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Effects of vitamin E on cardiovascular outcomes in people with mild-to-moderate renal insufficiency: Results of the HOPE Study

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Effects of vitamin E on cardiovascular outcomes in people with mild-to-moderate renal insufficiency: Results of the HOPE Study.

Background. A controlled trial reported cardiovascular benefits of vitamin E in terminal renal insufficiency. There are no data for renal insufficiency before the stage of terminal renal failure. We evaluated effects of vitamin E supplementation on cardiovascular and renal outcomes in 993 people with a serum creatinine ≥1.4 to 2.3 mg/dL.

Methods. Post-hoc analysis of a randomized trial that compared treatment with natural source vitamin E (400 IU/day) to placebo in 9541 people, 993 of which had renal insufficiency. Participants had either known cardiovascular disease or diabetes and at least one additional coronary risk factor. Exclusion criteria included a serum creatinine >2.3 mg/dL and dipstick-positive proteinuria. The primary study outcome after an average of 4.5 years was the composite of myocardial infarction, stroke, or cardiovascular death. Secondary outcomes included revascularizations, total mortality, and clinical proteinuria.

Results. In renal insufficiency, vitamin E supplementation had a neutral effect on the primary study outcome, on each component of the composite primary outcome, and on all secondary outcomes. Two hundred twenty-four primary outcomes, 23% of the vitamin E group and 22.1% of the placebo group, relative risk 1.03 (95% CI, 0.79–1.34; $P = 0.82$), were observed, and 585 secondary outcomes, including death in 17% and 18.8% of the vitamin E and placebo groups, respectively (RR 0.88, 95% CI, 0.66–1.18; $P = 0.40$). There was no effect of vitamin E on progression of proteinuria.

Conclusion. In people with mild-to-moderate renal insufficiency at high cardiovascular risk, vitamin E at a dose of 400 IU/day had no apparent effect on cardiovascular outcomes.

A full listing of the HOPE Investigators has been previously published (see reference 13).

Key words: renal insufficiency, vitamin E, antioxidants, coronary artery disease, nephropathy.

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Even in the absence of classic risk factors, people with renal disease have an elevated risk for cardiovascular disease [1–3]. This renal-cardiovascular association is well established for advanced renal insufficiency, especially for end-stage renal disease [2]. Recently, this association has also been reported for mild-to-moderate degrees of renal insufficiency [1, 3]. There are many potential causes that could explain why renal insufficiency is associated with a staggering cardiovascular risk [1, 3]. Oxidative stress has been hypothesized to be an important mechanism of atherogenesis in renal insufficiency. Renal insufficiency is associated with increased oxidative stress [4–6], and oxidative modification of low-density lipoprotein (LDL) is an important step in the development and progression of atherosclerosis in experimental studies [4, 5, 7].

In support of the foregoing information, small clinical studies have reported improved renal function and nerve conduction in patients receiving high-dose α-tocopherol [8, 9]. Moreover, one prospective trial examined if the antioxidant effect of supplementation with vitamin E can reduce the burden of atherosclerotic complications in people with end-stage renal disease. In fact, the Secondary Prevention with Antioxidants of Cardiovascular disease in End-stage renal disease (SPACE) trial reported a benefit of vitamin E on major cardiovascular outcomes in those patients [10]. These data in people with end-stage renal disease are at variance with the vast majority [11], but not all [12], of other major trials that observed a neutral effect of vitamin E on cardiovascular outcomes.

In the Heart Outcomes Prevention Evaluation (HOPE) study, 9541 patients at high risk for cardiovascular events were randomly allocated to natural source vitamin E 400 IU/day, or placebo, in addition to usual medical therapy. The study population included 993 people with mild-to-moderate renal insufficiency. The lack of effect of vitamin E on cardiovascular outcomes in the entire HOPE study population and in the diabetic

subgroup has been recently reported [13, 14]. In the present post-hoc analysis we tested the hypothesis that the subgroup with mild-to-moderate renal insufficiency benefited from vitamin E supplementation, as did people with more advanced renal insufficiency in the SPACE study [10].

METHODS

Detailed descriptions of the HOPE and Microalbuminuria, Cardiovascular and Renal Outcomes in the Heart Outcomes Prevention Evaluation Study (MICRO-HOPE) study designs and protocols have been published [15, 16]. In brief, we enrolled people with and without diabetes at high risk for cardiovascular events. The study was conducted in 19 countries in North and South America and in Europe. Patients were eligible if they were 55 years or older, had a history of cardiovascular disease (coronary artery disease, stroke, or peripheral arterial disease), or diabetes in the presence of at least one additional cardiovascular risk factor [total cholesterol >5.2 mmol/L, HDL cholesterol ≤0.9 mmol/L, hypertension (defined as use of medication(s) to treat high blood pressure or blood pressure at the time of recruitment >160 mm Hg systolic or >90 mm Hg diastolic), known microalbuminuria, or current smoking]. Key exclusion criteria included dipstick-positive proteinuria at baseline, serum creatinine >200 μmol/L (2.3 mg/dL), history of congestive heart failure, or known low left ventricular ejection fraction (<40%), hyperkalemia, uncontrolled hypertension, myocardial infarction, unstable angina, or stroke within one month prior to study enrollment, and use of or intolerance to vitamin E or ACE inhibitors. All study participants provided written informed consent, and the study protocol was approved by the Research Ethics Board of each participating center.

This publication refers to post-hoc analyses restricted to 993 participants with documented renal insufficiency at baseline. Recent data suggest that in individuals >55 years, a serum creatinine concentration ≥1.4 mg/dL (125 μmol/L) is a good indicator of a glomerular filtration rate <80 mL/min [17]. Therefore, prior to beginning this post-hoc analysis, a serum creatinine concentration ≥125 μmol/L (1.4 mg/dL) was used to differentiate people with and without renal insufficiency. Serum creatinine was measured locally at each of the 267 participating centers.

Study design and outcomes

The study had a 2 × 2 factorial design, with randomization to natural source vitamin E (RRR-α-tocopheryl acetate) 400 IU or placebo, and to 10 mg ramipril or placebo; both study drugs were administered once daily. After randomization, patients were evaluated at 1 month and thereafter every 6 months. As part of the MICRO-HOPE substudy, urinary albumin excretion was measured at baseline, and at study end (median 4.5 years) by measuring the albumin/creatinine ratio in the first morning urine sample. Microalbuminuria was defined based on definitions available in 1993 at the time of study initiation, as an albumin/creatinine ratio of 2 mg/mmol (18 mg/g creatinine) or higher [16]. Participants with albumin/creatinine ratio higher than 36 mg/mmol after randomization were asked to provide a 24-hour urine sample that was assayed in their local laboratory for total protein or urinary albumin. Results of these measurements were sent to the project office and all cases of overt nephropathy were adjudicated centrally.

The study outcomes have been defined previously [13, 15]. The primary study outcome was the composite of myocardial infarction, stroke, or death from cardiovascular causes. Secondary end points were total mortality, hospital admission for congestive heart failure, hospital admission for unstable angina, revascularization procedures, and the development of overt nephropathy. Overt nephropathy was diagnosed if the 24-hour urine albumin was 300 mg or more, if the 24-hour urine total protein excretion was 500 mg or more, or if the measured albumin/creatinine ratio was >36 mg/mmol and no 24-hour urine result was available [16].

Statistical analysis

Only data from the original intention-to-treat analysis [13] were used for this report. Because of HOPE's factorial design, all analyses were stratified for randomization to ramipril or placebo. Baseline characteristics were compared in participants treated with vitamin E or placebo using chi-square tests for discrete variables and *t* tests for continuous ones. Albumin/creatinine ratios were transformed to account for non-normality, and values were adjusted for the laboratories in which the assays were performed; they were compared using a Wilcoxon tests. Time-to-event by group was estimated by Cox regression stratified by center because the number of people with renal insufficiency varied significantly by center ($P = 0.006$). Kaplan-Meier curves were used to estimate survival and were compared by log-rank tests. All analyses were done using SAS 6.12 for Unix (Cary, NC, USA).

RESULTS

Patient characteristics

Of the total 9541 participants in the vitamin E arm of the HOPE study, 993 had documented renal insufficiency at baseline. Their mean age was 68.4 years, 126 (12.6%) were women, and 933 (94%) had a history of cardiovascular disease. Baseline characteristics of the HOPE study participants with renal insufficiency in the vitamin E and placebo groups were similar (Table 1).

Table 1. Baseline characteristics of participants of the vitamin E arm of the HOPE study with renal insufficiency

	Vitamin E $N = 499$	Placebo $N = 494$	P value
Demographic data			
Mean age (SD) *years*	68.6 (6.8)	68.3 (7.0)	0.4607
Female No. (%)	58.0 (11.6)	68.0 (13.8)	0.3106
Clinical characteristics History of No. (%)			
Myocardial infarction	292.0 (58.6)	295.0 (59.7)	0.7288
Coronary artery disease	443.0 (88.8)	425.0 (86.0)	0.1923
Stroke	49.0 (9.8)	36.0 (7.3)	0.1539
Peripheral vascular disease	118.0 (23.6)	117.0 (23.7)	0.9891
Any cardiovascular disease	474.0 (95.0)	459.0 (92.9)	0.1700
No cardiovascular disease	25.0 (5.0)	35.0 (7.1)	0.1700
Hypertension	272.0 (54.5)	278.0 (56.3)	0.5756
Diabetes	154 (30.9)	180 (36.4)	0.0630
Hypercholesterolemia	316.0 (63.3)	323.0 (65.4)	0.4984
Low HDL-cholesterol	115.0 (23.0)	109.0 (22.1)	0.7114
Current smoking	57.0 (11.4)	47.0 (9.5)	0.3261
Baseline measurements mean (SD)			
Body mass index (SD) kg/m^2	27.5 (4.0)	27.7 (4.4)	0.3279
Heart rate (SD) *beats/min*	66.5 (11.4)	67.0 (11.3)	0.4574
Systolic blood pressure (SD) *mm Hg*	140.1 (20.2)	140.6 (19.8)	0.6688
Diastolic blood pressure (SD) *mm Hg*	78.7 (10.8)	78.9 (11.3)	0.8202
Ankle/arm blood pressure index *SD*	0.8 (0.4)	0.8 (0.4)	0.7236
Waist/hip ratio	0.9 (0.1)	0.9 (0.1)	0.6904
Waist circumference (SD) *cm*	98.8 (11.4)	98.8 (11.0)	0.9134
Creatinine (SD) *μmol/L*	138.7 (16.9)	138.8 (16.2)	0.9199
Other drugs No. (%)			
Acetylsalicylic acid/other antiplatelet agents	403.0 (80.8)	401.0 (81.2)	0.8685
Beta-blockers	249.0 (49.9)	226.0 (45.7)	0.1905
Calcium-channel blockers	126.0 (25.3)	130.0 (26.3)	0.7012
Diuretics	113.0 (22.6)	120.0 (24.3)	0.5405
Hypolipidemic agents	147.0 (29.5)	147.0 (29.8)	0.9180
Vitamin C supplements	22.0 (4.4)	18.0 (3.6)	0.5398
Beta-carotene supplements	6.0 (1.2)	7.0 (1.4)	0.7661
Multivitamins	31.0 (6.2)	28.0 (5.7)	0.7167

The effects of vitamin E on cardiovascular outcomes and all-cause death

Vital status was ascertained at study end in all patients in the vitamin E group and in 99.9% in the placebo group; 224 primary and 585 secondary outcomes were observed. A total of 115 (23%) of the 499 people with renal insufficiency who were assigned to receive vitamin E and 109 (22.1%) of those 494 assigned to placebo had a primary cardiovascular event, hazard ratio 1.03 ($P = 0.82$). Similarly, there were no significant differences between the study groups in the rates of myocardial infarction, stroke, or death from cardiovascular causes (Table 2 and Fig. 1).

There were also no differences between patients assigned to vitamin E and those assigned to placebo in any of the secondary outcomes and in the other cardiovascular outcomes examined (Table 2). The total number of deaths, 85 in the vitamin E group versus 93 in the placebo group, was similar (hazard ratio 0.88, $P = 0.40$).

Effect of vitamin E on albuminuria

Albumin/creatinine ratio was measured in 947 (95%) participants at baseline, and in 699 (86% of those alive, 699/815) at study end. The albumin/creatinine ratio did not differ significantly in the two study groups at baseline or at study end (Fig. 2). Progression of proteinuria, defined as new microalbuminuria and/or new clinical proteinuria/overt nephropathy, was not different between groups. Progression of proteinuria from nil to microalbuminuria or clinical proteinuria occurred in 105 and 110 participants in the placebo and vitamin E group, respectively ($P = 0.659$), and from microalbuminuria to clinical proteinuria in 25 participants each ($P = 0.890$).

DISCUSSION

This analysis of HOPE study participants with mild-to-moderate renal insufficiency shows that 4.5 years of therapy with natural source vitamin E (RRR-α-tocopheryl acetate) 400 IU/day has a neutral effect on cardiovascular outcomes. The results on cardiovascular outcomes appear robust because a substantial number of outcomes was observed. There were 224 primary and 585 secondary outcomes. Compliance with study drug was high and similar in patients randomized to active vitamin E and placebo [13].

Not shown in this paper, but reported previously [18], participants with renal insufficiency were older, as compared to the rest of the HOPE study population, more likely to be male, and had a higher baseline prevalence of hypertension, coronary artery disease, peripheral vascular disease, low HDL, and use of antiplatelet and antihypertensive agents. Systolic blood pressure, urine albumin, and waist-to-hip ratio were also higher in this group. The higher cardiovascular risk profile translated into a substantially increased rate of cardiovascular outcomes [18]. Based on the number of cardiovascular events, the present analysis should have the statistical power to detect an effect, if there was any, of vitamin E on cardiovascular disease.

The Secondary Prevention with Antioxidants of Cardiovascular disease in End-stage renal disease (SPACE) study [10] is at variance with the HOPE study results in people with renal insufficiency. The SPACE trial randomized 196 hemodialysis patients of the greater Tel Aviv area, mean age 65 years, all with documented cardiovascular disease, 43% with known diabetes, to vitamin E 800 IU/day or to placebo for a mean follow-up 17 months [10]. Patients assigned to vitamin E had a 54% risk reduction (95% CI, 22–73; $P = 0.014$) of the composite end point of myocardial infarction, ischemic stroke, peripheral vascular disease, and unstable angina, and experienced fewer myocardial infarcts. There were no significant differences in total mortality. Why did vitamin E fail to demonstrate benefit in people with

Table 2. Cardiovascular events in the vitamin E and placebo groups

Outcome	Vitamin E $N = 499$ N%	Placebo $N = 494$ N%	RR (95% CI)[a]	*P* value
Primary outcome				
Composite of myocardial infarction, stroke, or death from CV causes	115.0 (23.0)	109.0 (22.1)	1.03 (0.79–1.34)	0.82
Myocardial infarction[b]	81.0 (16.2)	83.0 (16.8)	0.95 (0.70–1.29)	0.76
Stroke[b]	26.0 (5.2)	25.0 (5.1)	1.00 (0.58–1.73)	1.00
Death from CV causes[b]	57.0 (11.4)	57.0 (11.5)	0.97 (0.67–1.40)	0.85
Secondary outcomes				
Total mortality	85.0 (17.0)	93.0 (18.8)	0.88 (0.66–1.18)	0.40
Unstable angina	76.0 (15.2)	77.0 (15.6)	0.95 (0.69–1.31)	0.77
Heart failure hospitalizations	31.0 (6.2)	28.0 (5.7)	1.08 (0.65–1.80)	0.77
Revascularization procedures	107.0 (21.4)	88.0 (17.8)	1.20 (0.91–1.60)	0.20
Other outcomes				
Any heart failure	83.0 (16.6)	63.0 (12.8)	1.32 (0.95–1.84)	0.09
Transient ischemic attacks	33.0 (6.6)	34.0 (6.9)	1.27 (0.75–2.14)	0.38
Unstable angina with ECG changes	27.0 (5.4)	32.0 (6.5)	0.81 (0.49–1.36)	0.43

[a]RR, relative risk; CI, confidence interval; N, number of people (percentage); CV, cardiovascular.
[b]A patient may have had more than one event.

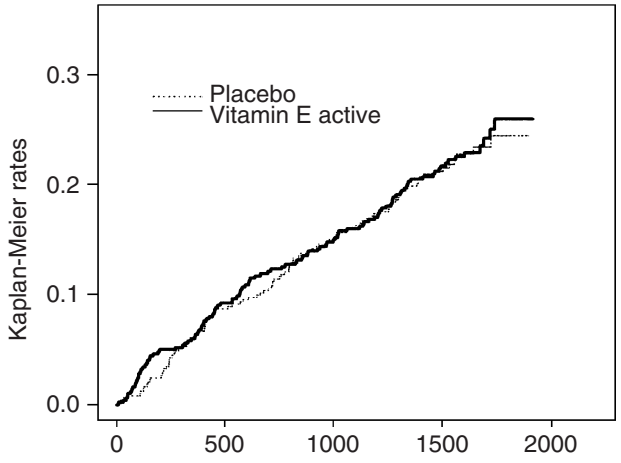

Fig. 1. Kaplan-Meier survival curves for the primary cardiovascular study outcome (myocardial infarction, stroke, cardiovascular death). The x-axis indicates the duration of follow-up in days.

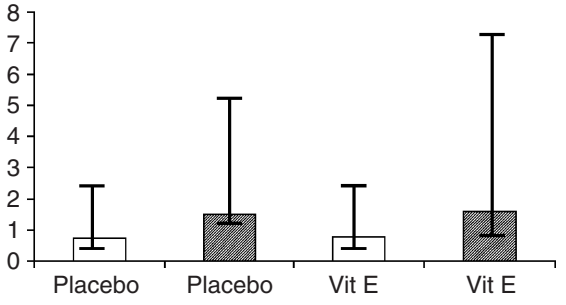

Fig. 2. Median urinary albumin/creatinine ratio including 25 and 75 percentiles at baseline (left) and at study end (right) in the placebo and vitamin E treated groups, respectively.

mild-to-moderate renal insufficiency while it was beneficial in people with end stage renal disease [10]? First, the population enrolled in the SPACE trial was at a higher cardiovascular risk than the present subgroup of the HOPE trial. The annual cardiovascular event rate of the SPACE trial was about 3 times that of our population [10]. Second, participants of the SPACE study were treated with a higher dose of vitamin E than in HOPE, and almost half of the population regularly consumed vitamin C. The vast majority of participants of the HOPE study did not consume vitamin C (see Table 1). It may well be that the higher antioxidative potential of higher vitamin E doses, combined with vitamin C, has different effects in people with terminal renal insufficiency compared to lower doses of vitamin E in people with mild-to-moderate renal insufficiency. There is some evidence that people with end-stage renal disease are exposed to a greater oxidative stress than other populations [4–7, 19, 20]. There is a hypothesis that the combined use of vitamins C and E has a superior antioxidant effect to vitamin E alone [21]. However, the recent results of the Heart Protection Study do not support a cardiovascular protective effect of vitamin E and C [22]. Third, the dietary intake of vitamins, including vitamin E, may be different in people with or without end-stage renal disease. The average diet of participants of the HOPE trial may have provided adequate supplies of vitamin E in a large proportion of individuals, but may have provided inadequate supplies in the population of the SPACE trial. In other words, the absolute difference of vitamin E intake between placebo and actively treated participants may be substantially greater in the SPACE than in the HOPE study. In both trials, there is no information on dietary intake of vitamin E at baseline. Fourth, the results of the SPACE trial may be a chance finding, because the majority of other large randomized trials did not find an effect

of vitamin E, alone or in combination with vitamin C, on cardiovascular events [11], and because SPACE studied a small sample compared with other trials [11], which resulted in large confidence intervals based on a broad composite end point.

In spite of the strong biologic rationale, the randomized clinical trials have, with few exceptions, failed to detect clear benefits of vitamin E supplementation on the progression of atherosclerotic lesions or on clinical outcomes [11]. Six recent, large randomized trials have evaluated the effects of vitamin E on major cardiovascular outcomes. The primary prevention trials include the Alpha-tocopherol Beta-carotene Cancer Prevention Study (ATBC) [23], the Collaborative Group of the Primary Prevention Project (PPP) [24], and Heart Protection Study [22]; the major trials in secondary prevention are the Cambridge Heart Antioxidant Study (CHAOS) [12], the GISSI Prevenzione trial [26], HOPE [13], and a subset of the ATBC trial [26]. Overall, these large randomized, controlled clinical trials failed to demonstrate consistent cardiovascular benefits of vitamin E supplementation, as were further supported by a recent meta-analysis [11].

Interestingly, vitamin E was shown to improve endothelial function in short-term studies [27, 28], and a large, long-term observational study reported reduced coronary atherosclerosis progression in women and men taking vitamin E supplements [29, 30]. Variable effects were reported on carotid atherosclerosis. The Study to Evaluate Carotid Ultrasound Changes in patients treated with Ramipril and vitamin E (SECURE), a HOPE substudy in 732 high-risk patients, showed no effect of vitamin E supplementation for 3 to 5 years on the progression of carotid atherosclerosis, assessed by ultrasound methods [31]. The Antioxidant Supplementation in Atherosclerosis (ASAP) trial [21], however, suggested benefits in hypercholesterolemic men treated with combined vitamin E and C supplementation, while finding no benefit in women.

Small clinical studies have reported improved renal function and nerve conduction in patients receiving high-dose α-tocopherol [8, 9]. The current study, the largest to date to evaluate the effects of vitamin E in people with renal insufficiency, showed neutral effects on proteinuria. The interpretation of those renal data is limited because urine albumin was measured only once at the beginning and at study end in all participants of the HOPE study. Although the drop-out rate of the HOPE study was very low [13], urine albumin values at study end were missing in about a third of the population because of death or missing values. It may be argued that those with missing values could be those with worse renal outcomes. However, baseline characteristics of those with and without missing values were identical (data not shown).

CONCLUSION

Our post-hoc analysis does not support the use of vitamin E to prevent cardiovascular complications in people with mild-to-moderate renal insufficiency. Other risk factors of premature atherosclerosis, such as high blood pressure and hyperlipidemia, should remain the focus of treatment.

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