

# Routine Vitamin Supplementation To Prevent Cardiovascular Disease: A Summary of the Evidence for the U.S. Preventive Services Task Force

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**Background:** Antioxidant vitamins are thought to play a role in atherosclerosis. Supplementation of these nutrients has been explored as a means of reducing cardiovascular morbidity and mortality.

**Purpose:** To assess the evidence of the effectiveness of vitamin supplementation, specifically vitamins A, C, and E;  $\beta$ -carotene; folic acid; antioxidant combinations; and multivitamin supplements, in preventing cardiovascular disease.

**Data Sources:** Cochrane Controlled Trials Registry and MEDLINE (1966 to September 2001), reference lists, and experts.

**Study Selection:** The researchers selected English-language reports of randomized trials and cohort studies that assessed vitamin supplementation in western populations and reported incidence of or death from cardiovascular events. They also included reports of good- or fair-quality clinical trials of primary and secondary prevention and good- or fair-quality prospective cohort studies. Studies that examined only dietary nutrients or did not provide separate estimates for supplements were not included.

**Data Extraction:** Two reviewers abstracted descriptive informa-

tion and data on cardiovascular outcomes and mortality from included studies. The researchers assessed study quality using predetermined criteria.

**Data Synthesis:** Evidence tables were constructed to summarize data from included studies. The researchers summarized the strength, level, and quality of the overall evidence for the effectiveness of each of the vitamin supplements in preventing or treating cardiovascular disease.

**Conclusions:** Some good-quality cohort studies have reported an association between the use of vitamin supplements and lower risk for cardiovascular disease. Randomized, controlled trials of specific supplements, however, have failed to demonstrate a consistent or significant effect of any single vitamin or combination of vitamins on incidence of or death from cardiovascular disease. Understanding the sources of these differences will permit researchers to better analyze the cohort study data and to better design long-term clinical trials.

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Approximately 60 million persons in the United States have some form of cardiovascular disease (CVD), and in 1996, CVD accounted for 41.4% of all deaths in the United States (1). While hypertension, diabetes, dyslipidemia, and smoking are leading risk factors, nutritional status plays a substantial role in the development of atherosclerotic CVD. Antioxidant nutrients, including vitamin C, vitamin E, and  $\beta$ -carotene, are thought to play a role in atherosclerosis (2–5). Some experts believe that mild to moderate deficiencies of these vitamins, although not severe enough to cause classic deficiency diseases, may be involved in the development of CVD (3, 4, 6). Therefore, it is thought that antioxidant supplementation may help reduce the incidence or progression of atherosclerotic CVD.

The biological basis of antioxidant use to prevent atherosclerotic heart disease is based largely on the oxidative modification hypothesis of atherosclerosis (6). According to this hypothesis, lipid peroxidation or oxidative modification of low-density lipoprotein is the initiator of atherosclerosis. Antioxidants capable of inhibiting lipid peroxidation should support primary and secondary prevention and consequently reduce cardiovascular events, including myocardial infarction.

This evidence review was conducted for the U.S. Preventive Services Task Force (USPSTF) to serve as the foundation for its recommendations on vitamin supplementation for disease prevention. This article addresses a key question posed by the Task Force: Does supplementation with vitamin A, vitamin C, vitamin E,  $\beta$ -carotene, or a

multivitamin reduce cardiovascular death, all-cause mortality, or cardiovascular events in the general adult population of the United States and in a population with evidence of atherosclerotic heart disease?

## METHODS

### Literature Search and Study Selection

#### Search Strategy

We searched the Cochrane Controlled Trials Registry and MEDLINE for relevant papers published in English from 1966 to September 2001, using Medical Subject Headings and keywords for the individual nutrients (vitamin A, vitamin C, vitamin E,  $\beta$ -carotene, folic acid) and for multivitamin and antioxidant supplements, combined with terms for CVD, coronary artery disease, myocardial infarction, and related risk factors (blood pressure, hypertension, hyperlipidemia, homocysteine). We examined reference lists of review articles (6–15) and asked experts for additional references. Finally, we searched MEDLINE using the acronyms or full titles of the major trials and cohort studies to identify additional publications.

#### Study Selection

The scope of this review was developed with input from the USPSTF. We included reports of randomized trials and prospective cohort studies from U.S. and European populations that assessed use of vitamin supplements and reported incidence of or death from cardiovascular events. We included only studies that measured intake of

vitamins from supplements, not from foods; most supplements provide single or limited nutrient combinations, whereas dietary sources are nutritionally complex and complicate data interpretation. Only cohorts that reported specifically on vitamin supplement use with risk ratios independent of dietary intake were included. Both primary and secondary prevention trials were considered but were analyzed separately. Studies conducted in specific populations that were not widely generalizable, such as a cohort with end-stage renal disease, were excluded. Only cohort studies rated as being of good to fair quality, according to predetermined criteria from a system developed by the current USPSTF (16), were included. Studies were excluded if they contained no original data, were not relevant (for example, addressed vitamin deficiency disease), did not report data on the specified outcomes, or took place in an acute care setting. Case-control studies were excluded because of retrospective data collection.

Two reviewers read titles and abstracts of 2758 identified articles and selected 306 as possibly relevant. Full-text articles of these citations were retrieved for further review. Of these, 38 articles, representing 10 cohort studies and 20 randomized, controlled trials (RCTs), were selected for inclusion in evidence tables. An additional 25 articles were included for background and context.

#### Data Abstraction, Validity Assessment, and Synthesis

We abstracted the following descriptive information: population, setting, sample size, supplement (dose, formulation, and frequency), control group intervention, length of follow-up, follow-up rate, confounding factors, factors controlled for in analyses, method of ascertaining adherence, adherence rate, and adverse effects. We recorded data on the following outcomes: cardiovascular events, myocardial infarction, restenosis, change in angina, cardiovascular mortality, and all-cause mortality. Study quality was assessed by using the standards of the current USPSTF (16). For RCTs, we summarized study quality using the Jadad score, which rates trials on a scale of 1 to 5 on the basis of adequacy of randomization method, blinding, and other criteria (17). Data abstraction and quality assessment were conducted independently by at least two reviewers. Disagreements were resolved by consensus or by a third reviewer. Finally, we summarized the strength, level, and quality of the overall evidence tables for the effectiveness of each of the vitamin supplements in preventing CVD.

#### Included Studies

We included 11 reports from 10 prospective cohort studies (18–28), 12 reports from 10 randomized trials of primary prevention of CVD (29–40), and 15 reports from 12 randomized trials of secondary prevention of CVD (41–55). The principal epidemiologic cohort studies (Table 1) included the Nurses' Health Study (87 245 female nurses followed for >10 years) (18, 19), the Health Professionals' Follow-up Study (39 910 male health professionals followed for 4 years) (20), the Iowa Women's

Health Study (34 486 Iowa women followed for 7 years) (21), and a cohort of 83 639 male physicians invited to participate in the Physicians' Health Study (27). Other studies include the Established Populations for Epidemiologic Studies of the Elderly (11 178 men and women >65 years of age) (23); the first National Health and Nutrition Examination Survey (NHANES I) (22), which followed a similar number of participants; and a study of more than 1 million people recruited for a mortality study by the American Cancer Society (25). These studies were all rated as good or fair using the USPSTF rating scale (16). Most had follow-up rates above 90% after 4 or more years, used well-defined outcomes, and adjusted for relevant confounders.

The RCTs of primary prevention (Table 2) principally comprised large factorial trials, including an antioxidant supplement with a co-intervention (angiotensin-converting enzyme inhibitor, aspirin, or lipid-lowering agent) examining CVD incidence or mortality. Of these nine trials, only four had the primary objective of preventing CVD: the Heart Outcomes Prevention Evaluation (HOPE) (35), the Women's Health Study (30), the Primary Prevention Project (36), and the Heart Protection Study (40). The others were designed to test whether antioxidants would prevent cancer or reduce progression of age-related eye disease; cardiovascular events were analyzed as a secondary end point. With one exception (36), all primary prevention trials were double-blind and placebo controlled.

Among secondary prevention trials, 10 of 12 examined the effects of vitamin supplementation in patients enrolled on the basis of preexisting CVD (Table 3). Two studies analyzed subgroups with previous coronary disease (41–44). In addition, two major trials analyzed primary and secondary prevention together (35, 40). Jadad scores for these studies ranged from 3 to 5 on the 5-point scale, indicating fair to good quality.

#### Role of the Funding Source

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## RESULTS

### Vitamin A

One good-quality cohort study evaluated the effect of vitamin A supplementation on incident coronary death (21). Participants in the highest quartile of vitamin A use did not have a lower risk for coronary death than those in the lowest quartile. There are no data from clinical trials on the effect of vitamin A supplements on atherosclerotic CVD.

### Vitamin C

In three of four cohort studies, vitamin C supplementation was not associated with coronary heart disease mor-

Table 1. Cohort Studies of the Association between Vitamin Supplement Use and Cardiovascular Disease Risk\*

Study, Year (Reference)	Quality Score	Description	Outcomes and Comparison
Stampfer et al. (Nurses' Health Study), 1993 (18)	Good	87 245 female U.S. nurses, age 34–59 y, with no history of cancer, angina, MI, stroke, or other CVD; 552 cases of major coronary disease; 97.1% follow-up at 8 y	Major coronary disease (nonfatal MI or death due to coronary disease) in users vs. nonusers
Rimm et al. (Nurses' Health Study), 1998 (19)	Good	80 082 female U.S. nurses, same as above plus no hypercholesterolemia or diabetes; 658 cases of nonfatal MI and 281 coronary deaths; 98% follow-up for mortality at 14 y	Incident nonfatal MI and coronary death in users (4–7 pills/wk) vs. nonusers
Rimm et al. (Health Professionals' Study), 1993 (20)	Good	39 910 male U.S. health professionals age 40–75 y; 667 incident cases of coronary disease; 96% follow-up at 4 y	Incident coronary disease (fatal coronary disease, nonfatal MI, CABG, angioplasty) in users vs. nonusers
Kushi et al. (Iowa Women's Health Study), 1996 (21)		34 486 women, age 55–69 y, from the general population of Iowa women; 242 incident coronary deaths; follow-up virtually complete (according to National Death Index) at 7 y	Incident coronary death in quintile 4 (>250 IU/d) vs. quintile 1 (nonusers)  Quintile 5 (>1000 mg/d) vs. quintile 1 (nonusers) Quintile 4 (>10 000 IU/d) vs. quintile 1 (nonusers)
Enstrom et al. (NHANES I Epidemiologic Follow-up Study), 1992 (22)	Good	11 348 men (39%) and women, age 25–74 y; representative sample of the noninstitutionalized U.S. population; 92% (in women) to 94% (in men) follow-up at 10 y	Cardiovascular mortality; standardized mortality ratio of regular supplement users  All-cause mortality; standardized mortality ratio of regular supplement users
Losonczy et al. (Established Populations for Epidemiologic Studies of the Elderly), 1996 (23)	Good	11 178 men and women age >65 y in 4 communities; 1101 coronary disease deaths; follow-up rate for mortality virtually complete (according to National Death Index) at 6 y	Coronary disease mortality in users vs. nonusers  All-cause mortality in users vs. nonusers
Klipstein-Grobusch et al. (Rotterdam Study), 1999 (24)	Good	4802 residents of one district in the Netherlands, age 55–95 y; 173 MIs; 94% follow-up at a mean of 4 y (range, 3–7 y)	Incident fatal and nonfatal MI in users vs. nonusers
Watkins et al. (Cancer Prevention Study II), 2000 (25)	Fair	1 063 023 U.S. residents recruited by American Cancer Society volunteers; follow-up virtually complete (according to National Death Index) at 7 y	Cardiovascular mortality in users vs. nonusers  All-cause mortality in users vs. nonusers
Knekt et al. (Finnish Mobile Clinic Study), 1994 (26)	Good	5133 men and women in Finland, age 30–69 y, free of known heart disease at baseline; 244 CHD deaths; 100% follow-up at a mean of 14 y (range, 12–16 y)	Cardiovascular mortality in users of supplements containing vitamin E and/or vitamin C vs. nonusers
Muntwyler et al. (Physicians' Health Study Screening Cohort), 2002 (27)	Good	83 639 male physicians with no history of CVD who responded to a letter inviting participation in the Physicians' Health Study; follow-up virtually complete (according to the National Death Index) at 4 y	CVD and CHD mortality in users and nonusers
Hodis et al. (Cholesterol Lowering Atherosclerosis Study), 1995 (28)	Good	Analysis of secondary prevention in randomized clinical trial of patients with repeated angiography at 2 y; study compares coronary artery disease progression with aggressive cholesterol reduction vs. placebo; cohort analysis assessed supplemental vitamin use	Change in minimal luminal diameter assessed 2 y apart in supplement users (vitamin E ≥100 IU/d, vitamin C ≥250 mg/d) and the obverse

\* BMI = body mass index; CABG = coronary artery bypass grafting; CHD = coronary heart disease; CVD = cardiovascular disease; MI = myocardial infarction; NHANES = National Health and Nutrition Examination Survey.

† Quetelet index is a measure of BMI.

‡ RTI International, Research Triangle Park, North Carolina.

Table 1—Continued

Factors Adjusted for in Analysis†	Multivariate Relative Risk (95% CI)				
	Vitamin A	Vitamin C	Vitamin E	Antioxidant Combinations	Multivitamin Preparations
Age, time period, quetelet index, smoking, alcohol intake, menopausal status, postmenopausal hormone use, exercise, regular use of aspirin, hypertension, high cholesterol level, diabetes, total energy intake, use of vitamin E supplements, use of multivitamin supplements			0.63 (0.45–0.88)		0.87 (0.70–1.07)
Age; time period; BMI; smoking; menopausal status; hormone replacement therapy; aspirin; vitamin E supplements; physical activity; hypertension; parental history of MI at age <65 y; alcohol; and quintiles of intake of fiber, alcohol, and saturated, polyunsaturated, and trans fat					0.76 (0.65–0.90)
Age, smoking, BMI; total calories, dietary fiber, alcohol consumption, hypertension, regular aspirin use, physical activity, parental history of MI at age <60 y, profession			0.75 (0.61–0.93)		
Age, total energy intake, BMI, waist-to-hip ratio, pack-years of smoking, hypertension, diabetes, oral contraceptive use, estrogen replacement therapy, physical activity, alcohol intake, marital status, education			1.09 (0.67–1.77)		
	1.29 (0.70–2.39)	0.74 (0.30–1.83)			
Adjusted to standardized U.S. population by using SUDAAN‡		0.52 (0.39–0.69)			
Adjusted to standardized U.S. population by using SUDAAN‡		0.74 (0.62–0.88)			
Age, sex, race, education, alcohol use, smoking history, aspirin use, CHD, stroke, diabetes, cancer, hypertension, and BMI		0.99 (0.74–1.33)	0.59 (0.37–0.93)	0.52 (0.28–0.97)	1.11 (0.91–1.36)
		1.09 (0.93–1.28)	0.73 (0.58–0.91)	0.63 (0.46–0.86)	1.03 (0.91–1.16)
Unclear				0.49 (0.21–0.99)	
Age; race; marital status; BMI; smoking; employment; exercise; education; aspirin use; diuretic use; liquor, wine, beer, or coffee consumption; vegetable index; history of diabetes, hypertension, heart disease, stroke, estrogen use				Men: 0.94 (0.88–1.01) Women: 0.90 (0.82–0.99)	Men: 0.99 (0.93–1.06) Women: 0.97 (0.90–1.05)
All of the above plus cancer, kidney disease, cirrhosis				Men: 0.98 (0.96–1.01) Women: 0.95 (0.92–0.98)	Men: 1.05 (1.02–1.08) Women: 1.02 (1.00–1.05)
Age, smoking, cholesterol level, hypertension, BMI, energy intake				0.55 (0.18–1.73)	
History of hypertension, history of hypercholesterolemia, current and past smoking, alcohol intake, physical activity, BMI, complementary vitamins, randomization status		CVD mortality: 0.88 (0.70–1.12) CHD mortality: 0.86 (0.63–1.18)	CVD mortality: 0.92 (0.70–1.21) CHD mortality: 0.88 (0.61–1.27)		CVD mortality: 1.07 (0.91–1.25) CHD mortality: 1.02 (0.83–1.25)
Unadjusted		No difference in progression of stenosis in users	Significantly less progression of stenosis in users (P = 0.04)		

Table 2. Randomized, Controlled Trials of Vitamin Supplementation for Primary Prevention of Cardiovascular Disease\*

Study, Year (Reference)	Jadad Score	Description	Treatment and Other Interventions
<b>Vitamin E</b>			
ATBC Cancer Prevention Study Group, 1994 (32)	5	29 133 Finnish male smokers, age 50–69 y; no current use of vitamin A, vitamin E, or $\beta$ -carotene; no severe angina, malignant condition, or other medical problems	Vitamin E, 50 IU/d, and $\beta$ -carotene, 20 mg/d, in 2 $\times$ 2 factorial design
Rapola et al. (ATBC Cancer Prevention Study), 1996 (33)	5	Same as above	Same as above
Virtamo et al. (ATBC Cancer Prevention Study), 1998 (34)	5	27 271 men, same as above except patients with previous MI excluded	Same as above
Yusuf et al. (HOPE Study), 2000 (35)	5	9541 men and women at 129 centers in 19 countries, age >55 y, with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes, plus one cardiovascular risk factor	Vitamin E, 400 IU/d from natural sources, and ACE inhibitor (ramipril, 10 mg) in 2 $\times$ 2 factorial design
Primary Prevention Project, 2001 (36)	3	4495 Italian men and women attending a general practitioner's office or outpatients attending a hospital-based hypertension clinic; age >50 y with one of the following cardiovascular risk factors: hypertension, hypercholesterolemia, diabetes mellitus, obesity, family history of early MI (age <55 y), age >64 y	Synthetic $\alpha$ -tocopherol, 300 IU/d, and aspirin, 100 mg/d, in 2 $\times$ 2 factorial design
Hodis et al. (VEAPS), 2002 (39)	5	353 patients age >40 y with high LDL levels and no symptoms or signs of CVD; no history of hypertriglyceridemia, diabetes or regular vitamin E use; primary outcome measure was change in carotid artery intima-media thickness	Tocopherol, 400 IU/d
<b><math>\beta</math>-Carotene</b>			
ATBC Cancer Prevention Study Group, 1994 (32)	5	29 133 Finnish male smokers, age 50–69 y; no current use of vitamin A, vitamin E, or $\beta$ -carotene; no severe angina, malignant condition, or other medical problems	$\beta$ -carotene, 20 mg/d, and vitamin E, 50 IU/d, in 2 $\times$ 2 factorial design
Rapola et al. (ATBC Cancer Prevention Study), 1996 (33)	5	Same as above	Same as above
Virtamo et al. (ATBC Cancer Prevention Study), 1998 (34)	5	27 271 men, same as above except patients with previous MI excluded	Same as above
Hennekens et al. (Physicians' Health Study), 1996 (29)	4	22 071 male U.S. physicians, age 40–84 y; no history of cancer, MI, stroke, or cerebral ischemia	$\beta$ -Carotene, 50 mg on alternate days, and co-intervention with aspirin, 325 mg, in 2 $\times$ 2 factorial design
Greenberg et al. (Skin Cancer Prevention Study), 1996 (31)	3	1188 U.S. men and 532 U.S. women <85 y of age with previous nonmelanoma skin cancer; multicenter trial to prevent skin cancer recurrence	$\beta$ -Carotene, 50 mg/d
Lee et al. (Women's Health Study), 1999 (30)	4	39 876 U.S. female health professionals, age >45 y; no history of cancer, coronary heart disease, or cerebrovascular disease	$\beta$ -Carotene, 50 mg on alternate days, and co-intervention with aspirin, 100 mg, and vitamin E, 600 IU/d, in 2 $\times$ 2 $\times$ 2 factorial design
<b>Antioxidant combinations</b>			
Omenn et al. (CARET), 1996 (37)	4	4060 West Coast U.S. male asbestos workers, age 45–74 y, first exposure to asbestos $\geq$ 15 y previously plus asbestos-related lung disease or high-risk job for 5 years, and 14 254 U.S. men and women age 50–69 y who were heavy smokers, had $\geq$ 20 pack-years of smoking, were current smokers, or quit <6 y previously	$\beta$ -Carotene, 30 mg/d, and retinol (retinyl palmitate), 25 000 IU/d
AREDS, 2001 (38)	5	4757 U.S. participants, age 55–80 y, recruited from ophthalmology clinics; no major CVD or cancer in recent past	Vitamin C, 500 mg/d, vitamin E, 400 IU/d, and $\beta$ -carotene, 15 mg/d; some patients with age-related macular degeneration also assigned to receive zinc, 80 mg, and copper, 2 mg, vs. placebo; 66% of the cohort chose to take a multivitamin (Centrum <sup>†</sup> ) in addition
Heart Protection Study, 2002 (40)	5	20 536 adults age 40–80 y in United Kingdom with blood cholesterol level $\geq$ 3.5 mmol/L and history of coronary artery disease, other occlusive arterial disease, diabetes, or treated hypertension; those with previous high-dose vitamin E supplementation or life-threatening disease excluded; participants must have shown adherence in 2-mo prerandomization adherence period	Synthetic vitamin E, 600 mg/d, vitamin C, 250 mg/d, and $\beta$ -carotene, 20 mg/d, in 2 $\times$ 2 factorial trial; co-intervention with simvastatin

\* Values in square brackets are 95% CIs. ACE = angiotensin-converting enzyme; ATBC = Alpha-Tocopherol Beta-Carotene; CARET = Carotene and Retinol Efficacy Trial; CVD = cardiovascular disease; HOPE = Heart Outcomes Prevention Evaluation; LDL = low-density lipoprotein; MI = myocardial infarction; RR = relative risk; VEAPS = Vitamin E Atherosclerosis Prevention Study.  
<sup>†</sup> Wyeth Consumer Healthcare, Berks, United Kingdom.

Table 2—Continued

Duration of Follow-up	Follow-up Rate	MI	CVD	CVD Mortality	All-Cause Mortality
5–8 y (median, 6.1 y)	Case ascertainment “essentially complete”				RR, 1.02 [0.95–1.09]
Maximum, 7 y; median, 4.7 y	73%		For angina: RR, 0.91 [0.83–0.99]		
5–8 y (median, 6.1 y)	Case ascertainment “essentially complete”	RR, 1.04 [0.89–1.22]	RR, 0.98 [0.87–1.10]	RR, 0.90 [0.75–1.08]	
5 y	99.90%	RR, 1.02 [0.90–1.15]	RR, 1.05 [0.95–1.22]	RR, 1.05 [0.90–1.22]	RR, 1.00 [0.89–1.13]
Mean ± SD, 3.6 y ± 1.0 y (median, 4 y)	99.30%	RR, 0.89 [0.52–1.58]	RR, 0.94 [0.77–1.16]	RR, 0.86 [0.49–1.52]	RR, 1.07 [0.77–1.49]
3 y	73% followed for 3 y	Vitamin group: 5 events Placebo group: 4 events ( <i>P</i> value not cited)	Vitamin group: 8 events Placebo group: 10 events ( <i>P</i> > 0.2)	Vitamin group: 1 event Placebo group: 1 event ( <i>P</i> value not cited)	Vitamin group: 2 events Placebo group: 1 event ( <i>P</i> value not cited)
5–8 y (median, 6.1 y)	Case ascertainment “essentially complete”				RR, 1.08 [1.01–1.16]
Maximum, 7 y; median, 4.7 y	73%		For angina: RR, 1.06 [0.97–1.16]		
5–8 y (median, 6.1 y)	Case ascertainment “essentially complete”	RR, 1.06 [0.90–1.24]	RR, 1.03 [0.91–1.16]	RR, 0.99 [0.83–1.19]	
Mean, 12 y	99.99%	RR, 0.96 [0.84–1.09]	RR, 1.0 [0.91–1.09]	RR, 1.09 [0.93–1.27]	RR, 1.02 [0.93–1.11]
Median, 8.2 y	98%			RR, 1.16 [0.82–1.64]	RR, 1.03 [0.82–1.30]
Median, 2.1 y of treatment plus 2 y of follow-up	100%	RR, 0.84 [0.56–1.27]	RR, 1.14 [0.87–1.49]	RR, 1.17 [0.54–2.53]	RR, 1.07 [0.74–1.56]
5.5 y	98% for mortality			RR, 1.26 [0.99–1.61]	RR, 1.17 [1.03–1.33]
Mean, 6.3 y	97.7% completed the trial	Reported chest pain Vitamin group: 19.8% Placebo group: 22.8% ( <i>P</i> = 0.01)	RR, 1.06 [0.84–1.33]		
5 y	99.7% followed for morbidity			RR for vascular mortality, 1.05 [0.95–1.15]	RR, 1.04 [0.97–1.12]

Table 3. Randomized, Controlled Trials of Vitamin Supplementation for Secondary Prevention of Cardiovascular Disease\*

Study, Year (Reference)	Jadad Score	Description	Treatment and Other Interventions
<b>Vitamin C</b>			
Tomoda et al., 1996 (54)	1	119 patients, age 35–80 y, with stable or unstable angina at a single center in Japan; angiographic evidence of $\geq 1$ coronary lesion with $>75\%$ diameter; successful coronary angioplasty, no recent MI ( $<8$ wk), no use of coronary stent, no angioplasty for restenosis	Vitamin C, 500 mg/d
<b>Vitamin E</b>			
Anderson and Reid, 1974 (45)	4	48 patients from a single center in Toronto, Ontario, Canada, with stable angina and no change in medication or health status in previous 3 mo	d- $\alpha$ -tocopherol succinate, 400 IU/d
Gillilan et al., 1977 (46)	3	52 patients from a single center in Baltimore, Maryland, with stable, effort-related angina plus previous MI by Q wave and/or $>75\%$ occlusion of $\geq 1$ coronary artery on angiography; all had ECG evidence of ischemia; crossover design	d- $\alpha$ -tocopherol succinate, 1600 IU/d
DeMaio et al., 1992 (47)	2	100 patients from one practice in Atlanta, Georgia, with successful angioplasty to reduce restenosis; 84% were men	Vitamin E as d- $\alpha$ -tocopherol, 1200 IU/d
Stephens et al. (CHAOS), 1996 (48)	4	2002 patients from one center in East Anglia, United Kingdom, with angiographically proven coronary artery disease; 84% were men	Vitamin E, 800 IU/d, for the first cohort ( $n = 546$ ), vitamin E, 400 IU/d, for the second cohort ( $n = 489$ )
Rapola et al. (ATBC Cancer Prevention Study), 1997 (44)	4	1862 Finnish male smokers, age 50–69 y, with previous MI; no current use of vitamin A, vitamin E, or $\beta$ -carotene; no severe angina, malignant condition, or other serious illness	Same as above
Rapola et al. (ATBC Cancer Prevention Study), 1998 (43)	4	1795 Finnish male smokers, age 50–69 y, with mild angina, no current use of vitamin A, vitamin E, or $\beta$ -carotene; no severe angina, malignant condition, or other serious illness	Vitamin E, 50 IU/d, and $\beta$ -carotene, 20 mg/d, in $2 \times 2$ factorial design
GISSI-Investigators, 1999 (49)	2	11 334 patients from multiple centers in Italy with recent ( $<3$ mo) MI; open-label study Same as above	Synthetic $\alpha$ -tocopherol, 300 IU/d, and n-3 PUFA, 1 g/d, in $2 \times 2$ factorial design; two-way analysis Same as above, four-way analysis (vitamin E vs. control)
<b><math>\beta</math>-Carotene</b>			
Gaziano et al. (Physicians' Health Study), 1990 (41)	4	333 male U.S. physicians, age 40–84 y, with chronic stable angina and/or coronary revascularization; no history of cancer, MI, stroke, cerebral ischemia, or nonadherence in run-in phase	$\beta$ -Carotene, 50 mg on alternate days; co-intervention with aspirin in $2 \times 2$ factorial design
Gaziano et al. (Physicians' Health Study), 1996 (42)	4	Same as above	Same as above
Rapola et al. (ATBC Cancer Prevention Study), 1997 (44)	4	1862 Finnish male smokers, age 50–69 y, with previous MI; no current use of vitamin A, vitamin E, or $\beta$ -carotene; no severe angina, malignant condition, or other serious illness	Same as description given under "Vitamin E"
Rapola et al. (ATBC Cancer Prevention Study), 1998 (43)	4	1795 Finnish male smokers, age 50–69 y, with mild angina; no current use of vitamin A, vitamin E, or $\beta$ -carotene; no severe angina, malignant condition, or other serious illness	$\beta$ -Carotene, 20 mg/d, and vitamin E, 50 mg/d, in $2 \times 2$ factorial design
<b>Antioxidant combinations</b>			
Tardif et al. (MVP Study), 1997 (50)	3	255 patients from a single center in Canada who had $\geq 50\%$ stenosis and successful angioplasty; 77% were men	$\beta$ -Carotene, 60 000 IU/d, and vitamin C, 1000 mg/d, plus $\alpha$ -tocopherol, 1400 IU/d, vs. probucol, 500 mg/d, in $2 \times 2$ factorial design; all patients were prescribed AHA Step 1 diet
Rodes et al. (MVP Study), 1998 (51)	3	189 patients from a single center in Canada who had angioplasty of coronary artery, diameter $<3$ mm	Same as above
Brown et al., 2001 (52)	4	160 patients from Seattle, Washington, and from Canada who had clinical coronary disease (previous MI, coronary intervention, or confirmed angina); $>3$ coronary stenoses of $>30\%$ or 1 $>50\%$ ; and low HDL and high triglyceride levels	Vitamin E, 800 IU, vitamin C, 1000 mg, natural $\beta$ -carotene, 25 mg, plus selenium, 100 mg/d; co-intervention with simvastatin, 10–20 mg/d, plus niacin, 2000 mg
Waters et al. (WAVE Trial), 2002 (55)	5	423 postmenopausal women in 7 U.S. and Canadian centers who had angiographic evidence of $\geq 1$ coronary artery with 15%–75% stenosis	Vitamin E, 400 IU/d, plus vitamin C, 500 mg/d, vs. conjugated equine estrogens, 0.625 mg/d, in a $2 \times 2$ factorial trial; women without hysterectomy also received progesterone with estrogen
<b>Multivitamins</b>			
Schnyder et al., 2001 (53)	4	206 patients from multiple centers in Switzerland, Germany, and California who had successful coronary angioplasty of $\geq 1$ artery with $>50\%$ stenosis	Folic acid, 1 mg/d, vitamin B <sub>12</sub> , 400 $\mu$ g/d, and pyridoxine, 10 mg/d

\* Values in square brackets are 95% CIs. AHA = American Heart Association; ATBC = Alpha-Tocopherol Beta-Carotene; CHAOS = Cambridge Heart Antioxidant Study; CV = cardiovascular; CVD = cardiovascular disease; ECG = electrocardiography; GISSI-P = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione; HDL = high-density lipoprotein; MI = myocardial infarction; MVP = Multivitamins and Probuco; PUFA = polyunsaturated fatty acid; RR = relative risk; WAVE = Women's Angiographic Vitamin and Estrogen.

tality (21–23) or all-cause mortality (23). In two studies in older samples (21, 23), vitamin C use did not protect against coronary disease or all-cause mortality after adjustment for relevant confounders (23). Similarly, vitamin C had no impact on cardiovascular or coronary heart disease mortality (27). However, in a good-quality follow-up study of NHANES I (22), regular use of a vitamin C supplement reduced the standardized mortality ratio for cardiovascular mortality by 48% and for all-cause mortality by 26%. In a cohort analysis of a secondary prevention trial of cholesterol reduction or coronary stenosis, vitamin C use ( $\geq 250$

mg/d) had no appreciable effect on progression of stenosis (28).

No randomized clinical trial of primary prevention has evaluated the effect of supplementation with vitamin C alone on CVD outcomes. One small, poorly controlled trial of secondary prevention with vitamin C suggested a reduced rate of coronary restenosis and reintervention (54).

### Vitamin E

Three good-quality cohort studies reported statistically significant associations between the use of vitamin E sup-

Table 3—Continued

Duration of Follow-up	Follow-up Rate	Restenosis	Change in Angina
4 mo	85%	Vitamin group: 22% of segments Placebo group: 39% of segments ( $P < 0.05$ )	
9 wk	All followed but 25% excluded from analysis		Improvement in angina in 5 of 18 patients (vitamin group) vs. 3 of 18 patients (placebo group) ( $P$ value not analyzed)
6 mo	92%		Improvement in angina in 4 of 48 patients (vitamin group) vs. 3 of 48 patients (placebo group) ( $P > 0.05$ )
4 mo	Follow-up on 86% of patients completing protocol; unclear how many were randomly assigned into trial	Vitamin group: 18 of 52 patients (34.6%) Placebo group: 24 of 48 patients (50%)	
Median, 1.5 y	98%		
5–8 y (median, 5.3 y)	Not reported; data obtained from national registry		
5–8 y	48% at 5 y		Severe angina: RR, 1.14 [0.84–1.53]
3.5 y	99.9%		
Not reported	Not reported		
12 y	Not reported		
5–8 y (median, 5.3 y)	Not reported; data obtained from national registry		
5–8 y	48% at 5 y		Severe angina: RR, 1.15 [0.85–1.57]
5–7 mo	90%	Vitamin group: 40.3% of segments Placebo group: 38.9% of segments ( $P > 0.2$ )	
5–7 mo	95%	Vitamin group: 45.1% of segments Placebo group: 37.3% of segments ( $P > 0.2$ )	
3 y	91% for angiography, 99% for CV events	Vitamin group: 1.8% progression of stenosis Placebo group: 3.9% progression of stenosis ( $P = 0.16$ )	
Mean, 2.8 y	79% for angiography, 97% for clinical status	Progression of minimal luminal diameter Vitamin group: $-0.044$ mm/y Placebo group: $-0.028$ mm/y ( $P > 0.2$ )	
6 mo	86% for angiography, 96% for clinical outcomes	Vitamin group: 19.6% Placebo group: 37.6% ( $P = 0.01$ ); RR, 0.52 [0.32–0.86]	

Continued on following page

plements and lower rates of CVD mortality (23) and nonfatal CVD events (18, 19). In the all-female Nurses' Health Study, use of a vitamin E supplement was associated with an adjusted risk reduction of 37% for major coronary heart disease (nonfatal myocardial infarction and coronary disease mortality) after 8 years of follow-up (18). Less than 2 years of use had no significant impact on cardiovascular risk, and a minimum dosage of 100 IU/d was necessary to observe risk reduction. In the all-male Health Professionals' Follow-up Study, a similar adjusted risk reduction of 25% was observed for incident coronary disease

(coronary disease mortality, nonfatal myocardial infarction, coronary artery bypass graft surgery, or angioplasty) when supplement users were compared with nonusers after 4 years (20). Men who took a supplement containing at least 100 IU/d for at least 2 years had greater adjusted risk reduction than nonusers (relative risk, 0.63 [95% CI, 0.47 to 0.84]). This statistically significant reduction in death from coronary heart disease and all-cause mortality was also observed in an elderly U.S. population (23). In a cohort analysis of a secondary prevention trial of aggressive cholesterol reduction, participants who used at least 100

Table 3—Continued

Study, Year (Reference)	MI	CV Events	CVD Mortality	All-Cause Mortality
<b>Vitamin C</b>				
Tomoda et al., 1996 (54)	Vitamin group: 14% required reintervention Placebo group: 33% required reintervention ( <i>P</i> < 0.02)			
<b>Vitamin E</b>				
Anderson and Reid, 1974 (45)				
Gillilan et al., 1977 (46)		Vitamin group: 2 of 48 patients Placebo group: 2 of 48 patients ( <i>P</i> > 0.05)		
DeMaio et al., 1992 (47)				
Stephens et al. (CHAOS), 1996 (48)	Vitamin group: 14 events Placebo group: 41 events ( <i>P</i> < 0.001)	Vitamin group: 41 events Placebo group: 62 events ( <i>P</i> = 0.015)	Vitamin group: 27 patients Placebo group: 23 patients ( <i>P</i> > 0.2)	Vitamin group: 36 patients Placebo group: 26 patients ( <i>P</i> > 0.2)
Rapola et al. (ATBC Cancer Prevention Study), 1997 (44)	Nonfatal: RR, 0.62 [0.41–0.96] Fatal: RR, 1.83 [0.85–3.95] Total: RR, 0.81 [0.56–1.17]	RR, 0.90 [0.67–1.22]	RR, 1.33 [0.86–2.05]	
Rapola et al. (ATBC Cancer Prevention Study), 1998 (43)	RR, 0.83 [0.52–1.34]	RR, 0.95 [0.68–1.33]	RR, 1.08 [0.68–1.72]	
Gissi-Investigators, 1999 (49)		RR, 1.04 [0.88–1.22]	RR, 0.94 [0.81–1.10]	RR, 0.92 [0.82–1.04]
		RR, 1.02 [0.81–1.28]	RR, 0.80 [0.65–0.99]	RR, 0.86 [0.72–1.02]
<b>β-Carotene</b>				
Gaziano et al. (Physicians' Health Study), 1990 (41)		RR, 0.56 [0.31–0.99]		
Gaziano et al. (Physicians' Health Study), 1966 (42)	RR, 0.67 [0.36–1.08]	RR, 0.78 [0.50–1.21]	RR, 1.33 [0.78–2.26]	
Rapola et al. (ATBC Cancer Prevention Study), 1997 (44)	Nonfatal: RR, 0.67 [0.44–1.02] Fatal: RR, 3.44 [1.70–6.94] Total: RR, 1.11 [0.79–1.56]	RR, 1.11 [0.84–1.48]	RR, 1.75 [1.16–2.64]	
Rapola et al. (ATBC Cancer Prevention Study), 1998 (43)	RR, 0.98 [0.61–1.57]	RR, 1.08 [0.78–1.50]	RR, 1.18 [0.74–1.87]	
<b>Antioxidant combinations</b>				
Tardif et al. (MVP Study), 1997 (50)	Vitamin group: 1 event Placebo group: 0 events			
Rodes et al. (MVP Study), 1998 (51)				
Brown et al., 2001 (52)		Vitamin group: 21% Placebo: 24% ( <i>P</i> > 0.05; exact <i>P</i> value not given)		
Waters et al. (WAVE Trial), 2002 (55)	Vitamin group: 1.9% Placebo group: 1.9% ( <i>P</i> value not cited)	Vitamin group: 6.6% Placebo group: 3.8% ( <i>P</i> value not cited)	Vitamin group: 4.7% Placebo group: 1.9% ( <i>P</i> = 0.17)	Vitamin group: 7.5% Placebo group: 2.8% ( <i>P</i> = 0.047)
<b>Multivitamins</b>				
Schnyder et al., 2001 (53)	Vitamin group: 4.9% Placebo group: 7.4% ( <i>P</i> > 0.2)	Vitamin group: 10.8% Placebo group: 22.3% ( <i>P</i> = 0.047); RR, 0.48 [0.25–0.94]	Vitamin group: 1.0% Placebo group: 2.1% ( <i>P</i> > 0.2)	

IU of supplementary vitamin E per day had significantly less progression of stenosis than those who did not (28). However, two good-quality cohorts demonstrated no effect of supplementation on CVD mortality (21, 27). Supplemental vitamin E was not associated with coronary heart disease mortality in the Iowa Women's Health Study (21) or with cardiovascular or coronary heart disease mortality in the Physicians' Health Study (27).

Clinical trials have generally not demonstrated that vitamin E supplementation is beneficial to CVD outcomes. There are three major clinical trials of primary prevention,

two of good quality (the Alpha-Tocopherol Beta-Carotene [ATBC] Cancer Prevention Study Group [32] and the HOPE trial [35]) and one of fair quality (the Primary Prevention Project [36]). In the ATBC study, which comprised male smokers, vitamin E had no significant effect on coronary heart disease outcomes (34). The incidence of myocardial infarction, cardiovascular events, and cardiovascular mortality did not differ in participants randomly assigned to vitamin E compared with those assigned to placebo. The incidence of new-onset angina pectoris in vitamin E users was lower than that in all patients assigned

to  $\beta$ -carotene or placebo (relative risk, 0.91 [95% CI, 0.83 to 0.99]) but not in only those assigned to placebo (relative risk, 0.97 [CI, 0.85 to 1.10]) (33).

The HOPE trial tested the effect of 400 IU of vitamin E and an angiotensin-converting enzyme inhibitor versus placebo in participants at high risk for cardiovascular events (35). Individuals older than 55 years with a history of coronary artery disease, peripheral artery disease, or diabetes, plus a cardiovascular risk factor, were included. The trial therefore encompassed both primary and secondary prevention. After 4.5 years of vitamin E supplementation, no reduction was observed in myocardial infarction, cardiovascular events, cardiovascular mortality, or all-cause mortality overall or in any subgroup, including participants who had diabetes and those who smoked.

In the Primary Prevention Project, 4495 men and women older than 50 years of age attending general practice or hypertension clinics were randomly assigned to receive 300 IU of synthetic vitamin E or aspirin in an open-label, non-placebo-controlled  $2 \times 2$  factorial trial (36). After a median of 4 years, vitamin E supplementation had no significant impact on myocardial infarction, cardiovascular events, cardiovascular mortality, or all-cause mortality. Last, in a small study investigating progression of carotid artery intimal thickening, no difference in myocardial infarction, cardiovascular events, mortality, or all-cause mortality was observed with 300 IU of vitamin E given for 3 years (39).

Of the seven RCTs of vitamin E supplementation for secondary prevention of cardiac events (43–49), only one (48) demonstrated a strongly beneficial effect. Three small, relatively short trials evaluated evidence of restenosis of coronary arteries or improvement in angina (45–47). In two of these studies, one of which was of good quality (45) and one which was of fair quality (46), angina did not improve with vitamin E supplementation. In another, there was a suggestion of a reduced rate of restenosis with vitamin E supplementation compared with placebo, but the difference did not reach statistical significance (47).

The Cambridge Heart Antioxidant Study (48) was the only RCT to describe a significantly reduced risk for myocardial infarction and all cardiac events after 1.5 years of vitamin E supplementation. However, it was encumbered by design problems, including unbalanced randomization, incomplete follow-up, and a mid-study change in vitamin E dose (800 IU/d to 400 IU/d) (48, 56).

Other studies did not demonstrate reduced risk for CVD or cardiac events. In a subgroup of patients with mild angina at baseline in the ATBC study, vitamin E supplementation had no effect on progression to severe angina, major coronary events, or fatal coronary heart disease (43). In a separate analysis of an ATBC subgroup of patients with previous myocardial infarction, vitamin E supplementation significantly reduced nonfatal myocardial infarction but not fatal myocardial infarction (44). Considered together, all myocardial infarctions, cardiovascular

events, and cardiovascular mortality were not affected by vitamin E supplementation. The GISSI-P (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico—Prevenzione) study is the largest of the secondary prevention trials. It included more than 11 324 men and women in Italy who were randomly assigned in an open-label, non-placebo-controlled  $2 \times 2$  factorial study to receive supplements of vitamin E or n-3 polyunsaturated fatty acid (49). Combined primary and cardiovascular end points were not significantly reduced in the two-way or four-way analyses comparing vitamin E supplements with no treatment. In secondary analyses, vitamin E supplementation significantly reduced cardiovascular death, including cardiac, coronary, and sudden deaths, in the four-way but not the two-way analysis. Although this study was not blinded, the large sample size and practice setting lend credibility to the results.

### $\beta$ -Carotene

In six publications from four RCTs of primary prevention,  $\beta$ -carotene supplementation did not reduce risk for CVD events or death (29–34). The Women's Health Study's primary purpose was preventing incident cancer and CVD (30). The  $\beta$ -carotene arm of this trial was discontinued after a median of 2.1 years, and patient follow-up continued for 2 additional years.  $\beta$ -Carotene supplementation (50 mg on alternate days) had no significant effect on incident myocardial infarction, cardiovascular events, or all-cause and cardiovascular mortality. A subsequent nested case-control analysis of 130 women from the Women's Health Study showed no effect of treatment on outcome according to plasma  $\beta$ -carotene level at baseline (57). In the all-male Physicians' Health Study, there was no evidence of a direct effect of  $\beta$ -carotene (50 mg on alternate days) on incident myocardial infarction, cardiovascular events, or all-cause or cardiovascular mortality (29). Three separate analyses of the ATBC study (32–34) have indicated that 5 to 8 years of  $\beta$ -carotene supplementation (20 mg/d) had no effect on incident nonfatal myocardial infarction, incident angina, all major coronary events, or cardiovascular mortality. However, all-cause mortality rate was significantly increased by 8% with  $\beta$ -carotene, principally because of increased rates of ischemic heart disease and lung cancer. Last, in the Skin Cancer Prevention Study (31),  $\beta$ -carotene (50 mg/d) had no significant impact on all-cause or cardiovascular mortality after a median of 8.2 years.

In analyses of secondary prevention in the ATBC study,  $\beta$ -carotene supplementation had no significant effect on the development of severe angina, major coronary events, or fatal coronary heart disease in a subgroup of patients with angina at baseline (43). In a subgroup of patients with previous myocardial infarction, the incidence of fatal coronary heart disease was significantly increased with  $\beta$ -carotene (44). Although the overall risk for myocardial infarction was not affected, incidence of fatal myo-

cardial infarction also increased significantly with  $\beta$ -carotene. Finally, an analysis of the Physicians' Health Study indicated a significant reduction in major coronary events in a sample of patients with angina pectoris at baseline (41); with longer follow-up,  $\beta$ -carotene had no demonstrated effect on cardiovascular events or mortality (42). No observational study has analyzed the use of  $\beta$ -carotene supplements for the prevention of cardiovascular events.

### Antioxidant Vitamin Combinations

Three good-quality observational studies (23, 24, 26) and one observational study of fair quality (25) have evaluated the effect of an antioxidant combination on cardiovascular events without attempting to separate the individual components. In a study in the Netherlands of persons older than 55 years of age (24), use of an antioxidant supplement was associated with a significantly reduced 4-year risk for myocardial infarction compared with nonuse. Similarly, in a U.S. cohort study in elderly persons (23), use of vitamins C and E reduced coronary death and all-cause mortality. A good-quality cohort study of Finnish residents showed no significant effect of an antioxidant supplement on coronary mortality (26); however, only 3% of the study sample used an antioxidant supplement. One fair-quality study of more than 1 million men and women in the United States demonstrated modest reductions in CVD mortality among women using antioxidant supplementation who had no history of CVD. Similar reductions were not demonstrated among men (25). All-cause mortality was significantly reduced among women but was not reduced among men.

Three large, good-quality primary prevention trials of antioxidant combination therapy have reported no effect on major cardiovascular end points. In the Carotene and Retinol Efficacy Trial (CARET), the rate of cardiovascular death after 5.5 years of follow-up was not significantly higher with the supplement combination of  $\beta$ -carotene and retinol than with placebo (37). All-cause mortality was significantly increased, however, in persons taking the supplement combination. This trial was terminated before completion because of an increase in lung cancer incidence and death in the group receiving the supplement.

The Age-Related Eye Disease Study Group reported results of a trial of vitamin C, vitamin E, and  $\beta$ -carotene to prevent progression of age-related cataracts and macular degeneration (38). Morbidity and mortality outcomes were also collected. Vitamin C, vitamin E, and  $\beta$ -carotene had no effect on all-cause mortality; however, participants reported chest pain much less frequently with antioxidant supplementation than without it.

The Heart Protection Study (40) included more than 20 000 persons in a double-blind, placebo-controlled,  $2 \times 2$  factorial trial of a combination supplement of vitamin C, vitamin E, and  $\beta$ -carotene. Data on cardiovascular events, vascular mortality, and all-cause mortality were collected. The co-intervention was simvastatin. The antioxi-

dant supplement group and the placebo group did not differ in all-cause mortality, coronary mortality, and all-vascular mortality or in coronary events, coronary revascularization, or all major vascular events. There was no difference in the actuarial rate of events in early versus late follow-up between groups. When the trial was separated into primary and secondary prevention cohorts, the lack of any significant effect on major cardiovascular events remained.

Three good-quality studies of antioxidant vitamin supplementation for secondary prevention of CVD have been reported (50–52). In the Multivitamins and Probuco Study (50, 51), investigators tested an antioxidant medication (probuco), an antioxidant vitamin supplement (vitamin C, vitamin E, and  $\beta$ -carotene), and placebo. This study was terminated at the interim analysis because participants in the probuco group had achieved the critical benefit threshold for the primary end point, restenosis rate. The rate of restenosis in the antioxidant-only group did not differ from that in the placebo group. In a second study (52), patients with coronary heart disease, low levels of high-density lipoprotein cholesterol, and normal levels of low-density lipoprotein cholesterol were assigned to a  $2 \times 2$  factorial trial of simvastatin, antioxidants (vitamin C, vitamin E, natural  $\beta$ -carotene, and selenium), or placebo. Antioxidant therapy did not significantly affect the rate of restenosis or cardiovascular events 3 years later.

The Women's Angiographic Vitamin and Estrogen trial studied the progression of minimal luminal diameter in coronary arteries with 15% to 75% stenosis at baseline (55). A supplement of vitamins C and E was compared with placebo in a  $2 \times 2$  factorial trial with a co-intervention of estrogen. Progression of stenosis did not differ between patients randomly assigned to the vitamin supplement and those assigned to no supplement, and nor did myocardial infarction, cardiovascular events, or cardiovascular mortality. However, all-cause mortality was significantly higher in persons taking the antioxidant supplement. In summary, cohort studies show an association between antioxidant supplementation and reduced coronary heart disease morbidity and mortality, but no reduced risk is demonstrated in clinical trials of primary and secondary prevention.

### Multivitamin Combinations

Four cohort studies analyzed the relationship between the use of multivitamins and CVD. One good-quality study reported a significant reduction in coronary events with multivitamin use (19), two good-quality studies reported no significant effect on mortality (23, 27), and a fair-quality trial reported an increase in all-cause mortality among men (25). Discrepancies in these results may be due to unreported differences in the multivitamin combinations used. In an early analysis of the Nurses' Health Study, with follow-up to 8 years, multivitamin use had no significant effect on coronary events (18). However, a sub-

sequent analysis of this same cohort after 14 years showed an association between multivitamin use and reduced risk for coronary events (19). Women who reported using a multivitamin supplement on most days for at least 5 years had the lowest risk. In the Physicians' Health Study, there was no impact on cardiovascular or coronary heart disease mortality after 4 years (27). Similarly, a fair-quality report from a cohort of more than 1 million men and women demonstrated no benefit on cardiovascular mortality (25). All-cause mortality in this study was increased by multivitamin supplement use in men only. However, when a multivitamin supplement plus antioxidant was considered, cardiovascular mortality was significantly reduced in both men and women.

A secondary prevention trial of coronary heart disease compared the effects of a multivitamin combination (folate, vitamin B<sub>12</sub>, and pyridoxine) and placebo on restenosis at 6 months after angioplasty (53). The rate of restenosis was significantly reduced, as was the rate of cardiovascular events; neither incident myocardial infarction nor cardiovascular mortality was affected significantly.

### Safety

Adverse effects of vitamin supplementation are best measured in clinical trials. In most studies of vitamin supplementation, adverse effects were not reported as might be expected in a pharmacologic trial. The Heart Protection Study reported no difference in cognitive impairment, respiratory disease, and fracture when comparing antioxidant therapy with placebo (40). However, an increase in levels of plasma triglycerides, low-density lipoprotein cholesterol, and plasma total cholesterol was observed (40). Only a nonsignificant increase in triglyceride levels was noted in CARET (58). In the ATBC study (32) and CARET (59), a significant increase in lung cancer incidence and lung cancer mortality was observed in smokers and was ascribed primarily to  $\beta$ -carotene supplementation. A nonsignificant increase in nonhemorrhagic stroke with vitamin E supplementation was observed in the ATBC study, although this was not reported in other studies (32). Heavy smokers may represent a subgroup of the population who should use antioxidants with caution.

### DISCUSSION

There is minimal evidence that any single vitamin supplement, combined antioxidant supplement, or multivitamin combination has a significant benefit in the primary or secondary prevention of CVD (Table 4). For vitamin A and C supplements, the lack of consistent, clear benefit in cohort studies does not support future randomized clinical trials. No observational study has examined  $\beta$ -carotene and coronary death or events. However, in the clinical trials of  $\beta$ -carotene designed for primary prevention of cancer, there is no evidence of cardiovascular risk reduction and some evidence supporting an increase in overall mortality. Secondary prevention analyses demonstrate similar results.

**Table 4. Summary of the Evidence**

Supplement	Evidence
Vitamin A Cohort (1 study) Primary prevention Secondary prevention	No effect on coronary death No data No data
Vitamin C Cohort (5 studies)  Primary prevention Secondary prevention (1 study)	No effect on primary prevention of coronary heart disease in 3; decreased cardiovascular and all-cause mortality in 1; no effect on progression of coronary stenosis in 1; reduction in progression of coronary stenosis in 1 No data Decrease in restenosis and reintervention in one poor-quality trial
Vitamin E Cohort (5 studies)  Primary prevention (3 studies) Secondary prevention (7 studies)	Decrease in primary prevention of coronary events or death in 3; no effect in 2 No effect on cardiovascular events or cardiovascular or all-cause mortality No effect on restenosis, angina, or events in 6; decrease in myocardial infarction and cardiac events in 1; secondary analysis in 1 demonstrated reduction in cardiovascular death
$\beta$ -Carotene Cohort Primary prevention (4 studies)  Secondary prevention (2 studies)	No data No effect on myocardial infarction, cardiovascular events, cardiovascular mortality in 4; increase in all-cause mortality in 1 In 1, increase in fatal coronary heart disease and fatal myocardial infarction in subgroup with previous myocardial infarction; no effect on all myocardial infarctions; no effect on anginal change, cardiovascular events, or mortality in subgroup with angina at baseline; no effect on myocardial infarction, cardiovascular events, or mortality in 1
Antioxidants Cohort (4 studies)  Primary prevention (3 studies)  Secondary prevention (3 studies)	Decrease in myocardial infarction in 1; decrease in coronary death and all-cause mortality in 1; no effect on all-cause mortality and a decrease in cardiovascular mortality only in women in 1; no effect on cardiovascular mortality in 1 No effect on cardiovascular disease mortality in 2; increase in all-cause mortality in 1, no effect in 2; reduction in reported chest pain in 1 No effect on restenosis or events; increase in all-cause mortality in 1
Multivitamins Cohort (3 studies)  Primary prevention Secondary prevention (1 study)	No effect on coronary disease or cardiovascular mortality in 3; decrease in major coronary events in 1 with earlier analysis of no effect; no effect on all-cause mortality in 1, increase in men but not women in 1 No data Decrease in restenosis, cardiovascular events

For vitamin E in particular, the promise of benefit from basic science and animal studies, correlation studies of plasma vitamin levels and CVD, and nutritional surveys was not borne out in RCTs. Why have these findings not been confirmed in clinical trials? Examination of potential explanations requires exploration of the broader questions

of nutrition and chronic disease. Is it possible that the observational studies are correct, that the clinical trials are in error, and that vitamin E can treat and prevent CVD? In general, supplementation of vitamin E in clinical trials has been of relatively short duration: 6 years in the ATBC trial (32), 4.5 years in the HOPE study (35), and 4 years in the Primary Prevention Project (36). In contrast, observational studies have assessed 15 years of supplementation, although in small numbers of participants. It is noteworthy that in two observational studies, at least 2 years of supplement use was necessary to observe an effect, and there was a trend (albeit nonsignificant) for decreasing cardiovascular events with increasing duration of use (18, 20). Given that, it is reasonable to assume that the duration of supplementation in these three clinical trials was sufficient. However, because the dose and duration of supplementation vary considerably more in observational studies than in clinical trials, it is possible that longer periods of supplementation may reduce CVD risk.

A second explanation is that in randomized trials, dosages may have been suboptimal or pharmacologic delivery may have been inappropriate and may not have increased plasma or cellular levels sufficiently to induce a change in cardiovascular risk. A supplement is delivered as an isolated nutrient source, but in addition to usual dietary intake. For some nutrients, such as vitamins C and E, the usual supplement is many times greater than dietary intake, thus overpowering any effect of diet. In at least one cohort study, there was no evident dose response, indicating a potential threshold for vitamin E (18).

Many clinical trials, such as CARET and the ATBC study, were begun for primary prevention of cancer rather than CVD. While there is no evidence of misclassification of cardiovascular end points or less avid assessment compared with cancer end points, the issue of secondary analyses must be considered. Observational studies, such as the Nurses' Health Study (18, 19), the Iowa Women's Study (21), and the Health Professionals' Study (20), have analyzed multiple end points far more extensively than most clinical trials; this is an often-cited strength of observational cohorts. However, it is possible that the results of these trials are spurious because of the sheer number of analyses.

Many trials of supplementation were performed in high-risk samples, whereas observational studies were conducted in general, broad-risk samples. Cohorts for the ATBC study (43) included only male smokers, and the HOPE trial (35), Heart Protection Study (40), and Primary Prevention Project (36) included older persons with known coronary artery or vascular disease or cardiovascular risk factors. Although conducting a randomized trial in a high-risk population reduces the required sample size because of the higher event rate, it is possible that, because of age and risk characteristics, such participants are less amenable to cardiovascular event reduction with antioxidant supplementation. However, in the HOPE trial, the Heart

Protection Study, and the Primary Prevention Project trial, the co-interventions significantly reduced cardiovascular events within the same sample.

Is it more likely that the clinical trials are correct and the observational studies are in error? Considerable attention has been paid to this comparison (60, 61). Because individuals who choose to take supplements differ in many ways from those who do not, observational studies are more subject to misleading associations because of confounding. Persons who use vitamin supplements tend to be more highly educated and of higher socioeconomic status, are likely to have lower body mass index, are less likely to smoke, are more likely to perform vigorous exercise, are less likely to consume alcohol, are less likely to have familial history of early coronary disease, and are more likely to use hormone replacement therapy (18, 19, 62). Although these analyses have been adjusted for obvious differences, it is entirely possible that unmeasured differences remain between users of vitamin supplements and nonusers. Confounding may also be incompletely controlled in the cohort analyses. Because of this, greater weight must be given to results from randomized trials in consideration of evidence (63).

Evidence involving folic acid supplementation is more complex than that for other supplements. Positive effects of multivitamin supplementation are often ascribed to folic acid in the absence of other evidence. Consistent data in several cohorts link low plasma folate levels and high homocysteine levels with fatal coronary heart disease and link multivitamin use with lowered risk for cardiovascular events (64, 65). However, these studies were done before the U.S. food supply was fortified with folate. Monitoring the effect of this fortification on population folate or homocysteine levels will provide important evidence about whether vitamin supplementation would be beneficial in the new food composition environment. Clinical trials of folic acid supplementation for primary prevention of CVD are needed.

Five to 10 major clinical trials of antioxidant use for primary prevention of CVD are ongoing in North America and Europe. These trials will include tens of thousands of participants and will examine major cardiovascular events. Several small trials will examine coronary atherosclerosis. At the conclusion of these trials, sufficient data should exist to analyze the effects of antioxidant use on cardiovascular outcomes in different racial, ethnic, gender, and other minority groups. There is a similar number of ongoing studies of vitamin supplementation for secondary prevention of CVD in the United States and in Europe. These somewhat smaller trials are evaluating antioxidants as well as folic acid supplements.

Randomized, placebo-controlled trials remain the gold standard for medical therapeutics (63). However, evaluating the role of vitamin supplementation in the early stages of CVD requires trials of many years' duration. Epidemiologic cohort studies will continue to be extremely impor-

tant in guiding the role of vitamin supplementation in prevention of chronic disease. The largest established cohorts (the Nurses' Health Study, the Health Professionals' Follow-up Study, and the Iowa Women's Study) are now reaching a stage of maturity that will allow them to provide information on risks and benefits associated with behaviors occurring early in the atherosclerosis process (18–21). Conclusions drawn from epidemiologic studies will always be limited by concerns about underlying differences between users and nonusers. Attempts to analyze the large cohort studies in ways that replicate clinical trial designs would be extremely useful in elucidating the differences between findings from clinical trials and cohort studies. Understanding these sources will permit scientists to better use the cohort study data and to better design long-term clinical trials.

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