Vitamin E and Coronary Artery Disease

Anne P. Spencer, PharmD; Deborah Stier Carson, PharmD; Michael A. Crouch, PharmD

Various studies have evaluated the antioxidant effects of vitamin E in the prevention or treatment of coronary artery disease (CAD). In vitro data suggest that vitamin E protects against oxidation of low-density lipoprotein and decreases the deposition of atherogenic oxidized low-density lipoprotein in arterial walls. Various observational and epidemiological studies also suggest a relationship between vitamin E serum concentrations or intake and CAD. One prospective, randomized trial suggested that low-dosage vitamin E supplementation (50 IU/d) decreases the risk of angina in patients without previously diagnosed CAD. Another study, using high-dosage vitamin E supplementation (400 or 800 IU/d), demonstrated a decrease in the combined end point of nonfatal myocardial infarction and cardiovascular death in patients with established CAD. Discordant data, however, have been published that imply no cardiovascular benefit of low-dosage vitamin E supplementation (50 IU/d) and detrimental effects if vitamin E is combined with beta carotene. At this point, clinicians should emphasize a low-fat diet with high intake of fruits and vegetable sources containing vitamin E. Supplemental vitamin E may be considered in patients at high risk for CAD or with documented CAD, but the potential beneficial effects should be weighed against possible long-term adverse effects. If vitamin E supplementation is initiated, the literature suggests dosages of 100 to 400 IU/d, with the higher dosage considered in patients with documented CAD. Additional investigation is warranted to further define the role of vitamin E supplementation in CAD and to critically evaluate the optimal dosage, duration of use, and method of consumption (dietary vs supplemental).

In recent years, there has been a surge of interest regarding the use of vitamins to prevent or treat disease. Vitamin E, in particular, has been studied for various conditions, including hot flashes, hypercholesterolemia, fibrocystic disease, and hemolytic anemia. This vitamin has also been promoted to increase sexual potency, diminish wound scarring, augment resistance to infection, and decrease aging.1,2 Lately, researchers have placed specific emphasis on the effects of vitamin E in coronary artery disease (CAD).

Acute myocardial infarction (MI) is a leading cause of morbidity and mortality among adults in the United States. Acute MI occurs in more than 1.5 million people annually and is fatal in one third of these cases.3 In the last 40 years, much progress has occurred in the management of CAD and mortality has decreased. This progress is likely due to the impact of drug therapy and lifestyle modifications on people with hypertension and hyperlipidemia, as well as the widespread use of thrombolytic drugs, angioplasty, and coronary artery bypass surgery.4,5 Traditional risk factors, such as hypertension, hypercholesterolemia, and smoking, explain some but not all CAD risk.6,7 Recent studies provide insight into the contribution of antioxidants, particularly vitamin E, in CAD prevention and treatment. The purpose of this review is to critically evaluate the role of vitamin E in the management of CAD.
OXIDATIVE MODIFICATION HYPOTHESIS

Recent evidence demonstrates that oxidation of low-density lipoprotein (LDL) plays an important role in the development of atherosclerosis. This theory, termed the oxidative modification hypothesis, has fueled numerous epidemiological studies and clinical trials to determine the role of antioxidants in the prevention and treatment of CAD. Normally functioning LDL provides vital nutrients, such as vitamins and cholesterol, to peripheral cells to maintain cellular function. The entry of LDL into cells is regulated by external receptors. When the cell has received sufficient cholesterol, these receptors down-regulate and prevent further LDL uptake. Through this mechanism, cells avoid excess LDL accumulation.9

The development of atherosclerosis is characterized by the deposition of large amounts of lipids in arterial walls, primarily derived from LDL. Macrophages residing in the endothelial wall are the site of lipid deposition and accumulation.10 Macrophages possess 2 types of LDL receptors: one that recognizes native LDL and down-regulates after sufficient LDL has entered the cell, and another receptor that recognizes modified, or oxidized, LDL. The latter receptor is termed the scavenger receptor and is not subject to feedback inhibition by the cellular cholesterol content. This inability to terminate the uptake of oxidized LDL permits excessive accumulation of LDL in tissue macrophages and the subsequent formation of a foam cell in the arterial wall. These lipid-laden foam cells are believed to be the primary contributor to atherosclerotic CAD (Figure 1).10 In addition to its role in foam cell production, oxidized LDL has effects on platelet and endothelial function that further promote cardiovascular events.9,10

The theory that oxidized LDL promotes the development of atherosclerosis has prompted investigations of augmented antioxidant activity. Some believe oxidative damage occurs when the protective antioxidant systems are depleted or when these systems are inadequate to cope with increased levels of oxidative stress. The endogenous antioxidant system includes several enzymes and many lipophilic antioxidants, including α-tocopherol, beta carotene, and γ-tocopherol.9 These antioxidants prevent the oxidation of polyunsaturated fatty acids (PUFAs) that are bound to LDL. The primary component of vitamin E, α-tocopherol, is the most prevalent antioxidant in LDL.11 In vitro data suggest that endogenous vitamin E and beta carotene concentrations decline prior to lipoprotein oxidation and that vitamin E supplementation prevents this destructive oxidative reaction.12

VITAMIN E

Vitamin E exists as at least 8 naturally occurring compounds, including α-, β-, γ-, and δ-tocopherol and α-, β-, γ-, and δ-tocotrienol; α-tocopherol is the most active component in vitamin E and naturally occurs as 1 isomer. Dietary vitamin E is expressed in milligrams of α-tocopherol equivalents. The recommended dietary allowances (RDA) of vitamin E according to the National Research Council are 10 and 8 mg daily of α-tocopherol equivalents for men and women, respectively (approximately 13.5 and 10.8 IU/d).13 The reference daily intake (RDI), formerly the US recommended daily allowance (USRDA), is based on the activity of racemic synthetic α-tocopherol, the form in vitamin E supplements. The RDI for vitamin E is 30 IU.14 The National Research Council RDA is generally considered the more authoritative body; however, the RDI is used to determine vitamin supplements.14 In general, 60% of dietary vitamin E is derived from vegetable and seed oils, such as margarine, salad dressings, and shortenings. Soybean and wheat germ oils are particularly high in vitamin E, while corn, cottonseed, and sunflower oils are of intermediate content. Animal fats, such as butter and milk, contain negligible vitamin E, although eggs and liver are substantial sources of this nutrient. Grains, fruits, and leafy green vegetables account for the remaining dietary intake.1,2

Interestingly, olive oil, a major component of the “Mediterranean diet” that is associated with a decreased risk of CAD, contains minimal vitamin E compared with other vegetable oils.15 This diet is rich in fruit, vegetables, legumes, and grains, and olive oil is the primary source of fat. As a whole, this diet is high in monounsaturated fatty acids and low in saturated fatty acids, and it is rich in natural antioxidants.16,17 In vitro, olive oil has been shown to decrease LDL oxidation; however, this activity is not mediated by vitamin E but rather is attributed to polyphenol antioxidant compounds.17

Although small, short-term studies using vitamin E supplementation (100-800 IU/d) have shown no evidence of toxicity, recent findings warrant attention. A study involving α-tocopherol supplementation-
tion (50 IU/d) and its effects on the incidence of cancer found a higher mortality rate due to hemorrhagic stroke in patients receiving α-tocopherol supplementation than in patients receiving placebo (7.8 vs 5.2 deaths per 10,000 person-years). Additionally, high vitamin E intake is contraindicated in patients with coagulation defects caused by vitamin K deficiency, as it may promote hemorrhage. Therefore, caution should be exercised in patients receiving warfarin or who have a malabsorption syndrome that may decrease vitamin K absorption. While vitamin E supplementation is often stated to be safe, this finding is frequently based on either small, short-term studies or long-term studies with inadequate end points to address the health consequences of vitamin E supplementation. The true long-term safety of vitamin E supplementation is unknown.

CROSS-SECTIONAL STUDIES

An early study analyzed the lipid-adjusted serum concentrations of vitamin E from various European communities in relation to each area’s CAD mortality. Vitamin E concentrations were adjusted for serum lipid concentrations because this vitamin is highly bound to lipoproteins (micromoles of vitamin E per millimole of cholesterol). It is important to lipid-adjust serum vitamin E concentrations to accurately compare antioxidant activity. Eastern Finland, southwest Finland, Scotland, and southern Italy were included; 80 to 131 healthy men aged 40 to 49 years participated from each region. Eastern Finland had the highest CAD mortality rate (212 deaths per 100,000 men per year), southwest Finland and Scotland had intermediate mortality rates (146 and 140 deaths per 100,000, respectively), and southern Italy had the lowest mortality rate (43 deaths per 100,000). The 3 areas with intermediate to high CAD mortality (eastern Finland, Scotland, and southwest Finland) all had similar median lipid-adjusted serum vitamin E concentrations (3.41-3.53 μmol/mmol). On the other hand, Italy, which had the lowest CAD mortality rate, had a significantly higher median vitamin E concentration (4.81 μmol/mmol, P < .001). The lack of difference between vitamin E concentrations in the 3 areas with higher CAD mortality rates may be related to other CAD risk factors in eastern Finland, such as blood pressure, serum cholesterol level, smoking, and obesity. Of note, eastern Finland has one of the highest CAD mortality rates worldwide. The term Finland factor has been coined to encompass the yet undiscovered reason for this marked CAD increase.

A cross-cultural study examined the relationship between ischemic heart disease (IHD) mortality and lipid-adjusted serum vitamin E concentrations. Other classic coronary risk factors, such as blood pressure, cholesterol, and smoking, were also evaluated. Approximately 100 healthy men from 16 different European communities with different incidences of IHD mortality were studied. Through regression analysis, the inverse correlation of lipid-standardized vitamin E levels and mortality from IHD was r² = 0.62 (cholesterol, 5.7 mmol/L [220 mg/dL]; triglycerides, 1.25 mmol/L; P = .002) (Figure 2). In other words, 62% of the IHD mortality was attributable to variation in the standardized vitamin E concentrations.

In this investigation, IHD mortality was more strongly correlated with vitamin E concentration than with blood pressure (r² = 0.24), cholesterol level (r² = 0.29), number of cigarettes per day (r² = 0.02), serum vitamin A level (r² = 0.26), and vitamin C concentration (r² = 0.11). This study suggests that an individual’s vitamin E concentration may be more indicative of IHD mortality than classic risk factors.

EPIDEMIOLOGICAL DATA

Epidemiological studies have examined the relationship between vitamin E intake or serum vitamin E concentration and the rate of CAD (Table 1 and Table 2). Initial studies found no correlation between serum or plasma vitamin E concentrations and CAD death. The results from these studies, however, may be unreliable because samples were not stored in suitable environments for vitamin E stability. In addition, vitamin E measurements were not adjusted for cholesterol levels, which may result in overestimation of vitamin E levels in patients with elevated cholesterol concentrations. One of the studies was in a Finnish population, and the influence of the Finland factor may overshadow any vitamin E effect.

Further epidemiological studies examined lipid-adjusted serum vitamin E concentrations in patients who experienced some type of coronary event. Each study recruited matched controls. A study in Finnish men found no association between lipid-adjusted serum vitamin E level and a coronary end point, which was a positive stress test. One investigation reported an odds ratio of 2.68 (95% confidence interval [CI], 1.07-6.70) for a positive response on a chest pain questionnaire in the lowest vs the highest quintile of lipid-adjusted vitamin E concentration. The actual presence of angina was not verified following a positive response on the questionnaire, possibly resulting in the inclusion of some false-positive results. A third study found significantly decreased lipid-adjusted vitamin E concentrations in patients with a first acute MI as compared with controls (P = .001). All 3 studies were relatively small (64-175 cases) and included only men.

Two case-control studies evaluated the rate of MI in relation to serum vitamin E concentration. Both studies included male
and female subjects who were monitored for 6 to 14 years for the occurrence of MI. In 1 investigation, which included 46 German cases, no difference in mean lipid-adjusted serum vitamin E concentration was observed between cases and controls. A larger sample size may have been necessary to detect a difference between groups. Furthermore, the authors suggest that the relatively high concentrations of vitamin E (4.89 and 4.82 µmol/mmol in cases and controls, respectively) may have been at the level of maximum protective effect of vitamin E.29 This threshold effect means that low vitamin E levels constitute a risk factor for CAD, while levels above a certain threshold confer no additional protection. Based on several cross-sectional studies, it has been proposed that a lipid-adjusted vitamin E concentration of 4.8 µmol/mmol is the threshold above which there is no further decrease in CAD risk.31 Street and colleagues30 performed a similar study with 123 cases from the United States who consumed supplemental sources of vitamin E. Both the US Nurses’ Health Study and the Health Professionals Follow-up Study found evidence that cardiovascular protection is maximized at 100 IU/d, with little benefit derived with higher intake.33,34 It is important to realize that these 2 studies included only health care professionals, who may have healthier lifestyles in terms of diet, exercise, and health care access; this may introduce numerous confounding variables into the study results.

Subsequent longitudinal epidemiological studies evaluated the role of vitamin E intake in large patient populations. A study on vitamin E intake among 87 425 female nurses in the US Nurses’ Health Study was published in 1993.33 A dietary questionnaire was used to estimate vitamin E intake, and levels of intake were divided into quintiles. This study found an adjusted coronary disease relative risk (RR) of 0.66 (95% CI, 0.50-0.87; P<.001) for women consuming the highest versus lowest amount of vitamin E (median, 208 vs 2.8 IU/d). This study also found that the benefit was only evident with greater than 2 years of continued consumption. The benefit of vitamin E intake appeared to occur with both supplemental and dietary vitamin E.

A similar study in 39 910 men, the Health Professions Follow-up Study, reported an adjusted RR for CAD of 0.64 (95% CI, 0.49-0.83; P<.003) for men with a median vitamin E intake of 419 vs 6.4 IU/d.34 The decrease in cardiovascular mortality was primarily evident in men who consumed supplemental sources of vitamin E. Both the US Nurses’ Health Study and the Health Professionals Follow-up Study found evidence that cardiovascular protection is maximized at 100 IU/d, with little benefit derived with higher intake.33,34 It is important to realize that these 2 studies included only health care professionals, who may have healthier lifestyles in terms of diet, exercise, and health care access; this may introduce numerous confounding variables into the study results.

A 14-year study in a Finnish population found RRs of 0.68 and 0.35 for CHD-related death in men and women, respectively, in the tertiles of greatest vs lowest vitamin E consumption.35 The tertile boundaries are relatively close and indicate only a 25% difference in vitamin E consumption. These data are difficult to interpret, as the breadth of consumption represented within the tertiles is unknown. However, this result may indicate that cardiovascular benefit is seen with small increases of vitamin E consumption.

A final investigation regarding vitamin E intake evaluated postmenopausal women with no cardiovascular disease who completed questionnaires regarding vitamin E intake and supplementation.36 Compared with women in the lowest quintile of intake, women in the highest quintile of vitamin E intake had an RR of 0.38 (P = .004 for the trend) for death from CHD. In contrast to the US Nurses’ Health Study, this benefit was seen in women who consumed vitamin E in their diet, but not in those who used vitamin E supplementation.

Table 1. Case-Control Epidemiological Studies Evaluating Vitamin E Levels

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Study</th>
<th>Cases, No.</th>
<th>Controls, No.</th>
<th>Mean Serum Vitamin E†</th>
<th>Study Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>30- to 64-year-old Finnish men and women</td>
<td>Salonen et al,22 1985</td>
<td>92</td>
<td>92</td>
<td>1416 µmol/L (61 mg/dL)‡</td>
<td>30- to 64-year-old Finnish men and women</td>
</tr>
<tr>
<td>37- to 87-year-old Dutch men and women</td>
<td>Kok et al,24 1987</td>
<td>84</td>
<td>168</td>
<td>1997 µmol/L (86 mg/dL)‡</td>
<td>30- to 64-year-old Dutch men and women</td>
</tr>
<tr>
<td>54-year-old Finnish men</td>
<td>Salonen et al,22 1988</td>
<td>175</td>
<td>894</td>
<td>3.7</td>
<td>3.5</td>
</tr>
<tr>
<td>35- to 54-year-old British men</td>
<td>Riemersma et al,27 1991</td>
<td>110</td>
<td>394</td>
<td>3.7</td>
<td>3.9</td>
</tr>
<tr>
<td>&lt;45-year-old Swedish men</td>
<td>Rengström et al,28 1996</td>
<td>64</td>
<td>35</td>
<td>1.9</td>
<td>2.3</td>
</tr>
<tr>
<td>25- to 64-year-old German men and women</td>
<td>Hense et al,29 1993</td>
<td>46</td>
<td>184</td>
<td>5.0</td>
<td>4.8</td>
</tr>
<tr>
<td>23- to 58-year-old US men and women</td>
<td>Street et al,26 1994</td>
<td>123</td>
<td>246</td>
<td>4.4</td>
<td>4.6</td>
</tr>
<tr>
<td>35- to 57-year-old US men</td>
<td>Evans et al,30 1998</td>
<td>239</td>
<td>479</td>
<td>4630 µmol/L (199.4 mg/dL)‡</td>
<td>4200 µmol/L (180.9 mg/dL)‡</td>
</tr>
</tbody>
</table>

* CAD indicates coronary artery disease; CVD, cardiovascular disease; ECG, electrocardiogram; NA, not applicable; OR, odds ratio; CI, confidence interval; MI, myocardial infarction; and CHD, coronary heart disease.
† All values are micromoles of α-tocopherol per millimole of cholesterol, unless otherwise noted.
‡ These vitamin E values are not lipid adjusted.

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These longitudinal studies suggest that vitamin E intake and cardiovascular disease are related, yet raise additional questions: (1) What is the most appropriate dosage? Benefits have been associated with a very large range of vitamin E intake, from 7.1 to +19 IU/d, but intake of 100 IU/d or greater is most consistently associated with benefit. (2) How long must increased vitamin E be consumed to realize a benefit? Supplementation for greater than 2 years has most consistently been associated with a benefit, yet this has not been rigorously studied. (3) Which is better, dietary or supplemental vitamin E? Whether dietary or supplemental sources or both confer protection against CAD has not been answered, as conflicting results have been reported. Dietary vitamin E is primarily found in foods high in PUFAs, which are susceptible to lipid oxidation. It has been shown in both animals and humans that vitamin E requirements increase with increased PUFA intake. A ratio of milligrams of vitamin E to grams of PUFA has been suggested to quantify vitamin E dietary requirements more appropriately. While vitamin E intake increases with vegetable oil use, fish oils are remarkably low in vitamin E, although high in PUFAs. Theoretically, supplemental vitamin E will improve the vitamin E–PUFA ratio more effectively than dietary consumption of foods high in vitamin E and more effectively decrease lipid oxidation. Unfortunately, the available data have not clarified the relative importance of dietary vs supplemental vitamin E, as benefits of each method of consumption have been found. Furthermore, data suggest that γ-tocopherol, present in dietary but not supplemental vitamin E, plays a role in the oxidation of LDL. This adds confusion to the issue of dietary (all vitamin E components) vs supplemental (α-tocopherol only) vitamin E.

**PROSPECTIVE TRIALS**

One study evaluated the effect of vitamin E intake (supplemental and dietary, nonrandomized) on coronary artery lesion progression. Subjects were men who had previously undergone coronary artery bypass graft surgery and were randomized into a cholesterol-lowering diet and colestipol-niacin group or a placebo group. Although the vitamin E aspect of the study was not randomized and the dosages were not consistent, the investigators found decreased coronary artery lesion progression, as assessed with angiography, in patients consuming 100 IU/d or more of supplemental vitamin E compared with patients who had lower vitamin E intake (P = .04). Dietary vitamin E consumption was not found to have an effect on lesion progression.

Two prospective, randomized trials have evaluated coronary outcomes following vitamin E supplementation (Table 3). One study, the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study, was designed to evaluate the development of lung cancer, but also documented the coronary outcomes in several subgroups of Finnish men who were randomized to receive either placebo or α-tocopherol (50 IU/d). Several analyses have been performed based on this initial study. In the men initially free of CHD, a very modest decrease in the incidence of angina was noted over 4.7 years in patients taking vitamin E supplementation (RR, 0.91; 95% CI, 0.83-0.99; P = .04), while no effect was seen on the occurrence of major coronary events (fatal CHD or nonfatal MI).

Similarly, in patients with a history of angina, vitamin E supplementation had no effect on the recurrence or progression of angina, or on the incidence of major coronary events. In patients with a previous myocardial infarction, α-tocopherol supplementation produced no change in major coronary events, and α-tocopherol in combination with beta carotene actually resulted in increased mortality.

The small decrease in the incidence of angina and the lack of apparent benefit in the above analyses could be related to the low dosage of vitamin E (50 IU/d) used in the study, which is lower than the 100 IU/d suggested by epidemiological studies. The follow-up periods ranged from 4 to 6.1 years, which may have been too short a period to detect a difference in the development of the various cardiac end points, especially in the primary prevention analyses. In addition, all subjects were Finnish male smokers.
Table 2. Longitudinal Epidemiological Studies Evaluating Vitamin E Consumption

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Vitamin E Intake, IU/d</th>
<th>Study Population</th>
<th>End Points</th>
<th>Follow-up, y</th>
<th>Outcomes†</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Nurses’ Health Study, 1993</td>
<td>87,245</td>
<td></td>
<td>34- to 59-year-old US women free of diagnosed CVD</td>
<td>Nonfatal MI and coronary death</td>
<td>8</td>
<td>RR, 0.57 (95% CI, 0.41-0.78) for nonfatal MI and coronary death in vitamin E supplement users compared with nonusers; benefit seen with ≥100 IU/d for ≥2 y; no effect seen based on dietary vitamin E intake</td>
</tr>
<tr>
<td>Cambridge Heart Antioxidant Study, 1993</td>
<td>39,910</td>
<td></td>
<td>40- to 75-year-old US men free of diagnosed CHD</td>
<td>Nonfatal MI, CHD-related death, and coronary revascularization</td>
<td>4</td>
<td>RR, 0.59 (95% CI, 0.47-0.75) for nonfatal MI, CHD-related death, and coronary revascularization in the highest quintile of vitamin E consumption compared with the lowest; RR, 0.63 (95% CI, 0.47-0.84) for supplemental vitamin E ≥100 IU/d for ≥2 y; no effect seen based on dietary vitamin E intake</td>
</tr>
<tr>
<td>Knekt et al, 1994</td>
<td>5,133</td>
<td></td>
<td>30- to 69-year-old Finnish men and women free of known heart disease</td>
<td>Death from CHD</td>
<td>14</td>
<td>RR, 0.68 (95% CI, 0.42-1.11) and RR, 0.35 (95% CI, 0.14-0.88) for CHD-related death in men and women, respectively, in the highest tertile of dietary vitamin E intake compared with the lowest</td>
</tr>
<tr>
<td>Kushi et al, 1996</td>
<td>34,486</td>
<td></td>
<td>Postmenopausal US women without cardiovascular disease</td>
<td>Death from CHD</td>
<td>7</td>
<td>RR, 0.38 (95% CI, 0.18-0.80) for death from CHD in women consuming dietary vitamin E in the highest quintile compared with the lowest; the benefit was not seen when total vitamin E consumption from both supplemental and dietary sources was analyzed</td>
</tr>
</tbody>
</table>

* indicates cardiovascular disease; MI, myocardial infarction; RR, relative risk; CI, confidence interval; and CHD, coronary heart disease.
† Adjusted for various cardiovascular factors.

and these factors may have influences that render the data not applicable to the general population. As a whole, these results indicate that supplemental vitamin E at this dosage appears to have no clinically relevant effect for primary or secondary prevention of CAD and may be harmful if used in combination with beta carotene.

A second trial, the Cambridge Heart Antioxidant Study, evaluated higher dosages of vitamin E (400 or 800 IU/d). This trial included 2002 patients in the United Kingdom with angiographically proven CAD. Patients were randomized to receive a placebo or vitamin E supplementation and were evaluated for a mean of 1.4 years. End points were nonfatal MI, cardiovascular death, and death from any cause. This trial demonstrated a significant decrease in the combined end point of cardiovascular death and nonfatal MI (41 vs 64 events, \( P = .005 \)) in patients who received vitamin E. The RR for cardiac events was 0.53 (95% CI, 0.34-0.83) for patients receiving supplementation. The beneficial effects of vitamin E appeared to occur after 200 days of supplementation; however, there was no difference in overall mortality between groups.

The Cambridge Heart Antioxidant Study trial provided the most substantial evidence that vitamin E supplementation may decrease cardiac events in high-risk patients. Baseline data regarding coronary vessel stenosis and left ventricular impairment were provided, yet there was no information regarding past MIs, angina, or arrhythmias, which may have influenced the risk of cardiac events. The 2 groups were not equal at baseline with regard to gen-

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der, serum cholesterol level, systolic blood pressure, diabetes, and β-blocker use. The first patients randomized into the vitamin E group received 800 IU/d, while later patients received 400 IU/d. The reason for this dosage change was decreased drug availability, and all patients who received vitamin E were analyzed as a homogeneous group. There was an increase in noncardiovascular deaths in the vitamin E group compared with the placebo group (9 vs 3), but this was not analyzed or discussed. Although the decrease in the combined end point was marked, additional investigation is required to further explore the effects of vitamin E, since overall mortality was unaffected.

**CONCLUSIONS**

Epidemiological evidence supports the hypothesis that a relationship exists between vitamin E consumption and the incidence of CAD. In particular, data imply that a low vitamin E serum concentration is correlated with the development of CAD. Despite some epidemiological and in vitro data supporting the use of vitamin E, the findings of prospective, controlled trials are limited and inconclusive. Thus far, studies suggest that increased intake of this vitamin may attenuate the development of CAD; however, the optimum dosage, duration of use, and method of consumption (dietary vs supplemental) remain undetermined. The incidence of adverse effects and long-term outcomes associated with vitamin E supplementation have not been carefully investigated, and some data suggest possible detrimental effects.

While it is too early to provide definitive guidelines for vitamin E intake, we feel that the following are reasonable recommendations based on the current data. A low-fat diet with high intake of fruit and vegetable sources containing vitamin E should be emphasized for all patients. Vitamin E supplementation may be considered in those at increased risk for CAD or with documented CAD, although this should be weighed against possible unknown long-term adverse effects. If vitamin E supplementation is initiated, a dosage of at least 100 IU/d appears necessary to derive cardiovascular benefit. Additional data from a prospective trial imply that a dosage of 400 IU/d is more appropriate in patients with documented CAD. Importantly, recommendation of the higher dosage of vitamin E is based on only 1 study, and this dosage has not been compared with a lower dosage (eg, 100 IU/d). The outcomes of additional prospective, randomized trials are necessary to more appropriately define the role of vitamin E in CAD and to critically evaluate the optimal dose, duration of use, and method of consumption (dietary vs supplemental).

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**Table 3. Prospective, Randomized Trials Evaluating Vitamin E Administration**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Vitamin E Intake, IU/d</th>
<th>Study Population</th>
<th>End Point</th>
<th>Follow-up, y</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapola et al, 1995</td>
<td>29 133</td>
<td>50</td>
<td>Finnish men aged 50-69 y, all smokers, no CHD</td>
<td>Incidence of angina</td>
<td>4.7</td>
<td>RR, 0.91 (95% CI, 0.83-0.99) of angina in men taking vitamin E supplementation</td>
</tr>
<tr>
<td>Virtamo et al, 1998</td>
<td>27 251</td>
<td>50</td>
<td>Finnish men aged 50-69 y, all smokers, no history of MI</td>
<td>First major coronary event (nonfatal MI, fatal CHD)</td>
<td>6.1</td>
<td>No difference in major coronary events</td>
</tr>
<tr>
<td>Rapola et al, 1998</td>
<td>1795</td>
<td>50</td>
<td>Finnish men aged 50-69 y, all smokers, with angina</td>
<td>Recurrence and progression of angina (nonfatal MI, fatal CHD)</td>
<td>4.0</td>
<td>No difference in recurrence or progression of angina or major coronary events</td>
</tr>
<tr>
<td>Rapola et al, 1997</td>
<td>1862</td>
<td>50</td>
<td>Finnish men aged 50-69 y, all smokers, with prior MI</td>
<td>First major coronary event (nonfatal MI, fatal CHD)</td>
<td>5.3</td>
<td>No difference in major coronary events; mortality was higher if vitamin E was combined with beta carotene or if beta carotene was used alone</td>
</tr>
<tr>
<td>Stephens et al, 1996</td>
<td>2002</td>
<td>400, 800</td>
<td>Men and women in the United Kingdom with CAD</td>
<td>Nonfatal MI; cardiovascular death from any cause</td>
<td>1.4</td>
<td>RR, 0.53 (95% CI, 0.34-0.83) for nonfatal MI or cardiovascular death in patients receiving vitamin E supplementation; no difference in overall mortality</td>
</tr>
</tbody>
</table>

*CHD indicates coronary heart disease; RR, relative risk; CI, confidence interval; MI, myocardial infarction; and CAD, coronary artery disease.
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