Supplementary Online Content

Dysken MW, Sano M, Asthana S, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA Cooperative randomized trial. *JAMA*. doi:10.1001/jama.2013.282834.

Correction: This eFigure was corrected online February 5, 2014.

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Physical Exam, Medical History, Laboratory Tests and Concomitant Medications at Baseline by Treatment Group

Characteristic	Vitamin E (N=152)	Memantine (N=155)	Vitamin E + Memantine (N=154)	Placebo (N=152)
Physical Exam, mean ± SD				
Body Mass Index	26.6 ± 4.5	26.4 ± 4.2	27.2 ± 4.6	26.6 ± 4.6
Systolic Blood Pressure	134 ± 17	136 ± 18	134 ± 17	133 ± 16
Diastolic Blood Pressure	73 ± 11	72 ± 10	73 ± 11	72 ± 11
Laboratory Values, mean ± SD				
International normalized ratio (INR)	1.0 ± 0.1	1.1 ± 0.7	1.0 ± 0.1	1.0 ± 0.1
HDL Cholesterol, mg/dL	49 ± 14	49 ± 17	47 ± 14	48 ± 11
LDL Cholesterol, mg/dL	95 ± 33	96 ± 33	94 ± 31	99 ± 31
Total Cholesterol, mg/dL	169 ± 38	168 ± 38	166 ± 36	172 ± 38
Triglycerides, mg/dL	129 ± 77	126 ± 71	136 ± 81	133 ± 62
Fasting Glucose, mg/dL	111 ± 47	105 ± 26	108 ± 31	110 ± 37
Homocysteine, μmol/dL	13.1 ± 4.4	13.6 ± 5.2	13.7 ± 5.3	14.0 ± 4.7
Thyroid-stimulating Hormone, μIU/mL	2.1 ± 1.3	2.0 ± 1.1	2.1 ± 1.6	2.3 ± 1.5
Vitamin B12, pg/mL	592 ± 292	627 ± 338	610 ± 356	586 ± 296
Creatinine Clearance, ml/min	63 ± 22	62 ± 22	65 ± 24	62 ± 24
Creatinine Clearance, N (%) < 30 ml/min	4 (3)	7 (5)	4 (3)	7 (5)
Medical History, N (%)				

Glaucoma or Cataract	57 (38)	60 (39)	52 (34)	53 (35)
Diabetes	41 (27)	39 (25)	45 (29)	42 (28)
Emotional Problems	42 (28)	33 (21)	47 (31)	44 (29)
Musculoskeletal Problems	43 (28)	39 (25)	34 (22)	50 (33)
Heart Disease *	41 (27)	28 (18)	34 (22)	43 (28)
Sleep Disorder	27 (18)	23 (15)	21 (14)	16 (11)
Cerebrovascular Disease	12 (8)	15 (10)	16 (10)	18 (12)
Chronic Pain Syndrome	20 (13)	11 (7)	10 (6)	12 (8)
Peripheral Vascular Disease	18 (12)	10 (6)	9 (6)	13 (9)
Parkinson's Disease	3 (2)	2 (1)	3 (2)	2 (1)
Renal Disease (Moderate/Severe)	1 (1)	0 (0)	1 (1)	0 (0)
Smoker (current or past)	94 (62)	95 (62)	100 (65)	98 (64)
Concomitant Medications, N (%)				
Statins	90 (60)	97 (63)	93 (60)	100 (66)
Aspirin	96 (63)	89 (57)	99 (64)	91 (60)
Other Antiplatelets, Anticoagulants, or Thrombolytics	9 (6)	6 (4)	13 (8)	15 (10)
Anticholinergics (Excluding TCAs)	7 (5)	7 (5)	6 (4)	6 (4)
Tertiary Tricyclic Antidepressants	5 (3)	5 (3)	5 (3)	3 (2)
Other Antidepressants	51 (34)	51 (33)	52 (34)	59 (39)
Antipsychotics	10 (7)	10 (6)	5 (3)	12 (8)
Sedatives/Hypnotics	8 (5)	13 (8)	8 (5)	8 (5)
Skeletal Muscle Relaxants	8 (5)	5 (3)	9 (6)	5 (3)

Vitamin C †	16 (11)	18 (12)	15 (10)	10 (7)
Other Antioxidants ‡	20 (13)	22 (14)	15 (10)	17 (11)

* Heart Disease includes a history of myocardial infarction, congestive heart failure, and/or angina.

† 14 participants were on vitamin C and at least one other antioxidant

‡ Other possible antioxidants included vitamin A, vitamin B6, vitamin B12, folate, zinc, selenium, lycopene, and magnesium.

eTable 2. Number and Frequencies of apolipoprotein ε2, ε3 and ε4 alleles overall and by treatment group.

Alleles — N* (%)	Vitamin E	Memantine	Vitamin E + Memantine	Placebo	Overall
ε2	4 (2.1)	9 (4.3)	6 (2.7)	15 (7.3)	34 (4.1)
ε3	129 (67.2)	131 (62.4)	156 (70.3)	133 (64.6)	549 (66.1)
ε4	59 (30.7)	70 (33.3)	60 (27.0)	58 (28.2)	247 (29.8)

***** N = the number of alleles.
Chi-square test two-sided p = 0.09; Fisher's Exact test two-sided p = 0.12.

eTable 3. Number and frequencies of apolipoprotein ε4 alleles overall and by treatment group.

Number of ε4 Alleles — N (%)	Vitamin E (N=96)	Memantine (N=105)	Vitamin E + Memantine (N=111)	Placebo (N=103)	Overall (N=415)
0	47 (49.0)	48 (45.7)	59 (53.2)	55 (53.4)	209 (50.4)
1	39 (40.6)	44 (41.9)	44 (39.6)	38 (36.9)	165 (39.8)
2	10 (10.4)	13 (12.4)	8 (7.2)	10 (9.7)	41 (9.9)

Chi-square test two-sided p = 0.85.

eTable 4. Number and frequencies of apolipoprotein ε genotypes overall and by treatment group.

APOε genotypes — N (%)	Vitamin E (N=96)	Memantine (N=105)	Vitamin E + Memantine (N=111)	Placebo (N=103)	Overall (N=415)
ε2/ ε2	0	0	0	0	0
ε2/ ε3	2 (2.1)	5 (4.8)	3 (2.7)	9 (8.7)	19 (4.6)
ε2/ ε4	2 (2.1)	4 (3.8)	3 (2.7)	6 (5.8)	15 (3.6)
ε3/ ε3	45 (46.9)	43 (41.0)	56 (50.5)	46 (44.7)	190 (45.8)
ε3/ ε4	37 (38.5)	40 (38.1)	41 (36.9)	32 (31.1)	150 (36.1)
ε4/ ε4	10 (10.4)	13 (12.4)	8 (7.2)	10 (9.7)	41(9.9)

Chi-square test two-sided p = 0.45; Fisher's exact test two-sided p = 0.52.

eTable 5. Missing Data Sensitivity Analyses for the Primary Outcome: Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory

	Vitamin E	Memantine	Vitamin E + Memantine	Placebo
Missing Data Sensitivity Analysis 1*				
Least Squares Means Change ±SE	-13.81 ±1.10	-14.97 ±1.10	-15.21 ±1.11	-16.96 ±1.11
Mean Difference Compared to Placebo (95% CI)	3.15 (0.92, 5.38)	1.99 (-0.23, 4.20)	1.75 (-0.48, 3.99)	-
Unadjusted P-Value	0.006	0.08	0.12	-
Adjusted P-Value	0.03	0.39	0.49	-
Missing Data Sensitivity Analysis 2†				
Least Squares Means Change ±SE	-13.82 ±1.11	-14.99 ±1.10	-15.21 ±1.11	-16.95 ±1.11
Mean Difference Compared to Placebo (95% CI)	3.13 (0.89, 5.36)	1.96 (-0.26, 4.18)	1.74 (-0.51, 3.98)	-
Unadjusted P-Value	0.006	0.08	0.13	-
Adjusted P-Value	0.04	0.42	0.52	-

***** Original mixed model with data imputed for the first missing score following the last observed outcome based on the slope for each treatment group.

† Model is adjusted for baseline factors that were independently predictive of missing data, Age and baseline outcome score, to adjust the treatment effect based on the missingness mechanism.

eTable 6. Mean Changes in the Alzheimer's Disease Cooperative Study/Activities of Daily Living Measure during the 4-year Study Period as Compared with Baseline for those with Mild Impairment (Baseline Mini-Mental State Examination score 20 to 26) compared to those with Moderate Impairment (Baseline Mini-Mental State Examination score 12 to 19)*

Outcome	Vitamin E	Memantine	Vitamin E + Memantine	Placebo
Mild impairment, N	106	105	110	89
Moderate impairment, N	46	50	44	63
Least Squares Means Change ±SE for those with Mild impairment	-13.39 ±1.20	-14.16 ±1.20	-13.77 ±1.19	-15.11 ±1.29
Least Squares Means Change ±SE for those with Moderate impairment	-14.78 ±1.68	-16.85 ±1.64	-19.16 ±1.77	-19.60 ±1.47
Mean Difference (95% CI) Compared to Placebo for those with Mild impairment	1.72 (-1.05, 4.50)	0.96 (-1.82, 3.73)	1.34 (-1.42, 4.10)	-
Mean Difference (95% CI) Compared to Placebo for those with Moderate impairment	4.82 (1.03, 8.62)	2.75 (-0.99, 6.48)	0.44 (-3.52, 4.39)	-
Interaction p = 0.38*				

*Test of interaction of treatment effect by Alzheimer's disease severity level defined by MMSE.

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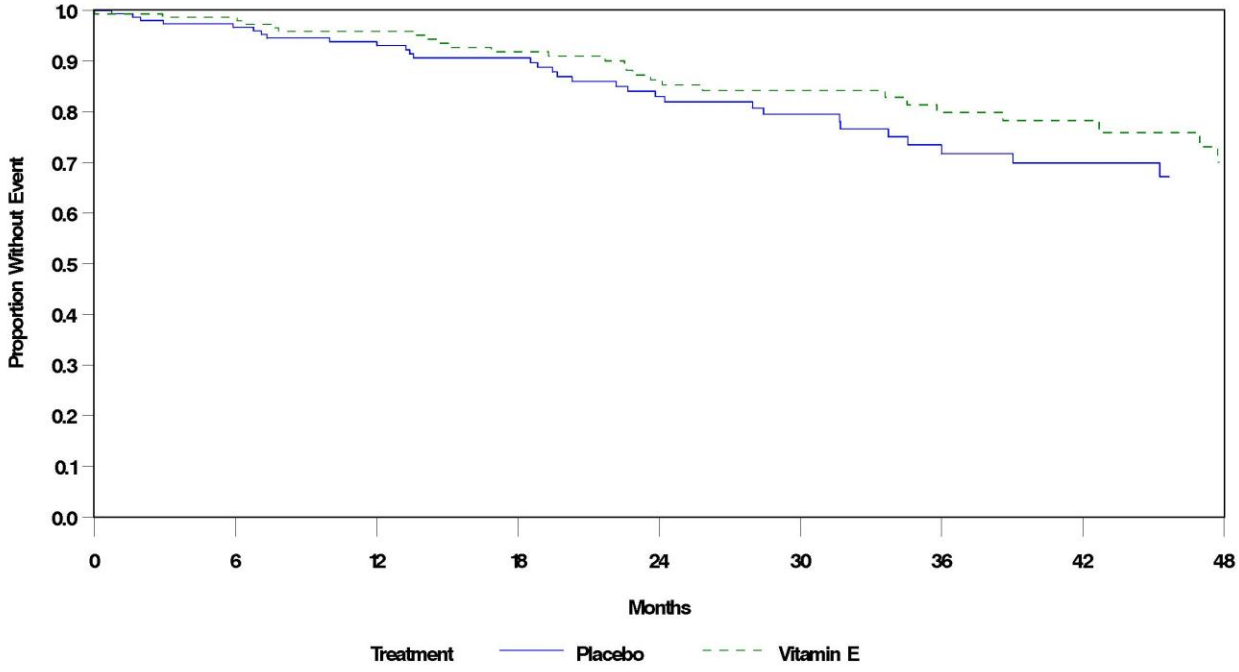
eFigure. Kaplan-Meier Estimates of Survival of Vitamin E, Memantine and the Combination compared to Placebo.

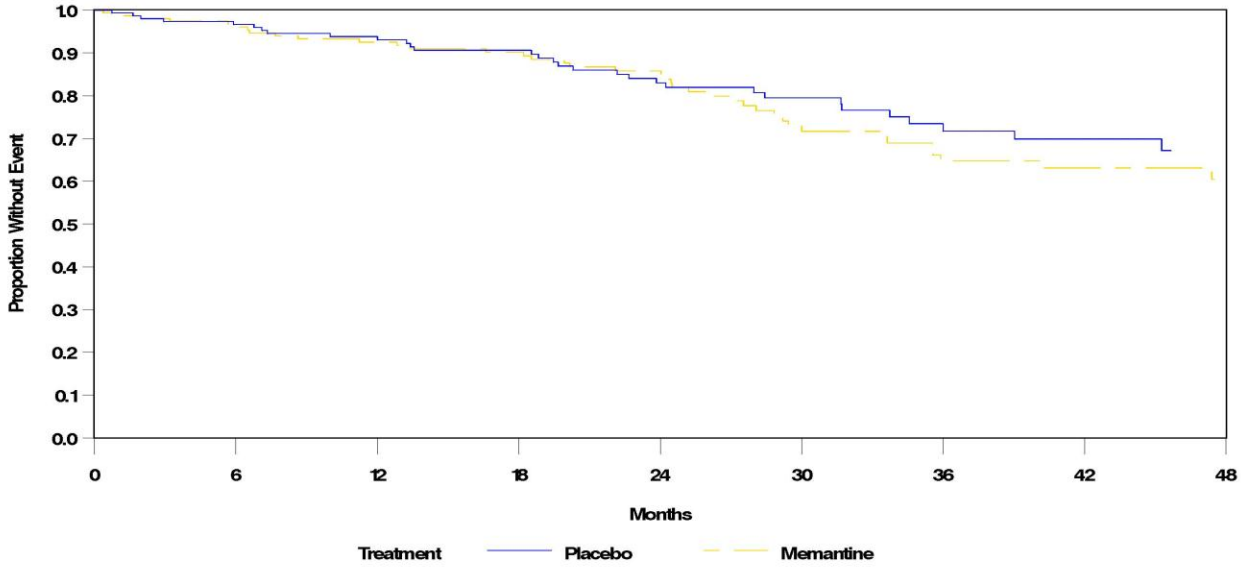
Vitamin E vs. Placebo



Placebo								
At Risk:	142	126	112	80	65	46	38	25
Failed:	5	9	13	21	24	28	30	31
Vitamin E								
At Risk:	146	138	110	90	78	54	48	23
Failed:	2	6	11	17	19	22	23	26

Log–Rank Chi–Square = 1.0340 P–value = 0.3092 N = 304 Failed = 57

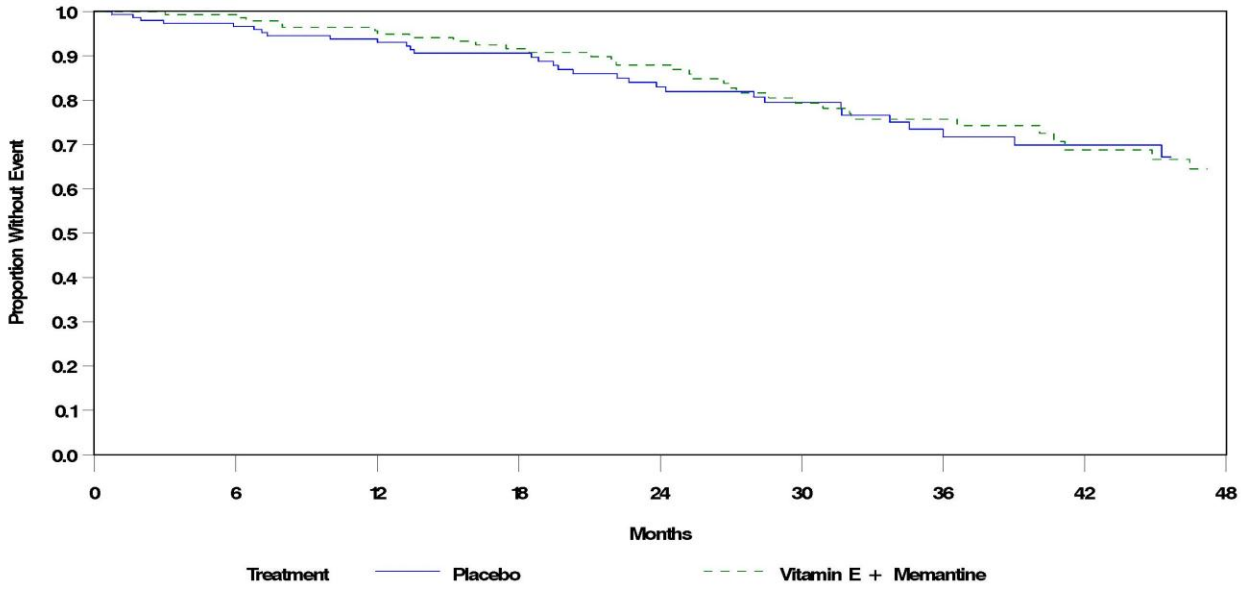
Memantine vs. Placebo



Memantine								
At Risk:	145	124	111	91	60	47	38	23
Failed:	5	11	14	19	31	36	38	39
Placebo								
At Risk:	142	126	112	80	65	46	38	25
Failed:	5	9	13	21	24	28	30	31

Log—Rank Chi—Square = 0.5344 P—value = 0.4648 N = 307 Failed = 70

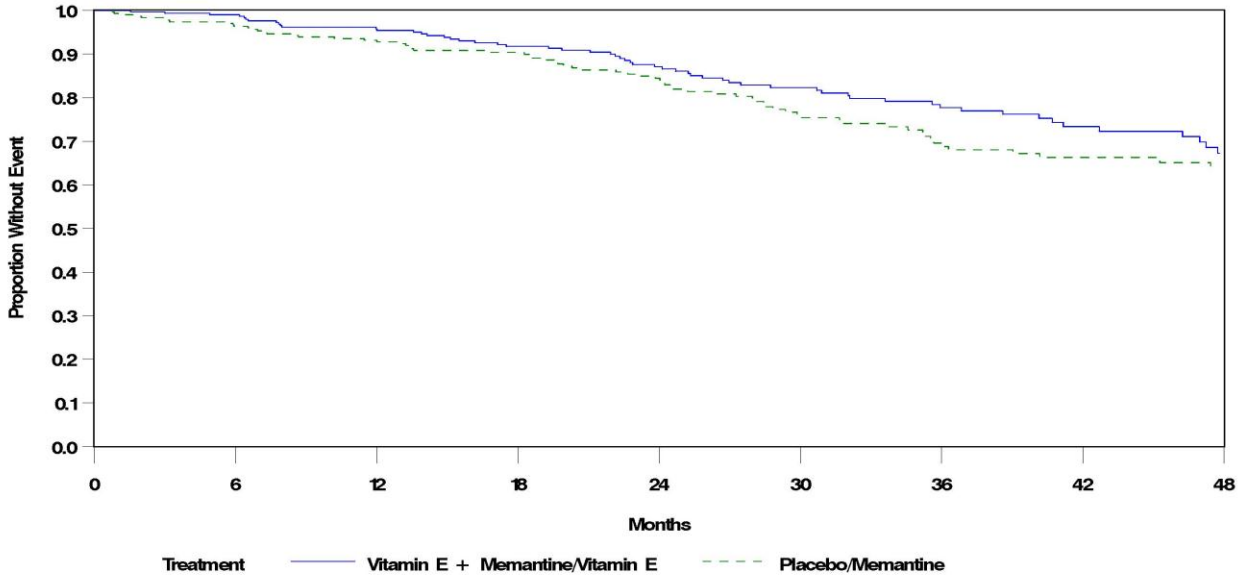
Vitamin E + Memantine vs. Placebo



Placebo								
At Risk:	142	126	112	80	65	46	38	25
Failed:	5	9	13	21	24	28	30	31
Vitamin E + Memantine								
At Risk:	149	125	110	92	70	62	36	30
Failed:	1	6	11	15	22	26	30	32

Log—Rank Chi—Square = 0.0641 P—value = 0.8002 N = 306 Failed = 63

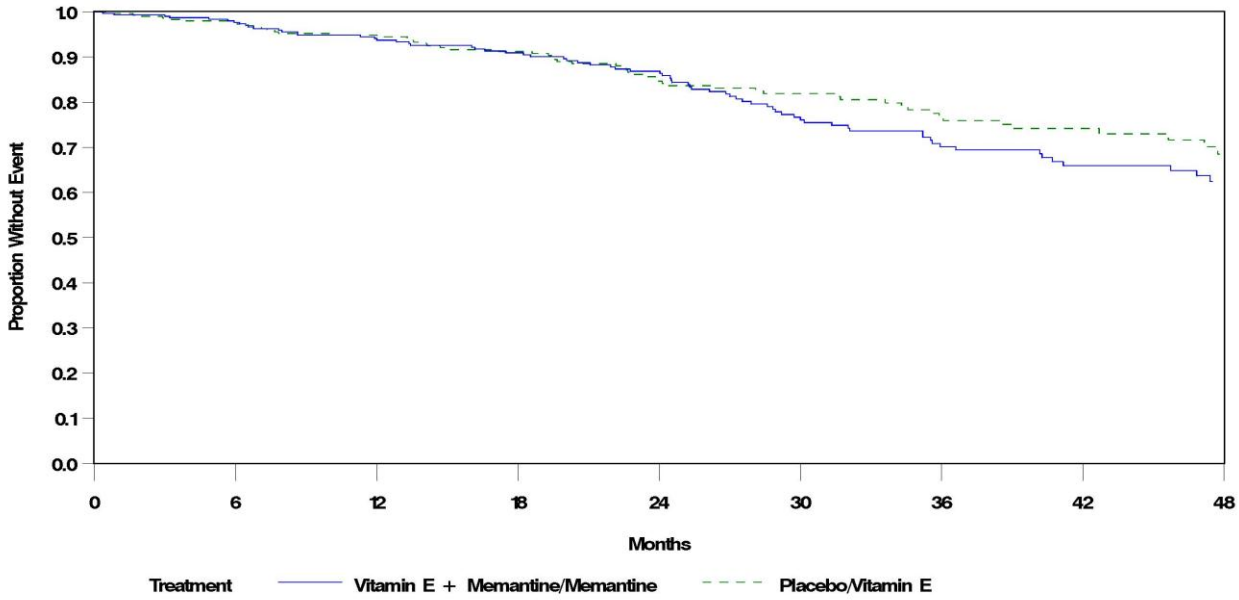
Vitamin E and Vitamin E + Memantine vs. Placebo and Memantine



Placebo/Memantine								
At Risk:	287	248	217	171	120	91	74	42
Failed:	10	20	27	40	55	64	68	70
Vitamin E + Memantine/Vitamin E								
At Risk:	294	251	219	178	140	107	75	50
Failed:	3	12	22	32	41	48	53	58

Log—Rank Chi—Square = 2.0587 P—value = 0.1513 N = 613 Failed = 128

Memantine and Vitamin E + Memantine vs. Placebo and Vitamin E



Placebo/Vitamin E								
At Risk:	286	261	216	170	137	97	85	41
Failed:	7	15	24	38	43	50	53	57
Vitamin E + Memantine/Memantine								
At Risk:	290	249	221	181	129	101	73	50
Failed:	6	17	25	34	53	62	68	71

Log—Rank Chi—Square = 1.1711 P—value = 0.2792 N = 613 Failed = 128