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A Randomized Factorial Trial of Vitamins C, E, and Beta-Carotene in the Secondary Prevention of Cardiovascular Events in Women:

Results from the Women's Antioxidant Cardiovascular Study (WACS)

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Abstract

Background—Randomized trials have largely failed to support an effect of antioxidant vitamins on risk of cardiovascular disease (CVD). Few trials have examined interactions among antioxidants, and no previous trial has examined the individual effect of vitamin C on CVD.

Methods—WACS tested the effects of vitamins C (500 mg daily), E (600 IU every other day), and beta-carotene (50 mg every other day) on the combined outcome of myocardial infarction (MI), stroke, coronary revascularization, or CVD death among 8,171 female health professionals at increased risk in a 2×2×2 factorial design. Participants were 40 years or older with a prior history of CVD or three or more CVD risk factors, and were followed an average 9.4 years, from 1995-96 to 2005.

Results—1,450 women experienced one or more CVD outcomes. There was no overall effect of vitamin C (RR=1.02, 95% CI=0.92-1.13, p=0.71), vitamin E (RR=0.94, 95% CI=0.85-1.04, p=0.23),

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or beta-carotene (RR=1.02, 95% CI=0.92-1.13, p=0.71) on the primary combined endpoint, or on the individual secondary outcomes of MI, stroke, coronary revascularization, or CVD death. A marginally significant reduction in the primary outcome with active vitamin E was observed among the pre-specified subgroup of women with prior CVD (RR=0.89, 95% CI=0.79-1.00, p=0.04; p-interaction=0.07). There were no significant interactions between agents for the primary endpoint, but those randomized to both active vitamin C and E experienced fewer strokes (p for interaction=0.03).

Conclusion—There were no overall effects of vitamins C, E or beta-carotene on cardiovascular events among women at high risk for CVD.

Trial Registration—clinicaltrials.gov Identifier: NCT00000541

INTRODUCTION

Oxidative damage may play a role in the development of cardiovascular disease, particularly through its effect on lipid peroxidation and DNA damage.[1] In addition, free radicals may damage arterial endothelium, encourage thrombosis, and alter vasomotor function.[2] Antioxidants scavenge free radicals, and limit the damage they can cause.[3] Diets high in fruit and vegetable intake, and thus rich in such antioxidants, have been associated with reduced rates of coronary heart disease and stroke.[4]

Vitamins C, E and beta-carotene are potential mediators of the apparent protective effect of a plant-based diet on cardiovascular disease (CVD). Observational epidemiologic studies of dietary intake of these vitamins provide some support for this hypothesis, particularly for vitamin E,[5-8] although results are not consistent. Some studies found lower event rates among those with higher plasma carotenoids,[9, 10] but others found no beneficial effects.[11, 12]

Several randomized trials have now examined the effects of these antioxidants, and results have generally been disappointing.[13] No trials, however, have examined the effect of vitamin C on CVD, except as part of an antioxidant cocktail. The Women's Antioxidant Cardiovascular Study (WACS) was designed to test the effect of three antioxidant agents, vitamins C, E, and beta-carotene, on prevention of CVD among women at high risk. It used a factorial design, enabling a comparison for each agent alone as well as interactions among them.

METHODS

Study Design and Participants

WACS is a randomized, double-blind, placebo-controlled trial evaluating the effects of vitamin C (500 mg/day synthetic vitamin C [ascorbic acid], provided by BASF Corporation [Mount Olive, NJ]), vitamin E (600 IU natural vitamin E [D-alpha-tocopherol acetate] every other day, provided by Cognis Corporation [La Grange, IL]), and beta-carotene (50 mg Lurotin every other day, provided by BASF) in the prevention of important vascular events in a 2×2×2 factorial design among high risk women with either a history of vascular disease or at least three cardiovascular risk factors. In 1998, approximately 2-3 years following randomization to the antioxidant arms, a folic acid/vitamin B_6/B_{12} component was added to the trial, expanding it to a four-arm factorial trial. This report describes the results of the three antioxidant interventions.

Details of the design have been reported previously.[14] Briefly, women were eligible if they were aged 40 years or older, postmenopausal or had no intention of becoming pregnant, had a self-reported history of CVD, or had at least three cardiac risk factors. The cardiac risk factors determining eligibility were self-reported diagnosis of hypertension, high cholesterol, or diabetes mellitus, parental history of premature myocardial infarction (MI) (before age 60), obesity (body mass index (BMI) ≥ 30 kg/m^2), current cigarette smoking, and inconsistent report of prior CVD. Women were excluded if they had a self-reported history of cancer (excluding nonmelanoma skin cancer) within the past ten years, any serious non-CVD illness, or were currently using warfarin or other anticoagulants. Potential participants also had to be willing to forgo individual supplements of vitamins A, C, E, and beta-carotene at levels beyond the U.S. recommended daily allowance (RDA) during the trial. 8,171 women were willing and eligible, were compliant during a 12-week run-in, and were randomized into the trial from June, 1995, through October, 1996 (Figure 1). The trial was approved by the institutional review board of the Brigham and Women's Hospital, Boston, MA, and was monitored by an external data and safety monitoring board.

Following randomization, every six months for the first year then annually, the women were sent monthly calendar packs containing active agents or placebos, along with questionnaires on compliance, side effects, and medical events. Study medications and end point ascertainment were continued in a blinded fashion until the scheduled end of the trial. Pill-taking for women not enrolled in the folic acid component ended as scheduled on January 31, 2005; women in the folic acid component completed pill-taking on July 31, 2005. The average follow-up from randomization to end of study was 9.4 years (range 8.3-10.1 years). Follow-up and validation of reported end points were completed in July, 2006. A search of the National Death Index was conducted for all participants through December, 2003; thus mortality information was virtually complete through 2003. As of the scheduled end of the trial in January or July, 2005, mortality follow-up was 93% complete. In terms of person-time, mortality information was complete for over 99% of person-years of follow-up. Morbidity status was known as of 8 years for 93% of survivors, and response to the final follow-up questionnaire among surviving women was 89%.

Compliance was assessed through self-report and defined as taking at least two-thirds of study pills. Reported compliance was, on average, 76% at 4 years and 68% at 8 years of follow-up for each antioxidant, with no significant difference between active and placebo groups at these times except for vitamin C at 8 years (70% vs. 67% in active vs. placebo, p=0.01). Average compliance over follow-up was approximately 73% for all active and placebo agents. In 1999, blood samples were obtained from 30 local participants to evaluate biomarkers for compliance. Blood levels were elevated in each active vs. placebo group (vitamin C: 1.88 vs. 1.26 mg/dL, p=0.007; vitamin E: 20.19 vs. 12.15 μg/mL, p=0.007; beta-carotene: 54.39 vs. 19.52 μg/mL, p=0.003).

Information was obtained on outside supplements of study medications for at least 4 days per month ("drop-ins"). Use of vitamin C supplements was approximately 10% at both 4 and 8 years, and did not differ by intervention group. Use of vitamin E supplements was 13% at 4 years and 12 % at 8 years, with no difference by randomized group. Use of supplements of beta-carotene or vitamin A averaged 2% at 4 and 8 years, and did not differ by beta-carotene assignment. When use of multivitamins containing more than 100% of the RDA was included in the definition of outside use, rates were approximately 3-5% higher for vitamin C, 4-8% higher for vitamin E, and 1-3% higher for beta-carotene, but again did not differ by randomized assignment.

End Point Definition

The primary outcome was a combined end point of CVD morbidity and mortality, including incident MI, stroke, coronary revascularization procedures (coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA)), and cardiovascular mortality. The individual components of MI, stroke, coronary revascularization, and CVD death were pre-specified secondary end points. Information on transient ischemic attack (TIA) and total mortality was also collected and reviewed.

Women reported relevant endpoints through questionnaire, letter, or phone call. Deaths were reported by family members, postal authorities or through the National Death Index. Written permission for medical records was sought from the participant, or next of kin in case of death. These were reviewed by an endpoints committee of physicians blinded to randomized treatment assignment. An MI was confirmed if symptoms met World Health Organization criteria and cardiac enzymes or diagnostic electrocardiograms were abnormal. Coronary revascularization (CABG or PTCA) was confirmed by medical record review. Confirmed stroke was defined as a new neurologic deficit of sudden onset that persisted for more than 24 hours or until death within 24 hours. Clinical information, computed tomographic scans, and magnetic resonance images were used to distinguish hemorrhagic from ischemic events. A confirmed TIA was defined as a neurologic deficit of sudden onset that lasted less than 24 hours. Death due to cardiovascular cause was confirmed by examination of autopsy reports, death certificates, medical records, and information obtained from the next of kin or other family members. Death from any cause was confirmed by the end points committee or on the basis of a death certificate. Only confirmed end points were included in these analyses, except for total mortality which included 66 reported deaths with no death certificate.

Statistical Analysis

Primary analyses were performed on an intent-to-treat basis, including all randomized women. Baseline characteristics were compared by randomized groups using t-tests, chi-square tests for proportions, and tests for trend for ordinal categories. Kaplan-Meier curves were used to estimate cumulative incidence over time by randomized group, and the log-rank test was used to compare curves. The Cox proportional hazards model was used to estimate the relative risk (RR), expressed as a hazards ratio, along with the 95% confidence interval (CI). Models included main effect terms for each of the three antioxidants along with age. Tests of proportionality of the hazards ratio over timeused an interaction term for treatment times the logarithm of time. To examine the impact of lack of compliance, a post-hoc sensitivity analysis censored women if and when they stopped taking at least two-thirds of their study medication, reported taking outside supplements containing study agents, or were missing compliance information. Analyses were conducted using SAS version 9 (SAS Institute, Cary, NC), using two-sided tests with a significance level of 0.05.

Interaction terms were used to test for additivity of the three antioxidant agents. All two-way interactions as well as a three-way interaction were tested, using multiplicative terms in the Cox model. In addition, we conducted subgroup analyses according to the presence or absence of major cardiovascular risk factors, including age, prior CVD, smoking, alcohol use, BMI, history of hypertension, high cholesterol or diabetes, parental history of MI before age 60, menopausal status and hormone therapy (HT) use, and current multivitamin use. Tests for effect modification by subgroup used interaction terms between subgroup indicators and randomized assignment, with a test for trend for ordinal subgroup categories, or a multi-degree-of-freedom test for unordered categories. Any significant modification of effect is described below.

RESULTS

8,171 women were randomized into the antioxidant arms of the trial, with a mean age of 60.6 years (SD=8.8). Of these, 5,238 (64%) had a prior cardiovascular event, and 2,933 (36%) had three or more CVD risk factors. Mean BMI was 30.3 (SD=6.7), and 1,269 women (16%) were current smokers, 1,564 (19%) had diabetes, 6,137 (75%) had a history of hypertension, and 5,950 (73%) had a history of high cholesterol at baseline. There were no statistically significant differences in baseline characteristics between the randomized groups, except history of high cholesterol by beta-carotene (Table 1).

During the average 9.4 year follow-up, 1,450 women experienced a confirmed CVD event, including 274 MIs, 298 strokes, 889 coronary revascularization procedures, and 395 cardiovascular deaths, with some experiencing more than one event. 995 women died during follow-up.

Vitamin C

There was no effect of vitamin C on the primary combined endpoint, with a relative risk (RR) of 1.02 (95% confidence interval (CI)=0.92-1.13, p=0.71) (Table 2). Cumulative incidence curves showed no variation of the effect over time (Figure 2), and the test for proportionality of the RR over time was not significant. Individual components of the primary end point also did not differ significantly, although there was some suggestion of a benefit for ischemic stroke. When participants were censored upon noncompliance, results were similar (RR=0.95, 95% CI=0.83-1.09, p=0.47). There were no significant effects of randomized vitamin C on the primary end point in any cardiovascular risk factor subgroup considered (Table 3).

Vitamin E

No differences were seen in the primary end point by randomized vitamin E assignment (RR=0.94, 95% CI = 0.85-1.04, p=0.23) (Table 2 and Figure 2), with no significant variation in the relative risk over time. We found a non-significant 16% reduction in total stroke, comprised of a 21% reduction in ischemic stroke (p=0.06) and an increase in hemorrhagic stroke based on small numbers. There was an overall 10% reduction in the combination of MI, stroke and CVD death, with a suggestion of a decrease (p=0.08) in benefit over time. No difference in total mortality by vitamin E group was found.

Censoring participants upon noncompliance led to a significant 13% reduction in the primary endpoint (RR=0.87, 95% CI = 0.76-0.99, p=0.04). Reductions in secondary study endpoints were also stronger, with a 22% reduction in MI (RR=0.78, 95% CI = 0.58-1.06, p=0.11), a 27% reduction in stroke (RR=0.73, 95% CI = 0.54-0.98, p=0.04), and a 9% reduction in CVD mortality (RR=0.91, 95% CI = 0.66-1.25, p=0.55). There was a 23% reduction in the combination of MI, stroke or CVD death (RR=0.77, 95% CI = 0.64-0.92, p=0.005). Among those with prior CVD the active vitamin E group experienced fewer major CVD events (RR=0.89, 95% CI = 0.79-1.00, p=0.04, p for interaction = 0.07) (Table 3).

Beta-Carotene

For beta-carotene, there was no difference in the primary end point (RR=1.02, 95% CI = 0.92-1.13, p=0.71) (Table 2 and Figure 2), with no variation over time. There were no significant treatment effects on individual secondary endpoints. There was a non-significant 14% increase in CVD mortality in the active group, with a significant decline over time in the effect on CVD deaths (p=0.04), but no difference in total mortality. When participants were censored upon noncompliance, the effect on the primary endpoint remained non-significant (RR for major vascular disease = 1.09, 95% CI = 0.96-1.24, p=0.18), but an increase in CVD mortality appeared to emerge (RR=1.48, 95% CI = 1.08-2.02, p=0.02).

No statistically significant subgroup effects were seen for the primary endpoint. In particular, in the pre-specified subgroup of smokers, we did not find any elevation in the risk of the primary endpoint (Table 3) or any of the individual components (data not shown).

Combinations of antioxidants

There were no significant two-way or three-way interactions among the agents for the primary endpoint. The effects for each of the combinations of active agents compared to the group with all three placebos is shown in Figure 3 (right). There were also no interactions for the secondary endpoints of MI or cardiovascular death. For stroke, we found a significant two-way interaction between vitamins C and E (p=0.03). Those in the active groups for both agents experienced fewer strokes compared to those in the placebo group for both agents (RR=0.69, 95% CI = 0.49-0.98, p=0.04) (Figure 3, left).

Side Effects

We examined reports of bleeding (including gastrointestinal bleeds, hematuria, easy bruising, epistaxis), of gastrointestinal symptoms (including peptic ulcer, gastric upset, nausea, constipation, diarrhea), or of fatigue or drowsiness. There were no statistically significant differences by any of the randomized antioxidant groups except for a small increase in reports of symptoms suggestive of gastric upset among those in the active beta-carotene group (2785 vs. 2717 reports, RR=1.06, 95% CI = 1.00-1.11, p=0.05).

DISCUSSION

In this large-scale randomized trial among high-risk women, we found no overall effects of vitamins E, C or beta-carotene on the primary endpoint of major vascular disease over a long-term follow-up of more than nine years. These null results are consistent with the majority of trials of these antioxidants in both primary and secondary prevention. When combinations of agents were examined, there were no significant interactions, except for a possible reduction in stroke among those taking both active vitamin C and active vitamin E. In contrast to a recent meta-analysis of antioxidant supplements,[15] we found no detrimental effects of any of these agents on total or CVD mortality.

No previous trial has considered the effect of vitamin C alone on CVD prevention. A few trials, however, have considered vitamin C as one component of an antioxidant cocktail, but have found no benefit for cardiovascular disease either in primary[16, 17] or in secondary[18, 19] prevention. Studies of atherosclerotic progression among patients with coronary disease[20] or hypercholesterolemia[21] have shown inconsistent results for combinations of vitamins C and E. The null results for the primary endpoint seen in WACS further limit enthusiasm for the role of vitamin C in cardiovascular risk protection.

For vitamin E, the lack of effect in primary prevention is consistent with results from three previous intervention trials of vitamin E as a single agent.[22-24] As in the Women's Health Study,[24] there was some suggestion of an early effect of vitamin E in WACS (Figure 2), but this diminished over time and was null overall. We also found no evidence of an increase in total mortality at the 600 IU every other day dose tested, as suggested for higher doses in a prior meta-analysis.[25] We did find a significant reduction in the primary endpoint in the subgroup of women with prior CVD. Previous trials of vitamin E in secondary prevention have been inconsistent, with significant decreases in CVD found in two trials of shorter 1.4 years duration.[26, 27] Later and longer trials have generally not upheld[26] this effect. Some found a reduction in secondary outcomes only,[28, 29] and another reported no effect at all in a combined high risk primary and secondary prevention population.[30, 31] Meta-analyses of patients with prior CVD enrolled in these trials may provide additional insights as to whether there may still be a role for vitamin E in the secondary prevention of cardiovascular disease.

For beta-carotene, we found no overall benefit or harm, a lack of effect that is consistent with studies using a similar 50 mg alternate day regimen.[32, 33] The ATBC[22] and CARET[34] trials found some increase in total and cardiovascular deaths among smokers or those exposed to asbestos, but we found little difference in these endpoints. Compliance-adjusted analyses found some increase in CVD mortality, but these were not adjusted for time-varying risk factors associated with compliance, and are more prone to bias than intent-to-treat analyses. Previous studies in secondary prevention had been small and inconsistent,[29, 35] and we found no evidence for benefit or harm in this pre-specified sub-group.

For vitamin E, there have been suggestions that γ-tocopherol is a more powerful antioxidant. Supplementation with α-tocopherol depletes γ-tocopherol, which may explain the lack of effect seen in vitamin E trials.[36] Single antioxidants may not reflect the complex vitamins and nutrients found in foods, which may explain the discrepancies between most intervention trials and studies of fruits and vegetables.[37] Trials using an antioxidant combination, however, also have not shown a clear benefit for CVD.[16-19] Questions concerning the complex nature of dietary effects on lipid peroxidation, however, are deserving of further study.

Limitations of the trial include the lack of complete follow-up and compliance. Mortality information follow-up was virtually complete through 2003, then 93% complete for the remaining two years. Overall, however, mortality follow-up as a percentage of person-time was over 99% complete. Although suboptimal, compliance in WACS over time is relatively comparable to several other trials of vitamin supplementation with at least four years duration in secondary,[19, 29] as well as primary[17, 38, 39] prevention.

In summary, results from WACS and other antioxidant trials have not found consistent preventive effects on CVD. Overall, we found no benefit on the primary combined endpoint for any of the antioxidant agents tested, alone or in combination. We also found no evidence for harm. While additional research into combinations of agents, particularly for stroke, may be of interest, widespread use of these individual agents for cardiovascular protection does not appear warranted.

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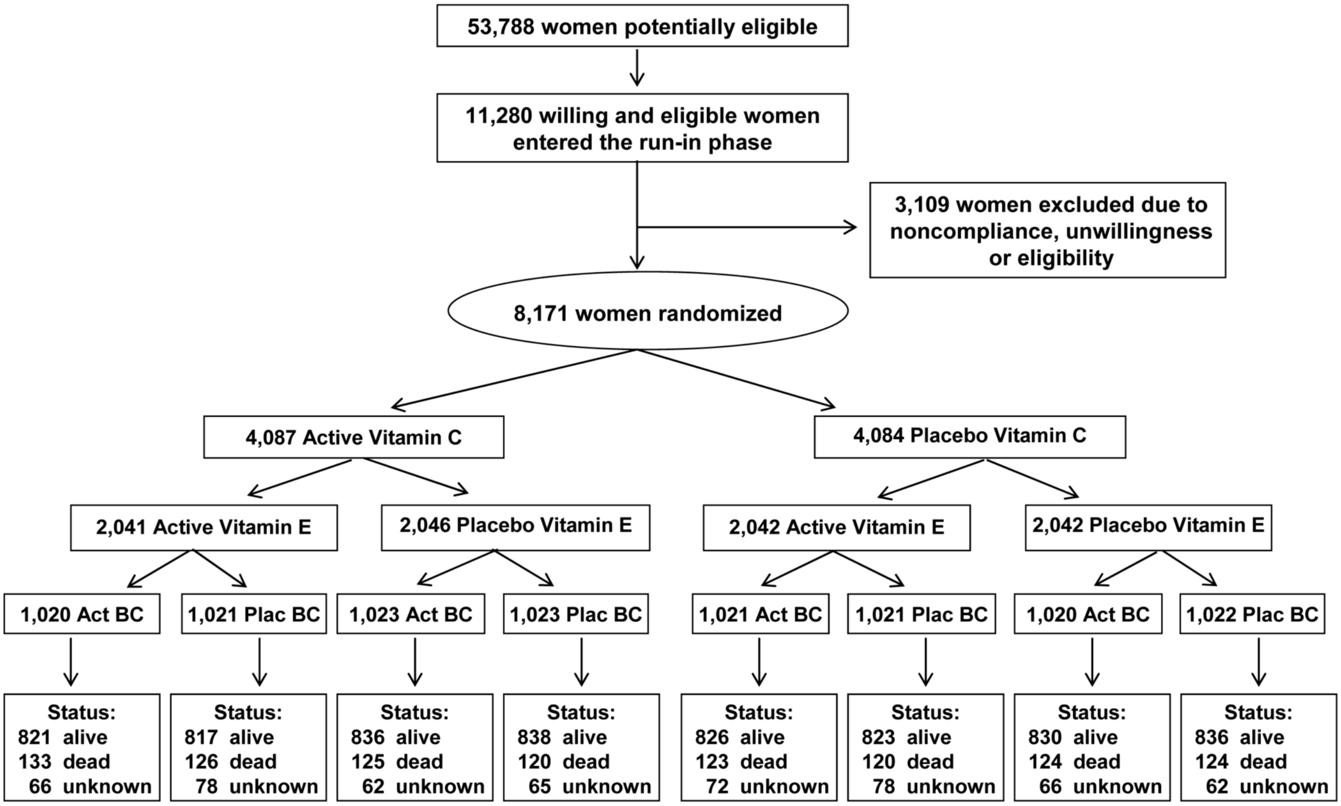

Figure 1.
Enrollment, randomization and follow-up of participants in the Women's Antioxidant Cardiovascular Study (WACS).

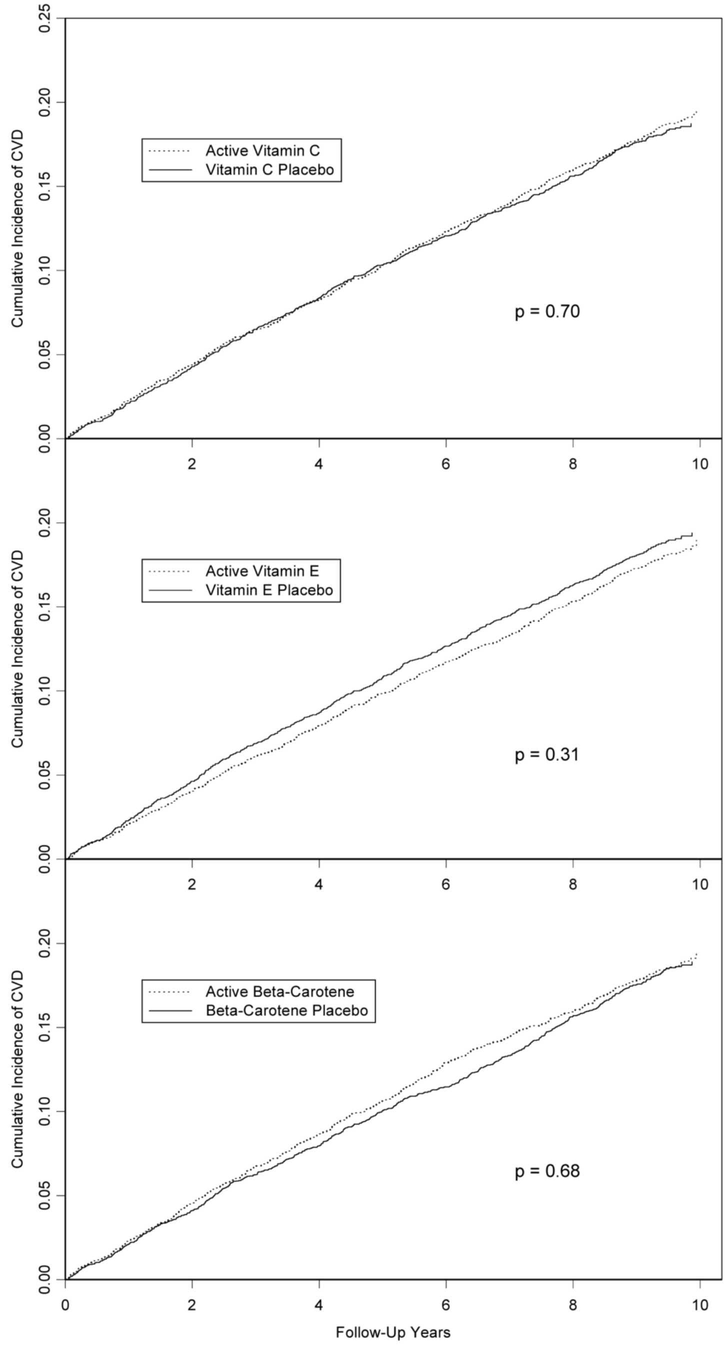

Figure 2.
Cumulative incidence of major vascular disease (myocardial infarction, stroke, coronary revascularization, or cardiovascular death), by randomized antioxidant intervention in the Women's Antioxidant Cardiovascular Study (WACS). P-value is from log-rank test.

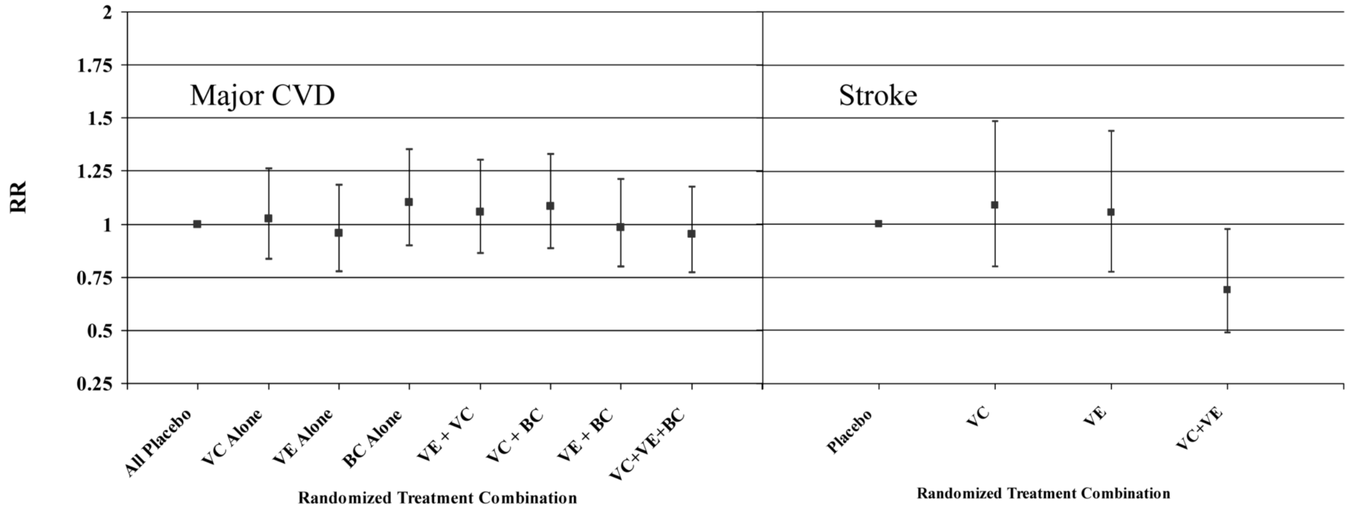

Figure 3.
Relative risk (RR) of major cardiovascular disease by eight combinations of all three active antioxidant assignments relative to the all placebo group (right); or of stroke by combinations of active vitamin C and vitamin E assignments relative to the groups with placebo vitamins C and E (left). VC = vitamin C, VE = vitamin E, BC = beta-carotene, CVD = cardiovascular disease.

Table 1

Comparison of baseline characteristics by randomized groups in the Women's Antioxidant Cardiovascular Study.*

		Vitamin C		Vitamin E		Beta-carotene	
Baseline Factor	**Total N**	**Active (N=4087)**	**Placebo (N=4084)**	**Active (N=4083)**	**Placebo (N=4088)**	**Active (N=4084)**	**Placebo (N=4087)**
Age (years), mean ± SD	8171	60.6 ± 8.8	60.6 ± 8.8	60.6 ± 8.9	60.6 ± 8.8	60.6 ± 8.9	60.6 ± 8.8
Age (years), %							
40-54	2400	29.4	29.4	29.3	29.4	29.4	29.4
55-64	2993	36.6	36.7	36.7	36.6	36.6	36.6
65+	2778	34.0	34.0	34.0	34.0	34.0	34.0
Health history, %†							
Prior CVD	5238	64.1	64.1	64.7	63.5	63.8	64.4
3+ risk factors	2933	35.9	35.9	35.3	36.5	36.2	35.6
History of hypertension, %							
Yes	6137	75.4	74.8	74.4	75.8	75.3	74.9
No	2034	24.6	25.2	25.6	24.2	24.7	25.1
History of high cholesterol, %							
Yes	5950	72.6	73.0	72.7	73.0	71.5	74.1§
No	2221	27.4	27.0	27.3	27.0	28.5	25.9
History of diabetes, %							
Yes	1564	19.4	18.9	18.7	19.6	19.2	19.1
No	6607	80.6	81.1	81.3	80.4	80.8	80.9
Parental History of MI, %‡							
Yes	3032	38.2	36.4	36.7	37.9	37.1	37.5
No	5097	61.8	63.6	63.3	62.1	62.9	62.5
Smoking status, %							
Current	1269	15.1	15.9	15.5	15.6	15.3	15.8
Past	3405	42.0	41.4	41.7	41.6	41.6	41.8
Never	3497	42.9	42.7	42.8	42.8	43.1	42.4
Alcohol use in past year, %							
Never	4514	56.1	54.4	54.7	55.8	55.6	54.9
0 - < 1/week	1008	12.3	12.4	12.1	12.6	12.3	12.4
1-6 / week	1964	23.9	24.2	24.9	23.2	23.7	24.4
Daily	685	7.8	9.0	8.3	8.5	8.4	8.4
Body mass index (kg/m^2), mean ± SD	8164	30.3 ± 6.7	30.3 ± 6.7	30.3 ± 6.6	30.3 ± 6.7	30.2 ± 6.7	30.4 ± 6.6
Body mass index, %							
<25 kg/m^2	1906	23.2	23.5	23.0	23.7	24.2	22.4
25-<30 kg/m^2	2339	29.1	28.2	29.2	28.1	28.4	28.9
30+ kg/m^2	3919	47.8	48.2	47.8	48.2	47.4	48.6
Menopause and HT use, %							
Premenopausal	653	8.1	8.2	8.2	8.0	7.8	8.5
Uncertain	1167	14.4	14.7	14.5	14.6	14.5	14.6
Postmenopausal, current HT	3083	39.2	37.7	38.8	38.1	38.7	38.2
Postmenopausal, no HT	3121	38.4	39.4	38.5	39.3	39.0	38.8
Current multivitamin use, %							
Yes	2192	26.5	27.5	27.1	26.9	26.9	27.1
No	5927	73.5	72.5	72.9	73.1	73.1	72.9

*Abbreviations: SD = standard deviation; CVD = cardiovascular disease; MI = myocardial infarction; HT = hormone therapy.

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† Prior CVD is history of MI, stroke, coronary revascularization, angina pectoris, or transient ischemic attack. 3+ risk factors denotes women with no prior CVD but with at least 3 of the following: hypertension, high cholesterol, diabetes mellitus, parental history of premature MI (before age 60), obesity (body mass index (BMI) $\geq$ 30 kg/m^2), current cigarette smoking, and inconsistent report of prior CVD.

‡ Before age 60.

§ p=0.007 for active vs. placebo.

Table 2

Relative risk of cardiovascular outcomes by randomized antioxidant intervention group in the Women's Antioxidant Cardiovascular Study.*

Outcome	Vitamin C				Vitamin E				Beta-carotene			
	N Active	N Plac	RR (95% CI)	p	N Active	N Plac	RR (95% CI)	p	N Active	N Plac	RR (95% CI)	p
Major CVD†	731	719	1.02 (0.92-1.13)	0.71	708	742	0.94 (0.85-1.04)	0.23	731	719	1.02 (0.92-1.13)	0.71
MI, stroke, CVD death	419	415	1.01 (0.88-1.16)	0.87	399	435	0.90 (0.78-1.03)	0.12	435	399	1.09 (0.95-1.25)	0.21
MI‡	140	134	1.05 (0.83-1.33)	0.70	131	143	0.91 (0.72-1.15)	0.44	135	139	0.97 (0.77-1.23)	0.82
Fatal	15	19	0.79 (0.40-1.55)	0.49	18	16	1.11 (0.57-2.18)	0.76	10	24	0.42 (0.20-0.87)	0.02
Nonfatal	125	115	1.09 (0.85-1.41)	0.50	113	127	0.88 (0.69-1.14)	0.34	125	115	1.09 (0.85-1.40)	0.51
Revascularization‡	446	443	1.01 (0.89-1.15)	0.88	438	451	0.96 (0.85-1.10)	0.59	438	451	0.98 (0.86-1.11)	0.71
Total CHD	510	489	1.05 (0.93-1.19)	0.46	491	508	0.96 (0.85-1.09)	0.52	500	499	1.01 (0.89-1.14)	0.92
Stroke‡	138	160	0.86 (0.69-1.08)	0.21	137	161	0.84 (0.67-1.05)	0.12	161	137	1.17 (0.93-1.47)	0.17
Ischemic	123	148	0.83 (0.66-1.06)	0.13	121	150	0.79 (0.62-1.01)	0.06	143	128	1.12 (0.88-1.42)	0.37
Hemorrhagic	13	12	1.09 (0.50-2.39)	0.83	15	10	1.47 (0.66-3.27)	0.35	17	8	2.13 (0.92-4.93)	0.08
Fatal	15	18	0.84 (0.42-1.67)	0.63	18	15	1.15 (0.58-2.28)	0.69	22	11	1.98 (0.96-4.07)	0.07
Nonfatal	123	142	0.87 (0.68-1.10)	0.25	119	146	0.80 (0.63-1.02)	0.08	139	126	1.10 (0.87-1.40)	0.42
TIA	203	218	0.93 (0.77-1.13)	0.49	205	216	0.94 (0.78-1.14)	0.54	201	220	0.91 (0.75-1.10)	0.35
CVD death‡	206	189	1.10 (0.90-1.33)	0.37	193	202	0.94 (0.77-1.15)	0.56	211	184	1.14 (0.94-1.39)	0.18
Total mortality	504	491	1.03 (0.91-1.17)	0.62	502	493	1.00 (0.89-1.14)	0.95	505	490	1.03 (0.91-1.17)	0.65

*Abbreviations: CVD = cardiovascular disease; MI = myocardial infarction; CHD = coronary heart disease (includes MI, revascularization, CHD death); TIA = transient ischemic attack; RR = relative risk; CI = confidence interval; Plac = Placebo.

†Primary outcome, includes MI, stroke, revascularization procedure or death due to cardiovascular cause.

‡Secondary outcome

Table 3

Relative risk of major cardiovascular outcomes by randomized intervention within subgroups in the Women's Antioxidant Cardiovascular Study.*

	Vitamin C				Vitamin E				Beta-carotene			
Baseline Factor	**Active**	**Placebo**	**RR (95% CI)**	**p**	**Active**	**Placebo**	**RR (95% CI)**	**p**	**Active**	**Placebo**	**RR (95% CI)**	**p**
Age (years)												
40-54	111	123	0.90 (0.70-1.17)	0.44	117	117	1.01 (0.78-1.30)	0.95	115	119	0.97 (0.75-1.25)	0.82
55-64	269	244	1.12 (0.94-1.33)	0.20	246	267	0.91 (0.77-1.09)	0.30	252	261	0.96 (0.81-1.15)	0.68
65+	351	352	0.99 (0.85-1.15)	0.91	345	358	0.94 (0.81-1.09)	0.39	364	339	1.08 (0.93-1.25)	0.31
Health history												
Prior CVD	592	567	1.05 (0.93-1.18)	0.43	558	601	0.89 (0.79-1.00)	0.04	580	579	1.02 (0.91-1.14)	0.77
3+ risk factors	139	152	0.93 (0.74-1.16)	0.51	150	141	1.13 (0.89-1.42)	0.32	151	140	1.06 (0.84-1.34)	0.60
Smoking status												
Current	139	158	0.92 (0.73-1.16)	0.48	151	146	1.05 (0.84-1.32)	0.68	152	145	1.12 (0.89-1.40)	0.34
Past or never	592	561	1.05 (0.94-1.18)	0.38	557	596	0.91 (0.81-1.02)	0.12	579	574	1.00 (0.89-1.12)	0.98
Alcohol use in past year												
Never	443	442	0.97 (0.85-1.11)	0.68	427	458	0.95 (0.83-1.08)	0.43	461	424	1.08 (0.95-1.23)	0.24
Ever	288	277	1.08 (0.92-1.28)	0.35	281	284	0.94 (0.79-1.11)	0.44	270	295	0.92 (0.78-1.09)	0.35
Body mass index												
<25 kg/m^2	192	170	1.17 (0.95-1.44)	0.14	167	195	0.88 (0.71-1.08)	0.22	197	165	1.09 (0.88-1.34)	0.43
25-<30 kg/m^2	229	225	0.98 (0.81-1.18)	0.82	233	221	0.98 (0.81-1.18)	0.81	210	244	0.89 (0.74-1.07)	0.21
30+ kg/m^2	310	323	0.97 (0.83-1.14)	0.73	307	326	0.94 (0.80-1.10)	0.43	323	310	1.08 (0.93-1.27)	0.32
History of hypertension												
Yes	583	591	0.98 (0.87-1.09)	0.68	570	604	0.95 (0.84-1.06)	0.35	595	579	1.01 (0.90-1.13)	0.87
No	148	128	1.21 (0.95-1.53)	0.12	138	138	0.93 (0.73-1.18)	0.54	136	140	1.03 (0.82-1.31)	0.78
Diabetes												
Yes	232	235	0.96 (0.80-1.15)	0.63	222	245	0.92 (0.77-1.11)	0.38	244	223	1.09 (0.91-1.31)	0.34
No	499	484	1.04 (0.92-1.18)	0.52	486	497	0.95 (0.84-1.08)	0.45	487	496	0.99 (0.87-1.12)	0.82
Menopause and HT use												
Premenopausal	26	30	0.92 (0.54-1.55)	0.74	31	25	1.26 (0.74-2.13	0.40†	24	32	0.82 (0.48-1.40)	0.47
Uncertain	77	65	1.16 (0.83-1.61)	0.39	60	82	0.70 (0.50-0.98)	0.04	74	68	1.06 (0.77-1.48)	0.71
Post, current HT	277	252	1.07 (0.90-1.27)	0.45	279	250	1.10 (0.93-1.31)	0.27	280	249	1.10 (0.92-1.30)	0.29
Post, no HT	337	359	0.96 (0.83-1.11)	0.59	328	368	0.88 (0.76-1.02)	0.08‡	338	358	0.96 (0.83-1.11)	0.60
Current multivitamin use												
Yes	173	194	0.89 (0.72-1.09)	0.26	179	188	0.92 (0.75-1.13)	0.42	183	184	0.99 (0.81-1.22)	0.94
No	551	518	1.07 (0.95-1.21)	0.28	525	544	0.96 (0.85-1.08)	0.46	540	529	1.02 (0.90-1.15)	0.76

*Abbreviations: CVD = cardiovascular disease; Vit = vitamin; Plac = placebo; RR = relative risk; CI = confidence interval; HT = hormone therapy; Post = postmenopausal. Baseline factors are defined as in Table 1.

†P for interaction < 0.05.

‡Among post-menopausal women, p < 0.05 for interaction comparing HT users vs. non-users.