

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.

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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.

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| 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 (%) | | | | |

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| | | | | |
|--|---------|---------|----------|----------|
| 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) |

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| | | | | |
|----------------------|---------|---------|---------|---------|
| 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 \pm SE | -13.81 \pm 1.10 | -14.97 \pm 1.10 | -15.21 \pm 1.11 | -16.96 \pm 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 \pm SE | -13.82 \pm 1.11 | -14.99 \pm 1.10 | -15.21 \pm 1.11 | -16.95 \pm 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)*

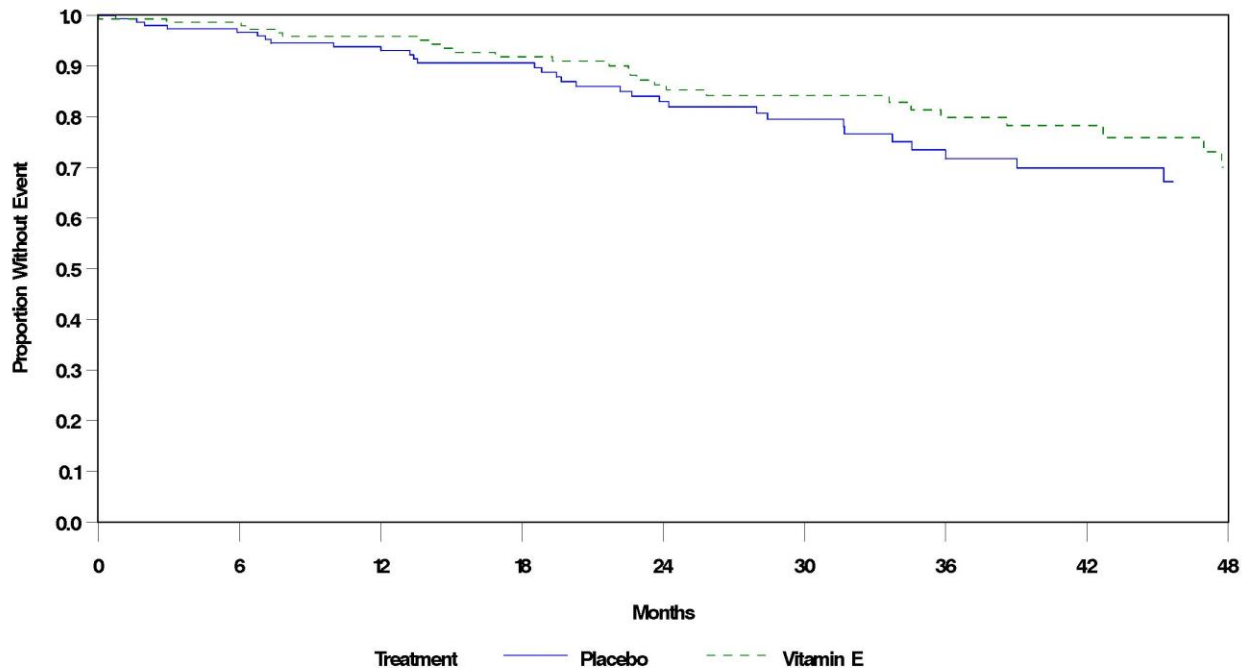
| Outcome | Vitamin E | Memantine | Vitamin E + Memantine | Placebo |
|---|-----------------------|-----------------------|------------------------------|-------------------|
| Mild impairment, N | 106 | 105 | 110 | 89 |
| Moderate impairment, N | 46 | 50 | 44 | 63 |
| Least Squares Means Change \pm SE for those with Mild impairment | -13.39 \pm 1.20 | -14.16 \pm 1.20 | -13.77 \pm 1.19 | -15.11 \pm 1.29 |
| Least Squares Means Change \pm SE for those with Moderate impairment | -14.78 \pm 1.68 | -16.85 \pm 1.64 | -19.16 \pm 1.77 | -19.60 \pm 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.

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

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

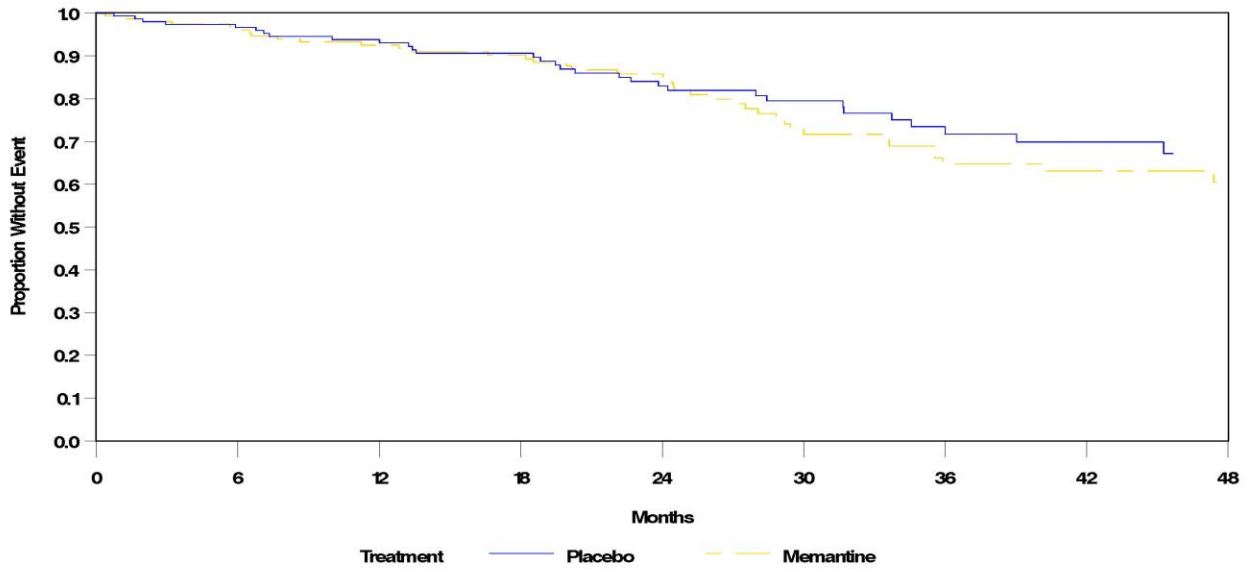
Vitamin E vs. Placebo



| | | | | | | | | |
|-----------|-----|-----|-----|----|----|----|----|----|
| 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 = 10340 P-value = 0.3092 N = 304 Failed = 57

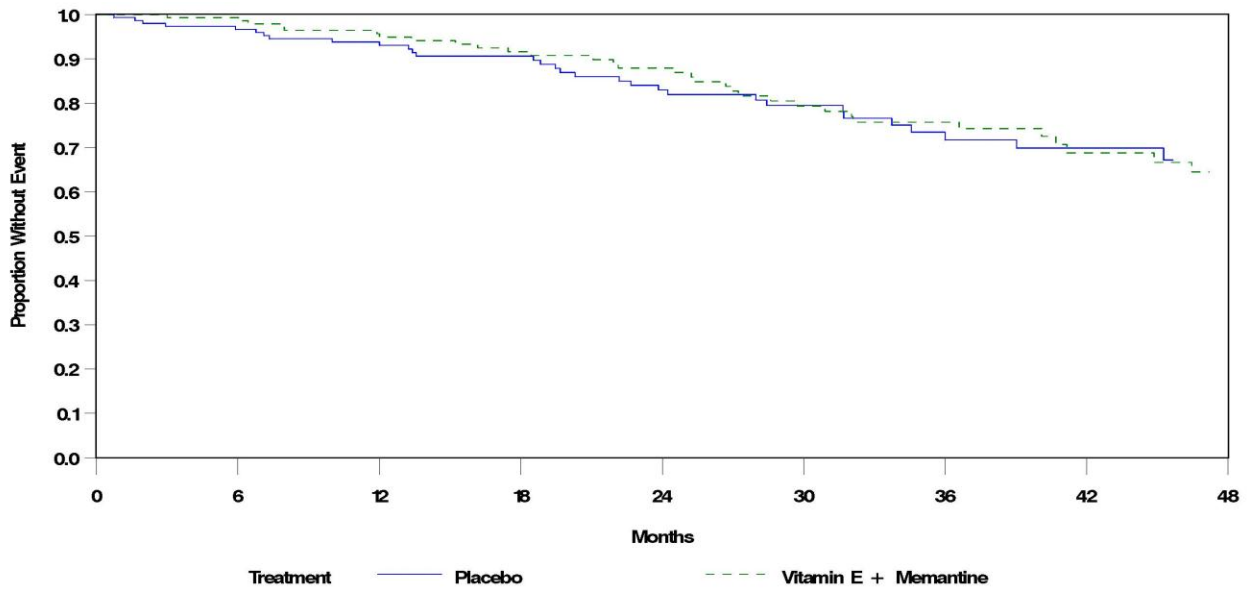
Memantine vs. Placebo



| | | | | | | | | | |
|-----------|-----|-----|-----|----|----|----|----|----|--|
| 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

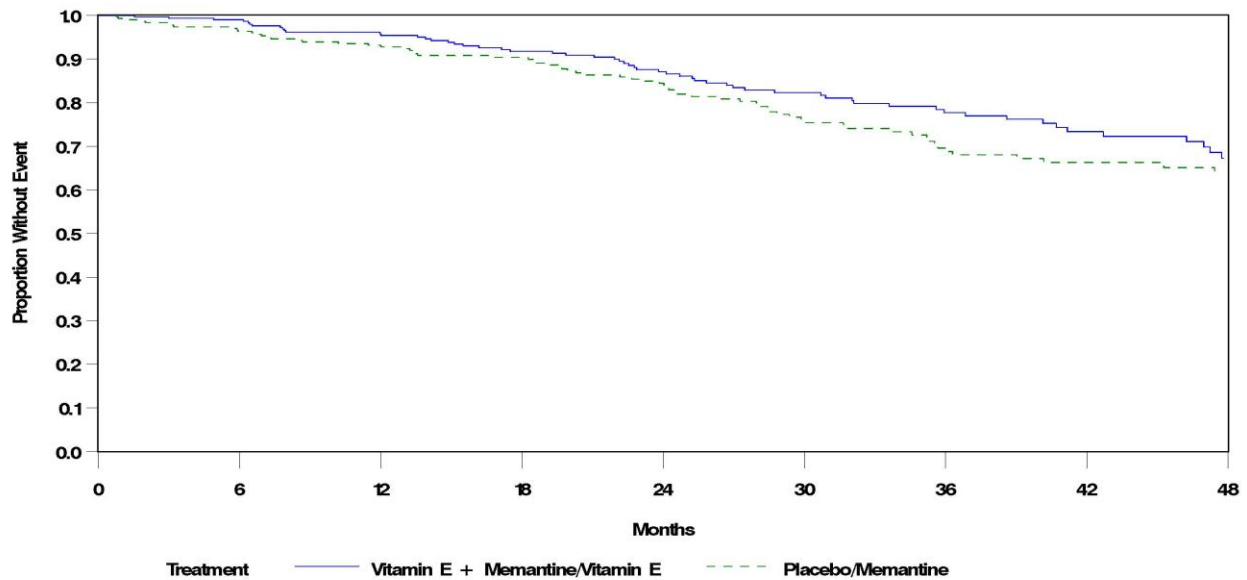
Vitamin E + Memantine vs. Placebo



| | | | | | | | | | |
|-----------------------|-----|-----|-----|----|----|----|----|----|--|
| 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

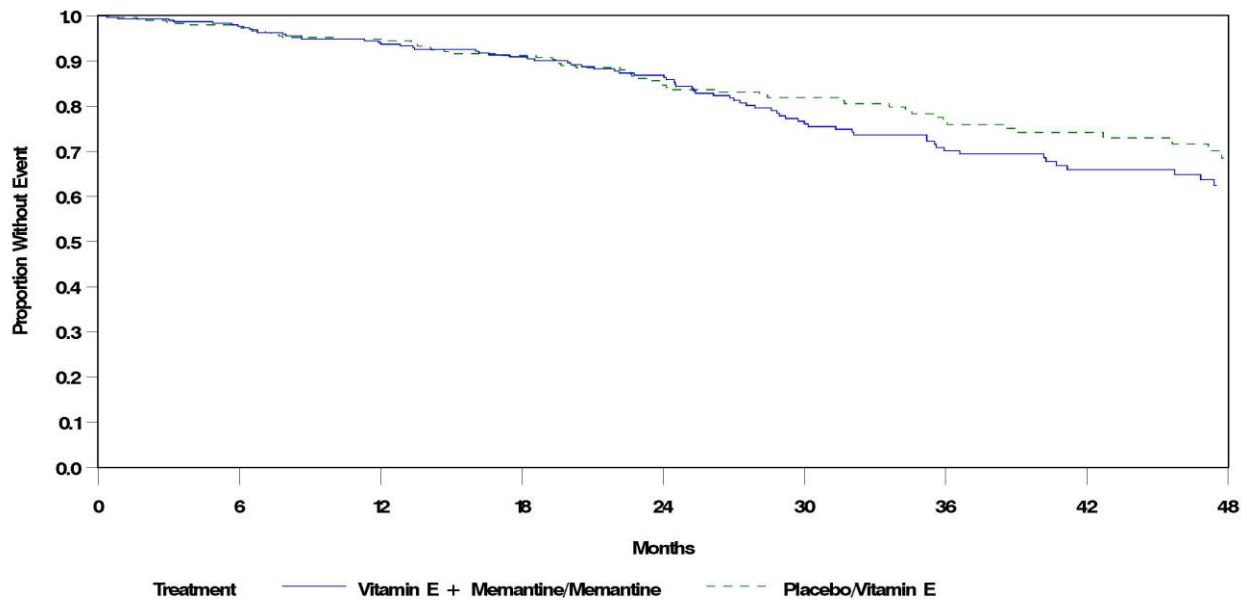
Vitamin E and Vitamin E + Memantine vs. Placebo and Memantine



| | | | | | | | | |
|---------------------------------|-----|-----|-----|-----|-----|-----|----|----|
| 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