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

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Epidemiology

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 (LDL) 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?*

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Reprints of the USPSTF recommendations based on this evidence review can be found in Routine Vitamin Supplementation to Prevent Cancer and Cardiovascular Disease: Recommendations and Rationale, available on the AHRQ Web site and in the *Guide to Clinical Preventive Services, Third Edition: Periodic Updates.*

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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 the 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 in nature 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 were excluded, such as a cohort with end-stage renal disease. Only cohort studies rated as being of good to fair quality by predetermined criteria from a system developed by the current USPSTF were included.[16] Studies were excluded if they contained no original data, were not relevant (eg, 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 2,758 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 (RTCs), 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 compliance, compliance 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 using the standards of the current USPSTF.[16] For randomized controlled trials (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 2 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 to prevent 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 more than 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,[23] (11,178 men and women older than 65 years), 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 (ACS).[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 cointervention (angiotensin-converting enzyme inhibitor, aspirin, or lipid lowering agent) examining CVD incidence or mortality. Of these 9 trials, only 4 were undertaken with the primary objective of preventing CVD: HOPE (Heart Outcomes Prevention Evaluation),[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 endpoint. 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 pre-existing CVD (Table 3). Two studies analyzed subgroups with prior coronary disease.[41–44] In addition, 2 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

This research was funded by the Agency for Healthcare Research and Quality (AHRQ) under a contract to support the work of the USPSTF. AHRQ staff and Task Force members participated in the initial design of the study and also reviewed interim analyses and the final manuscript.

Results

Vitamin A

One good quality cohort study evaluated the effect of vitamin A supplementation on incident coronary death.[21] Subjects in the highest quartile of vitamin A supplement use did not have a lower risk for coronary death compared with 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 3 of 4 cohort studies, vitamin C supplementation was not associated with coronary heart disease mortality[21–23] or all-cause mortality.[23] In 2 studies of 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 the 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 (≥250 mg/day) 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 supplements 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

Table 1. Cohort studies of the association between vitamin supplement use and cardiovascular disease risk

Study, publication, year (quality score)	Description	Outcomes, comparison
Nurses' Health Study Stampfer, 1993[18] (Good)	87,245 female US nurses, age 34–59, with no history of cancer, angina, myocardial infarction, stroke, or other cardiovascular disease; 552 cases of major coronary disease; 97.1% follow-up at 8 years.	Major coronary disease (nonfatal myocardial infarction or death due to coronary disease), in users vs. non-users.
Nurses' Health Study Rimm, 1998[19] (Good)	80,082 female US nurses, same as above plus no hypercholesterolemia or diabetes; 658 cases of nonfatal myocardial infarction and 281 fatal coronary deaths; 98% follow-up for mortality at 14 years.	Incident nonfatal myocardial infarction and coronary death, in users (4–7 pills/week) vs. non-users.
Health Professionals' Study Rimm, 1993[20] (Good)	39,910 male US health professionals age 40–75; 667 incident cases of coronary disease; 96% follow-up at 4 years.	Incident coronary disease (fatal coronary disease, nonfatal myocardial infarction, CABG, angioplasty). Comparing users vs. non-users.
Iowa Women's Health Study Kushi, 1996[21] (Good)	34,486 women age 55–69, from the general population of Iowa women; 242 incident coronary deaths; follow-up virtually complete (used National Death Index) at 7 years.	Incident coronary death, in Q4 (>250 IU/day) vs. Q1 (non-users). Q5 (>1000 mg/day) vs. Q1 (non-users). Q4 (>10,000 IU/day) vs. Q1 (non-users).
NHANES I Epidemiologic Follow-up Study Enstrom, 1992[22] (Good)	11,348 men (39%) and women age 25–74. Representative sample of the noninstitutionalized US population 92% (in women) to 94% (in men) follow-up at 10 years.	Cardiovascular mortality; standardized mortality ratio of regular supplement users. All-cause mortality; standardized mortality ratio of regular supplement users.

Table 1. Cohort studies of the association between vitamin supplement use and cardiovascular disease risk (cont.)

Factors adjusted for in analysis	Vitamin A	Vitamin C	Vitamin E	Anti-oxidant combinations	Multivitamin preparations
Age, time period, quetelet index†, smoking, alcohol intake, menopausal status, postmenopausal hormone use, exercise, regular use of aspirin, hypertension, high cholesterol, 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, body mass index, smoking, menopausal status, hormone replacement therapy use, aspirin, vitamin E supplements, physical activity, hypertension, parental history of myocardial infarction < age 65, alcohol, and quintiles of fiber, alcohol, and saturated, polyunsaturated, and *trans* fat.					0.76 (0.65–0.90)
Age, smoking, body-mass index, total calories, dietary fiber, alcohol consumption, hypertension, regular aspirin use, physical activity, parental history of myocardial infarction < age 60, profession.			0.75 (0.61–0.93)		
Age, total energy intake,body mass index, waist-to-hip ratio, pack year of smoking, hypertension, diabetes, oral contraceptive use, estrogen replacement therapy, physical activity, alcohol intake, marital status, education.			1.09 (0.67–1.77)		
Same as above.		0.74 (0.30–1.83)			
Same as above.	1.29 (0.70–2.39)				
Adjusted to standardized US population using SUDAAN.		0.52 (0.39–0.69)			
Adjusted to standardized US population using SUDAAN.		0.74 (0.62–0.88)			

Table 1. Cohort studies of the association between vitamin supplement use and cardiovascular disease risk (cont.)

Study, publication, year (quality score)	Description	Outcomes, comparison
Established Populations for Epidemiologic Studies of the Elderly Losonczy, 1996[23] (Good)	11,178 men and women in 4 communities ≥ age 65; 1101 coronary disease deaths; follow-up rate for mortality virtually complete (used National Death Index) at 6 years.	Coronary disease mortality in users vs. non-users. All-cause mortality, in users vs. non-users.
Rotterdam Study lipstein-Grobusch, 1999[24] (Good)	4802 residents of one district in the Netherlands age 55–95, 173 myocardial infarctions; 94% follow-up rate at mean 4 years (range 3–7 years).	Incident fatal and non-fatal myocardial infarction, in users vs. non-users.
Cancer Prevention Study II Watkins, 2000[25] (Fair)	1,063,023 US residents recruited by American Cancer Society volunteers, follow-up virtually complete (used National Death Index) at 7 years.	Cardiovascular mortality, in users vs. non-users. All-cause mortality, in users vs. non-users.
Finnish Mobile Clinic Study Knekt, 1994[26] (Good)	5133 men and women in Finland age 30–69, free of known heart disease at baseline; 244 CHD deaths; 100% follow-up at mean 14 years (range 12–16 years).	Cardiovascular mortality: users of supplements containing vitamin E and/or C vs. non-users.
Physicians' Health Study Screening Cohort Muntwyler, 2002[27] (Good)	83,639 male physicians who responded to a letter inviting participation in Physicians' Health Study, with no history of CVD. Follow-up virtually complete (National Death Index) at 4 years.	CVD and CHD mortality, in user and non-users.
Cholesterol Lowering Atherosclerosis Study Hodis, 1995[28] (Good)	Analysis of secondary prevention in randomized clinical trial of patients with repeat angiography at 2 years. Study compares coronary artery disease progression with aggressive cholesterol reduction vs. placebo. This cohort analysis uses assessed supplemental vitamin use.	Change in minimal lumenal diameter assessed 2 years apart in supplement users (vitamin E ≥ 100 IU/day, vitamin C ≥ 250 mg/day) and the obverse.

Table 1. Cohort studies of the association between vitamin supplement use and cardiovascular disease risk (cont.)

Factors adjusted for in analysis	Vitamin A	Vitamin C	Vitamin E	Anti-oxidant combinations	Multivitamin preparations
Age, sex, race, education, alcohol use, smoking history, aspirin use, CHD, stroke, diabetes, cancer, hypertension, and body mass index.		0.99 (0.74–1.33)	0.59 (0.37–0.93)	0.52 (0.28–0.97)	1.11 (0.91–1.36)
Age, sex, race, education, alcohol use, smoking history, aspirin use, CHD, stroke, diabetes, cancer, hypertension, and body mass index.		1.09 (0.93–1.28)	0.73 (0.58–0.91)	0.63 (0.46–0.86)	1.03 (0.91–1.16)
Adjusted; unclear for which variables.				0.49 (0.21–0.99)	
Age, race, marital status, body mass index, 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, hypertension, body mass index, energy intake.				0.55 (0.18–1.73)	
History of hypertension, history of hypercholesterolemia, current and past smoking, alcohol intake, physical activity, body mass intake, 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)		

Note: CABG indicates coronary artery bypass grafting; CHD, coronary heart disease; CVD, cardiovascular disease; LDL, low density lipoprotein; MI, myocardial infarction; NHANES, National Health and Nutrition Examination Survey; Q, question.

Table 2. Randomized controlled trials of vitamin supplementation for primary prevention of cardiovascular disease

Study, publication (Jadad score)	Setting/ population	Treatment (dose, formulation, frequency); other interventions
Vitamin E		
ATBC, ATBC Study Group, 1994[32] (5)	29,133 Finnish male smokers age 50–69 with no current use of vitamin A, E, or beta-carotene; no severe angina, malignancy, or other medical problems.	50 IU/day vitamin E and 20 mg/day beta-carotene in 2 x 2 factorial design.
ATBC Rapola, 1996[33] (5)	Same as above.	See above.
ATBC Virtamo, 1998[34] (5)	27,271 men, same as above except patients with prior MI excluded.	See above.
HOPE Study Yusuf, 2000[35] (5)	9,541 men and women at 129 centers in 19 countries, over age 55, with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes, plus one cardiovascular risk factor.	400 IU/day vitamin E from natural sources and ACE inhibitor (10 mg ramipril) in 2 x 2 factorial design.
Primary Prevention Project Collaborative Group of the Primary Prevention Project, 2001[36] (3)	4,495 Italian men and women attending general practitioner's office or outpatients attending hospital-based hypertension clinic; > age 50 with one of the following cardiovascular risk factors: hypertension, hypercholesterolemia, diabetes mellitus, obesity, family history of early MI (< age 55), or age > 64.	300 IU/day synthetic alpha-tocopherol and 100 mg/day aspirin in 2 x 2 factorial design.
Vitamin E Atherosclerosis Prevention Study (VEAPS Trial) Hodis, 2002[39] (5)	353 subjects ≥ 40 years with high LDL and no symptoms or signs of cardiovascular disease; no history of hypertriglyceridemia, diabetes or regular vitamin E. Primary outcome measure was change in carotid artery intima-media thickness.	400 IU/day tocopherol.
Beta-carotene		
ATBC, ATBC Study Group, 1994[32] (5)	29,133 Finland male smokers age 50–69 with no current use of vitamin A, E, or beta-carotene; no severe angina, malignancy, or other medical problems.	20 mg/day beta-carotene and 50 IU/day vitamin E in 2 x 2 factorial design.
ATBC Rapola, 1996[33] (5)	Same as above.	Same as above.

Table 2. Randomized controlled trials of vitamin supplementation for primary prevention of cardiovascular disease (cont.)

Duration of follow-up; follow-up rate	Myocardial infarction	Cardiovascular disease events	Cardiovascular disease mortality	All-cause mortality
5–8 years, median 6.1 years; case ascertainment essentially complete.				1.02 (0.95–1.09)
Maximum 7 years, median 4.7 years; 73%.		(Angina) 0.91 (0.83–0.99)		
5–8 years, median 6.1 years; case ascertainment essentially complete.	1.04 (0.89–1.22)	0.98 (0.87–1.10)	0.90 (0.75–1.08)	
5 years, 99.9%.	1.02 (0.90–1.15)	1.05 (0.95–1.22)	1.05 (0.90–1.22)	1.00 (0.89–1.13)
Mean 3.6 years ± 1.0 years; median 4 years 99.3%.	0.89 (0.52–1.58)	0.94 (0.77–1.16)	0.86 (0.49–1.52)	1.07 (0.77–1.49)
3 years, 73% followed for 3 years.	*Vitamin:* 5 *Placebo:* 4 p value not cited	*Vitamin:* 8 *Placebo:* 10 p=0.81	*Vitamin:* 1 *Placebo:* 1 p value not cited	*Vitamin:* 2 *Placebo*: 1 p value not cited
5–8 years, median 6.1 years; case ascertainment “essentially complete.”				1.08 (1.01–1.16)
Maximum 7 years, median 4.7 years; 73%.		(Angina) 1.06 (0.97–1.16)		

Table 2. Randomized controlled trials of vitamin supplementation for primary prevention of cardiovascular disease (cont.)

Study, publication (Jadad score)	Setting/ population	Treatment (dose, formulation, frequency); other interventions
Beta-carotene (continued)		
ATBC Virtamo, 1998[34] (5)	27,271 men, same as above except patients with prior MI excluded.	Same as above.
Physician's Health Study Hennekens, 1996[29] (4)	22,071 US male physicians age 40–84, with no history of cancer, MI, stroke, or cerebral ischemia.	50 mg beta-carotene on alternate days; cointervention with 325 mg aspirin in 2 x 2 factorial design.
Skin Cancer Prevention Study Greenberg, 1996[31] (3)	1,188 US men and 532 women with prior non-melanoma skin cancer, < age 85. Multicenter trial to prevent skin cancer recurrence.	50 mg/day beta-carotene.
Women's Health Study I-M Lee, 1999[30] (4)	39,876 US female health professionals, ≥ age 45; no history of cancer, coronary heart disease, or cerebrovascular disease.	50 mg beta-carotene on alternate days; cointervention with 100 mg aspirin and 600 IU/day vitamin E in 2 x 2 x 2 factorial design.
CARET Omenn, 1996[37] (4)	4,060 West Coast US male asbestos workers, age 45–74, first exposure to asbestos ≥ 15 yrs ago, plus asbestos-related lung disease or high-risk job for 5 years, and 14,254 US male and female heavy smokers age 50–69, ≥ 20 pack-years, current smokers or quit < 6 years ago.	30 mg/day beta-carotene and 25,000 IU/day retinol (retinyl palmitate).
AREDS, AREDS Study Group, 2001[38] (5)	4,757 US participants, age 55–80 years recruited from ophthalmology clinics, without major cardiovascular disease or cancer in recent past.	500 mg vitamin C, 400 IU vitamin E, 15 mg beta-carotene per day. Some patients with age-related macular degeneration also assigned to receive 80 mg zinc and 2 mg copper versus placebo. 66% of the cohort chose to take a multivitamin (Centrum™) in addition.
Heart Protection Study Heart Protection Collaborative Group, 2002[40] (5)	20,536 adults 40–80 years in UK with blood cholesterol ≥ 3.5 mmol/L and history of coronary artery disease, other occlusive arterial disease, diabetes, or treated hypertension; excluded with prior high dose vitamin E supplementation or life-threatening disease. Must have shown compliance in 2 month pre-randomization compliance period.	600 mg synthetic vitamin E, 250 mg vitamin C and 20 mg beta-carotene daily in 2 x 2 factorial trial. Cointervention with simvastatin.

Table 2. Randomized controlled trials of vitamin supplementation for primary prevention of cardiovascular disease (cont.)

Duration of follow-up; follow-up rate	Myocardial infarction	Cardiovascular disease events	Cardiovascular disease mortality	All-cause mortality
5–8 years, median 6.1 years; case ascertainment "essentially complete."	1.06 (0.90–1.24)	1.03 (0.91–1.16)	0.99 (0.83–1.19)	
Mean 12 years, 99.99%.	0.96 (0.84–1.09)	1.0 (0.91–1.09)	1.09 (0.93–1.27)	1.02 (0.93–1.11)
Median 8.2 years, 98%.			1.16 (0.82–1.64)	1.03 (0.82–1.30)
Median 2.1 years of treatment plus 2 years of follow-up, 100%.	0.84 (0.56–1.27)	1.14 (0.87–1.49)	1.17 (0.54–2.53)	1.07 (0.74–1.56)
5.5 years, 98% for mortality.			1.26 (0.99–1.61)	1.17 (1.03–1.33)
Mean 6.3 years, 97.7% completed the trial.	Reported chest pain: Vitamins: 19.8% Placebo: 22.8% (p=0.01)	1.06 (0.84–1.33)		
5 years, 99.7% followed for morbidity.			(Vascular Mortality) 1.05 (0.95–1.15)	1.04 (0.97–1.12)

Note: ATBC indicates Alpha-Tocopheral Beta-Carotene; AREDS, Age-Related Eye Disease Study; MI, myocardial infarction; CARET, Carotene and Retinol Efficacy Trial; HOPE, Heart Outcomes Prevention Evaluation; LDL, low-density lipoprotein; RR, relative risk.

Table 3. Randomized controlled trials of vitamin supplementation for secondary prevention of cardiovascular disease

Study, publication (Jadad score)	Setting/ population	Treatment Other medications or nutrients supplemented	Duration of follow-up; follow-up rate
Vitamin C			
Tomoda 1996[54] (1)	119 patients at a single center, Japan, age 35–80 with stable or unstable angina; angiographic evidence of ≥ 1 coronary lesion with > 75% diameter; successful coronary angioplasty, no recent MI (< 8 weeks), no use of coronary stent, no angioplasty for restenosis.	Vitamin C 500 mg/day	4 months, 85%.
Vitamin E			
Anderson 1974[45] (4)	48 Toronto patients from a single center, with stable angina and no change in medication or health status in previous 3 months.	400 IU/day d-alpha-tocopherol succinate	9 weeks; all followed but 25% excluded from analysis.
Gillilan 1977[46] (3)	52 patients from a single center in Baltimore, with stable, effort-related angina plus prior MI by Q wave and/or ≥ 75% occlusion of one or more coronary arteries on angiogram. All had ECG evidence of ischemia. Crossover design.	1600 IU/day d-alpha-tocopherol succinate	6 months, 92%.
DeMaio 1992[47] (2)	100 patients from one practice in Atlanta with successful angioplasty to reduce restenosis, 84% male.	1200 IU/day Vitamin E as d-alpha-tocopherol	4 months; follow-up on 86% of patients completing protocol, unclear how many randomized into trial.
CHAOS Stephens 1996[48] (4)	2002 patients from one center in East Anglia, UK with angiographically proven coronary artery disease, 84% male.	800 IU/day vitamin E for the first cohort (n=546), 400 IU/day for the second cohort (n=489)	Median 1.5 years; 98%.
ATBC Rapola 1997[44] (4)	1862 Finnish male smokers age 50–69, with prior MI, no current use of vitamin A, E, or beta-carotene; no severe angina, malignancy, or other serious illness.	Same as above.	5–8 years (median 5.3 years). Not reported but from national registry.
ATBC Rapola 1998[43] (4)	1795 Finnish male smokers age 50–69, with mild angina, no current use of vitamin A, E, or beta-carotene; no severe angina, malignancy, or other serious illness.	50 IU/day vitamin E and 20 mg/day beta-carotene in 2 x 2 factorial design.	5–8 years, 48% at 5 years.

Table 3. Randomized controlled trials of vitamin supplementation for secondary prevention of cardiovascular disease (cont.)

Relative Risk (95% Confidence Interval)					
Restenosis	**Change in angina**	**MI**	**CV events**	**CVD mortality**	**All-cause mortality**
Vitamin group: 22% of segments *Placebo:* 39% of segments ($p < 0.05$)			*Vitamin group:* 14% required reintervention *Placebo:* 33% required reintervention ($p < 0.02$)		
	Improvement in angina in 5/18 (vitamin group) vs 3/18 (placebo) (Not analyzed)				
	Improvement in angina in 4/48 (vitamin) vs 3/48 (placebo) p=NS			*Vitamin group:* 2 of 48 *Placebo:* 2 of 48 p=NS	
Vitamin group: 18/52 (34.6%) *Placebo:* 24/48 (50%) p=0.06					
		Vitamin group: 14 *placebo:* 41 p=0.0001	*Vitamin group:* 41 *placebo:* 62 p=0.015	*Vitamin group:* 27 *placebo:* 23 p=0.78	*Vitamin group:* 36 *placebo:* 26 p=0.31
		Nonfatal MI: 0.62 (0.41–0.96) *Fatal MI:* 1.83 (0.85–3.95) *Total MI:* 0.81 (0.56–1.17)	0.90 (0.67–1.22)	1.33 (0.86–2.05)	
	Severe angina: 1.14 (0.84–1.53)	0.83 (0.52–1.34)	0.95 (0.68–1.33)	1.08 (0.68–1.72)	

Table 3. Randomized controlled trials of vitamin supplementation for secondary prevention of cardiovascular disease (cont.)

Study, publication (Jadad score)	Setting/ population	Treatment Other medications or nutrients supplemented	Duration of follow-up; follow-up rate
Vitamin E (continue)			
GISSI-P Investigators 1999[49] (2)	11,334 patients from multiple centers in Italy with recent (≤ 3 months) MI. Open label study.	300 IU/day synthetic alpha tocopherol and 1 gram/day n-3 PUFA in 2 x 2 factorial design; 2-way analysis.	3.5 years, 99.9%.
	Same as above.	Same as above, 4-way analysis (vitamin E vs. control).	
Beta-carotene			
Physician's Health Study Gaziano 1990[41] (4)	333 US male physicians age 40–84, with chronic stable angina and/or coronary revascularization, no history of cancer, MI, stroke, cerebral ischemia, or noncompliance in run-in phase.	50 mg beta-carotene on alternate days; cointervention with aspirin in 2 x 2 factorial design.	Not reported.
Physician's Health Study Gaziano 1996[42] (4)	Same as above.	Same as above.	12 years. Not reported.
ATBC Rapola 1997[44] (4)	1862 Finnish male smokers age 50–69, with prior MI, no current use of vitamin A, E, or beta-carotene; no severe angina, malignancy, or other serious illness.	Same as above.	5–8 years, median 5.3 years. Not reported but from national registry.
ATBC Rapola 1998[43] (4)	1795 Finnish male smokers age 50–69, with mild angina, no current use of vitamin A, E, or beta-carotene; no severe angina, malignancy, or other serious illness.	20 mg/day beta-carotene and 50 mg/day vitamin E in 2 x 2 factorial design.	5–8 years, 48% at 5 years.
Antioxidant combinations			
MVP Study Tardif 1997[50] (3)	255 patients from a single center in Canada with ≥ 50% stenosis, who had successful angioplasty; 77% male.	60,000 IU beta-carotene, 1000 mg vitamin C, plus 1400 IU alpha-tocopherol daily v. probucol 500 mg/day in 2 X 2 factorial design. All prescribed AHA Step 1 diet.	5–7 months, 90%.

Table 3. Randomized controlled trials of vitamin supplementation for secondary prevention of cardiovascular disease (cont.)

Relative Risk (95% Confidence Interval)					
Restenosis	**Change in angina**	**MI**	**CV events**	**CVD mortality**	**All-cause mortality**
			1.04 (0.88–1.22)	0.94 (0.81–1.10)	0.92 (0.82–1.04)
			1.02 (0.81–1.28)	0.80 (0.65–0.99)	0.86 (0.72–1.02)
			0.56 (0.31–0.99)		
		0.67 (0.36–1.08)	0.78 (0.50–1.21)	1.33 (0.78–2.26)	
		Nonfatal MI: 0.67 (0.44–1.02) *Fatal MI:* 3.44 (1.70–6.94)	*Total MI:* 1.11 (0.79–1.56)	1.11 (0.84–1.48)	1.75 (1.16–2.64)
	Severe angina 1.15 (0.85–1.57)	0.98 (0.61–1.57)	1.08 (0.78–1.50)	1.18 (0.74–1.87)	
Vitamin group: 40.3% of segments *Placebo:* 38.9% of segments p=0.89		1 (vitamin group) vs 0 (placebo) p=NS			

Table 3. Randomized controlled trials of vitamin supplementation for secondary prevention of cardiovascular disease (cont.)

Study, publication (Jadad score)	Setting/ population	Treatment Other medications or nutrients supplemented	Duration of follow-up; follow-up rate
Antioxident combinations (continue)			
MVP Study Rodes 1998[51] (3)	189 patients from a single center in Canada with angioplasty of coronary artery diameter < 3 mm.	Same as above.	5–7 months, 95%.
Brown 2001[52] (4)	160 Seattle and Canadian patients with clinical coronary disease (prior MI, coronary intervention, or confirmed angina); ≥ 3 coronary stenoses of ≥ 30% or one ≥ 50%; and low HDL and high triglyceride levels.	800 IU vitamin E, 1000 mg vitamin C, 25 mg natural beta-carotene, plus 100 mg selenium/ day; cointervention with Simvastatin 10–20 mg/day plus niacin 2000 mg-4 gm/day in 2 x 2 factorial design.	3 years; 91% for angiography, 99% for CV events.
WAVE Trial Waters 2002[55] (5)	423 postmenopausal women in 7 US and Canadian centers with angiographic evidence of ≥ 1 coronary artery with 15–75% stenosis	400 IU vitamin E plus 500 mg vitamin C daily vs 0.625 mg conjugated equine estrogens in a 2 x 2 factorial trial. Women without hysterectomy also received progesterone with estrogen.	Mean 2.8 years; 79% for angiography; 97% for clinical status.
Multivitamins			
Schnyder 2001[53] (4)	206 patients from multiple centers in Switzerland, Germany, and California, with successful coronary angioplasty of ≥ 1 stenosis of ≥ 50%.	1 mg folic acid, 400 micrograms vitamin B12, 10 mg pyridoxine daily.	6 months: 86% for angiography, 96% for clinical outcomes.

Table 3. Randomized controlled trials of vitamin supplementation for secondary prevention of cardiovascular disease (cont.)

Relative Risk (95% Confidence Interval)					
Restenosis	**Change in angina**	**MI**	**CV events**	**CVD mortality**	**All-cause mortality**
Vitamin group: 45.1% of segments *Placebo:* 37.3% of segments p=0.37					
Vitamin group: 1.8% progression of stenosis *Placebo:* 3.9% progression of stenosis (p=0.16)			*Vitamin group:* 21% *Placebo:* 24% (p=NS; exact p value not given)		
Progression of minimal luminal diameter: *Vitamin group:* –0.044 mm/yr *Placebo group:* –0.028 mm/yr p=0.32		*Vitamin group:* 1.9% *Placebo group:* 1.9% p value not cited	*Vitamin group:* 6.6% *Placebo group:* 3.8% p value not cited	*Vitamin group:* 4.7% *Placebo group:* 1.9% p=0.17	*Vitamin group:* 7.5% *Placebo group:* 2.8% p=0.047
Vitamin group: 19.6% *Placebo:* 37.6% p=0.01 RR=0.52 (0.32–0.86)		*Vitamin group:* 4.9% *Placebo:* 7.4% (p=0.66)	*Vitamin group:* 10.8% *Placebo:* 22.3% p=0.047 RR=0.48 (0.25–0.94)	*Vitamin group:* 1.0% *Placebo:* 2.1% p=0.95	

Note: MI indicates myocardial infarction; CHAOS, Cambridge Heart Antioxidant Study; AHA, American Heart Association; ATBC, Alpha-Tocopherol Beta-Carotene; CV, cardiovascular; CVD, cardiovascular disease; ECG, electrocardiogram; GISSI-P, Gruppo Italiano per lo Studio della Sopravivenza nell'Infarto Miocardico—Prevenzione; HDL, high density lipoprotein; MVP, multivitamins and Probucol; PUFA, polyunsaturated fatty acid; RR, relative risk; WAVE, Women's Angiographic Vitamin and Estrogen.

cardiovascular risk and a minimum dose of 100 IU per day 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 per day for at least 2 years had greater adjusted risk reduction than nonusers (relative risk [RR], 0.63; 95% confidence interval [CI], 0.47 to 0.84). This 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 IU per day of vitamin E had significantly less progression of stenosis than those who did not.[28] However, 2 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 3 major clinical trials of primary prevention, 2 of good quality (the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study Group [ATBC][32] and the HOPE trial[35]) and 1 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 in all patients assigned to beta-carotene or placebo (RR, 0.91; 95% CI, 0.83 to 0.99), but not when compared only to those assigned to placebo (RR, 0.97; 95% 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 subjects at high risk for cardiovascular events.[35] Individuals older than 55 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, 4,495 men and women older than 50 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 x 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 and mortality, or all-cause mortality was observed with 300 IU of vitamin E given for 3 years.[39]

Of the 7 RCTs of vitamin E supplementation for secondary prevention of cardiac events,[43–49] only 1[48] demonstrated a strongly beneficial effect. Three small trials of relatively short duration evaluated evidence of restenosis of coronary arteries or improvement in angina.[45–47] In 2 of these studies, 1 of which was of good quality[45] and one of 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 (CHAOS) 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.[48] However, it was encumbered by design problems, including unbalanced randomization, incomplete follow-up, and a mid-study change in the vitamin E dose (800 IU to 400 IU per day).[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 Sopavivienza nell'Infarto miocarciso - 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 x 2 factorial study of vitamin E or n-3 polyunsaturated fatty acid.[49] Combined primary and cardiovascular endpoints were not significantly reduced in the 2-way or 4-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 4-way but not the 2-way analysis. Although this study was not blinded, the large sample size and practice setting lend credibility to the results.

Beta-Carotene

In 6 publications from 4 RCTs of primary prevention, beta-carotene supplementation did not reduce risk for cardiovascular disease 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 Physician's 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/day) had no effect on incident non-fatal myocardial infarction, incident angina, all major coronary events, or cardiovascular mortality. However, all-cause mortality 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/day) 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 with angina at baseline.[43] In a subgroup of patients with prior 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 myocardial infarction also increased significantly with beta-carotene. Finally, an analysis of the Physician's 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[23, 24, 26] observational studies and 1 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, use of an antioxidant supplement was

associated with a significantly reduced 4-year risk for myocardial infarction compared with nonuse.[24] Similarly, in a U.S. cohort study in elderly persons, use of vitamins C and E reduced coronary death and all-cause mortality.[23] 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, 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 people 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 subjects in a double-blind, placebo-controlled, 2 x 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 cointervention was simvastatin. The antioxidant 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 Probucol (MVP) Study,[50, 51] investigators tested an antioxidant medication (probucol), an antioxidant vitamin supplement (vitamin C, vitamin E, and beta-carotene), and placebo. This study was terminated at the interim analysis because those in the probucol group had achieved the critical benefit threshold for the primary endpoint, 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 x 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 (WAVE) 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 x 2 factorial trial with a cointervention of estrogen. Progression of stenosis did not differ between patients randomly assigned to the vitamin supplement and those assigned to no supplement, nor did myocardial infarction, cardiovascular events, or cardiovascular mortality. However, all-cause mortality was significantly increased with 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] 2 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 from 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 subsequent analysis of this same cohort after 14 years showed an association between multivitamin use and reduced risk of 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 reduced in both men and women.

A secondary prevention trial of coronary heart disease studied a multivitamin combination (folate, vitamin B12, 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 not 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 non-significant increase in triglyceride levels was noted in CARET.[58] In the ATBC[32] study 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 non-significant increase in non-hemorrhagic 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 for cardiovascular risk reduction and some evidence supporting an increase in overall mortality. Secondary prevention analyses demonstrate similar results.

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

Table 4. Summary of the evidence

Supplement	Evidence
Vitamin A	
Cohort (1 study)	No effect on coronary death.
Primary prevention	No data.
Secondary prevention	No data.
Vitamin C	
Cohort (5 studies)	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.
Primary prevention	No data.
Secondary prevention (1 study)	Decrease in restenosis and reintervention in one poor quality trial.
Vitamin E	
Cohort (5 studies)	Decrease in primary prevention of coronary events or death in 3, no effect in 2.
Primary prevention (3 studies)	No effect on cardiovascular events or cardiovascular or all-cause mortality.
Secondary prevention (7 studies)	No effect on restenosis, angina or events in 6, decrease in myocardial infarction and cardiac events in 1. Secondary analysis in 1 demonstrates reduction in cardiovascular death.
Beta-carotene	
Cohort	No data.
Primary prevention (4 studies)	No effect on myocardial infarction, cardiovascular events, cardiovascular mortality in 4. Increase in all-cause mortality in 1.
Secondary prevention (2 studies)	In 1, increase in fatal coronary heart disease and fatal myocardial infarction in subgroup with prior 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)	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.
Primary prevention (3 studies)	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.
Secondary prevention (3 studies)	No effect on restenosis or events. Increase in all-cause mortality in 1.
Multivitamins	
Cohort (3 studies)	No effect on coronary disease or cardiovascular mortality in 3 studies. 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.
Primary prevention	No data.
Secondary prevention (1 study)	Decrease in restenosis, cardiovascular events.

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 were 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 3 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 also 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 carried out 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 cointerventions significantly reduced cardiovascular events within the same population.

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 non-users. 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 the lowered risk of cardiovascular events.[64, 65] However, these studies were undertaken prior to 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 cardiovascular disease 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 important 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 taking place 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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