

CAT Presentation by Robert Valleau

Vitamins C & E in Cardiovascular Disease Prevention

Citation: Sesso H., et al. Vitamins E and C in the Prevention of Cardiovascular Disease in Men: The Physicians' Health Study II Randomized Controlled Trial. JAMA, Nov 12, 2008; 300:2123-2133

Context: Basic research suggests Vitamin E and C have a positive effect in preventing cardiovascular disease. The Physicians Health Study II (PHS II) was designed to demonstrate the efficacy of vitamin E and C in the prevention of cardiovascular disease in a low risk population of male physicians aged 50 and older.

Study Description: The PHS II is a randomized, double blind, placebo-controlled factorial trial of Vitamin E and Vitamin C that began in 1997 and continued to Aug 2007. It involved 14,641 male physicians over 50 years old, one group given Vitamin E 400 IU and placebo Qday and one group Vitamin C at 500mg and placebo Qday, one group given both Vitamin E and C doses, and one group with two placebos. These individuals were followed for a mean time period of 8 years. Among the groups a total of 1245 cardiovascular events occurred during this time point (equivalent to 11 per 1000 person-years). Composite end-points included the following; non-fatal myocardial infarction, non-fatal stroke, and cardiovascular disease death.

Research Question: Over an 8 year period does supplementation of Vitamin E and/or Vitamin C, decrease the risk of major cardiovascular events among older men with relatively low risk for cardiovascular events.

Importance of question: Should we as physicians recommend, or even prescribe, vitamin E and C supplementation to individuals of relatively low risk of cardiovascular events. We should know whether or not possible risks outweigh possible benefits.

Validity: Male eligible subjects were enrolled and randomized with intention to treat into PHS II. 7000 new physicians and 7641 from PHS I were enrolled. PHS I and II had the same eligibility criteria. Randomization was concealed. Subjects had regular and complete follow-up. This F/u was in a blinded fashion. Adherence was taking at least 2/3 of study agents. There were no significant differences in the adherence b/w the groups. Groups randomized were similar with regards to prognostic or risk factors.

Results: Large scale trial of 8 years duration showed that neither Vitamin E, nor Vitamin C, nor both vitamins combined was associated with a reduction in risk of major cardiovascular events.

Vitamin E – There was no effect of Vit E on the primary end point of major cardiovascular events. The overall rates of major cardiovascular events were 10.8 and 10.9 per 1000 person-years in the active and placebo respectively. Notably there was a statistically significant increased risk of hemorrhagic stroke. There were 39 hemorrhagic strokes in the active Vit E group and 23 hemorrhagic strokes in the placebo (HR 1.74, 95% CI 1.04-2.91, p=0.04).

Vitamin C – There was no effect of Vit C on the primary end point of major cardiovascular events (HR 0.99, 95% CI, 0.89-1.11, p=0.91).

Vitamin E and C - No effect modification (p=0.99)

External Validity: These subjects, as physicians, may be patients who are more health conscious regarding exercise, diet, and overall lifestyle. It is interesting that ~77% of subjects were taking aspirin which may be higher than the normal population of males aged 55-75 with no previous cardiovascular events. The prophylactic use of aspirin may be contributory to a less than significant effect from these supplements.

Conclusion: Until further studies are conducted, I would not prescribe or recommend Vitamin E or Vitamin C supplementation. No benefit was shown. The risk of increased hemorrhagic stroke in the Vitamin E study is a real concern. Further studies on a population that is not on aspirin therapy prophylactically would be helpful. Longer study duration may be needed to show effects.