Effects of Hormone Replacement Therapy and Antioxidant Vitamin Supplements on Coronary Atherosclerosis in Postmenopausal Women

A Randomized Controlled Trial

David D. Waters, MD
Edwin L. Alderman, MD
Judith Hsia, MD
Barbara V. Howard, PhD
Frederick R. Cobb, MD
William J. Rogers, MD
Pamela Ouyang, MD
Paul Thompson, MD
Jean Claude Tardif, MD
Lyall Higginson, MD
Vera Bittner, MD
Michael Steffes, MD, PhD
David J. Gordon, MD, PhD
Michael Proschan, PhD
Naji Younes, PhD
Joel I. Verter, PhD

Context Hormone replacement therapy (HRT) and antioxidant vitamins are widely used for secondary prevention in postmenopausal women with coronary disease, but no clinical trials have demonstrated benefit to support their use.

Objective To determine whether HRT or antioxidant vitamin supplements, alone or in combination, influence the progression of coronary artery disease in postmenopausal women, as measured by serial quantitative coronary angiography.

Design, Setting, and Patients The Women's Angiographic Vitamin and Estrogen (WAVE) Trial, a randomized, double-blind trial of 423 postmenopausal women with at least one 15% to 75% coronary stenosis at baseline coronary angiography. The trial was conducted from July 1997 to January 2002 in 7 clinical centers in the United States and Canada.

Interventions Patients were randomly assigned in a 2×2 factorial design to receive either 0.625 mg/d of conjugated equine estrogen (plus 2.5 mg/d of medroxyprogesterone acetate for women who had not had a hysterectomy), or matching placebo, and 400 IU of vitamin E twice daily plus 500 mg of vitamin C twice daily, or placebo.

Main Outcome Measure Annualized mean (SD) change in minimum lumen diameter (MLD) from baseline to concluding angiogram of all qualifying coronary lesions averaged for each patient. Patients with intercurrent death or myocardial infarction (MI) were imputed the worst rank of angiographic outcome.

Results The mean (SD) interval between angiograms was 2.8 (0.9) years. Coronary progression, measured in mean (SD) change, worsened with HRT by 0.047 (0.15) mm/y and by 0.024 (0.15) mm/y with HRT placebo ($P=.17$); and for antioxidant vitamins by 0.044 (0.15) mm/y and with vitamin placebo by 0.028 (0.15) mm/y ($P=.32$). When patients with intercurrent death or MI were included, the primary outcome showed an increased risk for women in the active HRT group ($P=.045$), and suggested an increased risk in the active vitamin group ($P=.09$). Fourteen patients died in the HRT group and 8 in the HRT placebo group (hazard ratio [HR], 1.8; 95% confidence interval [CI], 0.75-4.3), and 16 in the vitamin group and 6 in the vitamin placebo group (HR, 2.8; 95% CI, 1.1-7.2). Death, nonfatal MI, or stroke occurred in 26 HRT patients vs 15 HRT controls (HR, 1.9; 95% CI, 0.97-3.6) and in 26 vitamin patients and 18 vitamin controls (HR, 1.5; 95% CI, 0.80-2.9). There was no interaction between the 2 treatment interventions.

Conclusion In postmenopausal women with coronary disease, neither HRT nor antioxidant vitamin supplements provide cardiovascular benefit. Instead, a potential for harm was suggested with each treatment.

JAMA. 2002;288:2432-2440 www.jama.com

IN NUMEROUS OBSERVATIONAL STUDIES over the past 30 years, postmenopausal estrogen replacement therapy, with or without a progestin, has been consistently associated with a reduced risk of coronary events, both in women with and without evidence of coronary disease.[1-5] Estrogen exerts beneficial effects on blood lipids, low-density lipoprotein (LDL) oxidation, vascular function, and on some aspects of the coagulation system.[6] Yet hormone replacement therapy (HRT) was not shown to be beneficial in the only 2 randomized, placebo-controlled trials of postmenopausal women with coronary disease.[7-9] Furthermore, the only large primary prevention trial of HRT re-

Author Affiliations are listed at the end of this article. **Corresponding Author and Reprints:** David D. Waters, MD, Division of Cardiology, Room 5G1, San Francisco General Hospital, 1001 Potrero Ave, San Francisco, CA 94110 (e-mail: dwaters@medsfgh.ucsf.edu).

ported to date, the Women's Health Initiative, was stopped prematurely because overall risk exceeded benefit, including an increased risk of nonfatal myocardial infarction (MI) and coronary death, which was the study's primary outcome.[10] As a result of this discrepancy between clinical trial results and other evidence, guidelines do not offer consistent, explicit recommendations for the use of this therapy in postmenopausal women.[11]

Like HRT, antioxidant consumption, either dietary or in the form of vitamin supplements, has been associated with a reduced risk of coronary disease in epidemiological studies.[12-16] In a coronary angiographic trial, participants who took supplemental vitamin E (not as part of the trial) demonstrated less lesion progression.[17] Theoretically, antioxidants inhibit a key component of atherogenesis (oxidation of LDL cholesterol within the vessel wall), and other mechanisms have been demonstrated in animal experiments, including preservation of nitric oxide activity, inhibition of leukocyte adhesion, reduction of cellular oxidative injury, and inhibition of platelet adhesion.[18]

Five randomized, placebo-controlled trials of vitamin E in patients with or at risk for coronary disease have been completed,[19-23] and all but the smallest and shortest[20] reported no benefit. Although the antioxidant effects of vitamins E and C may be synergistic, vitamin C was combined with vitamin E in only 1 of these trials.[23] In addition to inhibiting LDL oxidation through a variety of mechanisms, vitamin C also exhibits other anti-atherosclerotic effects in animal models.[24]

To study possible benefits left unexplored by previous studies, the Women's Angiographic Vitamin and Estrogen (WAVE) Trial tested the combination of relatively high doses of vitamins E and C. Patients were randomized to HRT and/or antioxidant vitamins in a placebo-controlled 2×2 factorial design. The study population consisted of postmenopausal women with documented coronary disease, and the end point was the change in minimum lumen diameter (MLD) of qualifying coronary lesions.

METHODS

Study Participants

Women were recruited between July 1997 and August 1999 at 7 clinical sites in the United States and Canada. The institutional review board at each site approved the study. The study design and methods have been reported previously.[25] Women were eligible if they provided informed consent, were postmenopausal, and if a coronary angiogram performed within 4 months of study entry (according to the study protocol) demonstrated 1 or more 15% to 75% coronary stenoses in an artery not subjected to intervention. The protocol also specified that if the angiogram was performed within 2 weeks of an MI, the qualifying segment could not be related to the infarct. Baseline films were reviewed by the Angiographic Core Laboratory (Stanford University, Stanford, Calif) to confirm angiographic eligibility. Postmenopausal status was defined as having had a bilateral oophorectomy at any age, being younger than 55 years old with a follicle-stimulating hormone level of 40 mIU/mL or higher, or being older than 55 years.

Major exclusion criteria were HRT use within 3 months; concurrent use of more than 60 mg/d of vitamins C or 30 IU/d of E and unwillingness to stop taking them; evidence of potential breast, uterine, or cervical cancer; uncontrolled diabetes or hypertension; MI within 4 weeks; prior or planned coronary artery bypass graft surgery; fasting levels of triglycerides higher than 500 mg/dL (5.65 mmol/L); creatinine level higher than 2.0 mg/dL (176.8 µmol/L); symptomatic gallstones; New York Heart Association class IV heart failure or a left ventricular ejection fraction known to be less than 25%; history of hemorrhagic stroke, bleeding diathesis, pulmonary embolus, idiopathic deep vein thrombosis; or untreated osteoporosis.

Randomization and Treatment

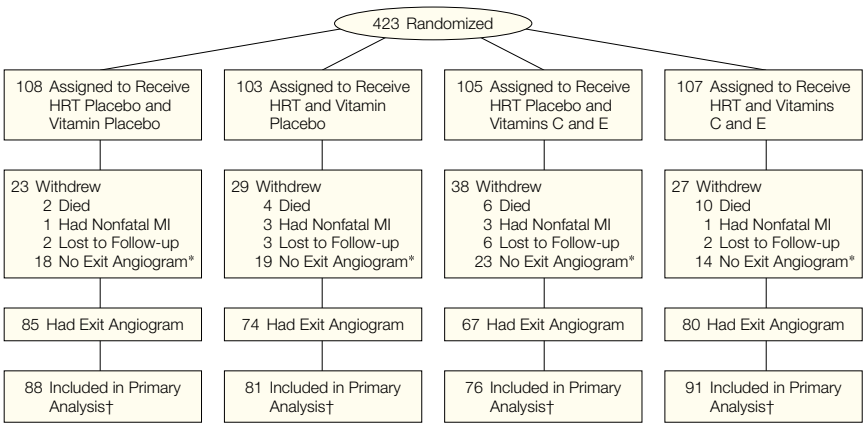
After enrollment, women were randomly assigned to 4 treatment groups of equal size stratified by clinical center and previous hysterectomy status (14 strata), using a permuted block design with fixed block sizes of 4. Women received 400 IU of vitamin E and 500 mg of vitamin C, or an identical-appearing placebo to be taken twice daily, with or without HRT. Women with a prior hysterectomy took 1 tablet containing conjugated equine estrogens (0.625 mg of Premarin; Wyeth Pharmaceuticals, Collegeville, Pa) or an identical placebo tablet daily; women who had not had a hysterectomy took 1 tablet containing conjugated equine estrogens and medroxyprogesterone acetate (0.625 mg/2.5 mg of Prempro, Wyeth Pharmaceuticals) or an identical placebo tablet daily.

Participants, the investigators at the central biochemistry and angiography laboratories, and staff at the clinical centers (except the clinic gynecologist when necessary) were blinded to treatment assignments. To preserve complete blinding of clinic staff, breast and gynecologic symptoms were evaluated and managed by a separate gynecologic coordinator and study gynecologist.

Follow-up Procedures

All women were contacted by telephone 1 month after randomization and returned to the clinic for a follow-up visit at 3 months. Clinic visits thereafter were scheduled for 6-month intervals until the end of the trial. At each visit, symptoms were assessed, interim medical history ascertained, and adherence to medication checked by tablet/capsule counts. The following measurements and examinations were performed at baseline and every 12 months: height, weight, blood pressure level, waist circumference-to-hip ratio, pelvic examination, Papanicolaou test, mammography, and physical examination. Quality of life was measured and blood for central analysis obtained at baseline, 18 months, and at the end of the study. Endometrial biopsy, or if not possible, transvaginal ultrasound, was performed 6 months after baseline for women who developed

Figure 1. Flow Diagram for WAVE Trial



Asterisk indicates most refused and some developed medical conditions that increased the risk of angiography. Dagger indicates the 30 women who died or experienced nonfatal myocardial infarction (MI) were assigned per protocol a worst score in the primary outcome analysis.

any bleeding while taking the study medication. The clinic gynecologist interpreted the results and consulted with the patient.

Clinical events were systematically captured to monitor safety. At each visit, study nurses asked each woman about any hospitalization and reported events were recorded on a study data collection form. Appropriate documentation was obtained for all protocol clinical events. Based on standard criteria,[9] 4 members of the steering committee who were blinded to the treatment assignment classified all potential MIs and deaths.

Study exit angiograms were scheduled and obtained a mean (SD) of 2.8 (0.9) years after the initial study (January 2001 through January 2002). We attempted to perform both the baseline and follow-up angiograms under similar, optimal conditions. Coronary injections were to be performed after the administration of 0.4 mg of sublingual or intracoronary nitroglycerin using nonionic contrast media and a 6F catheter or larger, and all coronary arteries were visualized in a minimum of 2 standardized orthogonal projections. Intercurrent angiograms done for clinical indications were reviewed to determine whether revascularization had been performed. These films were used for angiographic end-point analysis in patients for whom an exit angiogram could not be obtained. Clinically indicated coronary angiograms performed within 6 months before the scheduled exit angiogram were counted as the exit angiogram and not repeated unless a subsequent coronary event occurred.

Of the 423 women enrolled, 306 underwent a follow-up angiogram and did not die or have a nonfatal MI. Twenty-two women died, 8 had a nonfatal MI, 74 had their scheduled exit visit but did not have an exit angiogram, and 13 were recorded as lost to follow-up prior to their scheduled exit visit. Of these 13, five were known to be alive between randomization and 1 year, 3 between 1 and 2 years, and 5 between 2 and 3 years. The distribution of patients within these categories per treatment group is listed in FIGURE 1. Clinical status at the scheduled exit visit was known for all but 3% of the study cohort. Of the 30 women who died or had a MI, 14 had an intercurrent film.

Among the women with angiographic follow-up, those assigned to HRT took 67% of their prescribed medication according to pill counts, and those assigned to HRT placebo took 70%. The corresponding figures were both 84% for antioxidant vitamins and vitamin placebo. Nine women assigned to placebo estrogen crossed over to open-label estrogen, and 1 woman assigned to placebo vitamin supplements crossed over to open-label vitamins.

Angiographic Measurements

Angiographic core laboratory staff were blinded to treatment assignment. Computer-assisted quantitation of stenosis and segment dimensions was performed on cine film recordings using custom modified 35-mm cine projectors with an integrated megapixel digitizing camera, as previously described.[25,26] Angiograms recorded on CDs using the standard DICOM format provided direct digital imaging data. Angiographic images of individual lesions were selected from orthogonal views that best visualized the stenosis and that maximized the degree of stenosis for eccentric lesions. The factors influencing the choice of a specific frame were adequacy of vessel opacification, avoidance of vessel overlap, similarity of views between baseline and follow-up studies, and similar timing within the cardiac cycle.

For stenosis quantitation, the operator identified the lesion-containing segment length, the proximal and distal extent of the lesion, and the location of proximal and distal vessel diameter references, and outlined approximate vessel wall boundaries to facilitate computer quantitation. References were selected to be physiologically relevant to the lesion by identifying only those that are not separated from the stenosis by any substantial branch vessel. Dimensional calibration was based on contrast-filled catheter size as specified by the clinical sites. The quantitation program determined final vessel boundaries based on first and second derivative–edge-finding algorithms from which the MLD, mean lumen diameter, and percentage stenosis (based on available reference diameters) were computed. When remeasured by the same technician, the mean (SD) change in MLD was –0.004 (0.22) mm; when remeasured by a different technician, the change was 0.005 (0.081) mm.

Statistical Analyses

The sample size calculation, as previously described,[25] was based on the results of previous coronary angiographic trials that evaluated cholesterol-lowering therapy. Our sample size of 423 women would provide a power of approximately 90% to detect an effect size of at least 0.33 (corresponding to a change in MLD of approximately 0.1 mm), using a 2-tailed test and assuming that 20% of the women would not undergo a follow-up angiogram. The primary study end point (identified at the beginning of the trial) is based on change in the mean MLD of all qualifying segments of WAVE participants, and on the incidence of MI and death. Angiographic progression and clinical events analyzed separately were identified as secondary end points. WAVE qualifying segments were defined as segments with 15% to 75% stenoses at baseline or new lesions at follow-up. The annualized mean change in the MLD from baseline to concluding angiogram (or to intercurrent angiogram prior to revascularization) was calculated for all available WAVE qualifying lesions and averaged for each patient. The primary end point in the treated and control group was compared using a nonparametric rank test based on the Van der Waerden scores.[27] Patients with intercurrent death or MI were assigned the worst ranks. All analyses were intention-to-treat. For those participants who did not undergo follow-up angiography and did not die or have an MI, baseline angiography was carried forward for analysis and change over time was zero. Intergroup comparisons of baseline features and clinical outcomes were done using *t* tests, χ^2 tests, or Fisher exact tests as appropriate. Adjusted analyses of the primary end point were performed by least squares regression of the Van der Waerden scores against a treatment indicator and other appropriate covariates. Statistical analyses were performed using SAS statistical software (Version 8, SAS institute Inc, Cary, NC). All tests were 2-sided with $\alpha = .05$.

RESULTS

Baseline Characteristics

The baseline features of the study population are summarized in TABLE 1. The mean age was 65 years and one third of the women were nonwhite (predominantly black). More than one third of the patients were diagnosed as having diabetes, and the mean fasting blood glucose level for the entire group was 126 mg/dL (7 mmol/L). The mean body mass index of the women was high (30.7), as was the average level of fasting serum triglycerides (162 mg/dL; 1.83 mmol/L). Although nearly 60% of the women were being treated with cholesterol-lowering drugs, the mean LDL cholesterol level was 118 mg/dL (3.06 mmol/L), which is higher than the level recommended for patients with coronary disease.

Table 1. Baseline Characteristics*

Characteristic	HRT Intervention			Vitamins C and E Intervention		
	Active (n = 210)	Placebo (n = 213)	*P* Value	Active (n = 212)	Placebo (n = 211)	*P* Value
Age, mean (SD), y	65 (9)	66 (9)	.21	65 (9)	65 (9)	.72
Race						
White	136 (65)	144 (68)	.52	138 (65)	142 (67)	.65
Black	64 (31)	55 (26)		63 (30)	56 (27)	
Other	10 (5)	13 (6)		10 (5)	13 (6)	
History						
Myocardial infarction	96 (46)	85 (40)	.26	91 (43)	90 (43)	.96
Diabetes	89 (42)	65 (31)	.01	77 (37)	77 (37)	.97
Hypertension	162 (77)	157 (74)	.51	163 (77)	156 (74)	.48
Current smoker	39 (19)	39 (19)	.98	45 (21)	33 (16)	.14
Hysterectomy†	124 (59)	123 (58)	.88	124 (59)	123 (59)	.97
Oopherectomy	76 (36)	78 (37)	.84	78 (37)	76 (36)	.84
Hormone replacement use	83 (40)	75 (35)	.42	81 (38)	77 (36)	.74
Medication						
Aspirin	176 (84)	183 (86)	.47	177 (84)	182 (86)	.50
β-blocker	130 (62)	135 (64)	.71	133 (63)	132 (63)	.92
Calcium channel blocker	97 (46)	82 (39)	.12	90 (43)	89 (42)	.92
Lipid-lowering drug	122 (58)	126 (59)	.78	123 (58)	125 (59)	.84
Angiotensin-converting enzyme inhibitor	85 (41)	83 (39)	.75	74 (35)	94 (45)	.04
Nitrate	77 (37)	71 (34)	.49	71 (34)	77 (37)	.54
Diuretic	77 (37)	83 (39)	.60	86 (41)	74 (35)	.23
Physical examination, mean (SD)						
Blood pressure, mm Hg						
Systolic	140 (21)	138 (21)	.45	138 (20)	140 (21)	.43
Diastolic	76 (10)	75 (11)	.32	76 (11)	76 (10)	.51
Body mass index	31.1 (6.1)	30.3 (6.6)	.21	30.3 (6.6)	31.2 (6.1)	.17
Waist-to-hip ratio	0.86 (0.07)	0.86 (0.07)	.96	0.86 (0.07)	0.87 (0.07)	.35
Laboratory data, mean (SD)						
Cholesterol, mg/dL‡						
Total	202 (45)	198 (40)	.25	198 (43)	201 (42)	.50
Low-density lipoprotein	120 (39)	117 (37)	.43	118 (38)	119 (38)	.94
High-density lipoprotein	50 (13)	50 (13)	.75	51 (13)	49 (13)	.21
Triglycerides, mg/dL§	170 (119)	154 (79)	.10	151 (94)	173 (106)	.02
Estrone, ng/dL	2.8 (2.5)	2.6 (2.0)	.40	2.7 (2.1)	2.6 (2.4)	.85
Glucose, mg/dL‖	134 (73)	119 (53)	.01	125 (59)	128 (68)	.68
Insulin, uIU/mL	26 (36)	20 (16)	.03	23 (36)	23 (18)	.90
Glycosylated hemoglobin A_{1C}, %	6.8 (1.8)	6.5 (1.8)	.10	6.6 (1.8)	6.7 (1.8)	.91

*Values are expressed as number (percentage) unless otherwise indicated. HRT indicates hormone replacement therapy.
†Women with a previous hysterectomy received estrogen alone; all others took estrogen plus progesterone.
‡To convert to mmol/L, multiply by 0.0259.
§To convert to mmol/L, multiply by 0.0113.
‖To convert to mmol/L, multiply by 0.0555.

The active and placebo HRT groups were well-balanced with respect to baseline characteristics, with the exception of a statistically significantly higher prevalence of diabetes and higher fasting blood glucose levels in the HRT group. The randomization process to active or placebo vitamins resulted in a good balance for all characteristics except for a lower rate of angiotensin-converting enzyme inhibitor usage and lower levels of serum triglycerides in the active vitamin group.

Table 2. Coronary Angiographic Outcomes by Treatment Group*

	Placebo/ Placebo (n = 87)	HRT/ Placebo (n = 77)	Placebo/Vitamins C and E (n = 71)	HRT/Vitamins C and E (n = 85)	*P* Value
Minimum lumen diameter, mean (SD), mm					
Baseline	2.01 (0.48)	1.96 (0.43)	1.96 (0.47)	2.02 (0.57)	.74
Follow-up	2.01 (0.50)	1.87 (0.42)	1.89 (0.58)	1.94 (0.53)	.32
Change per year	−0.010 (0.15)	−0.048 (0.14)	−0.042 (0.15)	−0.046 (0.16)	.30
Average lumen diameter, mean (SD), mm					
Baseline	2.50 (0.49)	2.46 (0.46)	2.46 (0.51)	2.56 (0.64)	.59
Follow-up	2.54 (0.50)	2.41 (0.42)	2.43 (0.60)	2.51 (0.55)	.37
Change per year	0.009 (0.16)	−0.024 (0.11)	−0.026 (0.15)	−0.029 (0.12)	.23
No. (%) and type of categorical minimum lumen diameter changes†					
Regression	19 (22)	14 (18)	13 (18)	15 (18)	.55
No change	35 (40)	28 (36)	26 (37)	34 (40)	
Progression	22 (25)	28 (36)	24 (34)	33 (39)	
Mixed	11 (13)	7 (9)	8 (11)	3 (3.5)	

*HRT indicates hormone replacement therapy.
†A change of 0.4 mm or more of a qualifying lesion was defined as regressed or progressed. If 1 or more lesions progressed and 1 or more regressed in the same patient, she was classified as mixed.

Table 3. Coronary Angiographic Outcomes Comparison

	Hormone Replacement Therapy Intervention			Vitamins C and E Intervention		
	Active (n = 162)	Placebo (n = 158)	*P* Value	Active (n = 156)	Placebo (n = 164)	*P* Value
Minimum lumen diameter, mean (SD), mm						
Baseline	1.99 (0.51)	1.99 (0.47)	.92	1.99 (0.53)	1.99 ± 0.45	.94
Follow-up	1.90 (0.48)	1.95 (0.54)	.37	1.92 (0.55)	1.94 ± 0.47	.69
Change per year	−0.047 (0.15)	−0.024 (0.15)	.17*	−0.044 (0.15)	−0.028 (0.15)	.32†
Average lumen diameter, mean (SD), mm						
Baseline	2.51 (0.56)	2.49 (0.50)	.92	2.52 (0.59)	2.48 (0.47)	.58
Follow-up	2.46 (0.50)	2.49 (0.55)	.61	2.47 (0.57)	2.48 (0.47)	.97
Change per year	−0.027 (0.11)	−0.007 (0.16)	.20	−0.028 (0.13)	−0.006 (0.14)	.16
No. (%) and type of categorical minimum lumen diameter changes‡						
Regression	29 (18)	32 (20)	.17	28 (18)	33 (20)	.49
No change	62 (38)	61 (39)		60 (38)	63 (38)	
Progression	61 (38)	46 (29)		57 (37)	50 (31)	
Mixed	10 (6)	19 (12)		11 (7)	18 (11)	

*P = .045 when the worst angiographic outcomes are imputed to patients with intercurrent death or nonfatal myocardial infarction (primary end point of the trial; n = 336).
†P = .09 when the worst angiographic outcomes are imputed to patients with intercurrent death or nonfatal myocardial infarction (primary end point of the trial; n = 336).
‡A change of 0.4 mm or more of a qualifying lesion was defined as regressed or progressed. If 1 or more lesions progressed and 1 or more regressed in the same patient, she was classified as mixed.

Changes in Lipid and Vitamin Levels

In women assigned to HRT, levels of LDL cholesterol decreased by 18 mg/dL (0.47 mmol/L) ($P<.001$) or 9.5% after randomization, and levels of high-density lipoprotein (HDL) cholesterol increased by 4.3 mg/dL (0.11 mmol/L) ($P<.004$) or 8.6%. Levels of triglycerides increased by 11.9% ($P=.10$). Vitamins had no effect on blood lipid levels. Vitamin E levels increased from 1.22 mg/dL at baseline to 2.42 mg/dL at follow-up ($P<.001$) in women assigned to the vitamin group; vitamin C levels increased from 8.66 to 11.50 mg/dL ($P<.002$). Serum levels of vitamins E and C did not change in women assigned to placebo vitamins.

Angiographic Outcomes

Coronary angiographic outcomes (shown in TABLE 2 for each of the 4 treatment groups) were based on 1328 qualifying lesions in the 320 women who had a follow-up angiogram. The decrease in MLD and mean lumen diameter was greater in each of the 3 groups containing an active treatment compared with the double placebo group, but these trends were not statistically significant. No statistically significant interaction between treatments was observed for any of the angiographic outcomes ($P=.31$ for interaction for MLD change).

The factorial design revealed no interaction between treatments, so groups with specific interventions were combined (TABLE 3). The MLD worsened in the HRT group by 0.047 (0.15) mm/y vs 0.024 (0.15) mm/y for the HRT placebo group, but the difference was not statistically significant ($P=.17$). When results were inputed as the worst possible outcome for those who died or had an intercurrent MI, women in the active HRT group had an increased risk ($P=.045$). However, this outcome was partially explained by differences in prevalence of diabetes. After adjusting for diabetes and diabetes-related vari-

ables, the risk was no longer significant ($P=.07$). Among women who were compliant with HRT or HRT placebo treatment at 12 months, risk was increased in the active HRT group ($P=.04$).

Vitamin treatment was associated with a statistically nonsignificant difference in MLD (–0.044 [0.15] mm/y vs –0.028 [0.15] mm/y for controls) ($P=.32$). However, after imputing values to the women with events (the primary end point), the difference between the treatment groups approached statistical significance ($P=.09$). After adjustment for baseline differences in angiotensin-converting enzyme inhibitor usage and levels of triglycerides, $P=.054$.

The effect of treatment in patients with and without diabetes, current smokers and nonsmokers, whites and nonwhites, and women who had and had not received a hysterectomy are shown in TABLE 4. Neither HRT nor vitamin treatment had a different effect in any subgroup than in the entire population. Overall, MLD worsened more in diabetic than nondiabetic patients (0.069 [0.15] vs 0.014 [0.14]; $P=.001$).

Clinical Events

Clinical events in each of the 4 treatment groups are listed in TABLE 5. The mortality rate was lowest in the double placebo group, highest in the group receiving both active treatments, and intermediate in the other 2 groups ($P=.08$ for general association). There was no statistically significant interaction between HRT and antioxidant vitamin treatments in terms of clinical events ($P=.39$ for interaction for death and $P=.16$ for nonfatal MI).

TABLE 6 and FIGURE 2 show that the composite end point of death and nonfatal MI was more common in women randomized to HRT compared with HRT placebo, but these differences did not attain statistical significance. Similarly, death, nonfatal MI, or stroke was diagnosed in 26 patients in the HRT group compared with 15 in the HRT placebo group (hazard ratio [HR], 1.9; 95% confidence interval [CI], 0.97-3.6; $P=.07$). Fourteen patients died in the HRT group and 8 in the HRT placebo group (HR, 1.8; 95% CI, 0.75-4.3). During the first year of follow-up, 5 of the 6 deaths ($P=.09$) and 12 of the 18 death/nonfatal MIs ($P=.14$) occurred in the HRT group.

All-cause mortality was significantly higher in women assigned to antioxidant vitamins compared with vitamin placebo, 16 vs 6 (HR, 2.8; 95% CI, 1.1-7.2; $P=.047$). A trend in the same direction was seen for cardiovascular deaths, 10 vs 4 ($P=.17$). Death or nonfatal MI (Figure 2) occurred in 20 vitamin and 10 vitamin placebo women

Table 4. Coronary Angiographic Outcomes for Selected Predefined Subgroups by Treatment*

		HRT Intervention			Vitamins C and E Intervention		
	No. of Patients	Active	Placebo	*P* Value	Active	Placebo	*P* Value
Diabetes							
Yes	124	–0.067 (0.14)	–0.071 (0.17)	.89	–0.064 (0.16)	–0.073 (0.15)	.74
No	194	–0.032 (0.16)	–0.023 (0.13)	.10	–0.032 (0.15)	0.003 (0.14)	.08
Current smokers							
Yes	51	–0.059 (0.14)	–0.005 (0.10)	.13	–0.034 (0.14)	–0.036 (0.11)	.97
No	267	–0.045 (0.15)	–0.026 (0.16)	.33	–0.047 (0.16)	–0.025 (0.15)	.24
White race							
Yes	214	–0.037 (0.13)	–0.023 (0.14)	.43	–0.047 (0.16)	–0.015 (0.11)	.09
No	105	–0.067 (0.18)	–0.028 (0.17)	.26	–0.040 (0.15)	–0.056 (0.21)	.66
Hysterectomy†							
Yes	182	–0.053 (0.14)	–0.041 (0.17)	.61	–0.054 (0.17)	–0.040 (0.15)	.57
No	136	–0.040 (0.16)	0.001 (0.11)	.09	–0.033 (0.13)	–0.007 (0.14)	.28

*Values are expressed as mean (SD) change in minimum lumen diameter in millimeters per year unless otherwise indicated. HRT indicates hormone replacement therapy.
†Women with a previous hysterectomy received estrogen alone; all other took estrogen plus progesterone.

Table 5. Clinical Events by Treatment Group*

Event	Placebo/Placebo (n = 108)	HRT/Placebo (n = 103)	Placebo/Vitamins C and E (n = 105)	HRT/Vitamins C and E (n = 107)	*P* Value for Trend
All deaths	2 (1.9)	4 (3.9)	6 (5.7)	10 (9.4)	.08
Cardiovascular deaths	2 (1.9)	2 (1.9)	4 (3.8)	6 (5.6)	.37
Nonfatal MI	1 (0.9)	3 (2.9)	3 (2.9)	1 (0.9)	.56
Death or nonfatal MI	3 (2.8)	7 (6.7)	9 (8.6)	11 (10.3)	.17
Cardiovascular death/nonfatal MI	3 (2.8)	5 (4.9)	7 (6.7)	7 (6.5)	.54
Stroke	3 (2.8)	4 (3.9)	1 (1.0)	5 (4.7)	.41
Death, nonfatal MI, or stroke	5 (4.6)	11 (10.7)	10 (9.5)	15 (14.0)	.12
PCI or CABG surgery	28 (25.9)	13 (12.6)	19 (18.1)	21 (19.6)	.10
Pulmonary embolus or deep vein thrombosis	2 (1.9)	1 (1.0)	2 (1.9)	3 (2.8)	.93
Cancer					
Breast	0 (0)	1 (1.0)	1 (1.0)	2 (1.9)	.66
Other	2 (1.9)	2 (1.9)	2 (1.9)	1 (0.9)	.92

*Values are expressed as number (percentage). HRT indicates hormone replacement therapy; MI, myocardial infarction; PCI, percutaneous coronary intervention; and CABG, coronary artery bypass graft.

(HR, 2.1; 95% CI, 0.99-4.5; *P*=.09). Death, nonfatal MI, or stroke occurred in 26 vitamin patients and 18 controls (HR, 1.5; 95% CI, 0.80-2.9). Cancer and other noncardiovascular events occurred infrequently during the trial, with no differences detected between the treatment groups.

COMMENT

This trial fails to demonstrate that either HRT or antioxidant vitamin supplements provide cardiovascular benefit to postmenopausal women with coronary disease. In fact, potential harm was seen for both treatments. The primary end point of the trial was defined as coronary angiographic change, with the worst ranks imputed to women who died or experienced nonfatal MI. This end point, which was selected before the trial, has the advantage of incorporating both clinical events and angiographic change, which is a predictor of future coronary events, into 1 end point. By this measure, the increased risk associated with HRT was statistically significant (*P*=.045) and the increased risk associated with antioxidant vitamins was of borderline statistical significance (*P*=.09). All-cause mortality was higher in women assigned to antioxidant vitamins compared with vitamin placebo (HR, 2.8; 95% CI, 1.1-7.2; *P*=.047).

Previous HRT Trials

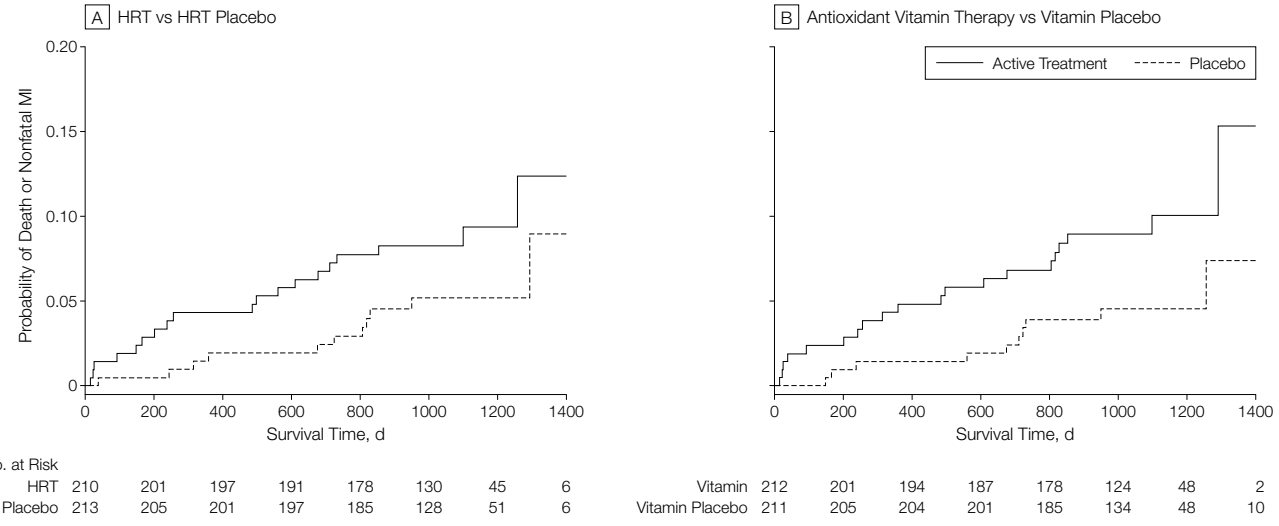
The Heart Estrogen/Progestin Replacement Study (HERS) demonstrated no reduction in coronary events after 4.1 years of treatment with HRT in 2763 postmenopausal women with coronary disease at baseline.[7] After 2.7 years of additional follow-up, with most women maintaining their assigned therapy, no cardiovascular benefit or harm was seen over a total of 6.8 years.[8] The relative risk of nonfatal MI or CHD death was higher in the HRT group during the first year of treatment, with a RH of 1.52 (95% CI, 1.01-2.29). In the Women's Estrogen for Stroke Trial (WEST), an increase in stroke with HRT was seen during the first 6 months of treatment.[28] This increase in risk early after initiation of HRT may account for the adverse effect of HRT in WAVE, since the mean duration of follow-up was 2.8 years. In the predominantly

Table 6. Clinical Events for Each Active Treatment Group Compared With Placebo*

	HRT Intervention			Vitamins C and E Intervention		
	Active (n = 210)	Placebo (n = 213)	*P* Value	Active (n = 212)	Placebo (n = 211)	*P* Value
All deaths	14 (6.7)	8 (3.8)	.20	16 (7.6)	6 (2.8)	.05
Cardiovascular deaths	8 (3.8)	6 (2.8)	.60	10 (4.7)	4 (1.9)	.17
Nonfatal MI	4 (1.9)	4 (1.9)	>.99	4 (1.9)	4 (1.9)	>.99
Death or nonfatal MI	18 (8.6)	12 (5.6)	.26	20 (9.4)	10 (4.7)	.09
Cardiovascular death or nonfatal MI	12 (5.7)	10 (4.7)	.67	14 (6.6)	8 (3.8)	.27
Stroke	9 (4.3)	4 (1.9)	.17	6 (2.8)	7 (3.3)	.79
Death, nonfatal MI, or stroke	26 (12.4)	15 (7.0)	.07	26 (12.3)	18 (8.5)	.26
PCI or CABG surgery	34 (16.2)	44 (20.7)	.14	40 (18.9)	38 (18.0)	.90
Pulmonary embolus or deep vein thrombosis	4 (1.9)	4 (1.9)	>.99	5 (2.4)	3 (1.4)	.72
Cancer						
Breast	3 (1.4)	1 (0.5)	.37	3 (1.4)	1 (0.5)	.62
Other	3 (1.4)	4 (1.9)	>.99	3 (1.4)	4 (1.9)	.72

*Values are expressed as number (percentage). HRT indicates hormone replacement therapy; MI, myocardial infarction; PCI, percutaneous coronary intervention; and CABG, coronary artery bypass graft.

Figure 2. Probability of Death or Nonfatal MI With Hormone Replacement Therapy (HRT) or Antioxidant Vitamin Therapy



Using the log-rank test, the hormone replacement therapy (HRT) comparison yielded *P*=.12; vitamin comparison, *P*=.049. MI indicates myocardial infarction.

healthy women participating in the Women's Health Initiative, an increased risk of cardiovascular events was recently reported after 5.2 years of combined HRT, with a relative risk of 1.29 (95% CI, 1.02-1.63).[10]

In the only previous coronary angiographic trial of HRT, the Estrogen Replacement and Atherosclerosis Trial, 309 women with coronary disease were randomized to estrogen alone, to estrogen plus continuous medroxyprogesterone, or to placebo.[9] Among the 248 women who underwent follow-up angiography, MLD over the 3.2 years of follow-up worsened by 0.09 (0.02) mm in both the placebo and unopposed estrogen groups, and by 0.12 (0.02) mm in the combined HRT group. These rates of progression were not reported as annual changes in MLD and are similar to the progression rates in WAVE.

No benefit in clinical end points, or a trend toward harm, has also been seen in several smaller trials.[29] Taken together, the evidence clearly indicates that HRT does not reduce coronary events in women with established coronary disease, and that it probably is harmful over the short term.

Previous Antioxidant Vitamin Trials

The effect of vitamin E supplements on coronary events has been evaluated in 4 clinical trials,[19-22] and in only the smallest and shortest of them was any benefit seen.[20] Overall, the relative risk among the 52 000 subjects enrolled in these trials was 0.97 (95% CI, 0.92-1.02).[22] Therefore, vitamin E alone is unlikely to influence coronary events in patients at high risk, such as those enrolled in these trials.

The combination of high-dose vitamin E, vitamin C, and beta-carotene supplements was evaluated in the Heart Protection Study, a trial of 20 536 patients with coronary disease, atherosclerosis in other vascular beds, or high-risk features such as diabetes or treated hypertension.[23] Over 5.5 years of follow-up, coronary mortality was 6% higher and total mortality was 4% higher in the active treatment group—differences that were not statistically significant. The dose of vitamin C in WAVE was 4-fold higher than the dose in the Heart Protection Study.

Some indirect evidence suggests that antioxidant vitamin supplements might be harmful to patients with coronary disease. In one study of coronary patients with low HDL cholesterol, the combination of vitamins C and E plus beta-carotene and selenium blunted the increase in HDL cholesterol and LDL cholesterol particle size caused by simvastatin plus niacin treatment.[30,31] A trend toward coronary regression was observed in the simvastatin plus niacin group, whereas minimal coronary progression occurred when antioxidant vitamins were added.[29] Vitamins C, E, and beta-carotene also appeared to attenuate the reduced rate of restenosis after coronary angioplasty produced by pretreatment with probucol.[32]

In summary, data from other studies support the observation in the WAVE trial that treatment with high doses of vitamins C and E is not beneficial, and may even be harmful.

Limitations of the Trial

Approximately 20% of our patients did not contribute to the study end point because they did not have follow-up angiography or interim events. Among the women with angiographic follow-up, those assigned to active HRT took only 67% of the prescribed medication, compared with 84% in the active vitamin group. These 2 factors limit the power of our study to detect a treatment effect, particularly for HRT. However, among women who were taking HRT or HRT placebo treatment at 12 months, risk was increased in the active HRT group ($P=.04$).

The primary end point of our trial was a change in coronary artery dimensions, with the worst angiographic outcome imputed to patients who died or suffered interim infarctions. Coronary progression has been shown in previous angiographic trials to be a strong, independent predictor of future coronary events,[33,34] and thus should be a valid surrogate end point. Imputing an unfavorable angiographic outcome to patients with interim events avoids the problem inherent in ignoring the outcomes of these patients for the primary end point of the trial.

Clinical Implications

The results of this trial add to the accumulating evidence that neither HRT nor antioxidant vitamin supplements improve the clinical course of coronary disease in postmenopausal women. This information is important because both of these treatments are commonly used in this circumstance, with the expectation of benefit, based on observational data and theoretical concepts.

Furthermore, these results strengthen the evidence that HRT causes cardiovascular harm during the first year or 2 of treatment. The increase in total and cardiovascular mortality in women taking high doses of vitamins C and E was unexpected. While this may represent a chance finding, a trend toward an increase in mortality was observed in the Heart Protection Study.[23] Therefore, we conclude that postmenopausal women with coronary disease should be discouraged from using both HRT and high doses of vitamins C and E.

Author Affiliations: Division of Cardiology, San Francisco General Hospital and the University of California, San Francisco (Dr Waters); Cardiovascular Medicine Division, Stanford University, Stanford, Calif (Dr Alderman); Departments of Medicine (Dr Hsia) and Statistics (Drs Younes and Verter), George Washington University, Washington, DC; Department of Cardiology, Medstar Research Institute, Washington, DC (Dr Howard); Duke Center for Living, Duke University, Durham, NC (Dr Cobb); Division of Cardiology, University of Alabama, Birmingham (Drs Rogers and Bittner); Division of Cardiology, Johns Hopkins Bayview Medical Center, Baltimore, Md (Dr Ouyang); Division of Cardiology, Hartford Hospital, Hartford, Conn (Dr Thompson); Montreal Heart Institute, Montreal, Quebec (Dr Tardif); University of Ottawa Heart Institute, Ottawa, Ontario (Dr Higginson); Central Biochemistry Laboratory, University of Minnesota, Minneapolis (Dr Steffes); and National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md (Drs Gordon and Proschan).

Author Contributions: *Study concept and design:* Waters, Hsia, Howard, Cobb, Rogers, Ouyang, Tardif, Bittner, Gordon, Younes, Verter.
Acquisition of data: Waters, Howard, Cobb, Rogers, Ouyang, Thompson, Tardif, Higginson, Bittner, Steffes, Younes, Verter.
Analysis and interpretation of data: Waters, Alderman, Hsia, Howard, Cobb, Rogers, Ouyang, Tardif, Higginson, Bittner, Steffes, Gordon, Proschan, Younes, Verter.
Drafting of the manuscript: Waters, Howard, Younes, Verter.
Critical revision of the manuscript for important intellectual content: Waters, Alderman, Hsia, Howard,

Cobb, Rogers, Ouyang, Thompson, Tardif, Higginson, Bittner, Steffes, Gordon, Proschan, Younes, Verter.
Statistical expertise: Howard, Proschan, Younes, Verter.
Obtained funding: Hsia, Rogers, Ouyang, Tardif, Gordon, Verter.
Administrative, technical, or material support: Alderman, Hsia, Rogers, Ouyang, Thompson, Higginson, Steffes, Gordon, Verter.
Study supervision: Waters, Howard, Cobb, Thompson, Verter.
Funding/Support: Our research was funded by National Heart, Lung, and Blood Institute contracts NO1-HV-68165 to NO1-HV-68170 and General Clinical Research Center grant MO1 RR02715.
Clinical Sites: University of Alabama, Birmingham (William J. Rogers, MD, Vera Bittner, MD, Tommie Holmes, RN, Bobbie Hill, RN, Kathy Carter, RN, Holly E. Richter, PhD, MD); Hartford Hospital, Hartford, Conn (Paul Thompson, MD, David Waters, MD, Marilyn Siwy, RN, Jennifer DeDominics, RN, Joann Pazdar, LPN); Medstar Research Institute, Washington, DC (Barbara Howard, PhD, Lucy van Vorhees, MD, Joseph Lindsay, MD, Angela Silverman RN, NP); Johns Hopkins Bayview Medical Center, Baltimore, Md (Pamela Ouyang, MD, Roger S. Blumenthal, MD, Mark Keleman, MD, Ivan Barofsky, PhD, Jeanne Wingo, RN, Kathleen Snyder RN); Duke University, Durham, NC (Frederick R. Cobb MD, Eric Peterson, MD, Laura Drew, RN, Melva Strait, RN, Tina Harding, RN, Mary Jo Chapman, RN); University of Ottawa Heart Institute, Ottawa, Ontario (Lyall Higginson, MD, Elyse Sevigny, RN, Hetty Martin, RN); Montreal Heart Institute, Montreal, Quebec (Jean Claude Tardif, MD, Carole Jesina, RN, Martine Vaillancourt, RN).
Central Biochemistry Laboratory: University of Minnesota, Minneapolis (Michael W. Steffes, MD, PhD, Myron Gross, PhD, Jean Bucksa, Greg Ryders, Jennifer Hayes).
Central Angiographic Reading Laboratory: Stanford University, Stanford, Calif (Edwin L. Alderman, MD, Anne Schwarzkopf, Brooke Hollak, RN).
Drug Distribution Center: Health and Human Services Supply Service Center, Perry Point, Md (Tom Shaffer, Kathleen Scott).
National Heart, Lung, and Blood Institute: National Institutes of Health, Bethesda, Md (David Gordon, MD, PhD, Michael Proschan, PhD, Sharon Kraft).
Coordinating Center: George Washington University Biostatistics Center, Rockville, Md (Joel Verter, PhD, Naji Younes, PhD, Judith Hsia, MD, Mark Tripputi, Phyllis Reed, Seshu Pakalapati).

REFERENCES

1. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med.* 1991;20:47-63.
2. Grodstein F, Stampfer MJ, Manson JE, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease [published correction appears in *N Engl J Med.* 1996;335:1406]. *N Engl J Med.* 1996;335:453-461.
3. Sullivan JM, Vander Zwaag R, Hughes JP, et al. Estrogen replacement and coronary artery disease: effect on survival in postmenopausal women. *Arch Intern Med.* 1990;150:2557-2562.
4. Newton KM, LaCroix AZ, McKnight B, et al. Estrogen replacement therapy and prognosis after first myocardial infarction. *Am J Epidemiol.* 1997;145:269-277.
5. Sullivan JM, El-Zeky F, Vander Zwaag R, Ramanathan KB. Effect on survival of estrogen replacement therapy after coronary artery bypass grafting. *Am J Cardiol.* 1997;79:847-850.
6. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med.* 1999;340:1801-1811.
7. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA.* 1998;280:605-613.
8. Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study Follow-up (HERS II). *JAMA.* 2002;288:49-57.
9. Herrington DM, Reboussin DM, Brosnihan B, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med.* 2000;343:522-529.
10. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288:321-333.
11. Manson JE, Martin KA. Postmenopausal hormone replacement therapy. *N Engl J Med.* 2001;345:34-40.
12. Gaziano JM, Manson JE, Buring JE, Hennekens CH. Dietary antioxidants and cardiovascular disease. *Ann N Y Acad Sci.* 1992;669:249-258.
13. Stampfer MJ, Hennekens CH, Manson JE, Colditz GA, Rosner B, Willett WC. Vitamin E consumption and the risk of coronary heart disease in women. *N Engl J Med.* 1993;328:1444-1449.
14. Rimm EB, Stampfer MJ, Ascherio A, Giovannucci E, Colditz GA, Willett WC. Vitamin E consumption and the risk of coronary heart disease in men. *N Engl J Med.* 1993;328:1450-1456.
15. Enstrom JE, Kanim LE, Klein MA. Vitamin C intake and mortality among a sample of the United States population. *Epidemiology.* 1992;3:194-202.
16. Dagenais DR, Marchioli R, Yusuf S, Tognoni G. Beta-carotene, vitamin C and vitamin E and cardiovascular disease. *Curr Cardiol Rep.* 2000;2:293-299.
17. Hodis HN, Mack WJ, LaBree L, et al. Serial coronary angiographic evidence that antioxidant vitamin intake reduces progression of coronary artery atherosclerosis. *JAMA.* 1995;273:1849-1854.
18. Diaz MN, Frei B, Vita JA, Keany JF Jr. Antioxidants and atherosclerotic heart disease. *N Engl J Med.* 1997;337:408-416.
19. Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med.* 1994;330:1029-1035.
20. Stephens NG, Parsons A, Schofield PM, Kelly F, Cheeseman K, Mitchinson MJ. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). *Lancet.* 1996;347:781-786.
21. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet.* 1999;354:447-455.
22. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G, and the Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med.* 2000;342:145-153.
23. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet.* 2002;360:23-33.
24. Lynch SM, Gaziano JM, Frei B. Ascorbic acid and atherosclerotic cardiovascular disease. *Subcell Biochem.* 1996;25:331-367.
25. Hsia J, Alderman EL, Verter JI, et al. Women's Angiographic Vitamin and Estrogen Trial: design and methods. *Control Clin Trials.* In press.
26. Leung WH, Sanders W, Alderman EL. Coronary artery quantitation and data management system for paired cineangiograms. *Cathet Cardiovasc Diagn.* 1991;24:121-134.
27. Conover WJ. *Practical Nonparametric Statistics.* 2nd ed. New York, NY: John Wiley & Sons; 1971:318.
28. Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suisa S, Horowitz RI. A clinical trial of estrogen replacement therapy after ischemic stroke. *N Engl J Med.* 2001;345:1243-1249.
29. Waters DD. Estrogen and unstable angina: another bump for the bandwagon. *J Am Coll Cardiol.* 2002;39:238-240.
30. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med.* 2001;345:1583-1592.
31. Cheung MC, Zhao XQ, Chait A, Albers JJ, Brown BG. Antioxidant supplements block the response of HDL to simvastatin-niacin therapy in patients with coronary artery disease and low HDL. *Arterioscler Thromb Vasc Biol.* 2001;21:1320-1326.
32. Tardif JC, Côté G, Lespérance J, et al. Probucol and multivitamins in the prevention of restenosis after coronary angioplasty. *N Engl J Med.* 1997;337:365-372.
33. Waters D, Craven TE, Lespérance J. Prognostic significance of progression of coronary atherosclerosis. *Circulation.* 1993;87:1067-1075.
34. Azen SP, Mack WJ, Cashin-Hemphill L, et al. Progression of coronary artery disease predicts clinical coronary events: long-term follow-up from the Cholesterol Lowering Atherosclerosis Study. *Circulation.* 1996;93:34-41.