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FROM THE FAMILY PRACTICE INQUIRIES NETWORK

In patients with a previous CVA, do antioxidants protect against subsequent stroke?

Donald C. Spencer, MD, MBA

Clinical Associate Professor of Family Medicine University of North Carolina at Chapel Hill

Susan E. Meadows, MLS

Department of Family and Community Medicine University of Missouri–Columbia

EVIDENCE-BASED ANSWER

Most recent randomized controlled clinical trials have not found a benefit in antioxidants (vitamin C, vitamin E, and/or beta-carotene) for preventing cardiovascular disease, including stroke. These recent clinical studies have not confirmed earlier observational studies that suggested a benefit. No studies have assessed only stroke patients and stroke outcomes. (Grade of recommendation: A, based on randomized controlled clinical trials and a systematic review of antioxidants and cardiovascular disease.)

EVIDENCE SUMMARY

The Heart Outcomes Prevention Evaluation (HOPE) trial was a 4.5-year randomized controlled clinical trial of vitamin E or placebo in 9541 patients aged 55 years or older with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes and other cardiovascular disease risk factors. No difference was noted between vitamin E and placebo for the outcomes of stroke, death, or other cardiac outcomes for these high-risk patients.[1] In a randomized controlled clinical trial of 29,133 Finnish male smokers, the overall net stroke morbidity and mortality with antioxidants was not significantly different from placebo. However, a trend toward higher rates of subarachnoid hemorrhages was found (relative risk [RR] = 1.5; 95% confidence interval [CI], 0.97–2.32; numbers needed to harm [NNH] = 833), while the cerebral infarction rate was decreased (RR = 0.86; 95% CI, 0.75–0.99; numbers needed to treat = 239) by vitamin E. Beta-carotene increased intracerebral hemorrhage (RR = 1.61; 95% CI, 1.10–2.36; NNH = 546).[2] Subsequent subgroup analysis showed a significant decrease in cerebral infarction (RR = 0.33; 95% CI, 0.14–0.78) without increasing subarachnoid hemorrhage in hypertensive, diabetic men taking vitamin E.[3] Given the inherent methodological perils of subgroup analysis, this association requires further study before clinical implementation.

The Italian GISSI study of 11,324 patients with a recent myocardial infarction showed no effect of vitamin E on the combined outcomes of death, myocardial infarction, and stroke.[4] In the Heart Protection Study, 20,536 adults between the ages of 40 and 80 years with cardiovascular disease, stroke, or diabetes were given vitamin E, vitamin C, beta-carotene, or placebo for 5 years. No significant differences were noted between vitamins and placebo in fatal or nonfatal stroke (RR = 0.99; 95% CI, 0.87–1.12).[5]

Although prior observational studies have hinted at a link between antioxidants and improved cardiovascular outcomes, the recently published Health Professionals Follow-up Study found no benefit to vitamin C or E in preventing strokes, based on the dietary assessment of 43,738 men, aged 40 to 75 years, who were not known to have cardiovascular disease or diabetes.[6]

RECOMMENDATIONS FROM OTHERS

The American Heart Association Science Advisory and Coordinating Committee commented on antioxidant use in 1999. While their emphasis was on coronary heart disease, they concluded that the general population should "consume a balanced diet with emphasis on antioxidant-rich fruits and vegetables and whole grains," noting that "the absence of efficacy and safety data from randomized trials precludes the establishment of population-wide recommendations regarding vitamin E supplementation."[7] Some authors argue that the failure to demonstrate a benefit from antioxidants is due to inadequate antioxidant dosing, treatment length, or type of antioxidant.[8]

Read a Clinical Commentary by Dan Sontheimer, MD, MBA, online at **http://www.FPIN.org**.

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