

Date: January 5, 2005

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Re: **Vitamin E and Alzheimer's Disease**

A recent publication (Ann Intern Med 2004; 142:1-10) examined the number of deaths in 19 clinical trials of vitamin E, including a total of 136,000 subjects. These trials varied in the characteristics of the subjects enrolled, the dose of vitamin E used, the duration of treatment and the outcome measures studied. Many of the subjects enrolled in these trials had coronary artery disease or risk factors for cardiovascular disease. In about half of the studies, the active treatment under investigation was a combination of vitamin E plus other vitamins or minerals.

None of the individual studies showed an increase in risk of death for subjects on vitamin E alone. Similarly, when all 19 studies were examined together, there was no increase in the risk of death. However, when the studies were arranged by dose of vitamin E (above or below the 400 IU/day median dose), it appeared that individuals on low to moderate doses of vitamin E had a very slight protection against death while those on high dose vitamin E were at a very slightly higher risk of death. The majority of the deaths occurred in individuals who had known coronary artery disease. Further, only 30% of the metaanalytical sample were in high dose studies and 12 studies with fewer than 10 deaths were not included in the analyses. Since publication of this paper, a number of methodological issues have been raised and the conclusions have been questioned; further statistical analysis is in progress.

Two Alzheimer's Disease Cooperative Study trials have been completed looking at the effects of high dose vitamin E in patients with Alzheimer's disease (AD) or mild cognitive impairment (MCI). In the AD study, patients on high dose vitamin E for up to 24 months reached functional milestones more slowly than individuals on placebo. Vitamin E was not associated with increased risk of death; an identical number of subjects on vitamin E died (12) during the course of the trial compared to patients on placebo (12). In a second study looking at the effects of vitamin E for up to 36 months in patients with MCI, there was no overall benefit or increase in risk; the death rate was also identical in individuals on placebo (5) and vitamin E (5).

Based on the pooled data in the recent publication, it is difficult to draw firm conclusions or make recommendations. The benefits of vitamin E supplements for AD prevention are unproven, and individuals with MCI have not shown benefit from vitamin E. A cautious interpretation of the risk reported in the new publication would be that cognitively normal individuals and those with MCI should limit their intake of vitamin E. For individuals with AD, the results are much less clear.

The single randomized clinical trial of vitamin E in AD showed that high dose vitamin E is beneficial, without increased mortality, in the treatment of individuals at the moderate stage of disease.

Since this trial was much smaller than the published cardiovascular trials, a small degree of increased risk might have been missed. Lower doses of vitamin E have not been tested in AD. It is thus unclear whether the risk-benefit ratio warrants continued use of 2000 IU of vitamin E for AD, or whether a lower dose should be recommended. An additional caution is that the protective effects of statins on cardiovascular disease may be attenuated by co-administration of anti-oxidants, suggesting that individuals who are on statins should be cautious about using vitamin E. In our view, it is reasonable at present to maintain AD patients on 2000 IU of vitamin E per day unless coronary artery disease is present, in which case a reduction in dose might be considered by the treating physician.

Research studies will continue to investigate vitamin E at various doses, as well as combinations of antioxidants, and will take appropriate precautions to monitor the well being of research participants.