



Supplementation of Vitamins E and C for the Prevention of Cardiovascular Disease

By Kelly Delaney, Pharm.D.

Theory suggests that antioxidants may slow or prevent atherosclerotic plaque formation by inhibiting low-density lipoprotein cholesterol oxidation and modifying platelet activity, thereby reducing thrombotic events.¹⁻⁵ Antioxidants such as ascorbic acid, beta-carotene and vitamin E have been studied in numerous clinical trials to prove that supplementation reduces risk of cardiovascular events. However, trial results have been inconclusive about antioxidants as preventers of cardiovascular disease (CVD).^{1,2}

The Physicians' Health Study II (PHS II) published in November 2008 shed some light on antioxidants' role in preventing CVD in men. This randomized, placebo-controlled, prospective study evaluated long-term vitamin E and vitamin C supplementation among 14,641 US male physicians to prevent nonfatal myocardial infarction (MI), nonfatal stroke and cardiovascular mortality.

PHS II enrollment occurred between July 1997 and August 2007. PHS I participants were invited to participate along with US male physicians registered with the American Medical Association. Men were ineligible if they reported a history of cirrhosis, active liver disease, or reported a serious illness that might preclude participation. Men with a history of MI, stroke, or cancer were eligible to enroll. Participants must have been willing to forgo use of supplements containing vitamin E, vitamin C, beta-carotene, or vitamin A for the duration of the study. After a 12-week run-in phase, 7,641 PHS I participants and 7,000 new physicians were enrolled. Of these participants, 754 men reported a history of nonfatal MI or nonfatal stroke. Participants were randomized in a

2x2x2x2 factorial design to receive beta-carotene 50 mg every other day or placebo; then vitamin E 400 IU every other day or placebo; then vitamin C 500 mg daily or placebo; then multivitamin daily or placebo. For example, a patient might receive active beta-carotene, placebo vitamin E, active vitamin C, and a placebo multivitamin. Results of the beta-carotene randomization were not reported and the trial's multivitamin component is ongoing.

The effects of vitamin C and vitamin E on cardiovascular events and mortality are summarized in Tables 1 and 2. These results are combined from all active and placebo vitamin E or C groups regardless of concomitant vitamin therapy.²

Table 1. Vitamin E Supplementation Effects on Major Cardiovascular Events and Mortality²

Outcome Measure	Active n=7315	Placebo n=7326	HR (95% CI)
Major Cardiovascular events	620	625	1.01 (0.90-1.13)
Total MI	240	271	0.90 (0.75-1.07)
Total stroke	237	227	1.07 (0.89-1.29)
Ischemic stroke	191	196	1.00 (0.82-1.22)
Hemorrhagic stroke	39	23	1.74 (1.04-2.91)
Cardiovascular death	258	251	1.07 (0.90-1.28)
CHF	289	294	1.02 (0.87-1.20)
Angina	718	765	0.95 (0.85-1.05)
Revascularization†	675	709	0.96 (0.86-1.07)
Total mortality	841	820	1.07 (0.97-1.18)

Abbreviations: CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction
† Includes both coronary artery bypass graft and percutaneous transluminal coronary angioplasty

Table 2. Vitamin C Supplementation Effects on Major Cardiovascular Events and Mortality²

Outcome Measure	Active n=7329	Placebo n=7312	HR (95% CI)
Major Cardiovascular events	619	626	0.99 (0.89-1.11)
Total MI	260	251	1.04 (0.87-1.24)
Total stroke	218	246	0.89 (0.74-1.07)
Ischemic stroke	180	207	0.87 (0.71-1.07)
Hemorrhagic stroke	30	32	0.95 (0.57-1.56)
Cardiovascular death	256	253	1.02 (0.85-1.21)
CHF	293	290	1.02 (0.87-1.20)
Angina	718	765	0.93 (0.84-1.03)
Revascularization [†]	678	706	0.96 (0.86-1.06)
Total mortality	857	804	1.07 (0.97-1.18)

Abbreviations: CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction
[†] Includes both coronary artery bypass graft and percutaneous transluminal coronary angioplasty

Ten years after PHS II initiation, neither vitamin E nor vitamin C showed significant cardiovascular disease risk reduction. Major cardiovascular events occurred in 620 and 625 participants in the active and placebo vitamin E groups, respectively (Hazard Ratio [HR], 1.01 [95% CI, 0.90-1.13]; P=0.86). Individual outcome measure results are shown in Table 1. Among stroke subtypes, a statistical increase in hemorrhagic stroke was associated with vitamin E supplementation (HR, 1.74 [95% CI, 1.04-2.91]; P=0.04). In the vitamin C groups, 619 and 626 major cardiovascular events occurred in the active and placebo groups, respectively (HR, 0.99 [95% CI, 0.89-1.11]; P=0.91). Evaluation of the 2-way interaction between randomized vitamin E and vitamin C assignments found no significant risk reduction of major cardiovascular events (P=0.99).

The PHS II studied common antioxidants in a generalized patient population. PHS II participants included men diagnosed with hypertension, hypercholesterolemia, diabetes

mellitus, tobacco use and history of CVD. PHS II results found that neither vitamin E nor vitamin C significantly reduce cardiovascular events in men with relatively low-risk of CVD, a previously understudied population. PHS II results are similar to previous clinical trials and meta-analyses outcomes. Redundant lack of efficacy suggests that further evaluation of vitamin E and cardiovascular disease is not necessary.

References

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**Stressed Over Oxidative Stress?
 Vitamin E in the Prevention of
 Cardiovascular Disease:
 A Review of the Literature**

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 11:30 AM
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