Effects of Vitamin E on Cardiovascular and Microvascular Outcomes in High-Risk Patients With Diabetes

Results of the HOPE Study and MICRO-HOPE Substudy

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OBJECTIVES — Experimental and observational studies suggest that vitamin E may reduce the risk of cardiovascular (CV) events and of microvascular complications in people with diabetes. However, data from randomized clinical trials are limited. Therefore, we evaluated the effects of vitamin E supplementation on major CV outcomes and on the development of nephropathy in people with diabetes.

RESEARCH DESIGN AND METHODS — The Heart Outcomes Prevention Evaluation (HOPE) trial is a randomized clinical trial with a 2 × 2 factorial design, which evaluated the effects of vitamin E and of ramipril in patients at high risk for CV events. Patients were eligible for the study if they were 55 years or older and if they had CV disease or diabetes with at least one additional coronary risk factor. The study was designed to recruit a large number of people with diabetes, and the analyses of the effects of vitamin E in this group were preplanned. Patients were randomly allocated to daily treatment with 400 IU vitamin E and with 10 mg ramipril or their respective placebos and were followed for an average of 4.5 years. The primary study outcome was the composite of myocardial infarction, stroke, or CV death. Secondary outcomes included total mortality, hospitalizations for heart failure, hospitalizations for unstable angina, revascularizations, and overt nephropathy.

RESULTS — There were 3,654 people with diabetes. Vitamin E had a neutral effect on the primary study outcome (relative risk = 1.03, 95% CI 0.88–1.21; $P = 0.70$), on each component of the composite primary outcome, and on all predefined secondary outcomes.

CONCLUSIONS — The daily administration of 400 IU vitamin E for an average of 4.5 years to middle-aged and elderly people with diabetes and CV disease and/or additional coronary risk factor(s) has no effect on CV outcomes or nephropathy.

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Abbreviations: CV, cardiovascular; DAG, D-acetyl-glycerol; HOPE, Heart Outcomes Prevention Evaluation; MI, myocardial infarction; MICRO-HOPE, Microalbuminuria Cardiovascular Renal Outcomes–HOPE substudy; PKC, protein kinase C.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Atherosclerotic cardiovascular (CV) diseases are a major source of morbidity and mortality in people with diabetes. Oxidative modification of LDL is an important step in the development and progression of atherosclerosis in experimental studies (1). Diabetes is a condition associated with increased oxidative stress as a consequence of hyperglycemia. Therefore, the use of antioxidants in people with diabetes has been advocated (2). Vitamin E is the most prevalent naturally occurring antioxidant and has been shown to retard atherosclerosis in animal models (3). In addition to its antioxidant properties, vitamin E also reduces the cytotoxic effect of oxidized lipoproteins, smooth muscle cell proliferation, platelet adherence and aggregation, and inflammation, and it improves endothelial function (3,4). Moreover, observational studies have suggested that supplemental vitamin E users have lower rates of coronary events (5,6). Although most participants in these studies did not have diabetes, people with diabetes were not systematically excluded.

Vitamin E was also proposed for the prevention of microvascular complications of diabetes. Indeed, in animal models it decreases hyperglycemia-induced protein kinase C (PKC) activation and D-acetyl-glycerol (DAG) levels, which have been associated with abnormalities in the retinal, renal, and vascular tissues in diabetes (7).

Despite these data, several large randomized clinical trials have failed to confirm benefits for vitamin E in CV prevention (8–11). Such studies have enrolled few people with diabetes and, to date, there are no large published trials on the effects of vitamin E on either CV or microvascular outcomes in diabetes.

We recently published the results of the Heart Outcomes Prevention Evaluation (HOPE) trial, which found no CV benefits for vitamin E in individuals at high risk for CV events (12) In the current

Table 1—*Baseline characteristics of HOPE study participants with diabetes*

	Vitamin E (n = 1,838)	Placebo (n = 1,816)
Demographic data		
Mean age (SD) (years)	65.6 (6.5)	65.2 (6.5)
Female [*n* (%)]	689 (37.5)	669 (36.8)
Clinical characteristics		
History [*n* (%)]		
MI	658 (35.8)	667 (35.7)
Coronary artery disease	1,120 (60.9)	1,069 (58.9)
Stroke	127 (6.9)	117 (6.4)
Peripheral arterial disease	330 (18.0)	348 (19.2)
Any CV disease	1,283 (69.8)	1,228 (67.6)
No CV disease	555 (30.2)	588 (32.4)
Hypertension	1,015 (55.2)	1,016 (55.9)
Hypercholesterolemia*	1,186 (64.5)	1,198 (66.0)
Low HDL cholesterol†	363 (19.8)	366 (20.2)
Current smoking	252 (13.7)	297 (16.4)‡
Baseline measurements [mean (SD)]		
BMI (SD) (kg/m^2)	28.8 (4.7)	28.7 (4.8)
Heart rate (SD) (beats/min)	72.1 (11.2)	72.6 (11.1)
Systolic blood pressure (SD) (mmHg)	141.9 (19.5)	141.9 (19.4)
Diastolic blood pressure (SD) (mmHg)	79.4 (10.5)	79.8 (10.8)
Ankle/arm blood pressure index (SD)	0.97 (0.2)	0.96 (0.2)
Waist-to-hip ratio	0.93 (0.09)	0.93 (0.08)
Waist circumference (SD) (cm)	99.8 (12.6)	99.7 (12.5)
Creatinine (SD) (μmol/l)	93.2 (27.2)	94.3 (22.3)
Diabetes and glycemic control		
Type 2 diabetes [*n* (%)]	1,797 (97.8)	1,775 (97.7)
Mean duration of diabetes (SD) (years)	11.3 (10.0)	11.6 (10.9)
Mean HbA_{1c} (SD) (%)	7.41 (1.9)	7.50 (1.9)
Microalbuminuria [*n* (%)]	585 (31.8)	572 (31.5)
Diabetic therapy [*n* (%)]		
Diet alone	328 (17.8)	321 (17.7)
Oral agents alone	954 (51.9)	936 (51.4)
Insulin alone	459 (25.0)	475 (26.2)
Insulin plus oral agents	97 (5.3)	84 (4.6)
Other drugs [*n* (%)]		
Acetylsalicylic acid/other antiplatelet agents	1,077 (58.6)	1,045 (57.5)
β-Blockers	516 (28.1)	516 (28.4)
Calcium-channel blockers	819 (20.6)	789 (43.4)
Diuretics	362 (19.7)	349 (19.2)
Hypolipidaemic agents	819 (20.6)	414 (22.8)
Vitamin C supplements	92 (5.0)	100 (5.5)
β-Carotene supplements	20. (1.1)	20. (1.1)
Multivitamins	126 (6.9)	128 (7.0)

*Hypercholesterolemia was defined as total cholesterol > 5.2 mmol/l; †low HDL cholesterol was defined as HDL cholesterol ≤0.9 mmol/l; ‡$P < 0.05$.

report, we describe the effects of vitamin E on CV events, on microvascular outcomes, and on glycemic control in the HOPE study participants with diabetes.

RESEARCH DESIGN AND METHODS

— The HOPE study evaluated vitamin E in 9,541 patients at high risk for CV events. The study was designed to enroll a large proportion of diabetic patients (>35%), and analyses of the effects of vitamin E in the study participants with a baseline diagnosis of diabetes were preplanned. The Microalbuminuria Cardiovascular Renal Outcomes (MICRO-HOPE) was a substudy of the HOPE trial, which evaluated the effects of the study interventions on nephropathy. Detailed descriptions of the HOPE and MICRO-HOPE study designs and protocols have been published (12–14). A brief summary is listed below.

Study population

The HOPE trial enrolled people with and without diabetes at high risk for CV events. Patients were eligible if they were 55 years or older, had a history of CV disease (coronary artery disease, stroke, or peripheral arterial disease) or diabetes in the presence of at least one additional CV 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 time of recruitment >160 mmHg systolic or >90 mmHg diastolic, known microalbuminuria, or current smoking). Key exclusion criteria included dipstick-positive proteinuria, diabetic nephropathy, serum creatinine >200 μmol/l, history of congestive heart failure or known low left ventricular ejection fraction (<40%), hyperkalemia, uncontrolled hypertension, myocardial infarction (MI), unstable angina or stroke within 1 month before study enrolment, 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 presents analyses restricted to patients with a baseline diagnosis of diabetes. Diabetes status was established at baseline based on history and confirmation by source documentation. Participants were judged to have type 2 diabetes if the diagnosis was made at age 30 years or older or if they were not taking insulin.

Study design and outcomes

The study had a 2 × 2 factorial design with randomization to 400 IU natural source vitamin E (RRR-α-tocopheryl acetate) or placebo and to 10 mg of ramipril or placebo, both study drugs administered once daily. Mean follow-up was 4.5 years.

After randomization, patients were evaluated at 1 month and thereafter every 6 months. HbA_{1c} and serum creatinine were assayed for all HOPE study participants with a history of diabetes in each

Table 2—*CV events in the vitamin E and placebo groups*

Outcome	Vitamin E (n = 1838)	Placebo (n = 1816)	RR (95% CI)	P
Primary outcome				
Composite of myocardial infarction, stroke, or CV death	325 (17.7)	313 (17.2)	1.03 (0.88–1.21)	0.70
MI*	212 (11.5)	209 (11.5)	1.01 (0.83–1.22)	0.96
Stroke*	103 (5.6)	84 (4.6)	1.21 (0.91–1.62)	0.20
CV death*	142 (7.7)	145 (8.0)	0.97 (0.77–1.23)	0.82
Secondary outcomes				
Total mortality	218 (11.9)	232 (12.8)	0.93 (0.77–1.12)	0.44
Hospitalizations for unstable angina	227 (12.4)	199 (11.0)	1.13 (0.93–1.37)	0.21
Hospitalizations for heart failure	85 (4.6)	76 (4.2)	1.11 (0.81–1.51)	0.52
Revascularization procedures	279 (15.2)	278 (15.3)	0.99 (1.82–1.17)	0.95
Other CV outcomes				
Any heart failure†	241 (13.1)	201 (11.1)	1.21 (1.00–1.46)	0.05
Transient ischemic attacks	89 (4.8)	96 (5.3)	0.93 (0.70–1.25)	0.64
Unstable angina with ECG changes	72 (3.9)	78 (4.3)	0.91 (0.66–1.25)	0.91
Microvascular complications				
Overt nephropathy	146 (7.9)	131 (7.2)	1.12 (0.88–1.42)	0.37
New microalbuminuria	442 (35.3)	466 (37.5)	0.91 (0.79–1.03)	0.14
Dialysis	9 (0.5)	9 (0.5)	0.99 (0.81–1.22)	0.97
Laser therapy for diabetic nephropathy	182 (9.9)	182 (10.0)	0.99 (0.81–1.22)	0.96
New cataract/cataract surgery	304 (16.5)	318 (17.5)	0.97 (.88–1.21)	0.70
Limb infection	53 (2.9)	58 (3.2)	0.90 (0.63–1.31)	0.59

Data are n (%) unless otherwise indicated. *A patient may have had more than one event; †refers to open label use of an ACE inhibitor for the diagnosis of heart failure, hospitalization for heart failure or death due to heart failure.

study center's local laboratory at baseline and yearly thereafter. Urinary albumin excretion was measured at baseline, at 1 year, and at study end, by measuring the albumin-to-creatinine ratio in the first morning urine sample. Urine was stored at −70°C. Albumin-to-creatinine ratio was measured at four laboratories, which served as central laboratories for the study regions (Canada, U.K., Argentina, and Brazil). Microalbuminuria was defined based on definitions available in 1993 at the time of study initiation, as an albumin-to-creatinine ratio of 2 mg/mmol or higher (13). Participants with albumin-to-creatinine ratio >36 mg/mmol after randomization were asked to provide a 24-h 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. Overt nephropathy was diagnosed if the 24-h urine albumin was 300 mg or more, if the 24-h urine total protein excretion was 500 mg or more, or if the measured albumin-to-creatinine ratio was >36 mg/mmol and no 24-h urine result was available.

Definitions of the study outcomes have been previously published (12–14). The primary study outcome was the composite of nonfatal MI, stroke, or CV death. 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. All primary and secondary outcomes were adjudicated by an events adjudication committee unaware of the participants' assigned treatments. Additional outcomes were determined by history and summary records, which were obtained for all hospital admissions and were reviewed by the Project Office.

Plasma vitamin E levels were measured by liquid chromatography (Waters 625 LC system; Millipore, Milford, MA) at baseline and at 2 years in 163 randomly selected patients in the vitamin E group and in 34 randomly selected patients in the placebo group.

Statistical analysis

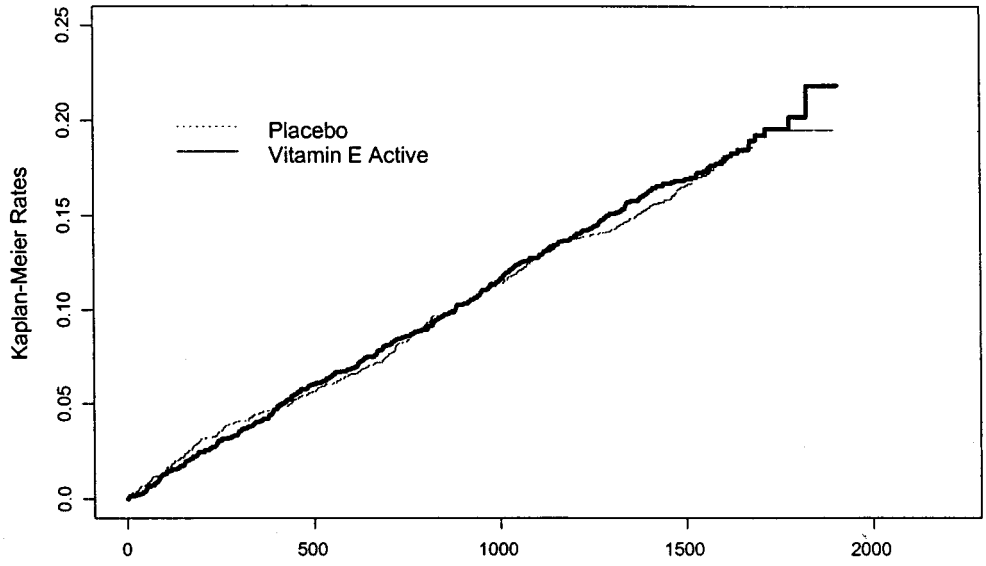
All analyses were carried out using SAS 6.02 (SAS Institute, Cary, NC) and were by intention to treat. Baseline characteristics were compared by t tests or χ^2 tests as appropriate. All outcome analyses were stratified according to randomization to ramipril or placebo by Cox regression in order to account for the factorial study design. Relative risks (RRs) and 95% CIs are reported for the primary, secondary, and other outcomes of interest. Kaplan-Meier curves were used to estimate survival and were compared by log-rank tests. Treatment effect in subgroups and potential interactions were evaluated by Cox regression analysis. Changes in continuous variables (HbA_{1c}, serum creatinine, albumin-to-creatinine ratio, and blood pressure) from baseline were compared by ANOVA, adjusted for baseline values. Results of HbA_{1c} were expressed as the percentage higher than the upper limit of normal for the assay used. Albumin-to-creatinine ratios were transformed to account for nonnormality, and values were adjusted for the laboratories in which the assays were performed.

RESULTS

Patient characteristics and compliance

There were 3,654 patients with diabetes at baseline. Their mean age was 65.4

Primary Outcome



Myocardial Infarction

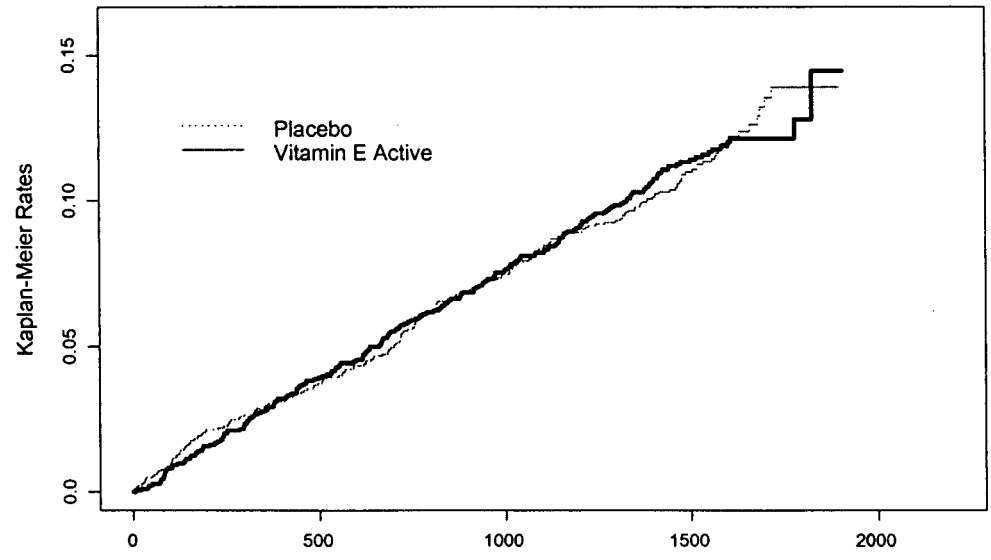
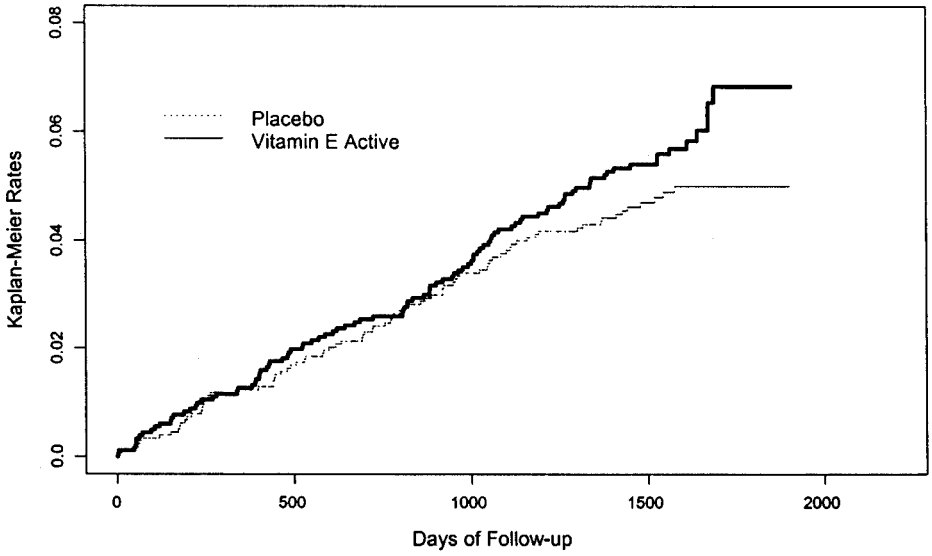


Figure 1—*Kaplan-Meier survival curves for the primary CV study outcome, MI, stroke, CV death, and total mortality. The x-axis indicates the duration of follow-up in days.*

years, 1,358 (37%) were women, and 2,511 (69%) had a history of CV disease. Baseline characteristics in the vitamin E and placebo groups were similar (Table 1). Compliance with study drug was high and similar in patients randomized to active vitamin E and to placebo. In the vitamin E group, 92.3% of patients were taking study drug at 1 year, 90.3% at 2

Stroke



Cardiovascular Death

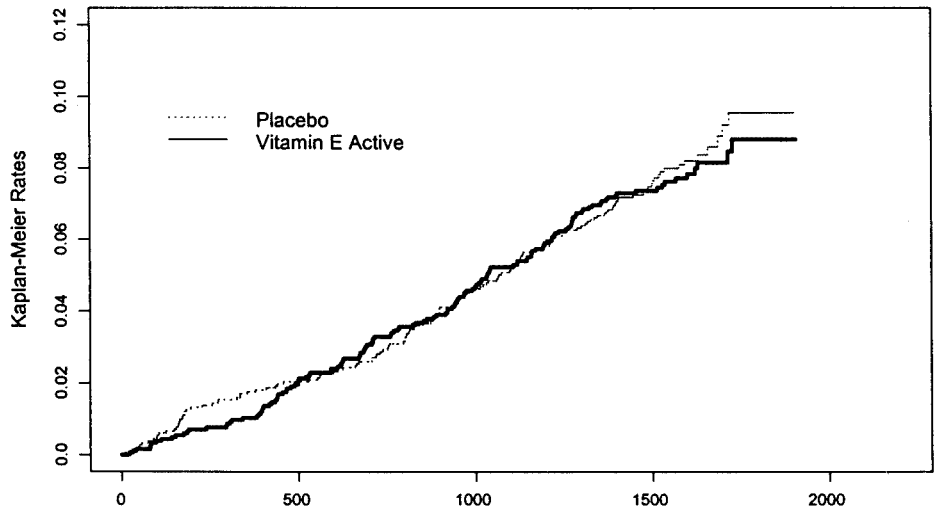


Figure 1—*Continued.*

years, 87.6% at 3 years, 84.6% at 4 years, and 83.4% at study end. In the placebo group, 90.6% of patients were taking study drug at 1 year, 88.7% at 2 years, 86.1% at 3 years, 83.3% at 4 years, and 81.3% at study end. Use of nonstudy vitamin E was very low, ranging from 0.7 to 3.3% of patients throughout the study, with no differences between the study groups. There were no significant side effects associated with vitamin E use. The most common reason for discontinuation of study drug was physician advice or patient refusal, which accounted for 17 and 19% of all cases of permanent drug discontinuation in the vitamin E and placebo groups, respectively.

Plasma vitamin E levels were similar

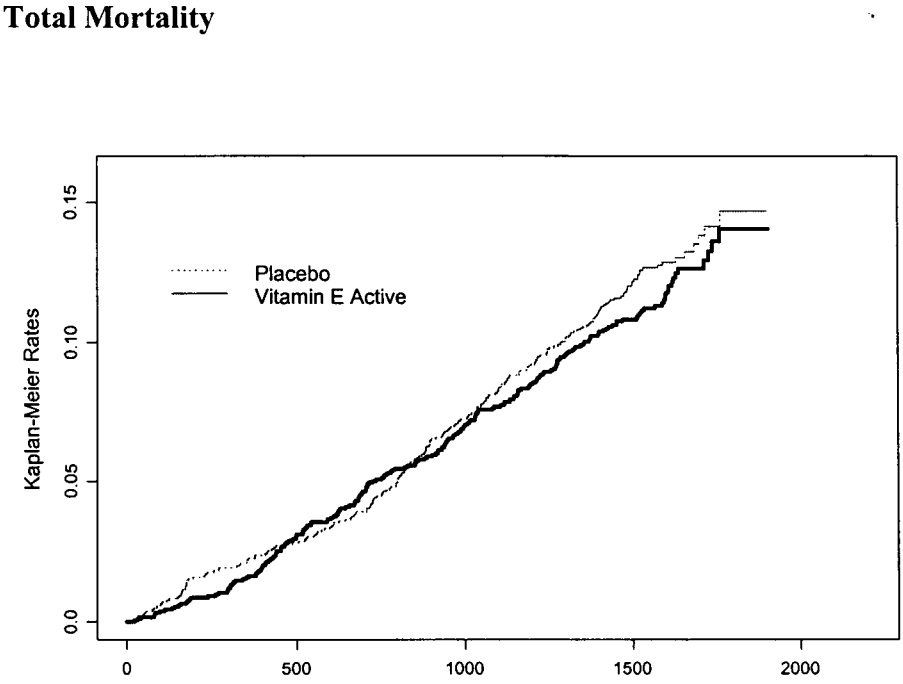


Figure 1—*Continued.*

at baseline: 28.1 ± 9.7 mmol/l in the vitamin E group and 29.8 ± 15.2 mmol/l in the placebo group. At 2 years, plasma vitamin E levels rose significantly in the vitamin E group to 48.7 ± 17.6 mmol/l ($P < 0.0001$) and remained unchanged in the placebo group (30.4 ± 21.1 mmol/l).

The effects of vitamin E on CV 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. There was no significant interaction between the study treatments (ramipril and vitamin E) for the primary ($P = 0.93$), secondary, and other study outcomes. In the active vitamin E group, 325 (17.7%) people with diabetes had a primary outcome event vs. 313 (17.2%) in the placebo group (RR 1.03, 95% CI 0.88–1.21; $P = 0.70$). Similarly, there were no significance differences between the study groups in the rates of MI, stroke, CV death, total mortality, and of all other secondary and additional CV outcomes (Table 2 and Fig. 1). There were also no significant treatment effects of vitamin E in any predefined subgroup. Subgroups analyzed included women, men, patients older and younger than 65 years of age, those with type 1 and with type 2 diabetes, with BMI above and below 27 kg/m^2, with and without a history of hypertension, smoking, hypercholesterolemia, microalbuminuria, CV disease, coronary artery disease, MI, stroke, peripheral arterial disease, on various therapies for glycemic control (diet alone, oral hypoglycemic drugs, insulin, or combined therapies) or for the management of CV diseases, hypertension and hypercholesterolemia, and those taking or not taking vitamin C and multivitamin supplements. Some of the pertinent subgroup analyses are illustrated in Fig. 2.

Effect of vitamin E on microvascular disease outcomes

Urinary albumin-to-creatinine ratio was measured in 3,574 (97.8%) participants at baseline, in 3,140 (88.9% of those alive) at 1 year, and in 2,740 (85.9% of those alive) at study end. The albumin-to-creatinine ratio did not differ significantly between the two study groups at baseline, at 1 year, or at study end. During follow-up, 361 (9.9%) study participants developed an albumin-to-creatinine ratio >36 mg/mmol and were asked to provide a 24-h urine collection to test for overt nephropathy. Results were available for 308 (85.3%) patients. In the vitamin E arm, 146 (7.9%) study participants developed overt nephropathy vs. 131 (7.2%) in the placebo arm ($P = 0.37$; this analysis uses as a definition of overt nephropathy the presence of significant proteinuria or albuminuria as defined above or albumin-to-creatinine ratio >36 mg/mmol). When a more stringent definition of overt nephropathy was used and the analysis was restricted to people in whom 24-h urine results were available, 120 (6.5%) in the vitamin E group vs. 109 (6.0%) in the placebo group developed nephropathy ($P = 0.45$). There were also no differences between the study groups in rates of new microalbuminuria, dialysis, history of laser therapy for diabetic retinopathy, combined outcomes related to microvascular disease, history of new cataract or cataract surgery, or hospital admissions for limb infection (Table 2). Serum creatinine was similar at baseline in both study groups (Table 1). The yearly changes in serum creatinine compared with the baseline values did not differ significantly between the study groups. At study end, serum creatinine increased by 1.92 μmol/l in the vitamin E group compared with baseline and by 3.39 μmol/l in the placebo group ($P = 0.24$).

Effects of vitamin E on glycemic control

At baseline, mean HbA_{1c} levels were similar in the vitamin E (7.41%) and the placebo groups (7.50%). Compared with

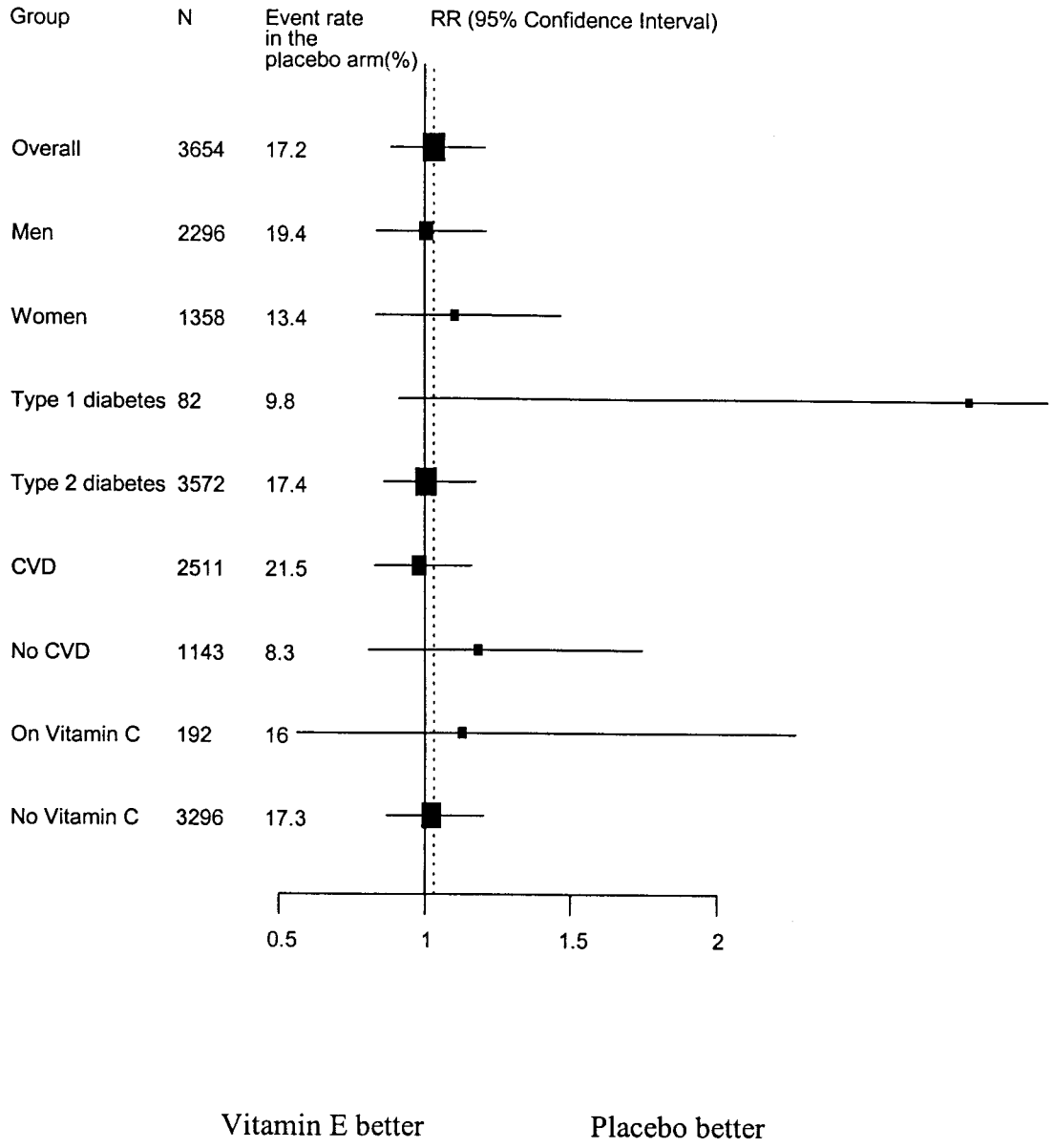


Figure 2—*Effect of vitamin E on the primary CV outcome in subgroups. The size of each symbol is proportional to the number of patients in each subgroup. CVD, CV disease.*

baseline, mean absolute HbA_{1c} values increased by absolute amounts of 1.96% higher than the upper limit of normal in the vitamin E group and of 2% in the placebo group at 1 year ($P = 0.89$). The change from baseline in HbA_{1c}, was similar for both groups at subsequent visits and at the end of the study (1.32% increase for vitamin E and 1.57% for placebo, respectively, $P = 0.78$). The number of hospital admissions for hyperglycemia (76 in the vitamin E vs. 76 in the placebo group, $P = 0.87$), for hypoglycemia (26 in the vitamin E vs. 37 in the placebo group, $P = 0.12$), and for diabetic ketoacidosis (8 in the vitamin E vs. 4 in the placebo group, $P = 0.27$) also did not differ significantly.

Effect of vitamin E on the development of new diabetes

There were 5,887 HOPE study participants without diabetes at baseline (2,799 in the vitamin E group and 2,827 in the placebo group). A diagnosis of new diabetes by history was obtained in 124 (4.2%) patients on active therapy vs. 137 (4.6%) on placebo ($P = 0.55$).

CONCLUSIONS— In our study, 400 IU/day of RRR-α-tocopheryl acetate administered for an average of 4.5 years to people with diabetes and at high risk for CV events had a neutral effect on CV outcomes, on microvascular complications, and on glycemic control.

The results on CV outcomes are very robust, with a large number of events and with consistent lack of benefit associated with vitamin E therapy on the composite primary outcome, on each component of the primary outcome, and on all secondary and additional CV outcomes for the

entire diabetic study population and for all subgroups evaluated.

In spite of the strong biological rationale for a fundamental role of oxidative stress in atherosclerosis and the supportive epidemiological data, randomized clinical trials have overall, with few exceptions, failed to detect clear benefits of vitamin E supplementation on the progression of atherosclerotic lesions or on clinical events (8–11, 15,16). While vitamin E was shown to improve endothelial function in short-term studies (4), there is no conclusive proof of long-term beneficial effects on human atherosclerosis (15), and a recent trial in patients with coronary disease and low HDL cholesterol suggested that combined antioxidant vitamin therapy may even diminish the benefits attained on coronary disease progression with a statin and niacin (16). Several previous large randomized trials have generally failed to demonstrate consistent CV benefits associated with vitamin E supplementation (8–11,17). Few people with diabetes were enrolled in these trials and none reported data separately for people with diabetes. Furthermore, none of these trials reported information on nephropathy and on other microvascular outcomes. More recently, the Heart Protection Study enrolled over 5,900 high-risk people with diabetes and showed no CV benefits for combined therapy with vitamins E, C, and β-carotene (18).

An epidemiological report suggested that vitamin E may prevent the development of diabetes (19), and a few small randomized trials showed improved glycemic control in people with diabetes receiving vitamin E supplements, while a number of other small randomized trials found no impact of vitamin E on glycemia (20). We found no effect of vitamin E on HbA_{1c} levels in patients with diabetes and no impact on the development of new diabetes in close to 6,000 individuals without diabetes at baseline.

Hyperglycemia-induced PKC activation has been proposed as an important pathway for the development of microvascular complications in diabetes (7). High doses of vitamin E decreased PKC activation and prevented or reversed abnormalities in the retinal and renal vessels and in mesangial cells in some animal models, although the published results are inconsistent (7,21,22). Small clinical studies have reported improved retinal blood flow, renal function, and nerve conduction in patients with diabetes receiving high-dose α-tocopherol (23,24). Our study, the largest to date to evaluate the effects of vitamin E on diabetic microvascular complications, showed neutral effects on renal function and on need for retinal laser therapy. While the lack of retinal photographs and/or retinal flow studies may be considered a limitation of the study and subtle early treatment effects on the retina may have been missed, urinary protein excretion and the development of diabetic nephropathy were carefully evaluated and the study had high power to detect clinically important benefits.

Several explanations have been proposed for the observed lack of benefit with vitamin E in recent large trials. Steinberg hypothesized that the effect of antioxidants in atherosclerosis is exerted primarily on early lesions and may be difficult to detect in middle-aged and elderly individuals with advanced disease, and that trials of longer duration than those designed to test pharmacological interventions may be required (25). Experimental data suggest that vitamin E can become pro-oxidative and that combined antioxidant vitamins can reduce the HDL_2-cholesterol subfraction (16). Some investigators advocate the use of higher doses of vitamin E, similar to those used in experimental animal studies, in which vitamin E was effective in preventing PKC activation and in reducing endothelial cell toxicity and markers of inflammation (4,7). Finally, it has been suggested that the average Western diet may provide adequate supplies of vitamin E in a large proportion of individuals and that it may be difficult to observe benefits in this population with the use of additional supplemental vitamin E intake (26).

Based on current evidence, the widespread use of supplemental vitamin E cannot be endorsed as a means to reduce vascular complications in people with diabetes. Our efforts should be directed toward the aggressive management of hyperglycemia and of additional risk factors for atherosclerosis and for microvascular damage.

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