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Effects of Ramipril and Vitamin E on Atherosclerosis The Study to Evaluate Carotid Ultrasound Changes in Patients Treated With Ramipril and Vitamin E (SECURE)

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Background—Activation of the renin-angiotensin-aldosterone system and oxidative modification of LDL cholesterol play important roles in atherosclerosis. The Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamin E (SECURE), a substudy of the Heart Outcomes Prevention Evaluation (HOPE) trial, was a prospective, double-blind, 3×2 factorial design trial that evaluated the effects of long-term treatment with the angiotensin-converting enzyme inhibitor ramipril and vitamin E on atherosclerosis progression in high-risk patients.

Methods and Results—A total of 732 patients ≥55 years of age who had vascular disease or diabetes and at least one other risk factor and who did not have heart failure or a low left ventricular ejection fraction were randomly assigned to receive ramipril 2.5 mg/d or 10 mg/d and vitamin E (RRR- α -tocopheryl acetate) 400 IU/d or their matching placebos. Average follow-up was 4.5 years. Atherosclerosis progression was evaluated by B-mode carotid ultrasound. The progression slope of the mean maximum carotid intimal medial thickness was 0.0217 mm/year in the placebo group, 0.0180 mm/year in the ramipril 2.5 mg/d group, and 0.0137 mm/year in the ramipril 10 mg/d group ($P=0.033$). There were no differences in atherosclerosis progression rates between patients on vitamin E and those on placebo.

Conclusions—Long-term treatment with ramipril had a beneficial effect on atherosclerosis progression. Vitamin E had a neutral effect on atherosclerosis progression. (*Circulation*. 2001;103:919-925.)

Key Words: atherosclerosis ■ angiotensin ■ carotid arteries ■ ultrasonics

Experimental and epidemiological data suggest that activation of the renin-angiotensin-aldosterone system and oxidative modification of LDL cholesterol play important roles in atherogenesis and that prolonged angiotensin-converting enzyme (ACE) inhibition and antioxidant vitamin E therapy may be beneficial.^{1,2} To date, only limited data exist from randomized clinical trials evaluating the impact of these interventions on human atherosclerosis. Therefore, we conducted a prospective, randomized, clinical trial that assessed the effects of ramipril and of vitamin E on atherosclerosis. The Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamin E (SECURE) is a substudy of the Heart Outcomes Prevention Evaluation (HOPE) trial, which included 9541 patients and evaluated the impact of these interventions on clinical outcomes.^{3,4}

Methods

The study design and baseline characteristics have been described in detail previously.⁵ A brief summary follows.

Patients

HOPE and its substudy SECURE enrolled subjects at a high risk for cardiovascular events.³⁻⁵ Patients were recruited between December 1993 and August 1995 from 6 Canadian centers that were selected based on expertise in B-mode carotid ultrasound (CUS) at 2 centers or proximity to these 2 centers, which performed all CUS examinations in all study patients. Patients were eligible if they were ≥55 years old, had vascular disease or diabetes and at least one additional cardiovascular risk factor, and adequate baseline CUS examinations. Adequate CUS examinations were defined throughout the study as those allowing reliable measurements from a minimum of 4 predefined carotid arterial segments. Exclusion criteria included heart failure, known low left ventricular ejection fraction (<0.40%), myocardial infarction, unstable angina or stroke within 1 month before study enrollment, use of an ACE inhibitor or vitamin E, uncontrolled hypertension (defined as a blood pressure [BP] >160/90 mm Hg), overt nephropathy, or major illness expected to affect trial participation. All patients provided written, informed consent, and the study protocol was approved by the Research Ethics Board of each participating center.

Study Design, Randomization, Interventions, and Follow-up

SECURE is a randomized, double-blind trial with parallel groups and a 3×2 factorial design. Initial assessment, including first

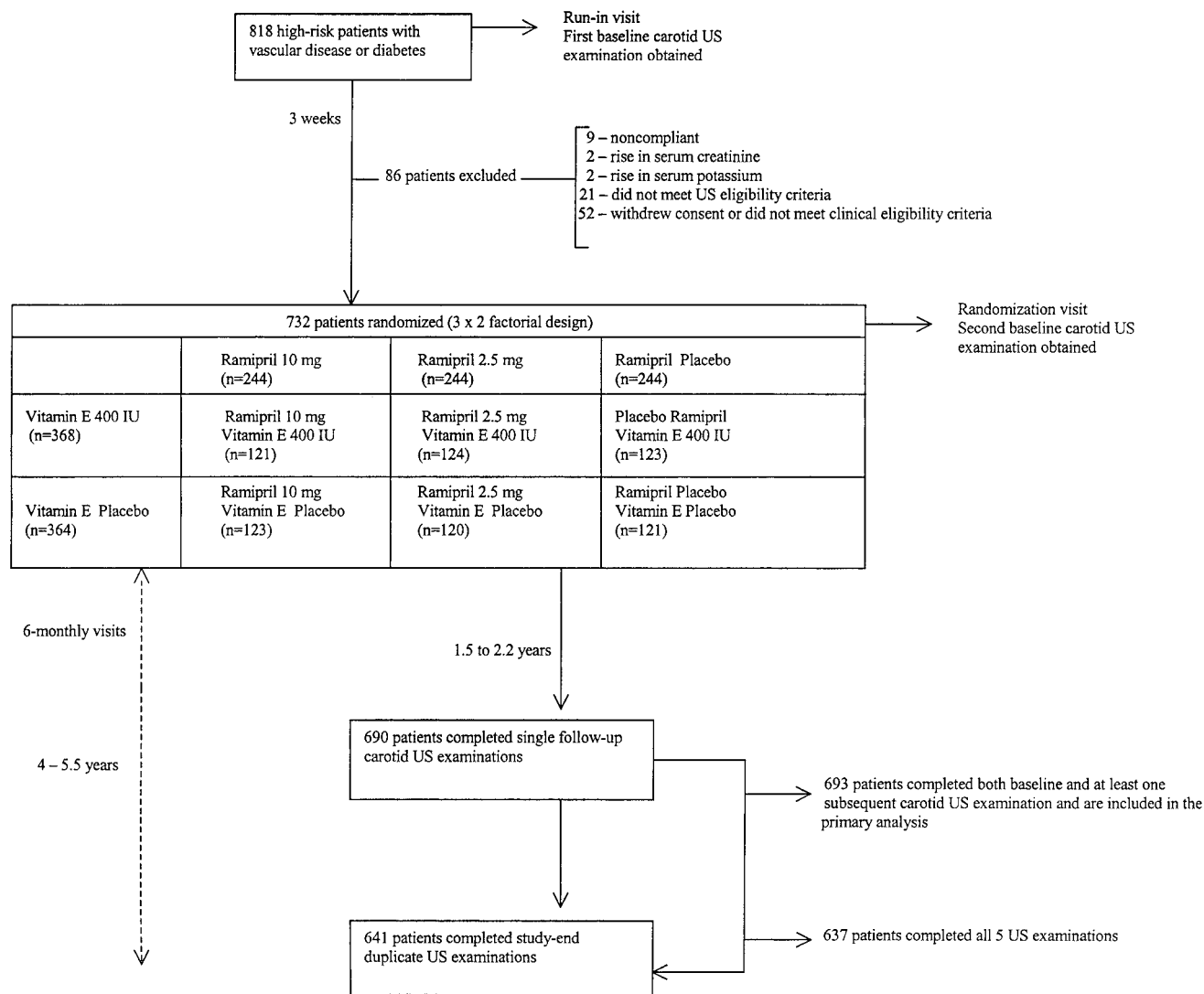
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Trial profile. US indicates ultrasound.

baseline CUS examination, was performed at the eligibility and run-in visit (Figure). Eligible patients entered a run-in period on active ramipril 2.5 mg/d (single-blind) for 7 to 10 days. This was followed by a serum creatinine and potassium measurement and by 10 to 14 days of ramipril placebo. Of the 818 patients who entered the run-in period, 86 patients were excluded from the trial within 3 weeks, and the remaining 732 patients were randomly assigned to ramipril 10 mg/d or ramipril 2.5 mg/d and to natural-source vitamin E (RRR- α -tocopheryl acetate) 400 IU/d or their matching placebos and had a second baseline CUS examination. For the ramipril 10 mg/d arm of the study, forced titration to the target dose or highest tolerated dose or matching placebo was performed over a 1-month period.

Follow-up visits occurred 1 month after randomization and every 6 months thereafter. All study-end visits and CUS examinations were completed by July 1, 1999. Systolic and diastolic BP were measured by experienced study nurses at randomization, 1 month, 2 years, and at study end using a standard sphygmomanometer and a standardized protocol (all study visits occurred during morning hours while study drug was taken in the evening, use of appropriate cuff size was ensured, and patients were supine for ≥ 5 minutes, thereafter 2 exact readings avoiding rounding were obtained from each arm, and the lowest readings from the right and the left arms were averaged).

B-mode CUS

Duplicate CUS examinations (maximum, 3 weeks apart) were performed at baseline and at study end 4 to 5 years (median, 4.5 years) after randomization, and a single follow-up CUS examination was obtained 1.5 to 2.2 years after randomization. The CUS methods have been reviewed in detail.⁵ High-frequency CUS imaging was performed by 3 trained and certified sonographers. Standardized CUS scanning and reading protocols were used.^{6,7} A circumferential longitudinal scan was performed to record the maximum intimal medial thickness (IMT) in each of 12 carotid artery segments (1-cm long), which were defined relative to the carotid flow divider as the near and far walls of the internal, bifurcation, and common left and right carotid arteries. All CUS measurements were performed by 2 certified readers who were unaware of treatment assignment. For each patient, the mean maximum IMT was computed as the average of the segment maximum IMTs across the 12 carotid arterial segments. The difference in the mean maximum IMT between the 732 paired baseline CUS examinations was 0.014 ± 0.17 mm, the mean absolute difference was 0.12 ± 0.11 mm, Pearson's correlation coefficient (r) was 0.87, and the intraclass correlation coefficient was 0.87. At study end, the mean difference in the mean maximum IMT between 641 paired CUS examinations was 0.004 ± 0.09 mm, the mean absolute difference was 0.06 ± 0.06 mm, r was 0.97, and the

intraclass correlation coefficient was 0.97. Detailed between- and within-sonographer and reader reproducibility assessments showed high reproducibility and absence of temporal drifts in reading.

Study Outcomes

The primary study outcome was the annualized progression slope of the mean maximum IMT. The secondary outcome was the annualized progression slope of the single maximum IMT among any of the 12 carotid segments. Clinical outcomes were recorded and analyzed as part of the HOPE study, which was adequately powered to evaluate the effect of the study interventions on clinical events.

Statistical Analysis

All analyses were by intention-to-treat and were done in SAS 6.12. There was no significant interaction between the study treatments for the primary or secondary CUS outcomes ($P=0.90$ and $P=0.61$, respectively, for interaction terms in the ANOVA models). Therefore, analyses were done to compare differences between ramipril overall and at each of the 2 doses versus ramipril placebo and between vitamin E versus vitamin E placebo. Baseline characteristics were compared by 1-way ANOVA and χ^2 tests as appropriate. The slopes of the mean maximum IMT and the single maximum IMT were computed for each patient from all serial CUS data by least-squares regression (after verifying the absence of significant deviations from linearity). The overall effect of ramipril, the effect of each dose of ramipril (2.5 and 10 mg/d), and the effect of vitamin E were analyzed by ANOVA, with the slope of the mean maximum IMT as the dependent variable and treatment assignment as the independent variables. Analyses adjusted for systolic and diastolic BP changes and with multivariate adjustment for variables found to influence the slope of the mean maximum IMT on univariate analysis, for imbalances in baseline variables, and for important design variables were performed by ANCOVA. Dunnett's test for comparison of multiple treatments against one control was used to adjust the level of statistical significance in the comparisons of the 2 doses of ramipril versus ramipril placebo.⁸ The prespecified primary analysis included all patients with an evaluable slope, ie, those who had completed the duplicate baseline CUS examinations and at least one subsequent examination.

Results

Baseline Characteristics, Follow-up, and Compliance

There were no differences in the baseline characteristics between the active treatment groups and their respective placebos, with the exception of smoking history, which was more common in the active vitamin E group (Table 1). The baseline characteristics of the 693 patients in the final primary analysis were similar.

Clinical follow-up was complete in all study patients. An adequate follow-up CUS examination was obtained in 690 patients 1.5 to 2.2 years after randomization. Of the initial 732 patients, 17 had died, 15 missed the follow-up CUS examination due to illness, and 10 moved, refused repeat CUS, or did not have a technically adequate examination. Three additional patients who did not complete the follow-up CUS examination had adequate study-end CUS studies. Therefore, the primary study analysis included 693 patients (95% of all randomized patients and 97% of randomized patients alive at the time of the first follow-up CUS assessment). Of these, 637 had completed all 5 scheduled CUS examinations (87% of all randomized patients and 95% of those alive at study end; Figure).

Compliance with study treatments is shown in Table 2. Only cough was a more common cause of permanent discontinuation of study drug in the active ramipril groups than in

the placebo group (1.6% in the ramipril placebo, 9.0% in the ramipril 2.5 mg/d, and 9.8% in the ramipril 10 mg/d groups). Vitamin E caused no significant side effects.

BP Changes

The mean BP at study entry was 132/76 mm Hg in all study groups. Both active ramipril groups reduced systolic and diastolic BP versus ramipril placebo, but there were no significant differences in BP changes between the ramipril 2.5 mg/d and 10 mg/d groups (Table 3). Vitamin E had no significant effect on BP.

Changes in Ultrasonographically Determined Carotid Atherosclerosis Progression

Among all baseline variables and relevant interaction terms, those found to influence the mean maximum IMT slope on univariate analysis were the baseline mean maximum IMT ($P=0.0002$), a history of high total cholesterol ($P=0.0002$) or of low HDL cholesterol ($P=0.008$), total and LDL cholesterol concentrations ($P=0.03$ and $P=0.01$, respectively), and treatment assignment to ramipril 10 mg/d ($P=0.028$). In the multivariate model, only baseline mean maximum IMT ($P<0.001$), history of dyslipidemia ($P=0.005$), and treatment assignment to ramipril 10 mg/d ($P=0.046$) were independent predictors of the mean maximum IMT slope.

The main study results are summarized in Table 4. Because the number of nonquantifiable carotid artery segments was low (average 5%), the primary study analysis was performed without imputation for missing CUS data. There was an overall effect of ramipril, which reduced the annualized slope of the mean maximum IMT versus ramipril placebo ($P=0.033$), and there was a strong trend for benefit in the ramipril 10 mg/d group versus ramipril placebo ($P=0.028$; Dunnett's correction for multiple comparisons results in an adjustment in the level of statistical significance to $P=0.027$).

We tested the robustness of our findings by additional analyses. In the analysis of 711 patients, including those in the primary analysis and an additional 18 with early death, debilitating myocardial infarction, or stroke who did not have a follow-up CUS and for whom rapid atherosclerosis progression (defined as the highest 10th percentile of the mean maximum IMT of the entire SECURE study population) was assumed, there was a reduced atherosclerosis progression rate for ramipril overall versus ramipril placebo ($P=0.019$, $P=0.027$ when controlling for BP changes, and $P=0.027$ after multivariate adjustment) and for the ramipril 10 mg/d group versus ramipril placebo ($P=0.015$, $P=0.022$ when controlling for BP changes, and $P=0.031$ after multivariate adjustment). Similar trends were noted in the analyses of the 637 study patients who completed all 5 CUS examinations ($P=0.068$ for the overall effect of ramipril versus ramipril placebo and $P=0.055$ for ramipril 10 mg/d versus ramipril placebo) and for the secondary CUS outcome measurement, the progression slope of the single maximum IMT. The absolute difference for this outcome between the ramipril 10 mg/d and the placebo groups was greater than that observed for the mean maximum IMT slope, but it did not reach statistical significance due to the greater variability of this

TABLE 1. Baseline Characteristics

	Ramipril			Vitamin E	
	Placebo (n=244)	2.5 mg/d (n=244)	10 mg/d (n=244)	Placebo (n=364)	Active (n=368)
Age, y	65.6±6.8	65.6±6.5	65.2±6.2	65.7±6.6	65.0±6.4
Female sex, %	21	27	24	24	23
BP, mm Hg	132±17/75±9	132±17/76±10	132±15/76±9	132±17/76±9	132±16/76±9
Heart rate, bpm	66±11	66±11	66±11	66±11	66±11
Body mass index, kg/m ²	28±4	28±4	28±4	28±5	28±5
History, %					
Coronary artery disease	85	87	81	85	84
Myocardial infarction	55	58	57	58	55
Stable angina pectoris	64	65	54	62	60
Unstable angina pectoris	34	34	30	34	32
Stroke or TIA	10	7	12	10	10
Peripheral vascular disease	42	39	38	37	41
Hypertension	34	35	40	35	37
Diabetes	35	32	35	32	36
Smoking					
Current	9	10	10	9	11
Current or former	74	75	76	70	80*
Elevated total cholesterol	48	46	47	46	48
Low HDL cholesterol	18	16	19	18	17
Medications, %					
β-Blockers	43	40	44	43	42
ASA/antiplatelet agents	86	85	82	85	83
Lipid-lowering agents	35	39	29	37	32
Diuretics	8	11	9	10	8
Calcium-channel blockers	44	43	40	40	45
Vitamin C	8	10	11	9	11
Beta carotene	1	1	2	1	2
Multivitamins	11	12	6	10	9
Hormone replacement therapy†	2	3	3	3	3
Laboratory tests, mmol/L					
Total cholesterol	5.3±1.2	5.3±1.0	5.3±1.0	5.3±1.0	5.3±1.1
Triglycerides	2.2±1.3	2.2±1.3	2.2±1.3	2.2±1.4	2.2±1.2
HDL cholesterol	1.0±0.3	1.0±0.3	0.9±0.3	0.9±0.3	1.0±0.3
LDL cholesterol	3.5±1.1	3.5±1.1	3.4±0.8	3.3±0.8	3.5±1.0
Carotid IMT, mm					
Mean maximum IMT	1.1462±0.34	1.1477±0.34	1.1603±0.32	1.1463±0.33	1.1564±0.33
Single maximum IMT	2.2653±0.92	2.2559±0.84	2.2678±0.79	2.2883±0.89	2.2379±0.81

Values are mean±SD or percent. TIA indicates transient ischemic attack; ASA, acetyl salicylic acid (aspirin).

* $P<0.05$.

†In women.

measurement. In the analysis of the 637 patients who completed all 5 CUS examinations, ramipril had a highly significant effect on the single maximum IMT slope ($P=0.003$ for the overall effect of ramipril versus placebo and $P=0.008$ for ramipril 10 mg/d versus placebo).

Vitamin E had a neutral effect on the primary and secondary CUS outcome measurements.

Clinical Outcomes

As expected in this relatively small substudy, there were no significant differences in the primary clinical outcome (the composite of cardiovascular death, myocardial infarction, and stroke), which occurred in 41 patients (16.8%) in the ramipril placebo, 34 (13.9%) in the ramipril 2.5 mg/d, and 31 (12.7%) in the ramipril 10 mg/d groups and in 55

TABLE 2. Compliance

Year	Ramipril*			Vitamin E†	
	Placebo	2.5 mg/d	10 mg/d	Placebo	Active
1	93	88	85	94	95
2	85	80	79	91	95
3	81	76	74	90	90
4	76	73	69	89	88
Study End	72	71	67	86	90

Values are percentages of patients taking >80% of study medications.

*Use of open-label ACE inhibitor any time during the study was 15.7% in the ramipril placebo, 13.5% in the ramipril 2.5 mg/d, and 13.3% in the ramipril 10 mg/d group.

†Use of open-label vitamin E at any time during the study was 6.2% in the placebo group and 5.5% in the active group.

patients (15.1%) in the vitamin E placebo and 51 (13.9%) in the active vitamin E groups. Reliable data on clinical outcomes are provided by the adequately powered parent HOPE study.^{3,4}

Discussion

The SECURE trial shows that long-term ACE inhibitor therapy retards the progression of human atherosclerosis, whereas vitamin E has a neutral effect.

The method used to evaluate treatment effects on atherosclerosis, B-mode CUS, is well-validated and has been increasingly used in clinical trials. It is a highly reproducible technique, which correlates with risk factors for coronary artery disease and with prevalent and incident coronary disease and stroke.⁹ Previous studies used various ultrasound instrumentation, scanning and reading procedures, and outcome measurements. We selected the change in the aggregate mean maximum IMT from 12 carotid arterial segments as the primary outcome in SECURE, because this aggregate measurement was shown to correlate best with angiographic coronary artery disease¹⁰ and to be sensitive to the detection of changes related to treatment effects.¹¹ We used measurements of segment maximum rather than segment mean IMT, because this approach minimizes missing data, focuses on the most diseased regions, and results in very stable measurements when averaged across the 12 arterial segments.^{7,11} The

CUS scanning and reading protocols have been extensively validated,^{6,7} and we achieved high measurement reproducibility.

Treatment with ramipril resulted in reduced atherosclerosis progression rates. This effect was noted in high-risk patients, the majority of whom were already on effective therapies, including aspirin (84%), lipid-lowering agents (34%), β -blockers (43%), diuretics (9%), nitrates (32%), and calcium-channel blockers (43%). Although the absolute differences in atherosclerosis progression rates between ramipril- and placebo-treated patients are small, the relative reduction in mean maximum IMT was 37% for ramipril 10 mg/d versus placebo, which is similar to the 32% reduction in the risk of stroke in HOPE. Similar magnitudes of change on atherosclerosis progression have been demonstrated in trials of cholesterol lowering, and they were associated with impressive reductions in clinical events, suggesting a stabilizing effect on the underlying disease process. The study was not powered to compare the 2 doses of ramipril. However, there was a trend suggesting a dose-dependent effect, with highest benefit in the ramipril 10 mg/d study group. Ramipril 10 mg/d is also the dose used in the large parent HOPE trial, where it had very clear benefits on a range of clinical end points.³

Ramipril had only a modest BP lowering effect in our study, because most study patients did not have a history of hypertension or had well-controlled BP; other antihypertensive and antianginal drugs were frequently used (>75% of patients). The beneficial effect of ramipril on atherosclerosis remained statistically significant after adjusting for a history of hypertension and for BP changes, suggesting the benefit is not fully explained by BP lowering and may be related to a direct vascular protective effect.

Increased tissue ACE activity has been demonstrated in human coronary artery lesions,¹² and long-term ACE inhibition has been shown to reduce atherosclerotic lesion area in the aorta, carotid, and coronary arteries in normotensive animal models of atherosclerosis.^{13,14} These antiatherogenic properties may be related both to the inhibition of tissue and circulating angiotensin II formation and to bradykinin potentiation, resulting in decreased proliferation and migration of smooth muscle cells, decreased accumulation and activation

TABLE 3. Systolic and Diastolic BP in the Ramipril Groups at Baseline and in Follow-up

	Baseline	1 Month	2 Years	Study End	Mean Change
Systolic BP, mm Hg					
Placebo	131.6 \pm 17.1	130.4 \pm 17.9	130.0 \pm 15.8	134.1 \pm 16.9	0.1 \pm 12.2
Ramipril 2.5 mg/d	131.7 \pm 17.0	126.1 \pm 17.0*	125.2 \pm 15.6*	130.8 \pm 16.7‡	-4.6 \pm 13.5*
Ramipril 10 mg/d	131.9 \pm 15.3	127.1 \pm 14.8‡	125.9 \pm 16.8‡	130.5 \pm 16.6‡	-4.1 \pm 12.4*
Diastolic BP, mm Hg					
Placebo	75.4 \pm 8.7	76.4 \pm 9.6	74.8 \pm 9.8	73.4 \pm 8.7	-0.4 \pm 7.3
Ramipril 2.5 mg/d	76.4 \pm 9.3	74.4 \pm 9.3*	73.0 \pm 9.6‡	72.7 \pm 9.0	-2.9 \pm 7.9*
Ramipril 10 mg/d	76.2 \pm 9.2	74.8 \pm 8.7‡	72.6 \pm 9.1*	72.6 \pm 8.9	-2.8 \pm 7.6*

Values are mean \pm SD.

* P <0.001; † P <0.01; ‡ P <0.05 for changes in BP from baseline compared with placebo; * P <0.001 for mean BP changes compared with placebo. There were no significant differences in BP changes between the 2 active ramipril groups.

TABLE 4. Progression Slopes for the Primary and Secondary CUS Outcome Measurements by Treatment Assignment in 693 Patients With an Evaluable Slope*

CUS Measurement	Ramipril†			Vitamin E	
	Placebo (n=227)	2.5 mg/d (n=232)	10 mg/d (n=234)	Placebo (n=344)	Active (n=349)
Mean maximum IMT slope	0.0217±0.0027	0.0180±0.0026	0.0137±0.0024‡	0.0174±0.0020	0.0180±0.0022
Single maximum IMT slope	0.0281±0.0095	0.0280±0.0096	0.0073±0.0087	0.0141±0.0076	0.0277±0.0075

Values are in mm/year and are mean±SEM.

*The slopes of the mean maximum IMT (in mm/year) in the 6 randomization cells were as follows: double placebo, 0.0205±0.0039; vitamin E placebo/ramipril 2.5 mg/day, 1.0184±0.0035; vitamin E placebo/ramipril 10 mg/day, 0.0135±0.0030; vitamin E active/ramipril placebo, 0.0229±0.0038; vitamin E active/ramipril 2.5 mg/day, 0.0175±0.0039; vitamin E active/ramipril 10 mg/day, 0.01385±0.0038. *P*=0.18 for vitamin E placebo/ramipril 10 mg/day (n=115) vs double placebo (n=114).

†Ramipril reduced the slope of the mean maximum IMT at *P*=0.033 (*P*=0.043 after adjustment for systolic and diastolic BP changes and *P*=0.046 after multivariate adjustment [for age, sex, baseline IMT, history of high total or low HDL cholesterol, history of smoking, use of cholesterol-lowering drugs, history of hypertension, BP changes, and baseline total and LDL cholesterol concentrations]).

‡*P*=0.028 for ramipril 10 mg/d vs placebo (*P*=0.037 after adjustment for BP changes and *P*=0.046 after multivariate adjustment).

of inflammatory cells, decreased oxidative stress, and increased endothelial nitric oxide formation, leading to improved endothelial function.¹

Previous randomized clinical trials evaluating the effects of ACE inhibition on human atherosclerosis include the angiographic substudy of the Quinapril Ischemic Event Trial (QUIET), the Simvastatin/Enalapril Coronary Atherosclerosis (SCAT) study, and the Prevention of Atherosclerosis with Ramipril Trial (PART-2).^{15–17} Two of these studies, QUIET and SCAT, used coronary angiography and reported no overall benefit with quinapril and enalapril, respectively, although in a subgroup analysis of QUIET, quinapril-treated patients with elevated LDL cholesterol had a reduced progression of coronary atherosclerosis. Differences in the results of SECURE and these studies may be related to the specific ACE inhibitor used, the ACE inhibitor dose, the study design, and the methods used for the assessment of atherosclerosis progression. The CUS measurements used in SECURE focus on the arterial wall and may be more sensitive than angiography. In PART-2, ramipril 5 to 10 mg/d had no effect on CUS IMT measurements; however, this study only evaluated changes in the mean far wall IMT of the common carotid arteries. The use of the aggregate IMT measurement in SECURE, which is derived from common, bifurcation, and internal carotid artery segments, may be more sensitive to change¹¹ and may account for the apparent differences in the results of these 2 trials.

Natural-source vitamin E 400 IU/d had a neutral effect on atherosclerosis progression. Compliance with vitamin E was high, the use of other nonstudy antioxidant vitamins was low, and the study was adequately powered to demonstrate a moderate treatment effect (80% power to detect a 48% reduction and 50% power to detect a 33% reduction in the primary outcome). Our original sample size calculation assumed a higher IMT progression rate based on the data available at the time of the study design. Therefore, a smaller treatment effect with vitamin E cannot be fully excluded.

We did not measure vitamin E levels or the effects of vitamin E on LDL oxidation in the SECURE trial. Previous studies have demonstrated, however, that natural-source vitamin E 400 IU/d leads to significant elevations in plasma and tissue levels of α -tocopherol and that similar or lower doses

can increase LDL resistance to oxidation^{18,19}; similar findings on LDL oxidation were observed in a separate substudy of HOPE (R. Hoeschen, MD, personal communication, 2000). Furthermore, the main aim of our study was to evaluate the effects of vitamin E supplementation, a therapy used by millions worldwide without knowledge of oxidative status.

Experimental data suggest an important role for the oxidation of LDL cholesterol in atherogenesis, and vitamin E is an efficient antioxidant that has been shown to reduce atherosclerosis in animal models,^{2,20} although these data are not fully consistent.²¹ An observational study reported reduced coronary atherosclerosis progression in individuals taking vitamin E supplements,²² and large epidemiological studies also suggest a cardioprotective effect of vitamin E. The Cambridge Heart Antioxidant Study showed a reduction in nonfatal events in patients treated with vitamin E after myocardial infarction,²³ but there was a trend toward increased mortality, and several larger, randomized clinical trials of longer duration failed to confirm benefits.^{4,24} To date, there are only limited data from randomized trials on the effects of vitamin E on atherosclerosis. A small study in 15 individuals with homozygous familial hypercholesterolemia found rapid progression of carotid IMT in vitamin E–treated subjects but regression of disease with statins.²⁵ Preliminary reports from the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study indicate no beneficial effect on carotid IMT changes with vitamin E alone or combined vitamin E and C supplementation in women, but a beneficial effect of combined therapy in hypercholesterolemic men who smoke.²⁶

The results of the SECURE trial on atherosclerosis are concordant with the results of the HOPE trial on clinical events. In conjunction, these studies demonstrate that ramipril reduces atherosclerosis progression and prevents major vascular events. By contrast, vitamin E administered for 4 to 6 years does not have a significant impact on atherosclerosis or on clinical events. The role of vitamin E alone or in combination with other antioxidants in various patient groups requires further investigation.

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References

1. Lonn EM, Yusuf S, Jha P, et al. Emerging role of angiotensin-converting enzyme inhibitors in cardiac and vascular protection. *Circulation*. 1994;90:2056–2069.
2. Steinberg D, Parthasarathy S, Carew TE, et al. Beyond cholesterol: modifications of low-density lipoprotein that increase its atherogenicity. *N Engl J Med*. 1989;320:915–924.
3. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on death from cardiovascular causes, myocardial infarction, and stroke in high-risk patients. *N Engl J Med*. 2000;342:145–153.
4. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of long-term vitamin E supplementation on cardiovascular events in 9541 high-risk persons. *N Engl J Med*. 2000;342:154–202.
5. Lonn EM, Yusuf S, Doris CI, et al. Study design and baseline characteristics of the Study to Evaluate carotid Ultrasound changes in patients treated with Ramipril and vitamin E (SECURE). *Am J Cardiol*. 1996;78:914–919.
6. Riley WA, Barnes RW, Applegate WB, et al. Reproducibility of noninvasive ultrasonic measurement of carotid atherosclerosis: the Asymptomatic Carotid Artery Plaque Study. *Stroke*. 1992;23:1062–1068.
7. Pitt B, Byington RP, Furberg CD, et al. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation*. 2000;102:1503–1510.
8. Dunnett CW. A multiple comparisons procedure for comparing several treatments with a control. *J Am Stat Assoc*. 1955;50:1096–1121.
9. O'Leary DH, Polak JF, Kronmal RA, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med*. 1999;340:14–22.
10. Crouse JR, Craven TE, Hagaman AP, et al. Association of coronary artery disease with segment-specific intimal-medial thickening of the extracranial carotid artery. *Circulation*. 1995;92:1141–1147.
11. Espeland MA, Craven TE, Riley WA, et al. Reliability of longitudinal ultrasonographic measurements of carotid intimal-medial thickness. *Stroke*. 1996;27:480–485.
12. Diet F, Pratt RE, Berry GJ, et al. Increased accumulation of tissue ACE in human atherosclerotic coronary artery disease. *Circulation*. 1996;94:2756–2767.
13. Chobanian AV, Haudenschild CC, Nickerson C, et al. Antiatherogenic effect of captopril in the Watanabe heritable hyperlipidemic rabbit. *Hypertension*. 1990;15:327–331.
14. Aberg G, Ferrer P. Effects of captopril on atherosclerosis in cynomolgus monkeys. *J Cardiovasc Pharmacol*. 1990;15:S65–S72.
15. Cashin-Hemphill L, Holmvang G, Chan RC, et al. Angiotensin-converting enzyme inhibition as antiatherosclerotic therapy: no answer yet: Quinapril Ischemic Event Trial. *Am J Cardiol*. 1999;83:43–47.
16. Teo KK, Burton JR, Buller CE, et al. Long term effects of cholesterol lowering and angiotensin-converting enzyme inhibition on coronary atherosclerosis: the Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT). *Circulation*. 2000;102:1748–1754.
17. MacMahon S, Sharpe N, Gamble G, et al. Randomized, placebo-controlled trial of the angiotensin converting enzyme inhibitor, ramipril, in patients with coronary or occlusive arterial disease. *J Am Coll Cardiol*. 2000;36:438–443.
18. Burton GW, Traber MG, Acuff RV, et al. Human plasma and tissue α -tocopherol concentrations in response to supplementation with deuterated natural and synthetic vitamin E. *Am J Clin Nutr*. 1998;67:669–684.
19. Devaraj S, Adams-Huet B, Fuller CJ, Jialal I. Dose-response comparison of RRR- α -tocopherol and all-racemic α -tocopherol on LDL oxidation. *Arterioscler Thromb Vasc Biol*. 1997;17:2273–2279.
20. Verlangieri AJ, Busch MJ. Effects of *d*- α -tocopherol supplementation on experimentally induced primate atherosclerosis. *J Am Coll Nutr*. 1992;11:131–138.
21. Godfried SL, Combs GF, Saroka JM, et al. Potentiation of atherosclerotic lesions in rabbits by a high dietary level of vitamin E. *Br J Nutr*. 1989;61:607–617.
22. Hodis HN, Mack WJ, LaBree L, et al. Serial coronary angiographic evidence that antioxidant vitamin intake reduces progression of coronary atherosclerosis. *JAMA*. 1995;85:1483–1492.
23. Stephens NG, Parsons A, Schofield PM, et al. Randomized controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). *Lancet*. 1996;347:781–776.
24. GISSI-Prevenzione trial. Dietary supplementation with *n*-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet*. 1999;354:447–445.
25. Raal FJ, Pilcher GJ, Veller MG, et al. Efficacy of vitamin E compared with either simvastatin or atorvastatin in preventing the progression of atherosclerosis in homozygous familial hypercholesterolemia. *Am J Cardiol*. 1999;84:1344–1346.
26. Salonen JT, Nyyssönen K, Salonen R, et al. Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study: a randomized study of the effects of vitamins E and C on 3-year progression of carotid atherosclerosis. *J Intern Med*. 2000;248:377–386.