Vitamin Supplementation and Cardiovascular Disease

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Abstract

• Objective: To review the evidence of the effectiveness of antioxidant vitamins for the prevention and treatment of cardiovascular disease (CVD).
• Methods: Qualitative assessment of the literature.
• Results: Data do not support the hypothesized cardioprotective effect of supplemental vitamin A, and there is a suggestion of toxicity with higher doses. Intervenional studies with β-carotene fail to support any benefit on CVD and many suggest harm from β-carotene supplementation. Observational studies of vitamin C supplementation have yielded variable results. Small interventional studies with surrogate endpoints and large prospective interventions overall have not shown a benefit of vitamin E on preventing CVD. Meta-analyses of these large studies corroborate the lack of effect of vitamin E. A benefit of folate on CVD risk has been demonstrated, but recent fortification of grains in the United States with folate might limit the translation of these study results into current practice. Nicotinic acid decreases the risk of CVD through its effect on lipids, but side effects limit its use. The majority of vitamin combination studies suggest no benefit, and several notable vitamin combination studies raise the concern that some combinations may cause harm. Perhaps the strongest beneficial effect with multivitamins is seen in those with or at risk for baseline vitamin deficiencies.
• Conclusion: Data from this review do not support the use of vitamins for primary or secondary prevention of CVD. Indeed, there is even the suggestion of possible harm in some groups. Thus, careful consideration is needed prior to prescribing or condoning supplemental vitamin use for the prevention or treatment of CVD.

Atherosclerotic cardiovascular disease (CVD) involving the coronary, cerebral, and peripheral vascular systems is the leading cause of death in the United States and is a major cause of morbidity. A better understanding of the atherosclerotic process has led to the development of more effective therapies for preventing CVD and to significant decreases in cardiovascular events and mortality, most notably when treatment with lipid-altering medications, including statins, is undertaken [1]. Although statin therapy has been shown to reduce relative risk in ischemic heart disease by up to 50% [2], there remains substantial room for improvement.

Lifestyle interventions addressing diet and physical activity must remain the cornerstone for treatment and prevention of vascular disease [3]. Many epidemiologic studies have demonstrated that increased intake of fruits and vegetables is associated with decreased risk of cardiovascular and cerebrovascular disease [4–9]. In addition, several studies have found an association between serum levels of various antioxidant vitamins and CVD [10,11]. Numerous lines of evidence support the oxidant role in atherosclerosis [2], including data showing that myeloperoxidase deficiency, which results in decreased oxidant production, is protective against atherosclerosis [12], while an elevated myeloperoxidase level is associated with the presence of atherosclerosis [13]. In addition to their antioxidant effects, vitamins may be related to improvement in other known cardiovascular risk factors, including blood pressure [14], homocysteine level [15], and lipid levels [16]. Therefore, specific interventions with vitamins deserve closer evaluation.

This review examines data on the effect of vitamin A, β-carotene, vitamin C, vitamin E, folate, nicotinic acid, and vitamin combinations on CVD. The proposed biologic mechanism for each vitamin and the available observational and interventional data are presented. In most cases, study findings are presented as relative risk (RR) with 95% confidence intervals (CI). A significant effect can be assumed when the 95% CI does not cross unity (ie, when the standard interval does not include 1).

Vitamin A (Retinol)

Low-density lipoprotein (LDL) particles carry vitamin A, although vitamin A is much less abundant in LDL than are...
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the other antioxidant vitamins [17,18]. Vitamin A may prevent CVD by reducing oxidation of LDL. Vitamin A-enriched LDL drawn from study participants who were given a single 20,000 IU oral supplement of vitamin A was more resistant to oxidation in an in vitro assay [18]. In another study, supplementation with 25,000 IU of vitamin A significantly decreased lipid peroxide levels [19]. However, while some cross-sectional and observational studies have found an association between serum vitamin A levels and risk of death from CVD [10,20], others have not found such an association [11,21–26]. Additionally, investigators have failed to between preclinical carotid atherosclerosis and vitamin A levels [27,28]. Interestingly, vitamin A levels have been found to be positively associated with hypertension [14].

The Iowa Women’s Health Study (IWHS) evaluated intake of both dietary and supplementary vitamin A and the risk for subsequent CVD in more than 34,000 women [29]. Overall, there was an inconsistent dose response between total vitamin A intake and CVD, and any hint of an effect was lost with control for other known risk factors. Analysis of vitamin A supplementation showed that participants in the next to lowest quintile of supplement intake (1–5000 IU/day) had a slight decrease in RR of death from CVD compared with the lowest quintile (no supplementation) (multivariate adjusted RR, 0.66 [95% CI, 0.44 to 1.01]). However, the risk of CVD was not different between the 2 highest quintiles of supplement intake and the lowest quintile [29].

A non–placebo-controlled study randomized asbestos workers from Australia (n = 512 per group) to either vitamin A (25,000 IU) or β-carotene (30 mg/day) [30]. At a median follow-up of 232 weeks, a slight but nonsignificant increase in death from CVD (RR, 1.72 [95% CI, 0.50–5.86]) was observed in the vitamin A group compared with the β-carotene group. Additionally, the vitamin A group experienced 45 adverse events, primarily elevated liver enzymes probably associated with treatment [30]. This study’s lack of a placebo group does not allow firm conclusions to be drawn regarding the effect of vitamin A on CVD. Additional intervention studies using vitamin A as part of an antioxidant cocktail will be discussed in later sections.

Summary
These limited data do not support the hypothesis that supplemental vitamin A is protective against CVD. There is a suggestion of toxicity when higher doses of vitamin A are administered.

β-Carotene
The dietary carotenoids are carried in the blood almost exclusively associated to lipoproteins [17]. Some of the dietary carotenoids, including β-carotene, can be converted to vitamin A by enzymes in the gastrointestinal tract [17]. Like vitamin A, the carotenoids are believed to protect against atherosclerosis via their antioxidant effects (eg, scavenging of peroxyl radicals and singlet oxygen) [17,31]. However, decreased susceptibility of LDL to oxidation in vitro has not always been demonstrated following β-carotene supplementation [32,33].

Observational Data
Several studies that assessed β-carotene intake from whole foods using food frequency questionnaires have demonstrated a protective effect [5,34,35]. In a sample of elderly patients from the Rotterdam Study, the group with the highest tertile of β-carotene intake had a lower risk for myocardial infarction (MI) (RR, 0.55 [95% CI, 0.34–0.83]) compared with the lowest intake tertile [35]. Similarly, a study of elderly patients in Massachusetts showed a lower risk for MI (RR, 0.25 [95% CI, 0.09–0.67]) in the highest versus lowest quartile of carotenoid intake [5]. These differences remained significant after controlling for other known risk factors, and were more pronounced when the use of supplements was incorporated [5,35]. Other prospective observational studies have corroborated these findings [22,34]. However, the IWHS did not show a beneficial effect of carotenoids, either from food sources or supplements, on prevention of CVD [29]. Likewise, the Health Professionals Follow-up Study (HPFS) found no association between risk of CVD and carotene intake in never smokers, although a protective association between carotene intake and CVD was seen in smokers [36]. Additionally, when risk for other vascular disease was evaluated in this study, no relationship between carotenoids and risk of stroke was demonstrated [37].

Studies that rely on intake data are fraught with difficulties, including confounding factors from the food itself (ie, intake of other beneficial macronutrients, micronutrients, or minerals) and the overall lifestyle associated with certain patterns of food intake. To control in part for some of these factors, studies have evaluated the effect of serum levels of β-carotene on CVD. Plasma carotene levels have been shown to be inversely associated with the risk of angina, albeit only before controlling for tobacco use [24]. In addition, patients with CVD have been shown to have lower plasma β-carotene levels and higher lipid peroxide levels compared with patients without CVD [23]. In the Basel Prospective Study, low plasma β-carotene levels were associated with an increased risk of CVD, including stroke, over 12-year follow-up [11]. The Lipid Research Clinics Coronary Primary Prevention Trial found that men in the highest quartile of serum carotene had a lower risk of CVD (RR, 0.64 [95% CI, 0.44–0.92]) compared with those in the lowest quartile, after adjustment for other known risk factors [38]. Finally, serum β-carotene was associated with a lower risk for hypertension (odds ratio [OR], 0.81 [95% CI, 0.73–0.89]) in the Third National Health and Nutrition Examination Survey (NHANES III) [14].
 Conversely, the Multiple Risk Factor Intervention Trial (MRFIT) has failed to show an effect of plasma carotenoids on risk for CVD [21]. Additionally, no correlation between β-carotene levels and carotid atherosclerosis was shown in a cross-sectional study from Australia [28].

Interventional Studies
Several trials of β-carotene supplementation have been conducted. In the uncontrolled study comparing vitamin A to β-carotene (30 mg/day, approximately equal to 4 carrots per day) in Australian asbestos workers [30], more deaths due to mesothelioma and a slight but nonsignificant decrease in ischemic heart disease were seen in the β-carotene group. However, without a placebo arm, no definitive conclusions regarding the effect of β-carotene on heart disease can be drawn from this study. The Physicians' Health Study assessed a β-carotene intervention [39], with 11,036 men receiving β-carotene (30 mg every other day, with or without aspirin on the alternate days) and 11,035 men receiving placebo (with or without aspirin). Significantly more yellowing of skin in the β-carotene group was the only adverse effect. After a mean follow-up of 12 years, β-carotene produced neither benefit nor harm overall with respect to CVD; however, in smokers there was a nonsignificant trend toward increased death from CVD (RR, 1.13 [95% CI, 0.80–1.61]) [39].

A study initially designed to evaluate the effect of β-carotene on prevention of skin cancer also evaluated the effect of baseline plasma β-carotene levels and supplementation with 50 mg/day of β-carotene on risk of all-cause death and death from CVD [40]. As in the studies discussed above, patients in the highest quartile of baseline β-carotene levels had a decreased risk of death from all causes (RR adjusted for other known risk factors, 0.62 [95% CI, 0.44–0.87]) and from CVD (adjusted RR, 0.57 [95% CI, 0.34–0.95]) compared with patients in the lowest quartile [40]. Conversely, supplementation after a median follow-up of 8.2 years did not alter total mortality (adjusted RR of death, 1.03 [95% CI, 0.82–1.30]) or CVD mortality (adjusted RR of death, 1.16 [95% CI, 0.82–1.64]). Although the difference in CVD mortality risk was far from significant (P = 0.41), the trend implies harm rather than benefit from β-carotene.

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) trial evaluated the effect of β-carotene on CVD in smokers (<40 cigarettes per day) and death from CVD [41]. Vitamin E and β-carotene, or placebo (approximately 7300 participants in each arm). Participants were followed for a median of 6.1 years. Overall, mortality was 8% higher in the combined β-carotene arms (P = 0.02), with increased mortality from ischemic heart disease compared with the other arms (77.1 versus 68.9 deaths per 10,000 patient-years) [41]. However, the increase in CVD came primarily from those with prior CVD, with an adjusted RR of 1.75 (95% CI, 1.16–2.64) for the β-carotene–only group [44]. There was no increase in new angina [43,45] and no increase in fatal coronary disease [42] in participants without previous CVD. However, data did not suggest a protective effect from this intervention in the population without previous CVD.

Finally, the Women’s Health Study evaluated the effect of β-carotene on CVD at a dose of 50 mg every other day [46]. Due to disappointing results in other trials, including the ATBC trial, this study was terminated prematurely after a median treatment duration of 2.1 years. Participants were followed for outcomes off treatment for an additional 2 years. No significant differences in MI, death from CVD, or other CVD outcomes were observed [46].

Summary
Contrary to findings in observational studies, interventional studies with β-carotene have not demonstrated a beneficial effect on CVD, and many of these studies suggest harm from β-carotene supplementation.

Vitamin C
The water-soluble vitamin C is not carried in the LDL particle as are the lipid-soluble vitamin A, β-carotene, and vitamin E [47]. However, evidence suggests that physiologic concentrations of vitamin C can act as an antioxidant in neutrophils [48] and that vitamin C might act to regenerate other antioxidants [49]. The antioxidant effects of vitamin C were demonstrated in a small secondary prevention trial where 1000 mg/day of vitamin C decreased lipid peroxide levels by 19.8% ± 10.8% [19]. Vitamin C may protect against atherosclerotic disease by other mechanisms, including decreased adhesion of monocytes to endothelial cells (a critical component of the production of the atherosclerotic lesion) [50]. However, this finding was not replicated in a similar study [51]. Vitamin C also may have a beneficial effect on endothelial vasomotor function [52,53], but it is possible that the improved vasomotor function occurs via its antioxidant properties.

Observational Data
Several cross-sectional studies have suggested a protective effect of vitamin C against CVD. Low plasma vitamin C levels were associated with risk of angina [24] and risk of CVD (RR, 2.23 [95% CI, 1.14–5.26]) in patients with low versus high vitamin C levels in 2 studies [23]. However, 2 other studies that used ultrasound imaging to evaluate for the presence of carotid artery lesions found no association between presence of disease and vitamin C levels [27,28].

Prospective observational studies also have yielded variable results. The IWHS [29], the Established Population for
Epidemiological Studies in the Elderly (EPESE) [54], the Physicians’ Health Study [55], a subgroup analysis of the Cholesterol-Lowering and Atherosclerosis Study (CLAS) [56], and the Rotterdam Study [35] all failed to show an association between vitamin C intake and risk for CVD. Although the HPFS suggested a possible benefit of vitamin C intake (RR, 0.83 [95% CI, 0.64–1.08]), this effect was lost after adjustment for risk factors and the use of other antioxidants [36]. The HPFS also failed to show an association between increased intake of vitamin C by either foods or supplements and cerebrovascular disease [37].

Conversely, several positive observational studies have been conducted. An analysis of the NHANES I study found that all-cause death was inversely related to vitamin C intake, and the risk of CVD was lower in both men (RR, 0.58 [95% CI, 0.41–0.78]) and women (RR, 0.75 [95% CI, 0.55–0.99]) with high vitamin C intake [57]. A second positive study followed Finnish men and women aged 30 to 69 years who had no CVD at entry. After a mean follow-up of 14 years, there was a decreased risk of death in women with the highest intake of vitamin C [34]. The Basel Prospective Study also found that those with low levels of vitamin C initially had an increased risk of ischemic heart disease and stroke over 12 years of follow-up [11]. In the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) [58], men with initial vitamin C deficiency by measurement of plasma levels had a significantly increased risk for CVD (RR, 4.0 [95% CI, 1.7–9.4]). However, no difference in risk for CVD was seen between those with levels just above deficiency and those with higher levels of vitamin C. Finally, the Nurses Health Study has followed more than 85,000 women for 16 years and evaluated for risk of CVD [59]. Participants with the highest intake of vitamin C had a moderately lower risk of coronary heart disease (multivariate adjusted RR, 0.73 [95% CI, 0.57–0.94]) when compared to those with the lowest intake of vitamin C. This effect persisted even after controlling for intake of other antioxidants. Interestingly, the effect was even stronger in the subgroup of women with diabetes (RR, 0.57 in highest versus lowest intake of vitamin C [95% CI, 0.37–0.88]).

Interventional Study
Only 1 interventional study of vitamin C with disease-specific outcomes has been published [60]. This secondary prevention study in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) included 60 control patients and 59 patients randomized to vitamin C 500 mg/day immediately following PTCA. The participants were restudied by angiography 4 months after the initial PTCA. The treatment group had a larger minimal lumenal diameter and a significantly lower rate of restenosis (~25% versus ~40% for placebo) or further intervention (14% versus 33% for placebo) [60].

Summary
Vitamin C has several biologically plausible mechanisms through which it might help to prevent CVD. Observational studies have yielded variable results, however. The most significant result is that, in studies of vitamin C plasma levels, those with vitamin C deficiency had the highest risk for CVD. The 1 published outcome study is promising, but the minimal outcome data limit recommendations for vitamin C supplementation.

Vitamin E
α-Tocopherol or vitamin E is the most abundant antioxidant present in the LDL particle [47]. Vitamin E can act as an antioxidant in vitro, but the effects in vivo have been variable. Vitamin E supplements (400 U/day) decreased lipid peroxide levels by 36.4% ± 1.17% [19]. Vitamin E supplementation increased LDL resistance to oxidation in vitro [33,61], but the protective effect was highly variable [61]. Studies that used more precise and quantitative measures of oxidation have failed to find an effect of vitamin E on lipid peroxidation [62]. Other potential mechanisms whereby vitamin E may decrease the risk of atherosclerosis include decreased adhesion of monocytes, inhibition of smooth muscle cell proliferation, decreased platelet adhesion, and improved vasodilatation [47,63]. The vasodilation effect is likely due, at least in part, to vitamin E’s antioxidant activity (similar to vitamin C) but also may occur through inhibition of protein kinase C activation and subsequent enhancement of nitric oxide synthase activation [47,63].

Observational Data
Several cross-sectional studies have suggested a protective effect of vitamin E against CVD. In 2 studies, plasma levels of vitamin E have been inversely associated with both risk for angina [24] and risk for coronary artery disease [23]. In addition, studies using carotid ultrasound imaging found a significant inverse association between intima-media thickness (IMT, a marker of vascular disease) and vitamin E intake in men and a similar, albeit nonsignificant, trend in women [28]. Vitamin E intake and plasma levels also have been shown to be inversely associated with carotid plaques [27]. Conversely, 2 case control studies have not demonstrated a beneficial effect of higher vitamin E levels on cardiovascular mortality or MI. A 9-year follow-up study from the Netherlands found no effect of vitamin E levels on cardiovascular mortality [26]. A case-control analysis of the MRFIT study also found no difference between the highest and lowest quartiles of plasma vitamin E levels in terms of MI or cardiovascular mortality [21].

Prospective observational studies have produced conflicting results regarding a protective effect of vitamin E against CVD. The Physicians’ Health Study found only a nonsignificant trend for decreased CVD in those who used supplemental vitamin E
factor such as aspirin, an angiotensin-converting enzyme also examined the effect of vitamin E (often also with another placebo group, 35% presence in the vitamin E group versus 50% in the vitamin E–only group (RR, 0.62 [95% CI, 0.41–0.96]), but a benefit was not seen in the vitamin E plus β-carotene group [44]. There was an increased incidence of fatal coronary heart disease in both vitamin E groups (RR, 1.58 [95% CI, 1.05–2.40] in vitamin E plus β-carotene; RR, 1.33 [95% CI, 0.86–2.05] for vitamin E only) [44].

The only large trial to demonstrate a positive effect of vitamin E on CVD was the Cambridge Heart Antioxidant Study (CHAOS) [72]. More than 2000 patients with proven CVD were randomized to either vitamin E (400 or 800 IU/day) or placebo and followed for a median of 510 days. The primary
endpoints were death from CVD and nonfatal MI. The vitamin E treatment group had a significant decrease in the combined primary endpoints (RR, 0.53 [95% CI, 0.34–0.83]), which was due to a large decrease in nonfatal MI (RR, 0.23 [95% CI, 0.11–0.47]). There was also a nonsignificant increase in death from CVD in the vitamin E group (RR, 1.18 [95% CI, 0.62–2.27]).

Meta-analyses

Finally, 2 meta-analyses have examined the effect of vitamin E on CVD. The first included the ATBC trial, CHAOS trial, GISSI study, and HOPE study and found no overall benefit of vitamin E supplementation on CVD (RR, 0.97 [95% CI, 0.92–1.02]) [71]. The second [73] included the above studies as well as the Heart Protection Study [74] and the Age-Related Eye Disease Study (AREDS) [75] (only combination vitamins were given in these 2 studies). This meta-analysis involved almost 82,000 patients and found no effect of vitamin E on total mortality (RR, 1.02 [95% CI, 0.98–1.06]), cardiovascular mortality (RR, 1.0 [95% CI, 0.94–1.06]), or any of the other endpoints evaluated, or after subdivision into primary and secondary prevention [73].

Summary

Although most cross-sectional and observational studies have shown a beneficial effect of vitamin E on preventing CVD, small intervention studies with surrogate endpoints and large prospective interventions overall have not shown a benefit. Meta-analyses of these large studies corroborate the lack of effect of vitamin E.

Folic Acid

Folic acid has been linked to CVD through its effect on homocysteine metabolism. It is well established that the mechanism explaining folate’s effect on CVD is its link with homocysteine. Deficiencies in folic acid result in elevated levels of the amino acid homocysteine, and it has been estimated that approximately two thirds of the cases of elevated homocysteine are due to a relative vitamin deficiency, most notably folate [76]. It was first noted that individuals with abnormal homocysteine metabolism and very high levels of homocysteine experienced premature atherosclerotic disease and that treatment to reduce the levels dramatically decreased the risk of CVD [77]. Subsequently, well over 100 prospective and cross-sectional studies have been published showing an overall positive correlation between homocysteine levels and CVD. A recent meta-analysis of 14 large prospective studies (including Framingham, Rotterdam, MRFIT, Women’s Health Study, and Physicians’ Health Study) found an increased risk of coronary heart disease (OR, 1.20 [95% CI, 1.14–1.25]) for every 5 μmol/L increase in homocysteine [15]. It has been proposed that elevated homocysteine causes CVD through increased platelet aggregation, endothelial toxicity and dysfunction, vessel wall abnormalities (including abnormal flow-mediated vasodilation), and increased proliferation of smooth muscle cells [15]. Some debate remains around the hypothesis that homocysteine increases the risk for CVD, notably because persons with severe metabolic disorders and extremely elevated homocysteine have primarily venous and not arterial disease, and because those with more modest abnormalities in homocysteine metabolism (eg, polymorphisms in the methylene-tetrahydrofolate reductase enzyme) do not seem to have increased risk of CVD [78]. Thus, folate might act independent of homocysteine, or folate might simply be a marker of other lifestyle alterations (including other nutrient intake) that modify CVD risk.

Observational Data

Low folic acid intake or serum levels have been associated with increased risk of CVD in numerous studies. In the Physicians’ Health Study, the risk of MI was increased (RR, 1.4 [95% CI, 0.9–2.3]) in men with the lowest serum folate levels (in the bottom 20% of all measurements) compared with men with the highest levels (in the top 80% of all measurements) [79]. The Atherosclerosis Risk in Communities study followed a middle-aged cohort of men and women over 3.3 years [80]. After adjusting for age, sex, and site, there was a decreased risk of coronary heart disease in those with the highest compared with the lowest folate levels (RR, 0.39 [95% CI, 0.1–1.06]) [80]. However, this effect was weakened after adjustment for other risk factors (RR, 0.66 [95% CI, 0.3–1.5]). An analysis of the NHANES I database [81] found no change in risk overall for fatal or nonfatal MI according to folate level, although an increased risk was demonstrated when 35- to 54-year-old patients with the lowest folate levels were compared to those in the same age-group with the highest levels (RR, 2.4 [95% CI, 1.1–5.2]) [81]. An analysis using data from the NHANES II Mortality Study [82] found that in patients without diabetes, the adjusted RR of CVD mortality was 2.28 (95% CI, 0.96–5.40) when the highest tertile of serum folate was compared with the lowest. Using a retrospective cohort analysis with a 15-year follow-up, the Nutrition Canada Study found an increased risk of CVD mortality (RR, 1.69 [95% CI, 1.10–2.61]) in those with the lowest compared with the highest serum folate levels [83]. Finally, the KIHD study found a decreased risk of acute coronary events in those with the highest compared with the lowest serum folate levels (RR, 0.30 [95% CI, 0.10–0.84]) [84].

Although these studies suggest that lower serum folate levels are associated with increased risk for CVD, their findings are limited by the fact that folate levels are not stable in frozen samples (ie, folate often degrades) [82]. In addition, serum folate only reflects recent intake and not body stores [85]. Using intake data, a case control study from Spain
Interventional Studies

One small study sheds some light on the effects of folate beyond homocysteine metabolism [89]. This randomized, placebo-controlled study found that the surrogate marker of flow-mediated dilation increased significantly both immediately (within 2 hours) and over the longer term (6 weeks) after administration of folate 5 mg daily [89]. However, the change in flow-mediated dilation did not correlate with changes in homocysteine. In fact, homocysteine levels decreased in both the treatment and placebo groups during the acute study, yet flow-mediated dilation did not increase in the placebo group [89].

There have been several additional interventional studies evaluating the effect of folate supplementation on prevention of CVD. In a small study that followed 38 patients with carotid artery atherosclerosis, plaque area increased by 0.31 ± 0.39 cm² per year prior to supplementation with folic acid (2.5 mg/day) and vitamins B₆ and B₁₂, and decreased by 0.05 ± 0.25 cm² per year after supplementation (P = 0.002) [90]. However, the lack of a control group and other potential confounding factors limit the generalizability of this study [90]. A study from the Netherlands involving siblings of patients with CVD (the siblings also were required to have elevated homocysteine after a methionine load) found that after 2 years of supplementation with folic acid 5 mg and vitamin B₆ there were fewer abnormal exercise tests in the treatment group compared with the placebo group (OR, 0.40 [95% CI, 0.17–0.93]) [91]. However, there was no difference in measures of peripheral vascular disease or stenosis of the carotid or femoral arteries by ultrasound imaging. Additionally, in 2 reports from the Swiss Heart Study, patients randomized to a vitamin B combination (including 1 mg/day of folic acid) following PTCA had less restenosis at 6 months (19.6% in treatment group versus 37.6% in control; RR, 0.52 [95% CI, 0.32–0.86]) [92]. At 11 months of follow-up, the proportion of patients needing repeat vascularization of the target lesion remained significantly less (9.9% versus 16%; RR, 0.62 [95% CI, 0.40–0.97]) [93]. However, not all studies have been positive. In almost 600 patients with stable CVD (most on aggressive statin treatment for more than 3 years before the study and all on aggressive treatment during the study), 0.5 mg of folic acid daily for 2 years did not affect any of the endpoints (including mortality, recurrent MI, stroke, or vascular procedure) [94].

Summary

Folate seems to have a potential for benefit, but the independence of this effect beyond changes in homocysteine is not well defined. Recent fortification of grain products in the United States with folate may limit the translation of these study results into current practice [95].

Nicotinic Acid

Pharmacologic doses of niacin greater than 1 g daily (typically > 3 g daily) have been shown to decrease cardiovascular events and even mortality over the long term [96,97]. The primary effect of nicotinic acid is likely a function of its beneficial effects on lipids (ie, increased high-density lipoprotein [HDL] cholesterol and decreased LDL cholesterol and triglycerides). This effect is specific to the nicotinic acid form of vitamin B₃ as niacinamide does not have any effect on lipids. However, nicotinic acid use in pharmacologic doses is limited in part by its side-effect profile, which includes flushing, hepatitis, peptic ulcer disease, decreased glucose tolerance, and gout. Interestingly, a recent small study found that low doses of nicotinic acid (50 mg/day) could have a significant effect on increasing HDL cholesterol when added to statin therapy, although any outcome from this remains to be proven [16]. In the HDL-Atherosclerosis Treatment Study (HATS) [98], a niacin “placebo” of 50 mg twice daily used by investigators to mimic the flushing seen in the treatment arm did not alter lipid profiles. However, these findings are from an unpublished report, and the study had no true placebo arm to ensure this very low dose had no effect.

Summary

Nicotinic acid decreases the risk of CVD through its effect on lipids, but side effects limit its use. Any effect of lower-dose niacin on lipids or prevention of CVD remains to be definitively shown.

Multivitamin Combinations

The demonstrated beneficial effect of diets rich in vitamins and minerals might be related to the interactions of more than one vitamin with supportive or complementary mechanisms of action (eg, supporting different antioxidant properties or one acting as an antioxidant and another improving lipids or vascular reactivity). Indeed, the Endothelial Assessment of Risk from Lipids in Youth trial showed that even in children with an inherited dyslipidemia, the addition of
vitamin C (250 mg) and vitamin E (200 IU) twice daily significantly improved endothelial function as measured by flow-mediated dilation [99]. In order to further to address the potential for combined effect of vitamins, several studies have examined the effect of 2 or more vitamins or of multivitamins on CVD risk.

Observational Data
The observational data on multivitamin use or combination vitamin use and CVD are conflicting, in part due to the variability of combinations and the differences in the populations evaluated. For example, the NHANES I [100] found that although more than 20% of their population were supplement users, there was no difference in mortality between users and nonusers over 10 years of follow-up. However, an EPIC study [54] found that those who used vitamin C and E supplements had decreased total mortality (RR, 0.58 [95% CI, 0.42–0.79]) and decreased mortality due to coronary disease (RR, 0.47 [95% CI, 0.25–0.87]). Additionally, the Cancer Prevention Study II [101] followed more than 1 million participants for 7 years, with death as the main outcome. It found that users of multivitamins and vitamins A, C, and/or E had the lowest risk of death, those who used only vitamins A, C, and/or E had an intermediate decreased risk, and those who used only multivitamins had a modest (and not always significant) lower risk. The Physicians’ Health Study [55] similarly found that users of vitamins E and C had a trend for decreased total CVD mortality (RR, 0.76 [95% CI, 0.54–1.06]), whereas users of multivitamins had no trend for protection (RR, 1.07 [95% CI, 0.91–1.25]). Finally, the Stockholm Heart Epidemiology Program [102], in a case control study of patients with their first MI, found that regular supplement users had a lower risk for MI compared with nonusers (OR, 0.78 [95% CI, 0.62–0.97] for males; 0.67 [95% CI, 0.49–0.93] for females). However, these results highlight a possible background effect because overall consumption of fruits and vegetables was low in this population, foods were not fortified with folate, and a low-dose multivitamin was used (ie, the recommended daily intakes). These factors again raise the possibility that vitamin supplementation might be most efficacious in those with (relative) deficiencies.

Interventional Studies
The results of several studies that evaluated the effect of combination therapy on both surrogate endpoints (eg, intima-media thickness or plaque progression) and hard endpoints (MI or death) have been published. Again the results are mixed, with a few studies suggesting a benefit and most studies suggesting no benefit or even harm. The Antioxidant Supplementation in Atherosclerosis Prevention study [103] from Scandinavia evaluated the progression of carotid atherosclerosis in a high-risk population treated with a “physiologic ratio” of vitamin E (182 mg daily) and vitamin C (500 mg daily) for a total of 6 years (3 years double-blind and 3 years open label). There was 29% less progression with the supplementation, but this was limited to years 3 to 6 of the study and limited to men. Additionally, the men had much lower vitamin levels at baseline, again suggesting perhaps that those with subclinical deficiencies benefited the most. In a study that followed atherosclerosis progression by intravascular ultrasound imaging after heart transplantation using combination vitamin E and vitamin C, less progression was seen with the multivitamin treatment [104]. However, this was a very small study (16 treated and 21 placebo with full evaluation) [104]. Finally, a multivitamin supplementation trial conducted in Limxian, China, followed almost 30,000 people for more than 5 years following randomization to various combinations of vitamins, including vitamin A, vitamin B6, niacin, vitamin C, vitamin E, and β-carotene [105,106]. It should be noted that this population is at high risk for vitamin deficiency and that the doses given in the study were 1 to 2 times the recommended daily allowance. Although there was little coronary heart disease in this population, cerebrovascular disease accounted for 25% of the mortality. Overall, there was a slight decrease in total mortality in the β-carotene and vitamin E group (RR, 0.91 [95% CI, 0.84–0.99]) [105]. In a subgroup analysis of those with esophageal dysphagia at baseline, there was a nonsignificant decreased risk of cerebrovascular mortality (RR, 0.62 [95% CI, 0.37–1.06]) [106].

Studies that have not shown a benefit of multivitamins include the Multivitamins and Probucol (MVP) trial [107], the AREDS study [75], and the Heart Protection Study [74]. In the MVP trial, participants scheduled to receive angioplasty were randomized to the antioxidant probucol and/or an antioxidant vitamin cocktail (30,000 IU β-carotene, 500 mg vitamin C, 700 IU vitamin E per day) prior to and following angioplasty. The participants were then reevaluated with angiography 5 to 7 months after the angioplasty. Although there was significantly less restenosis or angiographic progression of atherosclerotic disease with probucol, there was no beneficial or harmful effect with the multivitamins [107]. The AREDS study was designed to evaluate the effect of antioxidant vitamins (vitamin C 500 mg/day, vitamin E 400 IU/day, and β-carotene 15 mg/day) on age-related cataracts, but given its size (almost 5000 participants were enrolled) and duration (6.3 years average follow-up), cardiovascular outcomes also were ascertained. Overall, the AREDS study found no effect of vitamins on mortality (RR, 1.05 [95% CI, 0.78–1.40]). Although patients who took the vitamins had less frequent chest pain (19.8% versus 22.2%, P = 0.001), this study was not designed to appropriately evaluate chest pain, and this finding must be interpreted with caution. Finally, the Heart Protection Study evaluated the effects of simvastatin and antioxidant vitamins (vitamin E
600 mg, vitamin C 250 mg, β-carotene 20 mg) over 5 years in a 2 x 2 study design [74]. Simvastatin had dramatic beneficial effects, whereas the multivitamin had no effect on all-cause mortality (RR, 1.04 [95% CI, 0.97–1.12]), nonfatal MI or coronary death (RR, 1.02 [95% CI, 0.93–1.11]), or any major vascular event (RR, 1.0 [95% CI, 0.94–1.06]).

Some studies have raised concern that use of multivitamins may cause harm. In the Carotene and Retinol Efficacy trial, treatment of more than 18,000 smokers and asbestos workers for more than 4 years with [β-carotene 30 mg and vitamin A 25,000 IU resulted in increased all-cause death (RR, 1.17 [95% CI, 1.02–1.37]) and death from CVD (RR, 1.26 [95% CI, 0.99–1.61]) compared with placebo [108,109]. The Women’s Angiographic Vitamin and Estrogen trial [110] involved more than 400 postmenopausal women with angiographically identified CVD who were randomly assigned in a 2 x 2 factorial design to receive either placebo or vitamins (vitamin E 800 IU/day and vitamin C 1000 mg/day) or hormone replacement. In the vitamin groups, there was an increase in all-cause mortality (hazard ratio, 2.8 [95% CI, 1.1–7.2]) and death or nonfatal MI (hazard ratio, 2.1 [95% CI, 0.99–4.5]). The HATS [98] also had a 2 x 2 design that evaluated the effect of simvastatin and nicotinic acid (in pharmacologic doses of 2 g/day) compared with multivitamins (vitamin E 800 IU, vitamin E 1000 mg, [β-carotene 50 mg) on stenosis progression. This study found that the antioxidants dramatically blunted the beneficial effect of the simvastatin/ nicotinic acid combination and had no independent benefit. Finally, the ATBC trial [41–45] found a significantly increased risk of fatal coronary heart disease (RR, 1.58 [95% CI, 1.05–2.40]) and fatal MI (RR, 2.67 [95% CI, 1.30–5.48]) in the subgroup of participants with previous CVD treated with combination vitamin E and β-carotene [44]. Neither risk nor benefit of combination treatment was seen in those without previous CVD [42], or with respect to angina progression in those with previous angina [45] or new-onset angina [43].

Summary

Studies that assessed combinations of vitamins have yielded variable results. Perhaps the strongest beneficial effect is seen in those with or at risk for baseline vitamin deficiencies. The majority of vitamin combination studies suggest no benefit, and several notable vitamin combination studies raise the concern that some combinations may cause harm.

Conclusion

Recently, the U.S. Preventive Services Task Force summarized the data on antioxidant vitamins and made recommendations [111]. Their conclusion is consistent with the data presented in this review: although several cohort studies suggest possible benefit from vitamin supplementation, the lack of good interventional data with definitive CVD outcomes argues against recommending supplementation to prevent CVD. Conversely, the possible harm of vitamin supplementation with respect to total mortality and CVD shown in several studies (the majority of which included [β-carotene) raises some concern. Of note, several studies suggest benefit with smaller doses of vitamins [105] or in those with likely deficiencies [103]; thus, the results must be applied in the context of the individual patient. Finally, although the folate data are promising, the current fortification of grain products with folate limits any recommendations to add folic acid. Overall, these data do not support the use of vitamins for primary or secondary prevention of CVD and suggest possible harm in some groups. There remains a need for careful consideration prior to prescribing or condoning supplemental vitamin use for the prevention or treatment of CVD.

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References

44. Rapola JM, Virtamo J, Ripatti S, et al. Randomised trial of alpha-tocopherol and beta-carotene supplements on...
75. Age-Related Eye Disease Study Research Group. A randomised, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. Arch
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83. Morrison HI, S goal of the study was to examine the long-term effects of multivitamin and probiotic supplementation on atherosclerosis progression. The Kuopio Ischaemic Heart Disease Risk Factor Study. Eur J Clin Nutr 2000;54:424–8.

