



**DEPARTMENT OF VETERANS AFFAIRS  
CENTER FOR MEDICATION SAFETY  
VAMedSAFE: High-Dose Vitamin E ( $\geq$  400 IU/day)**

**I. ISSUE**

Authors of a recently published meta-analysis demonstrated that high-dose vitamin E may increase all-cause mortality.<sup>1</sup> As a result of their findings, the authors recommend avoidance of high-dose vitamin E.

**II. BACKGROUND**

There have been a number of large, long-term clinical trials evaluating the role of vitamin E in the prevention of certain chronic diseases. The premise for these trials was based upon the knowledge that vitamin E possesses antioxidant properties and its use may result in a reduced risk for certain chronic diseases including, among others, cardiovascular disease, cancer and Alzheimer's disease.

In the case of cardiovascular disease, investigators have failed to show a benefit of vitamin E in reducing morbidity or mortality associated with cardiovascular events. Over the past two years, there have been three published meta-analyses investigating the use of vitamin E either alone or combined with other vitamins in the prevention of cardiovascular disease.<sup>2-4</sup> In all three analyses, the effect of vitamin E supplementation had no statistically significant effect on cardiovascular outcomes including all-cause mortality, cardiovascular mortality, fatal or nonfatal myocardial infarction (MI) or blood lipids.

**III. DISCUSSION**

In a more recently published meta-analysis, investigators observed an increase in all-cause mortality in those users of high-dose vitamin E ( $\geq$ 400 IU/day) versus control or placebo. The analysis was performed with the intent of determining whether there was a dose-response relationship between vitamin E supplementation and all-cause mortality. Trials included in the meta-analysis were only those trials meeting several criteria. Those criteria included 1) randomized allocation, 2) use of vitamin E alone or vitamin E with other vitamins, 3) use of a control or placebo group, 4) study population consisting of men and/or non-pregnant women, 5) vitamin E use and study follow up duration of at least one year and 6) reporting of at least 10 deaths.

Of the 36 trials identified, 19 met the inclusion criteria and were selected. Sample size ranged from 196 to 29,584 study participants with an average study duration ranging from 1.4 to 8.2 years. In all 19 trials combined, there were 135,967 individuals participating and 12,504 reported deaths. The majority of trials consisted of populations at high risk for a chronic disease (cardiovascular disease), especially in those trials evaluating higher dosages ( $\geq$  400 IU daily). The dose of vitamin E supplementation in the 19 trials ranged from 16.5 IU to 2000 IU daily with a median dose of 400 IU per day. Trials investigating high-dose vitamin E were typically smaller and consisted of 30.1% (n=40,950/135,967) of total study participants in the included trials. Overall, vitamin E supplementation did not result in a difference in all-cause mortality versus control or placebo. However, the authors reported significant heterogeneity of study results and determined that the differences could be explained by variation in dose of vitamin E supplementation (see Table 1 for results). Sensitivity analyses were performed and the findings remained with low and high dose vitamin E. As part of the sensitivity analysis, each of the eleven high-dose vitamin E trials was removed and the results determined. After exclusion of each of the high dose trials, the difference in all-cause mortality remained suggesting that the events were not driven by one particular trial.

**Table 1. Results<sup>1</sup>**

Groups	Pooled Risk Difference between Vitamin E and Control / 10,000 Persons	95% CI / 10,000 Persons	Death Risk Ratio	95% CI	P-Value
Overall (Vitamin E)	10	-18 to 38	1.01	0.98-1.04	>0.2
Low Dose (<400 IU)	-16	-41 to 10	0.98	0.96-1.01	>0.2
High Dose (≥400 IU)	39	3 to 74	1.04	1.01-1.07	0.035

Average death risk in the control group across trials was 1022/10,000 persons

In their discussion, the authors state that other recent meta-analyses of randomized trials do not explore a dose-response relationship between vitamin E supplementation and benefit or harm. In addition, they admit that the populations of patients on high-dose vitamin E consisted primarily of patients with chronic diseases (cardiovascular disease) and therefore, the generalizability of their findings is unclear. However, from the data, the authors concluded that high-dose vitamin E supplementation should be avoided.

In the case of using vitamin E to slow cognitive deterioration in patients with Alzheimer's disease, authors of a Cochrane Database Systematic Review determined that there was insufficient evidence to support the efficacy of vitamin E in Alzheimer's disease. In their review, they identified only one trial that was considered to be of acceptable methodology.<sup>5</sup> In that trial, patients with moderate disease were randomly assigned to placebo, vitamin E 2000 IU/day, selegiline 10 mg/day, or both for two years. The authors of the systematic review found the results to be difficult to interpret but felt that there was sufficient evidence of possible benefit to justify further studies. There was also a statistically significant excess of falls in the vitamin E group compared with placebo, which also needs further investigation.<sup>6</sup>

In the case of preventing the onset of or reducing the severity of neuroleptic-induced tardive dyskinesia (TD), authors of a Cochrane Database Systematic Review determined from the available evidence that vitamin E did not improve symptoms of TD but may protect against deterioration. There was no evidence for vitamin E in those with early symptoms of TD.<sup>7</sup> In a recently published study of vitamin E 1200 IU/day versus placebo in 41 inpatients with TD, investigators observed a greater reduction from baseline in the Abnormal Involuntary Movement Scale (AIMS) in favor of vitamin E.<sup>8</sup>

#### IV. VA MEDSAFE RECOMMENDATIONS

1. Since there is an abundance of data suggesting that supplementation with vitamin E has no apparent benefit in preventing or reducing cardiovascular events but there are some data suggesting an increased risk in all-cause mortality, high-dose (≥400 IU) vitamin E should be removed from the VA National Formulary. VA MedSafe will request the MAP and VISN formulary leaders to remove high-dose vitamin E supplements from the VA National Formulary.
2. VA clinicians will be sent an information bulletin regarding these findings. The VA PBM-MAP recommends that high-dose vitamin E not be used for the purpose of cardiovascular disease prevention.
3. In those patients using high-dose vitamin E for other chronic disease indications, it is recommended that VA clinicians consider the evidence for benefit and risk of such therapy in individual patients.

#### V. USE OF VITAMIN E IN VHA

For the 4<sup>th</sup> quarter of this year, VA had dispensed high-dose vitamin E (400 IU units or greater) to 50,814 unique patients.

## VI. REFERENCES

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