Vitamin E Use is Associated with Improved Survival in an AD Cohort

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Background

- Vitamin E (alpha-tocopherol) is a lipid soluble vitamin with antioxidant properties which may decrease free-radical mediated damage in neuronal cells
- Many, but not all, observational studies suggest a protective effect of vitamin E for prevention of cognitive decline and AD
- One randomized clinical trial in moderately severe AD patients resulted in a significant delay in disease progression in patients assigned to 2000 IU/day of vitamin E compared to placebo.
- Recent meta analyses suggest slightly higher mortality risk with vitamin E.
- Until 2004, standard practice in the Baylor ADMDC was to recommend 1000 IU of vitamin E twice daily supplementation to all AD patients in addition to any other indicated anti-dementia drugs.
- Current study undertaken to determine if treatment with vitamin E was associated with higher mortality in an AD cohort.

Table 1. Patient Characteristics (n=847)

Variable	Mean ± SD or n (Percent)	Range
Age at First ADMDC Visit (years)	73.5 ± 8.6	43.2 – 93.9
Female (percent)	570 (67.3 %)	
Non-Hispanic White (percent)	741 (87.5%)	
Years of Education	13.4 ± 3.5	0 - 29
Duration of Symptoms (years)	3.8 ± 2.5	.5 - 20
Baseline MMSE	18.8 ± 6.8	1 - 30
Baseline Severity Category		
• Mild (MMSE ≥ 20)	439 (51.8%)	
• Moderate (MMSE 10-19)	309 (36.5%)	
• Severe (MMSE < 10)	99 (11.7%)	
Survival Time from First ADMDC Visit (years)	5.5 ± 2.8	.99 – 14.7

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Methods

Setting: Baylor Alzheimer's Disease and Memory Disorders Center, Baylor College of Medicine

Patients:

- Diagnosis of probable AD (based on NINCDS-ADRDA criteria), with or without concurrent cerebrovascular disease
- At least 1 comprehensive annual follow-up visit after the initial patient visit

Variables:

Independent Variable: Dementia medication history—recorded by clinician on standardized form at each visit and entered in electronic data base.

Dependent Variable: Vital status as of 12/31/2004 ascertained from Death Index

Covariates: Age, sex, years of education, duration of symptoms at the first patient visit, race/ethnicity (coded as non-Hispanic white vs other), baseline severity of dementia (mild, moderate, severe based on MMSE score), presence of CVD.

Analysis:

- Medication exposures were coded as a binary variable for each visit interval in a longitudinal data base.

  [*Note: Some regimens included memantine after 2003.The number taking memantine alone was too small to analyze and these patients were excluded from survival analyses. Approximately 5% of patients classified as taking vitamin E with or without a cholinesterase inhibitor during a visit interval could also be taking memantine.]*

- Time dependent Cox survival models were constructed to test the effects of the following independent medication exposure variables

1. Regimens including vitamin E ± a cholinesterase inhibitor compared to all other regimens.

2.a. Regimens including vitamin E ± a cholinesterase inhibitor compared to no drug treatment

2.b. Cholinesterase inhibitor alone compared to no drug treatment.

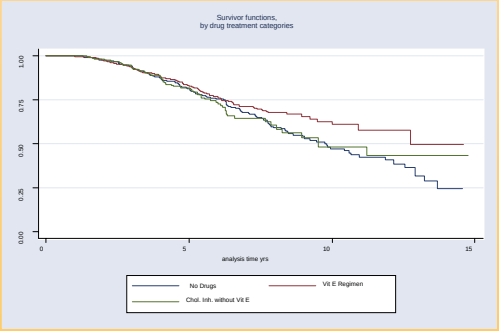
Results

Table 2. Distribution of Drug Exposure Categories at First, Second, and Last ADMDC Visit

	Vitamin E + Cholinesterase Inhibitor	Cholinesterase Inhibitor Without Vitamin E	Vitamin E Alone	No Drug Treatment	Total with Drug Exposure Recorded In Record	Exposure Undetermined	Total Patients in Cohort
First ADMDC Visit	**137** (18.5%)	**135** (18.2%)	**67** (9.1%)	**401** (54.2%)	**740**	**104** (12.3%)	**847**
Second ADMDC Visit	**428** (57.5%)	**121** (16.2%)	**53** (7.1%)	**143** (19.2%)	**745**	**87** (10.3%)	**847**
Final ADMDC	**310** (61.9%)	**65** (13.0%)	**47** (9.4%)	**79** (15.8%)	**501**	**50** (9.1%)	**552**

- 847 patients met basic inclusion criteria (see baseline characteristics in Table 1).
- At the first ADMDC visit, 54% of patients were not taking any anti-dementia medication, and just over 25% were taking vitamin E alone or with a cholinesterase inhibitor (Table 2). By the final visit, 62% were taking both vitamin E and a cholinesterase inhibitor, 9% were taking vitamin E alone,13% were taking a cholinesterase inhibitor without vitamin E, and 16% were not taking any drug. Drug exposure was uncertain for about 10% of patients during each follow-up interval.
- In a Cox survival model with all covariates included, drug regimens that included vitamin E were associated with a 26% reduction in mortality risk (HR=.74, 95% CI=.58, .93, p=.009). With non-significant covariates excluded, the hazard ratio was .71 (95% CI=.57, .89, p=.003).
- Patients on a cholinesterase inhibitor without vitamin E had no survival benefit (HR=1.20, 95% CI=.87, 1.65, p=.273), whereas those taking vitamin E with or without another antidementia drug had a 23% lower mortality risk compared to those not taking any drugs (HR=.77, 95% CI= .60, 1.00, p.=.051).

Figure 1



Conclusions

- No evidence that treatment with high doses of vitamin E had an adverse effect on survival in our AD cohort.
- Patients whose regimens included vitamin E tended to survive longer than those taking no drug, or a cholinesterase inhibitor alone.
- The survival benefits were only observed with long-term exposure (see Figure 1).
- High dose vitamin E treatment is controversial in light of recent cardiovascular trial results and meta analyses. Additional clinical trials with long-term follow up in AD patients may be warranted.

Table 3. Cox Survival Analysis: Hazard Ratios (± 95% CI) for Different Exposure Categories*

	HR	95% CI	p
Vitamin E Regimens vs. All Other Categories (n=764)			
Age	1.03	1.02, 1.05	<.001
Sex (1=male ; 0=female)	1.90	1.52, 2.37	<.001
Race (1=white ; 0=other race/ethnicity)	1.81	1.25, 2.62	.002
Baseline Severity			
• *Moderate vs. Severe*	.86	.63, 1.19	.376
• *Mild vs. Severe*	.52	.37, .72	<.001
Vitamin E Regimen	.71	.57, .89	.003
Vitamin E Regimens and Non Vitamin E Regimens vs. No Drug			
Age	1.03	1.02, 1.05	<.001
Sex (1=male ; 0=female)	1.93	1.54, 2.42	<.001
Race (1=white ; 0=other race/ethnicity)	1.83	1.26, 2.65	.001
Baseline Severity			
• *Severe (reference)*	--		
• *Moderate*	.84	.61, 1.67	.300
• *Mild*	.50	.36, .70	<.001
Drug Regimen			
• *No Drug (reference)*	--		
• *Vitamin E (alone or with other antidementia drug*	.77	.60, 1.00	.051
• *Cholinesterase Inhibitor Without Vitamin E*	1.20	.87, 1.6	.273

*Duration of symptoms, education, and CVD non-significant (p>.20) In all models; hazard ratios not shown