

# Supplemental Vitamins and Minerals for Cardiovascular Disease Prevention and Treatment

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**ABSTRACT:** Vitamins and minerals are dietary supplements used by almost half of the US adult population based on the presumption that they help prevent or treat cardiovascular disease. Many studies, including randomized trials, have investigated the possible role of these substances in cardiovascular disease. We reviewed the available data on multivitamins/multiminerals, antioxidants, folic acid, vitamin E, niacin (B3), and beta-carotene. Despite extensive investigation, the evidence to date fails to support the use of exogenous supplements of vitamins and minerals for the prevention or treatment of cardiovascular disease. Here, we review some of the common supplements used by adults for cardiovascular health and the available evidence for risks/benefits.

## INTRODUCTION

Vitamins and minerals are the most commonly used dietary supplements among adults in the United States. The National Health and Nutrition Examination Survey (NHANES) conducted on 37,958 adults from 1999 to 2012 showed that overall use remained stable during that time, with 49% reporting use of dietary supplements between 2011 and 2012.<sup>1</sup> Less than a quarter of the supplements used by adults are prescribed by a physician.<sup>2</sup> The common reasons for supplement use in adults are to maintain or improve overall health. Women are more likely to use supplements for “bone health” and men for “heart health or to lower cholesterol.”<sup>2</sup>

Cardiovascular disease (CVD) continues to be the leading cause of mortality across both sexes and all races and ethnicities in the United States.<sup>3</sup> Among deaths attributable to CVD, coronary heart disease is the highest contributor to mortality (43.8% of deaths) followed by stroke, high blood pressure, and heart failure.<sup>3</sup> Many of the traditional risk factors for CVD—such as obesity, poor nutrition, cigarette smoking, and physical inactivity—are thought to increase inflammation and oxidative stress, thereby contributing to atherogenesis. Micronutrients, including many vitamins and minerals such as selenium and zinc, are involved in pathways that can modulate inflammation and oxidative damage and thus are thought to play a role in reducing CVD risk.

Since vitamins and minerals cannot be generated *in vivo* and must be ingested through diet, deficiencies in these substances have known clinical disease states. However, the question of whether individuals without deficiencies in vitamins or minerals would benefit from supplementation has been the subject of innumerable investigations (Table 1). The US Preventive Services Task Force

(USPSTF) states that the current evidence for use of multivitamins or other nutrient supplements to prevent cardiovascular diseases is insufficient.<sup>4</sup> Several scientific associations recommend obtaining vitamins and minerals from the diet rather than in the form of supplements.<sup>5,6</sup> In this article, we review some of the common supplements used by adults for cardiovascular health and the available evidence for risks/benefits.

## MULTIVITAMINS AND MULTIMINERALS

Multivitamins/multiminerals (MVMMs) are the most commonly consumed dietary supplements among adults in the United States.<sup>7</sup> Forty-nine percent of the US population take at least one MVMM, with use more common among women compared to men.<sup>8</sup> Currently, the definition or categorization of MVMMs is not standardized. Previous NHANES surveys have defined “multivitamin” as a supplement with three or more vitamins with or without minerals.<sup>9</sup> Few studies have evaluated the effects of MVMM supplements on cardiovascular health. The Physicians Health Study II (PHS II) was a randomized, double-blind, placebo-controlled, 2x2x2 factorial trial that evaluated the benefits of a multivitamin (a commercially available multivitamin with 30 ingredients), vitamin E, or beta-carotene for prevention of cancer, cardiovascular disease, eye disease, and cognitive function among 14,641 male physicians aged  $\geq 50$  years. The multivitamin component of the trial extended for a median of 11.2 years and evaluated the incidence of major cardiovascular events (MACE), including nonfatal myocardial infarction (MI), nonfatal stroke, and cardiovascular disease mortality. Results showed no significant benefit of MVMMs over placebo on MACE, cardiovascular mortality, or total mortality.<sup>10</sup>

Multivitamins also did not reduce the incidence of total, ischemic, or hemorrhagic stroke, congestive heart failure and

SUPPLEMENT	TRIAL	INTERVENTION (MEDIAN FOLLOW-UP)	RESULTS (95% CI)
Multivitamin, Multimineral (MVM)	Physicians Health Study II (PHS II)	MVMM vs placebo (11.2 y)	Major cardiovascular events: HR 1.01; CI 0.91-1.10 All-cause mortality: HR 0.94; CI 0.88-1.02
Antioxidants	Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI. MAX)	Antioxidant combination vs placebo (7.5 y)	Ischemic cardiovascular events: HR 0.97; CI 0.77-1.20 All-cause mortality: HR 0.77; CI 0.57-1.00
Folic acid	Aspirin/Folate Polyp Prevention Study (AFPPS)	Folic acid vs placebo (10 y)	Incidence of MI: 2.7% vs 1.6% (P = .28) Stroke: 1.7% vs 1.0% (P = .42) Death: 1.9% vs 3.8% (P = .09)
	China Stroke Primary Prevention trial (CSPPT)	Enalapril daily vs enalapril plus folic acid daily (4.5 y)	Stroke: HR 0.79; CI 0.68-0.93 (P = .003)
Vitamin E	Women's Health Initiative (WHS)	Vitamin E vs placebo (10 y)	Major cardiovascular events: RR 0.91; CI 0.82-1.05 Cardiovascular death: RR 0.76; CI 0.59-0.98 (P = .03)
	Selenium and Vitamin E Cancer Prevention Trial (SELECT)	Selenium, vitamin E, selenium plus vitamin E, or placebo (5.5 y)	Cardiovascular events: RR 0.98; CI 0.88-1.09 Death: RR 0.93; CI 0.77-1.13
	Heart Outcomes Prevention Trial (HOPE)	Vitamin E vs placebo (6 y)	Major cardiovascular events: RR 1.04; CI 0.96-1.14 Death: RR 1.00; CI 0.91-1.10 Heart failure: RR 1.13; CI 1.01-1.26 (P = .03)
	Heart Outcomes Prevention Trial—The Ongoing Outcomes (HOPE-TOO)	Vitamin E vs placebo (4 y)	Major cardiovascular events: RR 1.05, CI 0.95-1.16 Death: RR 1.02; CI 0.92-1.15 Heart failure: RR 1.19; CI 1.05-1.35 (P = .007)
Niacin	Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH)	Niacin plus simvastatin vs placebo plus simvastatin (2 y)	Primary end point* HR 1.02; CI 0.87-1.21
	Heart Protection Study 2- Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE)	Extended-release niacin-laropiprant vs placebo in background of statin-based low-density lipoprotein-lowering therapy (3.9 y)	Major vascular events: RR 0.96; CI 0.90-1.03 Death from any cause: RR 1.09; CI 0.99-1.21
Beta-carotene	Alpha-Tocopherol Beta-carotene Cancer prevention study (ATBC)	Alpha-tocopherol, beta-carotene, beta-carotene plus alpha-tocopherol or placebo (6.1 y)	Mortality due to ischemic heart disease: 77.1/10,000 person years in beta-carotene arm vs 68.9/10,000 person years in placebo arm
	Beta-Carotene and Retinol Efficacy Trial (CARET)	Beta-carotene, retinol, beta-carotene plus retinol, or placebo (4 y)	Death from any cause: RR 1.18; CI 1.02-1.37 Death from cardiovascular causes: RR 1.26; CI 0.99-1.61

\* Composite of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome or symptom-driven coronary or cerebral revascularization

Table 1.

Major randomized controlled trials evaluating the cardiovascular benefits of supplemental vitamins and minerals.

angina, or coronary revascularization. Observational data for the association of MVMMs and cardiovascular events is variable. Prospective data from the Multiethnic Cohort Study has shown no association between multivitamin use and all-cause mortality or cardiovascular diseases.<sup>11</sup> On the other hand, prospective data from the 80,082 participants in the Nurses' Health Study showed a decreased incidence of coronary heart disease among multivitamin users.<sup>12</sup> The varying results could possibly be explained by the variable composition of the multivitamins used in the studies. A recent meta-analysis by Jenkins et al. showed no significant benefit of multivitamins on cardiovascular outcomes.<sup>13</sup> The USPSTF currently does not recommend use of multivitamins for prevention of cardiovascular diseases.<sup>4</sup>

## ANTIOXIDANTS

Micronutrients such as selenium, zinc, copper, and manganese are integral to the enzymatic system that is involved in the reduction of oxygen-free radicals.<sup>14</sup> It is possible that inadequate intake of these nutrients can result in proliferation of reactive oxygen species, which have an implication in a number of disease processes, including CVD. Similarly, vitamins A, C, E, and beta-carotene function as antioxidants by interacting with free radicals and preventing oxidative damage to macromolecules such as low-density lipoprotein (LDL).<sup>15</sup> Lipid peroxidation of LDL increases its atherogenicity; thus, vitamins A, C, E, and beta-carotene have a potential role in CVD risk modification. Several observational studies and a few randomized clinical trials (RCTs) evaluated the potential role of antioxidant mixtures in CVD prevention or treatment.<sup>16</sup>

SU.VI.MAX is a large, randomized, placebo-controlled trial conducted in France that randomized 13,017 adults to a single daily antioxidant supplement (combination of vitamins E and C, beta-carotene, selenium, and zinc) or a placebo.<sup>17</sup> After 7.5 years of median follow-up, no significant differences were found between the two groups in terms of all-cause mortality or incidence of ischemic cardiovascular disease. A recent meta-analysis of more than 20 RCTs showed no significant benefit of antioxidants for CVD prevention or treatment and a trend towards worsening all-cause mortality.<sup>13</sup>

## FOLIC ACID

Homocysteine is positively associated with an increased risk for CVD.<sup>18,19</sup> Folic acid can reduce the plasma levels of homocysteine and thus has a potential role in CVD risk modification.<sup>20</sup> The Aspirin/Folate Polyp Prevention Study is a double-blind placebo-controlled trial that randomized adults aged 21 to 80 years to folic acid (1 mg daily) or placebo. It also separately randomized participants to receive low-dose aspirin 81 mg or placebo. No difference was seen in the incidence of

CVD or all-cause mortality between the intervention and control groups.<sup>21</sup> The Vitamins to Prevent Stroke study is a placebo-controlled double-blind trial that randomized patients with a known history of stroke to B-complex vitamins and folic acid or a placebo.<sup>22</sup> No significant difference in the incidence of stroke, MI, or vascular death was found between intervention and control groups.

On the other hand, the recent China Stroke Primary Prevention Trial randomized 20,702 Chinese adults with hypertension but no prior history of MI or stroke to enalapril alone or enalapril with folic acid.<sup>23</sup> After a median follow-up of 4.5 years, the group taking enalapril with folic acid had a greater reduction in the incidence of ischemic stroke and composite cardiovascular events. The results were more pronounced in patients with low baseline folate levels. All-cause mortality did not differ significantly between the two groups. However, these results might not be generalizable for adults in other countries and can possibly be related to lack of folic acid fortification of foods in China.

Given these varying results, it can be concluded that folic acid can possibly be used for stroke prevention, especially in areas where folic acid fortification of foods is not routine.

## VITAMIN E

As discussed earlier, vitamin E can help prevent the oxidative damage of macromolecules such as LDL and has a potential role in CVD risk modification. Several RCTs have evaluated the potential cardiovascular benefits of vitamin E. The PHS II and SU.VI.MAX studies evaluated vitamin E supplementation along with other vitamins and antioxidants and did not find any significant cardiovascular benefit. The Women's Health Study randomized 39,786 healthy US women to vitamin E or placebo.<sup>24</sup> After an average follow-up of 10.1 years, fewer major cardiovascular events occurred in the vitamin E group compared to placebo, but the difference did not reach statistical significance. All cause-mortality was very low and did not differ in both groups. However, cardiovascular death was lower in the vitamin E group, which could be a chance finding given the low event rate or could possibly be due to different biological effects of vitamin E in women compared to men.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) randomized patients to vitamin E, selenium, selenium plus vitamin E, and placebo. All-cause mortality, cardiovascular events, and cardiovascular deaths did not differ significantly from placebo in the vitamin E arm.

The Heart Outcomes Prevention Evaluation (HOPE) was a randomized controlled trial that evaluated the effects of ramipril versus placebo and vitamin E versus placebo in 9,541 patients

at high risk for cardiovascular events. The study was conducted between 1993 and 1999, and the vitamin E arm was extended from 1999 to 2003 in the HOPE-TOO trial (Heart Outcomes Prevention Evaluation—The Ongoing Outcomes).<sup>25</sup> Both the HOPE and HOPE-TOO trials did not show any significant differences between the vitamin E and placebo group in terms of overall mortality or MACE.

Interestingly, adverse effects were noted in patients receiving vitamin E in some of these trials, but the effects were not reproduced in other similar trials. In PHS II, an increased number of hemorrhagic strokes were found in patients assigned to vitamin E, but this was not seen in the Women's Health Study or SELECT.<sup>10</sup> Furthermore, an increased risk of heart failure and heart failure admissions were noted in patients in the vitamin E group of both the HOPE and HOPE-TOO trials but not in other trials.<sup>25</sup>

### NIACIN (B<sub>3</sub>)

It is known that low levels of high-density lipoprotein (HDL) are an independent predictor of risk in coronary artery disease, as are increased levels of LDL. Niacin increases the level of HDL, and its role as a potential modifier of cardiovascular disease risk was evaluated in several studies. In the Coronary Drug Project, which evaluated the efficacy and safety of five lipid-modifying agents including niacin, 15-year follow-up showed a late mortality benefit for niacin compared to placebo.<sup>26</sup> However, similar benefit was not seen in RCTs that evaluated potential benefit of niacin in the background of statin therapy. The AIM-HIGH trial (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) randomized 3,414 patients with known coronary artery disease to extended-release niacin or placebo. All patients received simvastatin. Although niacin therapy increased the mean HDL levels, there was no significant difference in MACE between both groups.<sup>27</sup> Patients in the niacin group had more adverse events, including liver function test abnormalities, myopathy, and rhabdomyolysis, compared to placebo. The Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial randomized 25,673 patients with known vascular disease to niacin-laropiprant or placebo.<sup>28</sup> Both groups did not differ significantly in the incidence of MACE. However, the niacin group had an increased incidence of adverse effects similar to AIM-HIGH. A recent meta-analysis by Jenkins et al. showed that use of slow-release niacin in patients on statin therapy does not benefit CVD outcomes but does show an increased trend towards all-cause mortality.<sup>13</sup>

### BETA-CAROTENE

Beta-carotene is purported to be an anticancer agent and is believed to have some antioxidant properties as well. Both the

ATBC (Alpha-Tocopherol Beta-Carotene Cancer Prevention) and CARET (Beta-Carotene and Retinol Efficacy Trial) studies evaluated the efficacy of beta-carotene in cancer prevention in smokers, and CARET included individuals with occupational exposure to asbestos.<sup>29,30</sup> Both trials showed no benefit from beta-carotene in terms of the incidence of cardiovascular disease. The beta-carotene arm of the PHS II trial randomized 11,036 US physicians to beta-carotene or placebo and did not find significant differences in overall mortality or CVD between the intervention and control groups.<sup>31</sup> Similarly, the beta-carotene arm of the Women's Health Study showed no statistically significant differences in the incidence of MI, stroke, or cardiovascular deaths between the intervention and control groups.<sup>32</sup>

### HARMS OF VITAMIN/MINERAL SUPPLEMENTATION

Dietary vitamin and mineral supplements are not benign. Major and minor adverse effects have been reported in the RCTs discussed above. The ATBC and CARET trials evaluated the benefit of beta-carotene supplementation in individuals with a high baseline risk of developing lung cancer, and both trials reported an increased incidence of lung cancer in higher-risk subjects receiving beta-carotene.<sup>16</sup> The PHS II and Women's Health Study, however, did not show similar effects on lung cancer mortality with beta-carotene, probably due to the low baseline risk of lung cancer in the participants. The USPSTF currently recommends against use of beta-carotene for cancer prevention or cardiovascular diseases.<sup>4</sup>

As mentioned previously, an increased incidence of hemorrhagic stroke was reported in the vitamin E arm of PHS II but was not validated in other trials. In the SELECT trial, an increased risk of prostate cancer was reported after extended follow-up.<sup>33</sup> Similar effects on cancer incidence with vitamin E or selenium were not reported in other trials.

Two prospective cohort studies, the Iowa Women's Health study and the Nurses' Health Study, reported an increased incidence of hip fractures with excessive vitamin A use in post-menopausal women.<sup>34,35</sup>

Other reported minor adverse effects include hypercarotenemia or yellowing of the skin with beta-carotene, rashes and minor bleeding events with multivitamins, and gastrointestinal symptoms with selenium.<sup>16</sup>

### CONCLUSION

Vitamins and minerals are the most commonly used dietary supplements among adults in the United States. The most common reason cited for supplement use is to help maintain or

improve overall health. Randomized controlled trials and large-scale observational studies have failed to show any benefit of dietary supplements in preventing or treating cardiovascular disease. The USPSTF currently does not recommend use of multivitamins for prevention of cardiovascular diseases.

#### KEY POINTS

- The exogenous supplementation of vitamins and minerals in individuals without dietary deficiencies has shown no proven cardiovascular benefit to date.
- Folic acid has a possible role in stroke prevention, especially in populations with low baseline folate levels or in areas that lack folic acid fortification in foods.
- Beta-carotene should not be used for cardiovascular disease or cancer prevention; this is especially true for smokers due to an increased incidence of lung cancer.

#### Conflict of Interest Disclosure:

The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

#### Keywords:

vitamin supplements, minerals, vitamin E, folic acid, beta-carotene, cardiovascular disease risk

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