimilar to the other cohorts studied.

In the SPACE cohort, total mortality did not differ by treatment disorder, despite a significant reduction in fatal myocardial infarctions in the vitamin E group. This finding can be attributed to a non-significant increase in non-cardiac mortality in patients who received vitamin E. When each of the endpoints was examined separately, however, none was significantly different by treatment disorder. Nevertheless, both cases of death associated with haemorrhage occurred in the vitamin E group. In a controlled trial of low-dose (50 mg daily) vitamin E,

Table 3: Causes of death by treatment and disorder in SPACE cohort

(\(p=0.01\)). However, the addition of present smoking to the Cox model adjusted the relative risk towards 1 and widened the CIs so that the treatment effect was no longer significant (adjusted relative risk 0.36 [0.12–1.08], \(p=0.1\)).

Peripheral vascular disease, unstable angina, and ischaemic stroke

During follow-up, 11 incident peripheral vascular disease events were reported, eight in the placebo group and three in the vitamin E group. Although treatment with vitamin E was associated with a 62% reduction in incident peripheral vascular disease, results were not significant (0.38 [0.1–1.4], \(p=0.13\)). Patients with incident peripheral vascular disease were no more likely than others to have previously had peripheral vascular disease.

Unstable angina was considered for analysis only in patients with no history of unstable angina or myocardial infarction. Six cases of incident unstable angina occurred during follow-up, four in the placebo and two in the vitamin E group (0.51 [0.09–2.7], \(p=0.4\)).

Eleven cases of ischaemic stroke occurred during follow-up, six in the placebo group and five in the vitamin E group (0.85 [0.3–2.7], \(p=0.8\)). Four of these strokes were fatal, two in each treatment group (\(p=0.7\)).

Adverse effects

The following adverse effects were reported: difficulty swallowing capsules (three patients), gastrointestinal distress (three), and itching (two). There was no difference by treatment group in the number of side-effects reported (five vs three, \(p=0.7\)).

Causes of death

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Vitamin E (n=97)</th>
<th>Placebo (n=99)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deaths</td>
<td>31 (31.2%)</td>
<td>29 (29.3%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Cardiovascular disease*</td>
<td>9 (9.3%)</td>
<td>15 (15.2%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Sepsis</td>
<td>10 (10.3%)</td>
<td>8 (8.1%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td>5 (5.2%)</td>
<td>3 (3.0%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Haemorrhage†</td>
<td>5 (2.1%)</td>
<td>1 (0.2%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Cancer</td>
<td>0</td>
<td>2 (2.2%)</td>
<td>2.2</td>
</tr>
<tr>
<td>Other‡</td>
<td>5 (5.2%)</td>
<td>1 (0.2%)</td>
<td>2.2</td>
</tr>
</tbody>
</table>

*Includes fatal myocardial infarction, fatal ischaemic stroke, and sudden death.
†Includes intestinal haemorrhage and oesophageal varices haemorrhage in patient with hepatitis B. In the vitamin E group includes car accident, mesenteric thrombosis, died during surgery, intestinal necrosis complications post-transplant; in the placebo group, complications post-transplant.
‡Includes fatal myocardial infarction and fatal ischaemic stroke.
30 mg daily β-carotene, both, or placebo, vitamin E supplementation was associated with a 14% decrease in ischaemic stroke (relative reduction 1–25%, p=0.03). On the other hand, it was also associated with a 62% increase in intracerebral haemorrhage. That this effect might have been due to inhibition of platelet function induced by vitamin E independent of its antioxidant effect. Vitamin E inhibits protein kinase C. As a result, platelet-pseudopodia formation in response to agonist stimulation is decreased, leading to reduced platelet adhesion.  

High-dose vitamin E supplementation has been associated with inhibition of proatherogenic events: monocyte superoxide anion release; interleukin-1β from activated monocytes; lipid oxidation; platelet aggregation; in-vivo smooth-muscle-cell proliferation; and monocyte adhesion to the endothelium. Additionally, vitamin E may be associated with stabilization of atherosclerotic plaque, providing a mechanism through which vitamin E effectiveness may be explained even during short periods of follow-up.  

The benefits of vitamin E on clinically relevant endpoints have been reported in other high-risk patient populations. Antioxidant therapy would be expected to have a greater treatment effect on patients in greater oxidative stress, and haemodialysis patients are in need of a greater treatment effect on patients in greater populations. Antioxidant therapy would be expected to have a greater treatment effect on patients in greater oxidative stress, and haemodialysis patients are in need of a greater treatment effect on patients in greater populations.  

The accelerated cardiovascular-disease event rate observed in haemodialysis patients, contributed to by increased oxidative stress, would be expected to respond to antioxidant therapy. Our study is not the final word, and recommendations regarding vitamin E therapy in haemodialysis patients have not yet been established. Nevertheless, this study shows that in haemodialysis patients with prevalent cardiovascular disease supplementation with 800 IU per day reduced composite cardiovascular disease endpoints and myocardial infarction.  

Contributors  
Mona Boaz designed the study, developed the study protocol, designed forms and data management systems, participated in the analysis and interpretation of the data, and wrote most of the paper. Shmuel Smetana, Talia Weinstein, Uzi Gaftier, Adrian Iaina, Aaron Knecht, and Yehoshua Weissgarten oversaw the study sites, assisted with the development of site-specific protocols, oversaw quality assurance at the sites, and provided substantial input into the study design and protocols. Ziporah Matas developed and directed laboratory protocols, including the analysis and interpretation of all data stemming from the laboratory, associated quality assurance, and participated in the analysis, interpretation, and editing of the paper. Daniel Brunner, Menahem Fainaru, and Manfred S Green oversaw the design and execution of the study, supervised the analyses, and assisted in the interpretation and editing of the paper. All investigators had substantial input into the interpretation of the results and the critical revision of the paper.  

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