The Role of Vitamin Supplementation in the Prevention of Cardiovascular Disease Events

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ABSTRACT

The production, sale, and consumption of multiple vitamins is a multibillion-dollar industry. Most Americans take some form of supplement ostensibly for prevention of cardiovascular disease. It has been claimed that vitamin A retards atherogenesis. Vitamin C is an antioxidant and is thought to possibly decrease free radical-induced endothelial injury, which can lead to atherosclerotic plaque formation. Vitamin E has been extensively studied for its possible effects on platelet function as well as inhibition of foam-cell formation. Low levels of vitamin D have been thought to negatively impact myocardial structure and increase the risk for cardiovascular events. Increased intake of vitamin B6, B12, and folate has been associated with reduction of homocysteine levels; elevated homocysteine blood levels have been associated with the occurrence of stroke, heart attack, and cardiovascular death. The purpose of this study was to review the currently available literature for vitamin supplementation with respect to prevention of cardiovascular disease. Unfortunately, the current evidence suggests no benefit exists with vitamin supplementation in the general US population. Further research is needed to evaluate whether there are specific populations that might benefit from vitamin supplementation.

Introduction

Vitamins are commonly used for the prevention of cardiovascular disease (CVD) without clear evidence of benefit or risk. A great deal has been published on the role of vitamins; however, there is disagreement regarding mechanisms of potential benefit, efficacy, dosing, and target population. A number of studies of multivitamin supplementation in generally healthy people, for example, have failed to provide conclusive information while still hinting at possible benefit without an increase in all-cause mortality, cancer incidence/mortality, or CVD incidence/mortality. However, data from 2 recent randomized controlled trials (RCTs) failed to demonstrate any CVD benefit from routine supplementation.[1,2] For this reason it is important to evaluate critically the data for each vitamin, individually as well as in combination. The purpose of this review was to examine the latest clinical-trial data regarding vitamin supplementation and cardiovascular events, including myocardial infarction (MI) and cardiovascular death, from the last 10 years. The Table 1 summarizes trial data and meta-analysis data referenced.

Homocysteine-Targeted Therapy and Cardiovascular Events

Background and Possible Mechanisms

Dr. Kilmer McCully was the first to suggest elevated homocysteine as a risk factor for premature vascular disease, based on a study of children with congenital defects in amino-acid metabolism who were found to have early atherosclerosis.[3] In the years that followed, a number of observational studies emerged suggesting a causal relationship. One of the larger studies reported results from the Nurses' Health Study from 1980 of 80 082 women who were followed for 14 years and analyzed by estimated folate and vitamin B6 intake. Those in the highest quintiles of intake had a lower risk for nonfatal MI and cardiovascular death.[4] Still another large-scale meta-analysis of prospective studies of patients with defective homocysteine metabolism and those in whom serum homocysteine was measured yielded an oft-cited conclusion: that for every 3-μmol/L decrease in serum homocysteine, there should be a mean 16% reduction in risk for ischemic heart disease.[5] The final common pathway for possible benefit for folate, vitamin B6, and vitamin B12 for preventing CVD centers on serum homocysteine, and it has been postulated that elevated homocysteine causes endothelial dysfunction, promotes an innate autoimmune response, and causes accumulation of inflammatory monocytes in atherosclerotic plaques.[6]

Homocysteine-Lowering Therapy and Cardiovascular Events: Latest Clinical-Trial Data

In a recent trial, 12 064 predominantly male survivors of MI were randomized to receive placebo or supplemental folate 2 mg and vitamin B12 1 mg daily for a mean of nearly 7 years of follow-up. Despite even distribution of classic Framingham CVD risk factors between control and intervention groups, adequate size and power, and a mean reduction in plasma homocysteine by 3.8 μmol/L,

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Table 1. Summary of Large-Scale Clinical Trials for Vitamin Supplementation and CVD Prevention

Study	Intervention	No. of Patients	Characteristics	Follow-up, y	Outcomes	HR (95% CI)
Armitage et al, 2010[7]	Folate, 2 mg/d; vitamin B12, 1 mg/d	12 064	Mean age 64 years, history of MI	6.7	Composite: coronary death, MI, coronary revascularization	1.04 (0.97-1.12)
Hankey 2010[9]	Folate, 2 mg/d; vitamin B6, 25 mg/d; vitamin B12, 0.5 mg/d	8164	Mean age 63 years, recent TIA/CVA	3.4	Composite: stroke, MI, vascular death	0.91 (0.8-1.0)
Albert et al, 2008[8]	Folate, 2.5 mg/d; vitamin B6, 50 mg/d; vitamin B12, 1 mg/d	5442	Mean age 63 years, all F, known history of CVD or ≥3 CVD risk factors	7.3	Composite: MI, stroke, coronary revascularization, cardiovascular death	1.03 (0.9-1.19)
Hsia et al, 2007[24]	Calcium carbonate, 500 mg/d; vitamin D, 200 IU/d	36 282	Mean age 62 years, all F	7.0	Composite: MI, cardiovascular death	1.04 (0.92-1.18)
Törnwall et al, 2004[32]	Vitamin A, 20 mg/d; vitamin E, 50 mg/d (=111 IU/d); vitamin A + E	5768, 5794, 5741	Finnish M only, smokers, mean age 52 years	6.0	Composite: nonfatal MI, cardiovascular death	Vitamin A, 1.13 (1–1.28); vitamin E, 0.94 (0.83-1.07); A + E, 1.08 (0.95-1.22)
Cook et al, 2007[33]	Vitamin A, 50 mg every other day; vitamin C, 500 mg/d; vitamin E, 600 IU every other day	8171 total	Mean age 61 years, all F	9.4	Composite: cardiovascular death, MI, stroke, coronary revascularization, total mortality	Vitamin A, 1.02 (0.92-1.13); vitamin C, 1.02 (0.92-1.13); vitamin E, 0.94 (0.85-1.04)
Sesso et al, 2008[40]	Vitamin C, 500 mg/d; vitamin E, 400 IU every other day	14 641 total	Mean age 64 years, all M	8.0	Composite: nonfatal MI or stroke, cardiovascular death	Vitamin C, 0.99 (0.89-1.11); vitamin E, 1.01 (0.9-1.13)
Lee et al, 2005[54]	Vitamin E, 600 IU every other day (vitamin A arm stopped)	39 876	Mean age 55 years, all F, no known CVD	10.1	Composite: nonfatal MI/stroke, cardiovascular death	0.93 (0.82-1.05)
Vardi et al, 2012,[48] meta-analysis of post hoc data from 3 select vitamin E trials reporting Hp genotype	Vitamin E, 400–600 IU/d (intervention trials); Hp 2–2 gene; non–Hp 2–2 gene	Pooled: 2110, 2656	WHS study data[34]: age ≥40 years, F, DM; Milman et al, 2008[49]: age 69–70 years, DM; HOPE study data[50]: mean age 66 years, DM	8.0, 1.5, 4.5	Composite: total MI, total stroke, cardiovascular death	Hp 2–2, OR: 0.66 (0.48-0.9); non–Hp 2–2, OR: 1.11 (0.80-1.53)[a]
Sesso et al, 2012[1]	Daily multivitamin	14 641	Mean age 64 years, all M	11.2	Composite: nonfatal MI, nonfatal stroke, cardiovascular death	1.01 (0.91-1.1)
Lamas et al, 2013[51]	Daily compound multivitamin	1708	Median age 65 years, recent MI (within 6 wks of trial)	2.6	Composite: total mortality, recurrent MI, stroke, coronary revascularization, hospitalization for angina	0.89 (0.75-1.07)
Hercberg et al, 2010[2]	Multivitamin: vitamins A (6 mg), C (120 mg), E (30 mg), selenium (100 µg), zinc (20 mg)	12 741	Mean age 49 years	7.5	Ischemic CVD, overall mortality	0.95 (0.75-1.2); 0.77 (0.57-1.04)

Abbreviations: CI, confidence interval; CVA, cerebrovascular accident; CVD, cardiovascular disease; DM, diabetes mellitus; F, female; HOPE, Heart Outcomes Prevention Evaluation; Hp, haptoglobin; HR, hazard ratio; IU, international units; M, male; MI, myocardial infarction; OR, odds ratio; TIA, transient ischemic attack; WHS, Women's Health Study.
[a]For the entry for Vardi et al 2012, ORs and 95% CIs are listed instead of HRs.

there was no major difference in MI, cardiovascular death, stroke, or need for revascularization.[7] Similarly, in the Women's Antioxidant and Folic Acid Cardiovascular Study (WACS), a daily combination of 2.5 mg folate, 50 mg vitamin B6, and 1 mg of vitamin B12 for a mean of 7.3 years in a well-powered, comparably higher-risk cohort of female healthcare professionals also failed to affect incidence of cardiovascular events.[8] Of note, in the Vitamins to Prevent Stroke Trial (VITATOPS), supplementation with 2 mg of folate, 25 mg of vitamin B6, and 0.5 mg of vitamin B12 for a median of 3.4 years did not reduce the rate of the composite of stroke, MI, or vascular death in survivors of stroke or transient ischemic attack—a lack of benefit that persisted even in those patients with an elevated plasma homocysteine value at baseline.[9] Finally, a Cochrane review with 11 trials reporting baseline homocysteine levels revealed no difference in incidence of MI with vitamin supplementation.[10] Current evidence supports the association between elevated plasma homocysteine blood levels and CVD, but it does not support supplementation with folate or vitamins B6 or B12 for reducing cardiovascular risk in this patient population.

Vitamin D and Cardiovascular Events

Background and Mechanisms of Action

The vast majority of data published regarding the relationship of vitamin D and heart disease in the 1960s and 1970s explored the connection between high vitamin D intake, hypercalcemia, and increased risk of heart disease. A team from Michigan was one of the first to suggest a link between vitamin D depletion and changes in myocardial structure that might herald the development of compensated heart failure in experimental studies involving rats.[11] Since that time, a great deal of observational data have emerged linking lower serum 25-hydroxy vitamin D (25[OH]D) levels with cardiovascular events.[12–14] In a 10-year follow-up study, the Health Professionals Follow-up Study (HPFS), men without previous CVD and vitamin D deficiency (25[OH]D <15 ng/mL) exhibited a 2-fold increased rate of MI.[14] In the Framingham Offspring Study, low 25(OH)D (<15 ng/mL) is associated with incidence of CVD.[15] Kendrick et al performed a cross-sectional analysis of data from the Third National Health and Nutrition Examination Survey (NHANES), 1988 to 1994, of 16 603 individuals and found a strong and independent relationship of 25(OH)D deficiency with prevalence of CVD compared with individuals with higher levels of vitamin D.[16] The NHANES 2000 to 2004 survey showed that 25(OH)D levels <20 ng/mL in adults were associated with increased prevalence of coronary heart disease, heart failure, and peripheral vascular disease.[17] The hypothesized mechanisms of action behind this link are broadly categorized as direct and indirect, genomic and nongenomic. These include modulation of nitric oxide,[18] the renin-angiotensin axis,[19] vascular smooth-muscle function,[20] and immune function.[21] Several studies in vitamin D receptor knockout mice demonstrated increased surrogate markers for CVD including hypertension, left ventricular hypertrophy, and increased proteinuria. One of the leading hypotheses is vitamin D negative regulation on the renin-angiotensin-aldosterone system.[15]

There are, however, differences of opinion regarding what constitutes "adequate" dietary vitamin D intake. Recently, the Endocrine Society and the Institute of Medicine (IOM) released updated guidelines. And although they differ in the recommended daily intake and do not agree on the oft-cited serum level of <20 ng/mL as the cutoff for "deficiency" for the general population, there is at least agreement that there is insufficient evidence to support intake of vitamin D for the prevention of nonskeletal outcomes.[22,23]

Vitamin D: Clinical-Trial Data

Despite a long list of promising observational data, RCTs so far have not demonstrated a reduction in cardiovascular events with vitamin D supplementation. Findings from the Women's Health Initiative Calcium/Vitamin D Supplementation Study (WHI CaD) revealed that cardiovascular events (a prespecified secondary outcome) were no less frequent in those patients randomized to receive calcium with vitamin D after 7 years of follow-up.[24] A meta-analysis of 51 randomized trials (6 of which specifically reported incidence of MI, 6 of stroke) similarly failed to demonstrate benefit with vitamin D supplementation, even in planned subgroup analyses of trials involving vitamin D-deficient patients.[25]

While we await the results of the Vitamin D and Omega-3 Trial (VITAL),[26] it seems clear that there is insufficient evidence to support routine vitamin D supplementation specifically for prevention of cardiovascular events in both the general population and even in patients thought to have inadequate blood levels of vitamin D.

Vitamins A, C, and E and Cardiovascular Events

Observational data also lend strong support to conventional wisdom—that diets rich in fruits and vegetables are associated with improved cardiovascular health.[27] Vitamins A, C, and E, among other substances, have been singled out in an attempt to distill the responsible ingredients, though to date carefully done studies have not been supportive.

Vitamin A: Background and Possible Mechanisms of Action

The term "vitamin A" refers to a group of >500 different carotenoid compounds, the most prominent of which is β-carotene. The emergence of evidence illustrating the role of oxidized LDL in atherogenesis, as well as in vitro studies demonstrating the ability of β-carotene to prevent such oxidation, stimulated interest in "antioxidants" like vitamin A in prevention of heart disease.[28] Others have subsequently highlighted the discrepancy between older epidemiologic evidence linking serum β-carotene levels and decreased risk for cardiovascular events and the lack of supportive RCT data.[29] This might suggest alternate roles of vitamin A in a more complex model of atherosclerosis, and currently in addition to possible antioxidant properties, vitamin A (and the carotenoids in general) is hypothesized to slow atherogenesis by modulation of cytokine levels[30] and alteration of lipid metabolism.[31]

Vitamin A and Cardiovascular Events: Clinical-Trial Data

A number of recent RCTs have been undertaken to investigate the possible link between vitamin A and

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cardiovascular events. In a study involving extended follow-up of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study, a cohort of 23 144 male smokers randomized to receive α-tocopherol 50 mg and/or β-carotene 20 mg daily vs placebo was followed for 5 to 8 years for incident MI and fatal coronary heart disease.[32] For reasons that remain unclear, β-carotene was associated with increased risk of fatal coronary heart disease in individuals without a history of MI. The smaller WACS study of vitamins A, C, or E vs placebo in a cohort of women with a high prevalence of coronary artery disease (64%) also failed to show any improvement in composite endpoints, or in any of the components of major adverse cardiovascular events with vitamin A supplementation.[33] An increase in cardiovascular (but not total) mortality was observed in this group, but only when data were adjusted for compliance (ie, a non–intention-to-treat analysis). Finally, in the Women's Health Study (WHS), 39 876 women without known CVD were randomized to receive 50 mg of vitamin A every other day, 600 IU of "natural source" vitamin E every other day, aspirin, or placebo in what was originally a $2 \times 2 \times 2$ design.[34] The outcomes analyzed were incidence of invasive cancers and cardiovascular events, defined as nonfatal MI or stroke or cardiovascular death. The vitamin A arm of the trial was terminated early by the steering committee after a median of 2.1 years of treatment in light of null results regarding cancer incidence for a similar study of vitamin A and cancer incidence, as well as other studies (including the ATBC trial mentioned above) that suggested the potential for serious adverse cardiovascular effects.

Vitamin C: Background and Mechanism of Action

Vitamin C is perhaps one of the most prolific "antioxidant" supplements, but, as with vitamin A, it may also affect the genesis of atherosclerosis by other means, including effects on vascular remodeling,[35] endothelial function,[36] and lipid peroxidation.[37] Meta-analyses of prospective cohort data published in the last decade have suggested a relatively lower risk for incidence of CVD in those reporting greater intake of vitamin C supplements.[38] Subsequent RCTs have been less supportive.

Vitamin C: Clinical-Trial Data

In the WACS trial, ascorbic acid alone did not improve risk for composite cardiovascular events or its components. This is consistent with the majority of original data in the literature, and a meta-analysis by Myung et al of trial data from 7 studies of ascorbic acid showed no effect on incidence of cardiovascular events.[39] Interestingly, in the WACS trial, the combination of vitamin C and E did result in a decrease in rate of ischemic stroke (but not total stroke). In the Physicians' Health Study II (PHS-II), this combination did not change the total incidence of stroke.[40]

Vitamin E: Background and Mechanism of Action

Vitamin E, though technically a chemically heterogeneous group of tocopherols and trienol antioxidant compounds, refers to the form predominantly active in humans, α-tocopherol. As with vitamin C, recognition of the role of lipoprotein oxidation in atherogenesis generated interest in searching for a protective effect of vitamin E against heart disease. One such effort was a longitudinal cohort study from Finland, in which the dietary intake of vitamins A, C, and E were estimated in a large healthy group that was followed for a mean of 14 years—an inverse association was found between estimated vitamin E intake and cardiovascular death.[41] A similarly conducted, larger study of middle-aged to elderly US males used questionnaires to determine vitamin E intake and followed subjects for 4 years. Again, a significant trend toward reduced risk for cardiovascular death, nonfatal MI, or need for coronary artery bypass or coronary angioplasty was noted with any comparatively higher intake of vitamin E (ie, $\geq$60 IU daily, as compared with $<$7.5 IU daily, and at least 100 IU daily compared with no intake).[42] Vitamin E is hypothesized to exert its effects via inhibition of foam-cell formation,[43] platelet function,[44] and, at least with in vitro studies, free-radical scavenging.[45] Data from RCTs, however, have not been consistently supportive of such benefit.

Vitamin E and Cardiovascular Events: Clinical-Trial Data

Data are conflicting, with the majority of trials showing no benefit except in very specific subpopulations. In the previously mentioned ATBC cohort, 50 mg of daily synthetic supplemental α-tocopherol—equivalent to 111 IU of active α-tocopherol[46]—had no effect on incident MI or fatal CHD, both in those with a history of MI and in those without. There was, however, an increased rate of fatal hemorrhagic stroke (but not total stroke) in the 28 519 members of the cohort analyzed for this outcome.[47] Similarly, in the PHS-II trial mentioned previously, 400 IU every other day of synthetic vitamin E supplementation did not reduce the rate of major cardiovascular events or its endpoints, both in the entire cohort as well as in the subgroup with a history CVD. Similar to the ATBC findings, there was an increased risk of hemorrhagic stroke (but not total stroke) in the active vitamin E arm. Contrasting findings were found in the aforementioned WHS.[47] In the vitamin E arm, treatment with 600 IU every other day of vitamin E was associated with reduced major adverse cardiovascular events, total MI, and cardiovascular death, but only in patients age $\geq$65 years. The authors noted that this subgroup comprised only 10% of the total cohort, but contributed 31% of endpoints. Further argument for group selective effects can be found in a meta-analysis by Vardi et al of observational and trial data involving incident cardiovascular events and the effect of vitamin E in patients with diabetes mellitus and with haptoglobin (Hp) genotype 2–2.[48] In the observational data, the group found an increased incidence of nonfatal MI, stroke, and cardiovascular death with this particular genotype of diabetic patients, which the authors attributed to increased oxidative stress. Individual trial data used in this particular meta-analysis included data from a randomized trial by Milman et al of vitamin E in Hp 2–2 diabetic patients,[49] the Heart Outcomes Prevention Evaluation (HOPE) of use of ramipril or vitamin E for cardiovascular primary prevention,[50] and the WHS.[51] At the level of individual trial data, benefit in terms of reduced cardiovascular events with vitamin E supplementation was

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not uniformly statistically significant, but it was in the pooled analysis (Table). Despite this discrepancy, the various effects reported with vitamin E use across the studies reviewed thus far—that vitamin E might in some patients be associated with increased bleeding risk or improved cardiovascular outcomes in some genotypes but not others—still highlight unsaturated areas of research that will become particularly relevant as the scientific community's understanding of genome-wide associations deepens in the years to come.

Vitamins A, C, and E: Conclusion

Based on the inconsistent benefit in recent trial data and potential for adverse effects, it is concluded that there remains insufficient evidence for vitamin A, C, or E, singly or in combination, for prevention of cardiovascular events in a general population at risk. Study of the therapeutic potential of alternative members of the retinoid and tocopherol family of compounds, as well as genotype-targeted therapy, offers interesting avenues for continued research.

Combination Multivitamins and Cardiovascular Events

In an attempt to exploit the possibility that it is specific combinations of vitamins rather than 1 individual supplement alone that holds the key to potential cardiovascular benefit, a number of proprietary brands of multivitamins are marketed, each purporting various health benefits. The PHS-II group published one of the only 3 large-scale RCTs currently available from the last decade involving the effect of a multivitamin on cardiovascular outcomes.[1] In the trial, 14 641 male physicians were randomized to receive a common brand of multivitamin vs placebo and were followed for a median of 11 years. At the completion of follow-up, there was no between-group difference in major cardiovascular events, total MI, total stroke, cardiovascular death, or overall mortality. There was a reduction in total death from MI, which appeared to be driven by an observed reduction in fatal MI in those patients without an antecedent history of CVD. The authors suggest that the observed effect was due to chance, due to the low number of said events. This argument parallels the conclusions of the Supplementation in Vitamins and Mineral Antioxidants Study (SU.VI.MAX.) investigators, who noted a non-statistically significant trend toward an increased incidence of ischemic CVD in women who received a multivitamin supplement.[2] The recently published results from the multivitamin arm of the Trial to Assess Chelation Therapy (TACT) trial also showed no benefit of a particular combination of vitamins and minerals in preventing recurrent MI, stroke, hospitalization for angina, or need for revascularization in patients with a history of prior MI.[52]

Combination Multivitamins and Cardiovascular Events

The authors of this review agree with the findings of a recent review by Rembold et al[53] and those of Fortmann et al, who cited 2 of the above studies as part of their recommendation to the US Preventive Services Task Force against routine multivitamin and mineral supplementation for the prevention of cardiovascular events.[54]

Conclusion and Future Directions

Despite the mostly negative findings of multiple trials at this point in time, considerable opportunities for investigation remain in the search for those populations that might benefit from specific vitamin supplements for CVD prevention. At this time, however, despite observational data to the contrary, the overall weight of the evidence does not support routine vitamin supplementation for prevention of cardiovascular events for most individuals in the US population.

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