Aricept

Aricept®

Donepezil HCl 5mg & 10mg Tablets

How to Maximize the Effectiveness of ARICEPT

Eisai Korea Inc.

Clinical features of AD

Age over 65 years

No gait difficulties till late stage

Insidious onset

AD

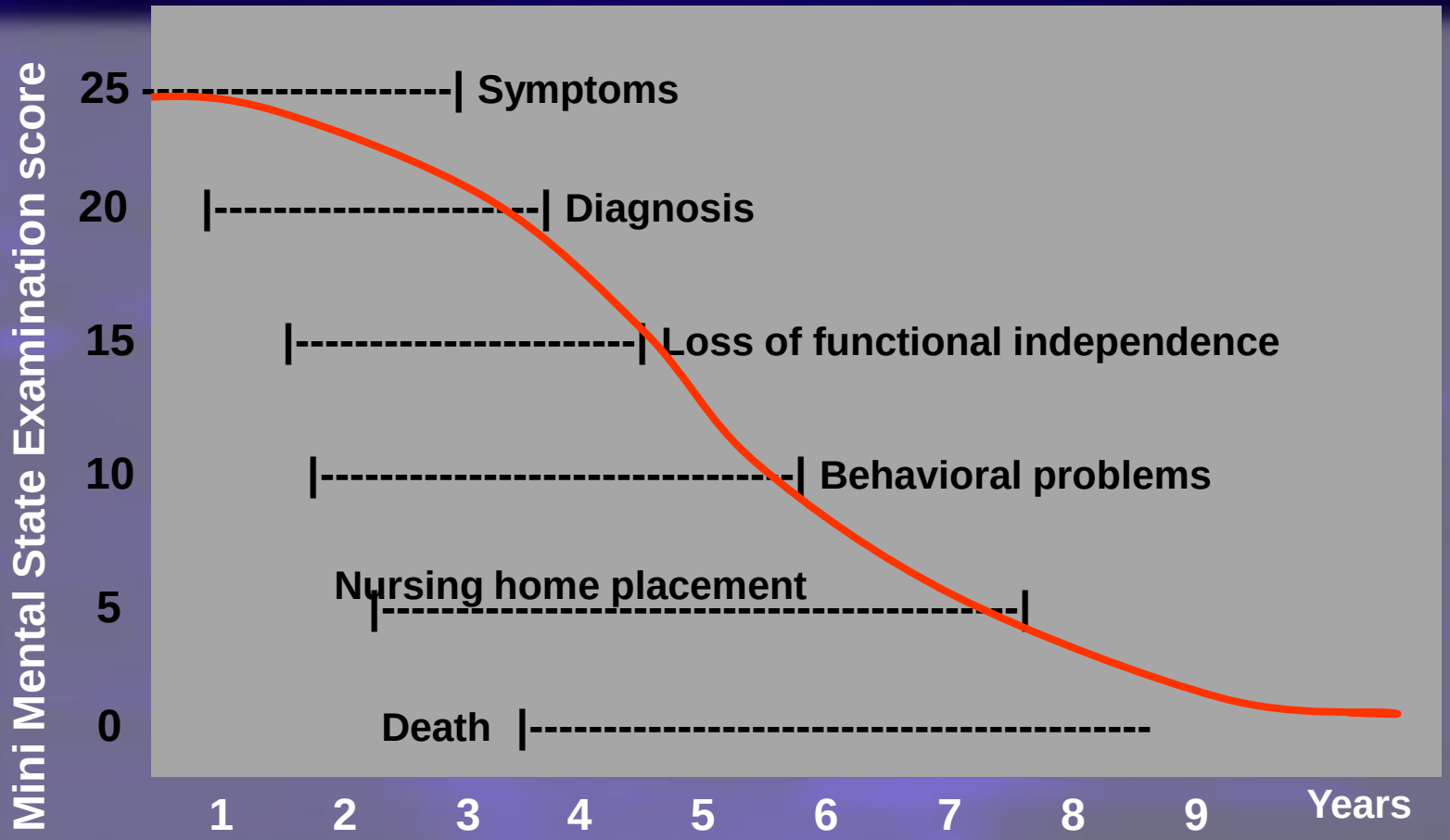
Behavioral signs
* Mood swings
* Agitation
* Wandering

Cognitive decline
* Memory loss
* Aphasia
* Apraxia
* Agnosia
* Executive dysfunction

Functional impairment
* IADL
* ADL

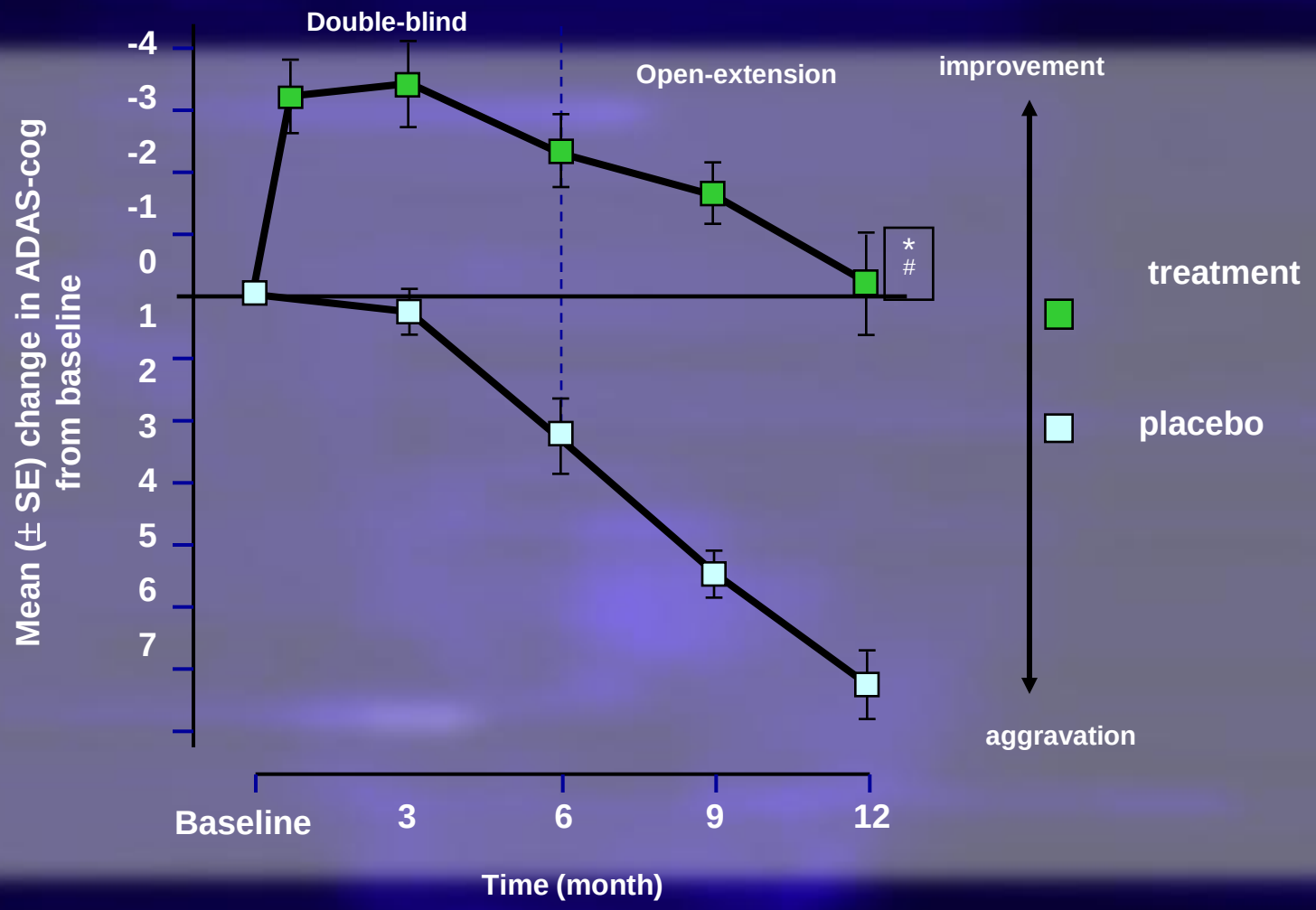
J Kor Med Assoc. 2002;45(4) : 356-360; JAMA. 1989;262(18):2251-6

Symptom Progression in AD



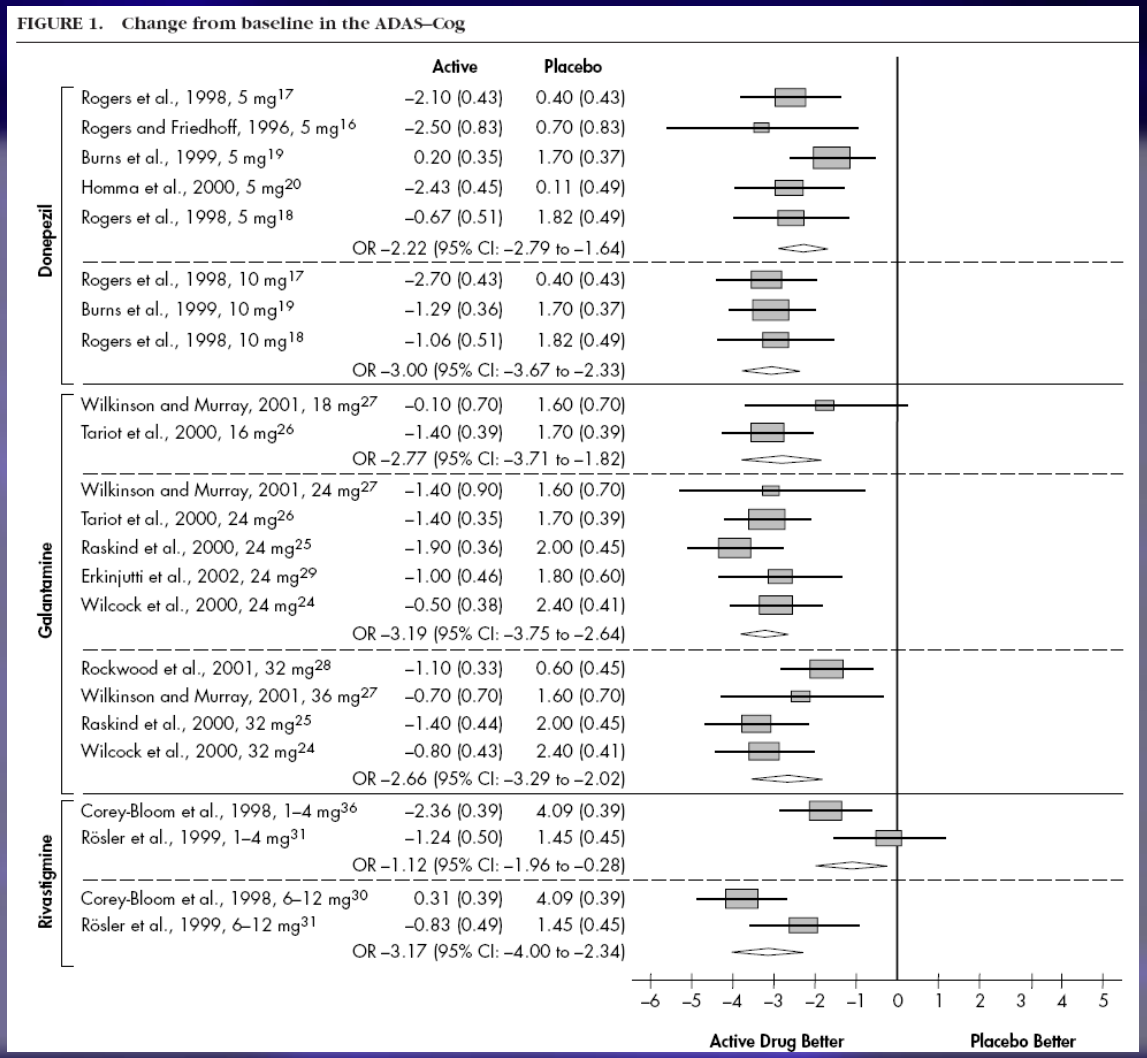
Feidman and Gracon, 1996

Effect of Cholinesterase Inhibitors



Effect of Short-Term Treatment

FIGURE 1. Change from baseline in the ADAS–Cog



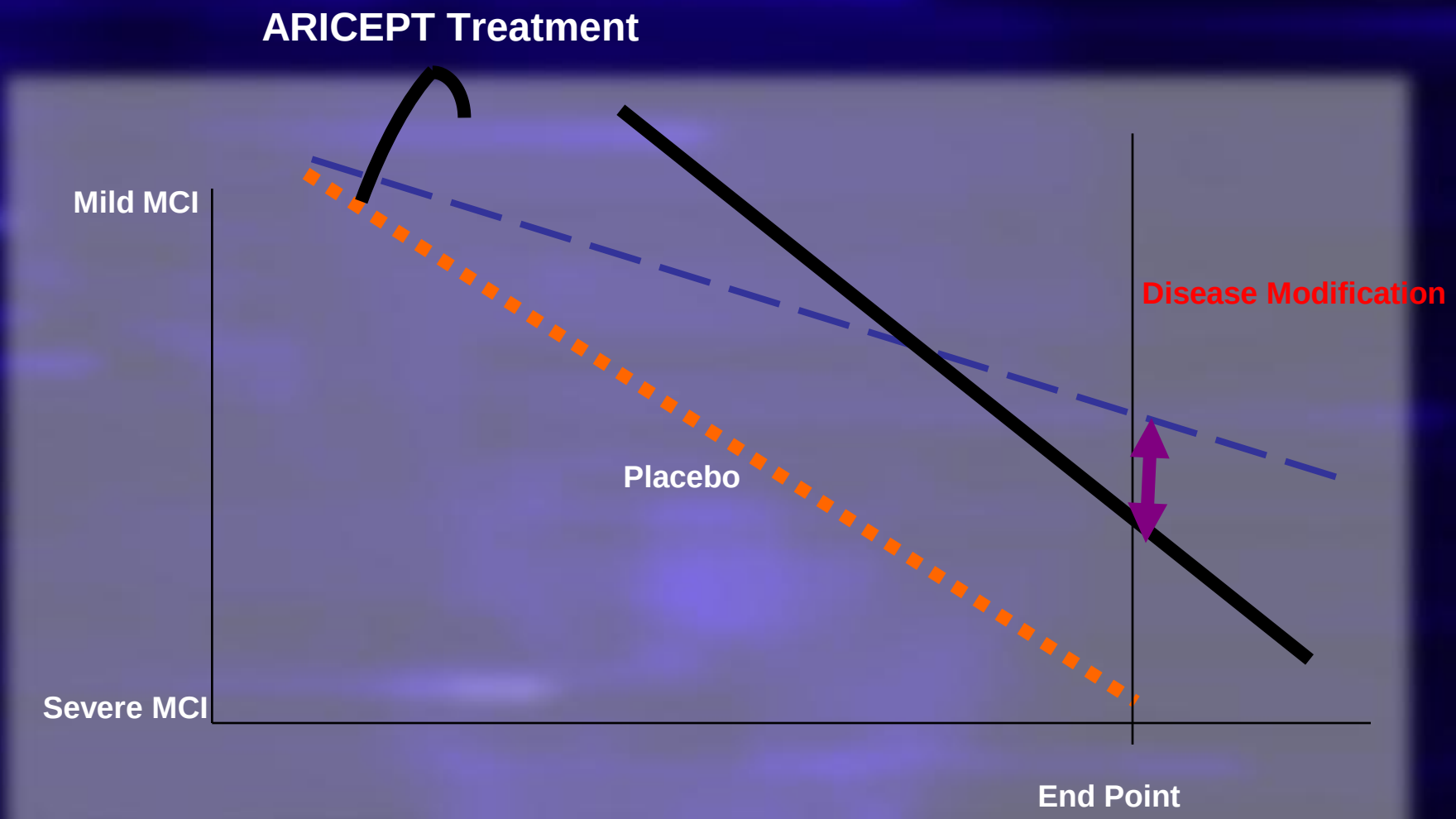
Riechie, Am J Geriatr Psychiatry 2004;12:358-369

Effect of long-Term Treatment

2-year data			
Doody et al. (19)	Donepezil (5–10 mg/day)	Open-label continuation of two placebo-controlled studies, total duration 144 weeks ($n = 763$)	ADAS-cog: declined by 10–12 points over 144 weeks
Grossberg et al. (10)	Rivastigmine (2–12 mg/day)	Meta-analysis of two open-label continuations of four placebo-controlled studies, total duration 104 weeks ($n = 2010$)	ADAS-cog: declined by 4–5 points less than predicted, had patients been left 'untreated
3-year data			
Klatte et al. (20)	Donepezil (5–10 mg/day) and vitamin E (1000 U/day)	Retrospective review of 130 patients over 3 years, compared with historical untreated patients	MMSE: 6.3-point decline over 3 years, compared with 9.1-point decline in the historical patients, indicating a slower cognitive decline in patients receiving donepezil and vitamin E
Raskind et al. (27)	Galantamine (24 mg/day)	Open-label continuation of two placebo-controlled studies, maximum total duration 36 months ($n = 194$)	ADAS-cog: mean change of 10.2 points compared with baseline (month 0); 50% less than that predicted for 'untreated' patients
4-year data			
Burns et al. (28)	Galantamine (24 mg/day)	Open-label continuation of two placebo-controlled studies, maximum total duration 48 months	ADAS-cog: mean annual decline approximately 50% less than that predicted for 'untreated' patients
5-year data			
Small et al. and Sano et al. (12,13)	Rivastigmine (2–12 mg/day)	Meta-analysis of two open-label continuations of four placebo-controlled studies, maximum total duration 260 weeks ($n = 2010$)	ADAS-cog: mean annual decline of 3.9 points; patients remaining on rivastigmine for 5 years declined by about 20 points less than predicted for model-based 'untreated' patients MMSE: mean annual decline of 1.7 points; patients remaining on rivastigmine for 5 years declined by 7 points less than predicted for model-based 'untreated' patients
Rogers et al. (24)	Donepezil (5–10 mg/day)	Open-label continuation of a placebo-controlled study, maximum total duration 254 weeks ($n = 133$)	ADAS-cog: mean annual decline of at least 6 points; similar to expected placebo decline of 7 points per year

Bullock, Int J Clin Pract, 2005, 59, 817–822

ARICEPT for slow progression of AD



Primary Prevention
Identification of High-Risk Individuals
Prevention of progression

Secondary Prevention
Early Identification
Early tx

Treatment
Minimize Disability
Treat Symptoms

Normal	Pre-Symptomatic AD	Mild Cognitive Impairment	Alzheimer Disease
No Pathology, No Symptoms	*Early Pathology, No Symptoms*	*AD Pathology, Amnesia*	*Extreme Pathology, Cognitive Impairment*

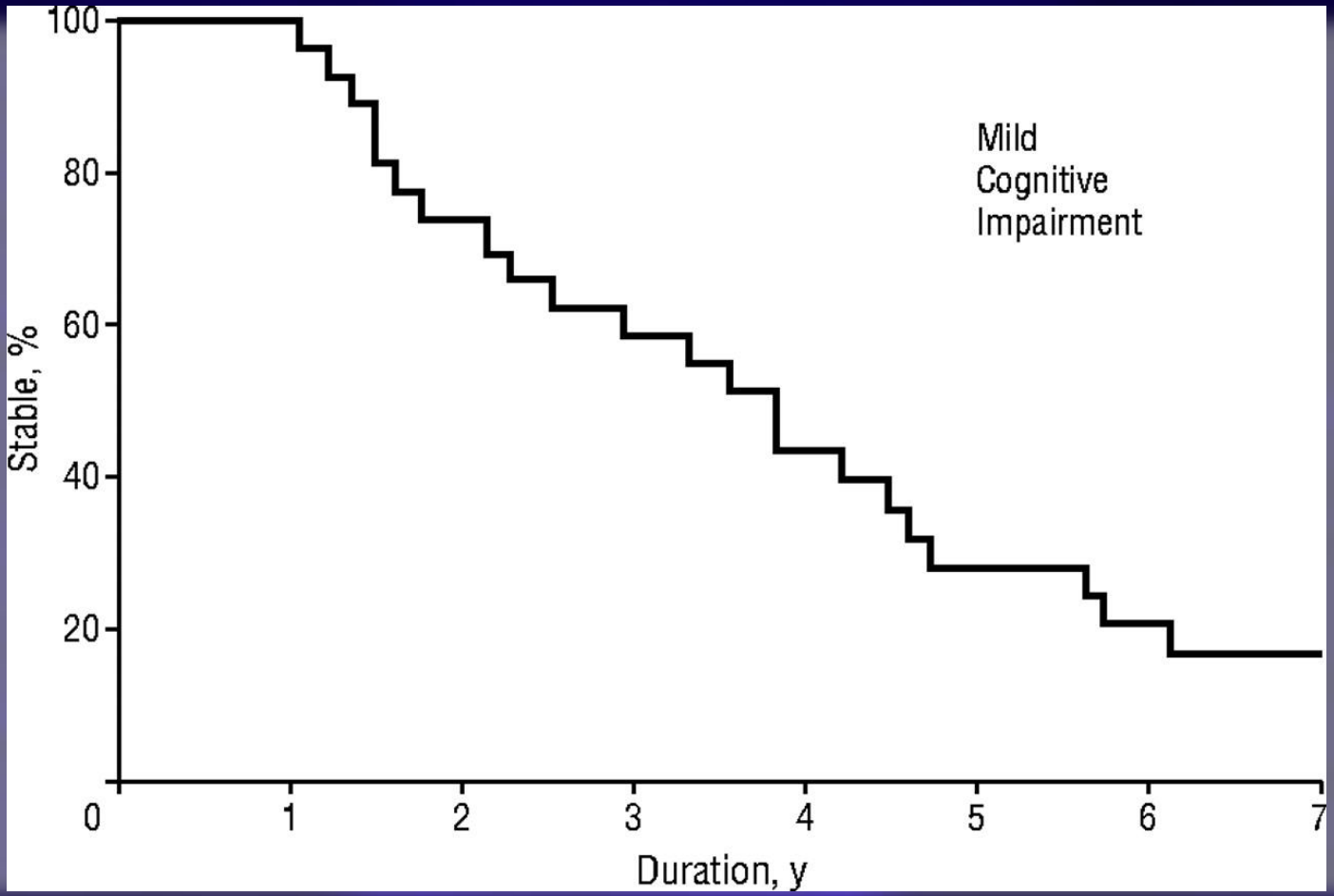
Disease Progression

Working Criteria for Mild Cognitive Impairment

- Subjective memory complaint and objective memory deficit
  (ie, delayed recall >1.5 SD below age and education norms)
- Preserved general cognitive ability (Mini-Mental State Examination [MMSE] ≥24)
- Intact activities of daily living (ADL)
- Not demented (Clinical Dementia Rating [CDR] 0.5)
- MCI may be regarded as incipient or prodromal Alzheimer's disease (AD)
- Patients with MCI progress to AD at a higher annual rate (10% to 15%) than normal elderly patients (1% to 2%)

Petersen RC et al. *The Neurologist.* 1995;1:326-344. Petersen RC et al. *Arch Neurol.* 2001;58:1985-1992. Grundman M, Petersen R. *Neurology*. 1996;46:A403. Flicker C et al. *Neurology*. 1991;41:1006-1009. Petersen RC et al. *JAMA*. 1995;273:1274-1278.

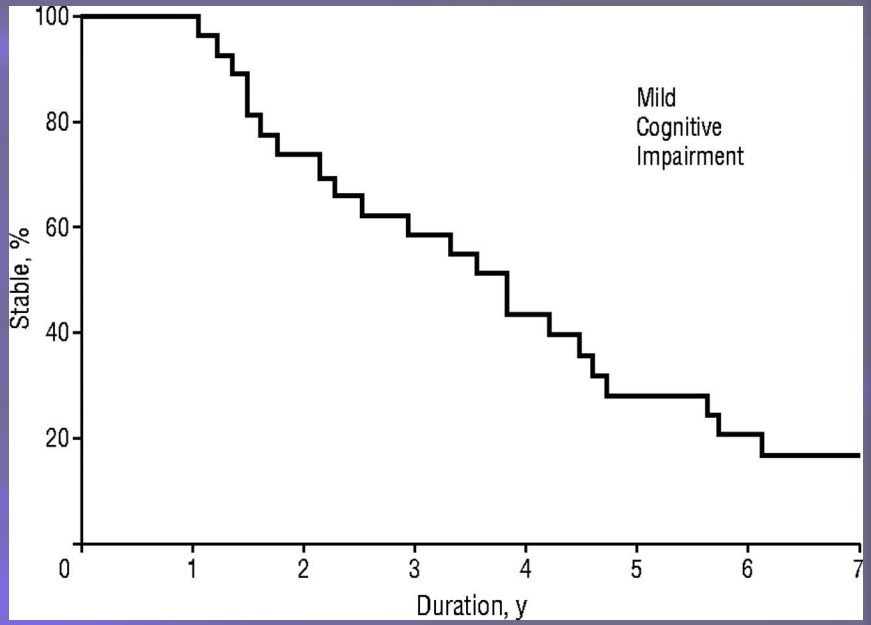
Survival curve of persons characterized as having a mild cognitive impairment for 6 years



Petersen, R. C. et al. Arch Neurol 2001;58:1985-1992.

Progression of MCI to AD

- ***10-15 % per year*** **by Petersen**
- ***26 % over two year*** **by Nordberg**
- ***50 % conversion to AD within 3-4 year*** **by Hanninen**



ARICEPT for Mild Cognitive Impairment

The NEW ENGLAND JOURNAL of MEDICINE

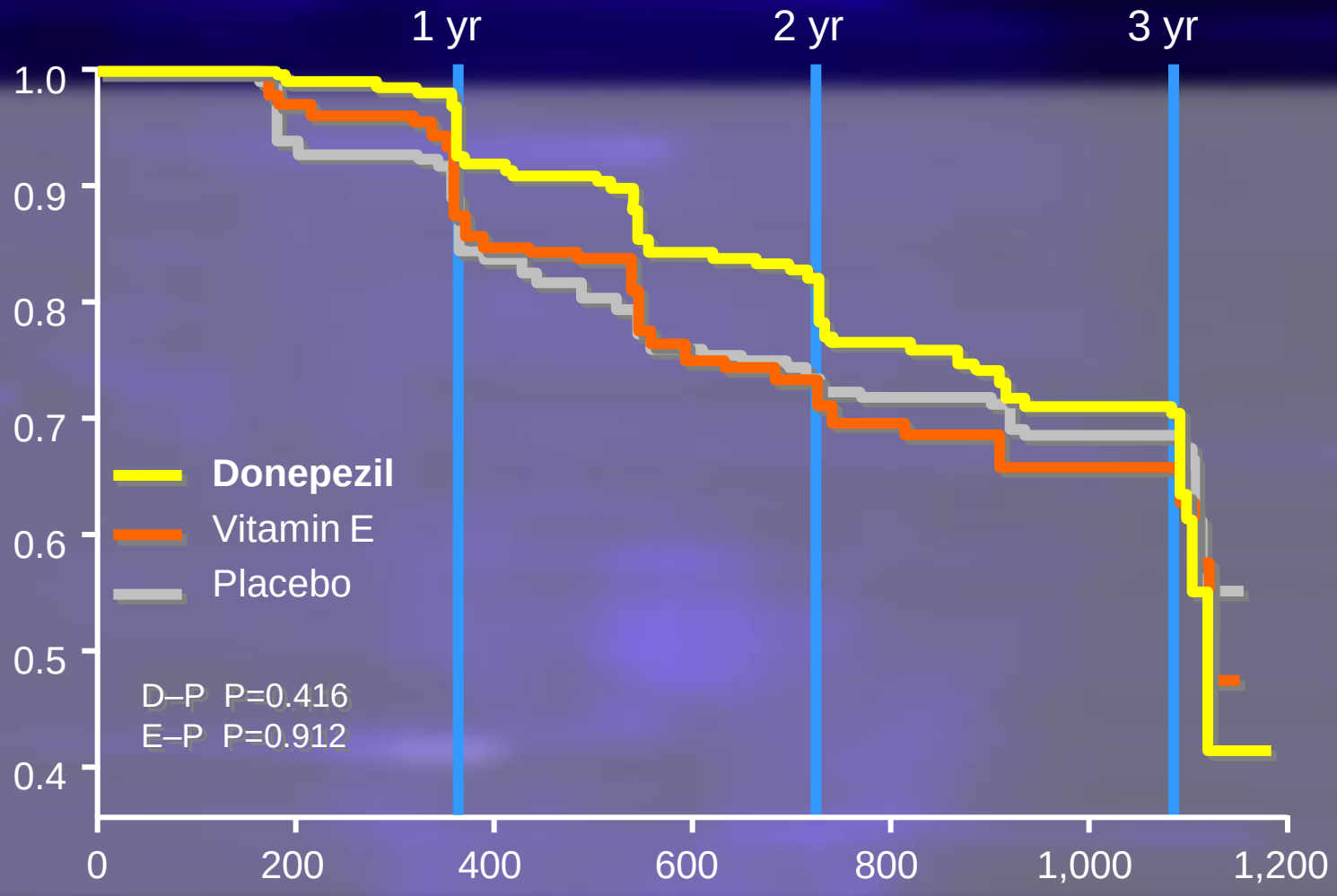
ESTABLISHED IN 1812 JUNE 9, 2005 VOL. 352 NO. 23

Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment

- *Design*: 3 years, randomized, multicenter, randomized, double-blind, placebo-controlled, parallel study

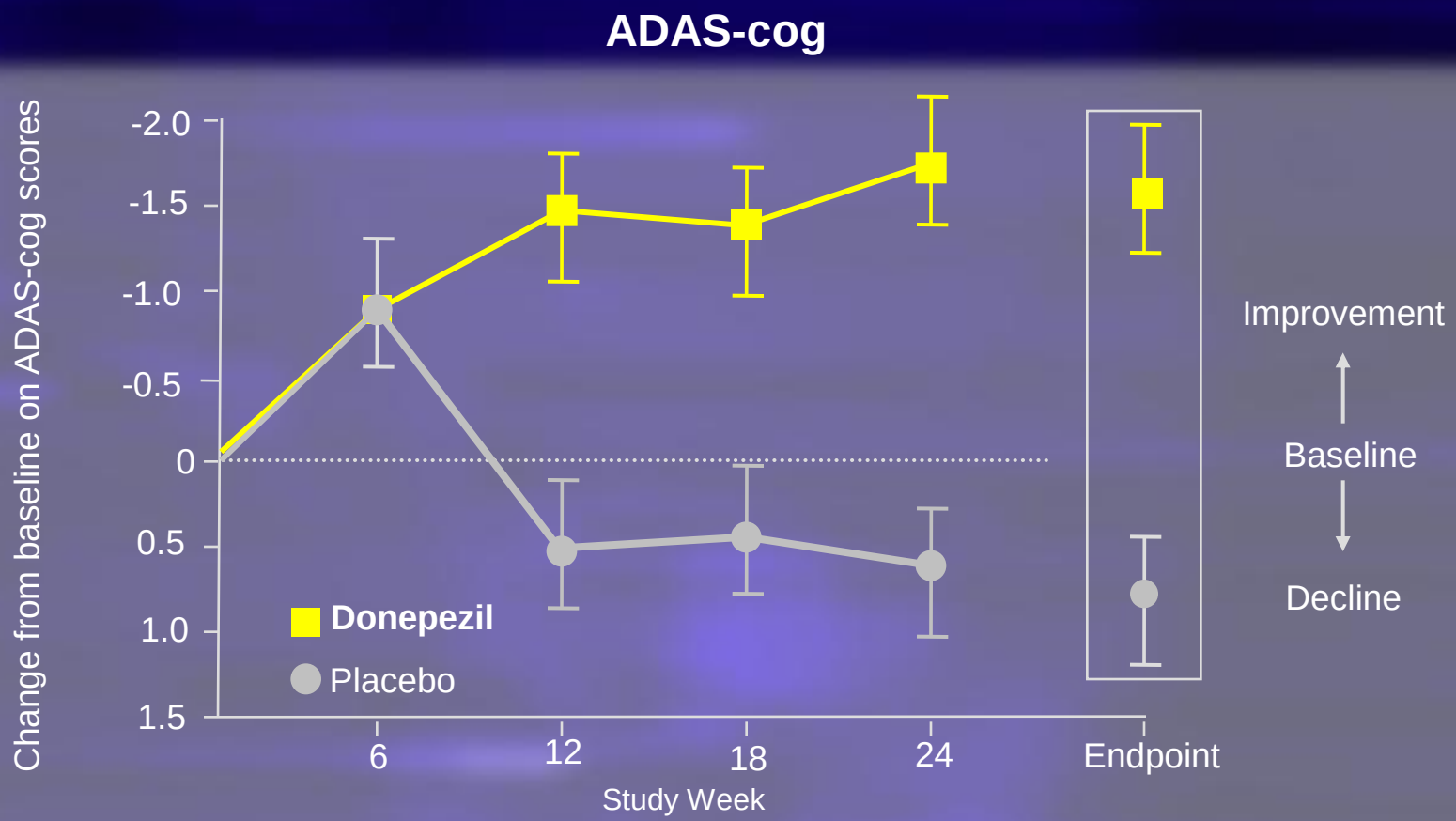
  (→ Open-label donepezil after conversion to AD)

ARICEPT delays conversion to dementia



N Eng J Med 352;23

Result of Early AD study (1)

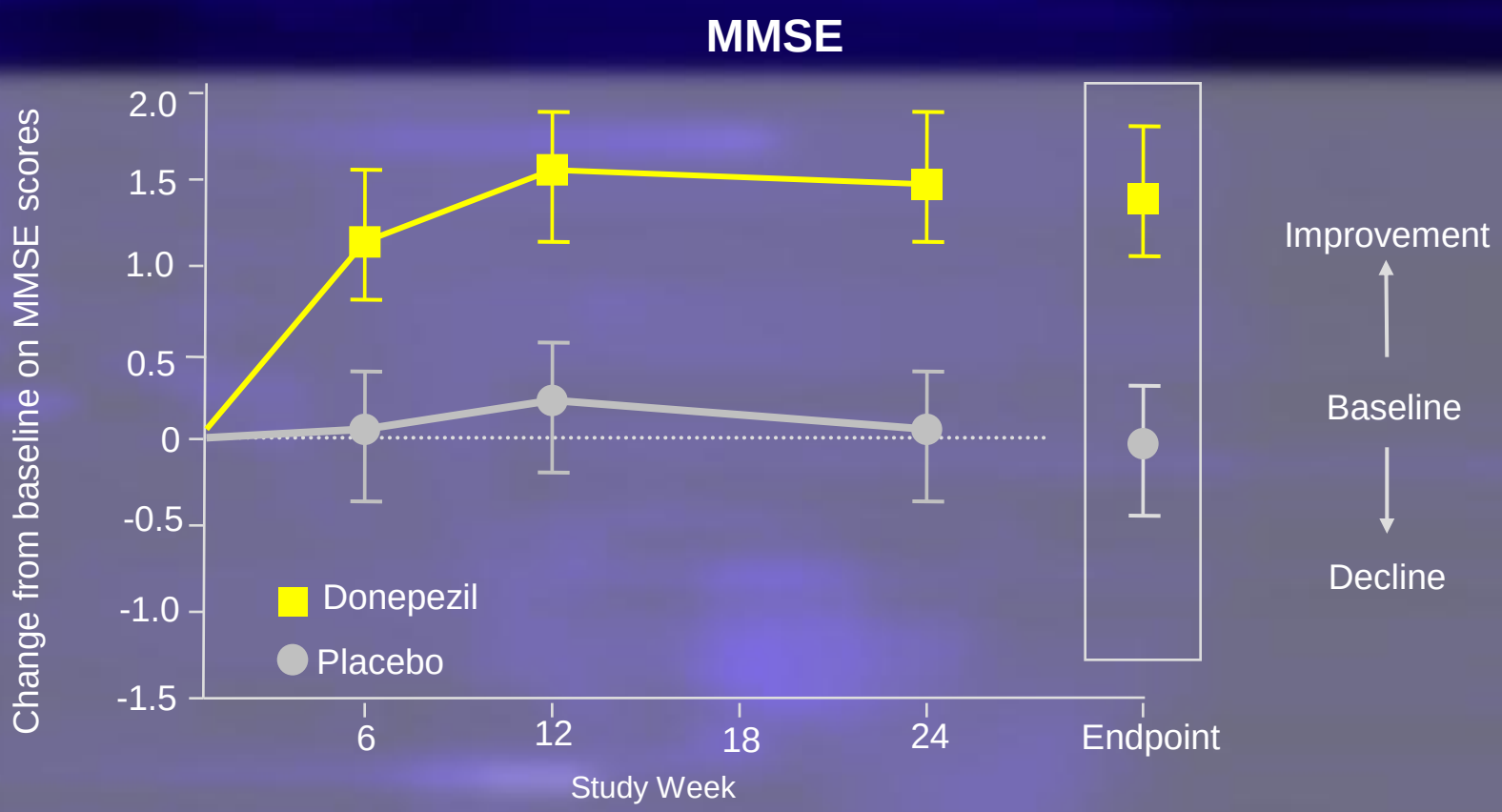


*Improvement ≥4 points : 16% placebo, 37% donepezil

*Improvement ≥7 points : 7% placebo, 10% donepezil

Arch Neurol. 2004;61:1852-1856

Result of Early AD study (2)



*** Improvements from week 6 (P=.02) through week 24 (P=.03)**

*** Difference 1.8 points (P = .002) at the end point**

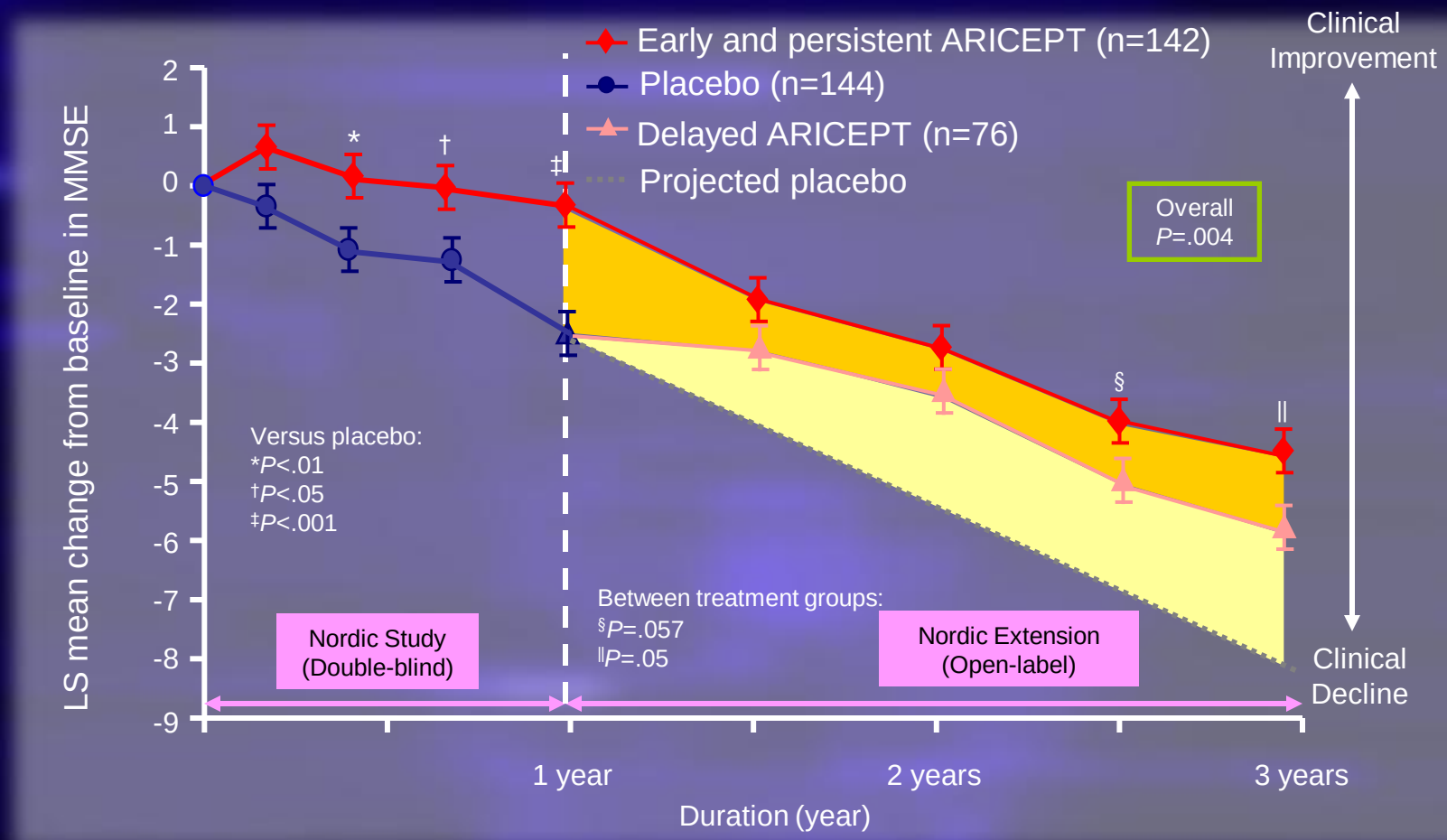
Arch Neurol. 2004;61:1852-1856

Effect of Early and continuous ARICEPT

3-Year Study of Donepezil Therapy in Alzheimer's Disease: Effects of Early and Continuous Therapy

B. Winblad[a] A. Wimo[b] K. Engedal[c] H. Soininen[d] F. Verhey[e]
G. Waldemar[f] A.-L. Wetterholm[g] A. Haglund[g] R. Zhang[h] R. Schindler[h]
for the Donepezil Nordic Study Group

Benefit of early and persistent treatment

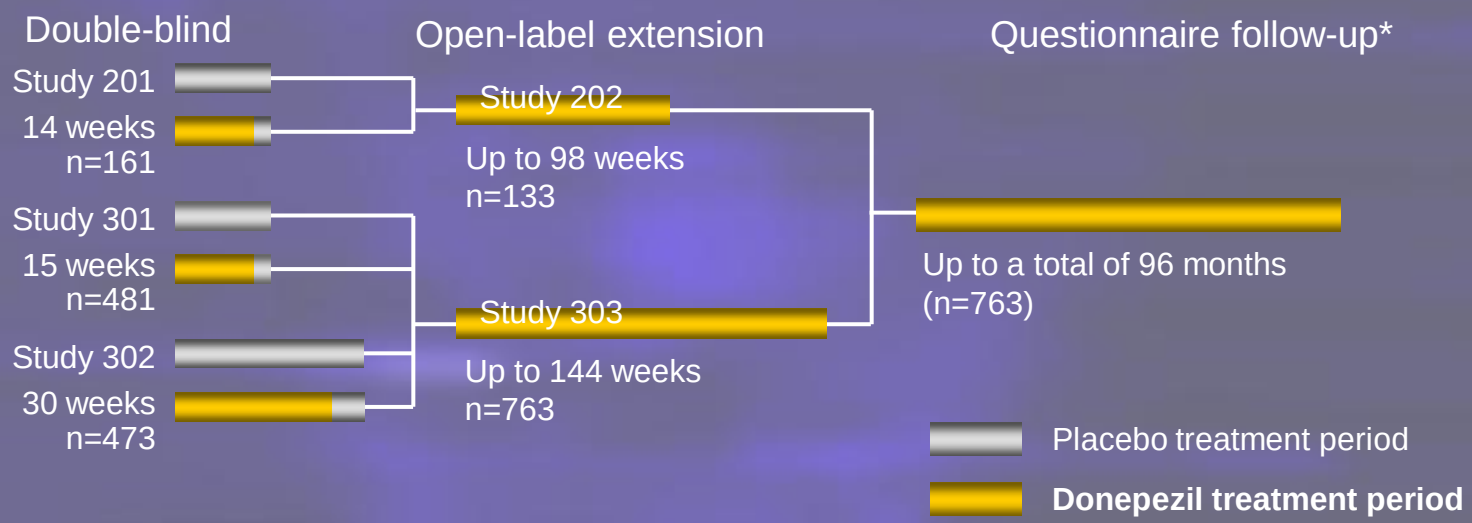


Neurology. 2001;57:489-495

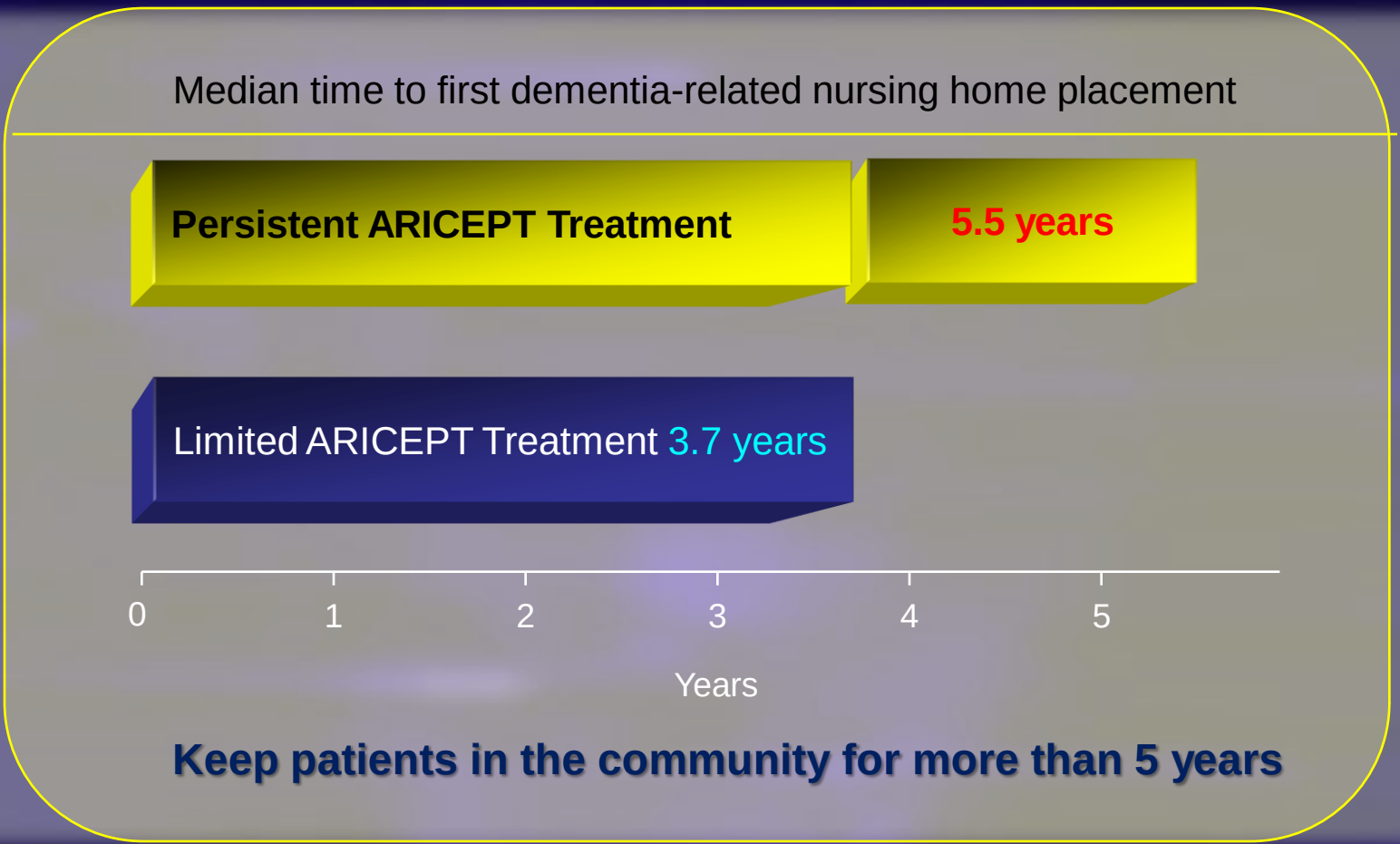
Efficacy of ARICEPT for DNHP

Donepezil Is Associated with Delayed Nursing Home Placement in Patients with Alzheimer's Disease

David S. Geldmacher, MD,[*†] *George Provenzano, PhD,*[‡] *Thomas McRae, MD,*[§] *Vera Mastey, MS,*[‖] *and John R. Ieni, PhD*[¶]



ARICEPT delayed 2 year to NHP



Geldmacher DS et al. J Am Geriatr Soc. 2003;51:937-944

Long-term efficacy of ARICEPT

ELSEVIER

European Neuropsychopharmacology 10 (2000) 195–203

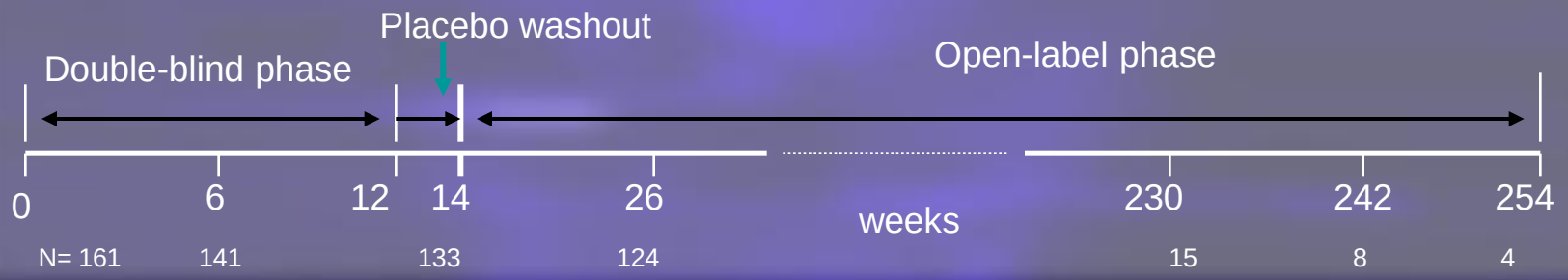
EUROPEAN NEURO-PSYCHOPHARMACOLOGY

www.elsevier.com/locate/euroneuro

Long-term efficacy and safety of donepezil in the treatment of Alzheimer's disease: final analysis of a US multicentre open-label study

S.L. Rogers[a,*], R.S. Doody[b], R.D. Pratt[c], J.R. Ieni[c]

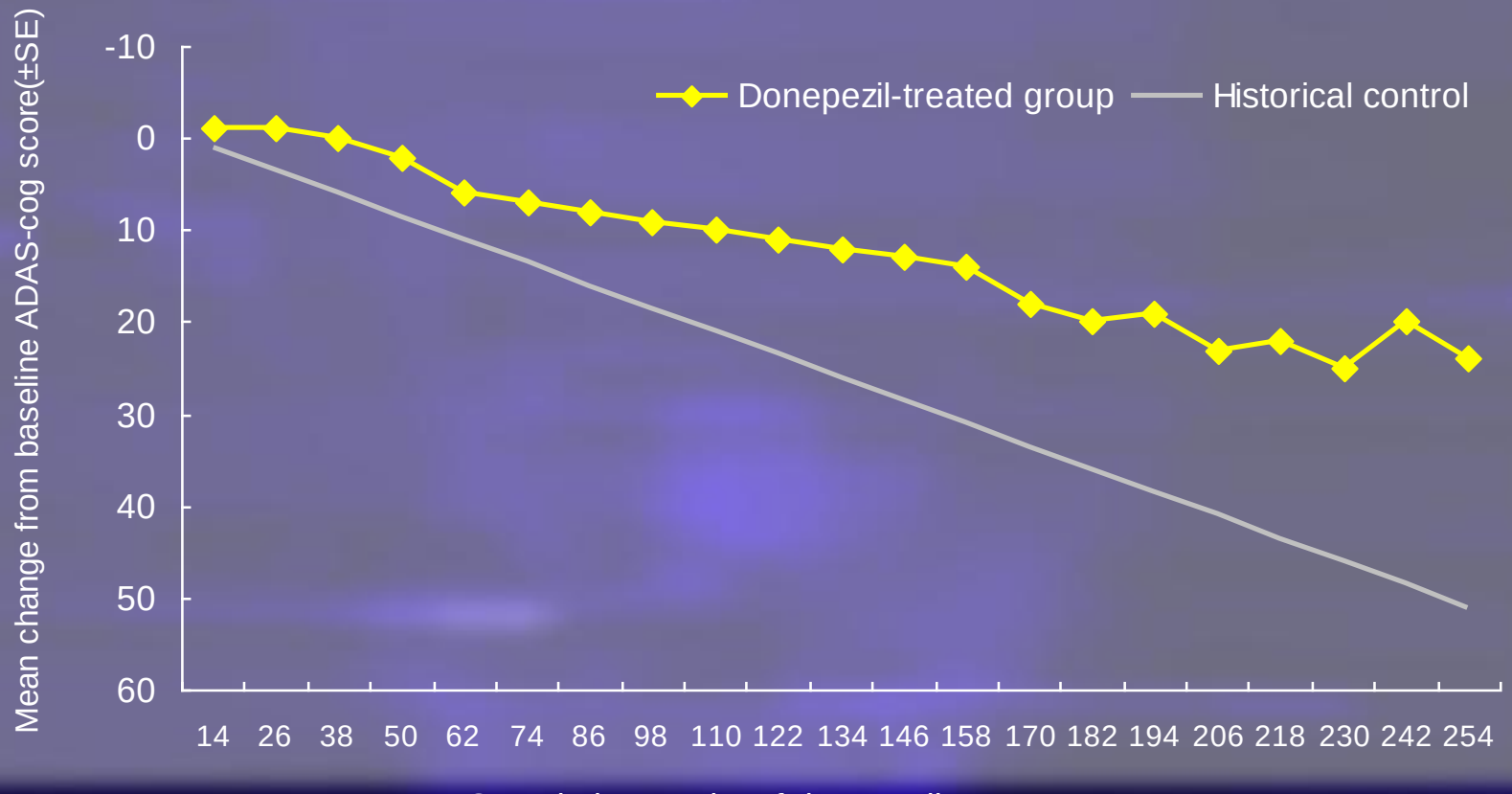
- *Design*: for up to cumulative 254 weeks *(4.9 years)*



Result of long-term efficacy of ARICEPT

ADAS-cog

→ *over 254 cumulative weeks*



Galantamine for AD and MCI

- Preliminary results of two 2-year, randomized, placebo-controlled trials of galantamine in a total of 2048 patients indicated **no significant differences in the rate of progression from MCI to AD**

Cochrane DatabaseSyst *Rev.* 2006; 1 :CD001747. Loy C, Schneider L

Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the InDDEx study

Howard H Feldman, Steven Ferris, Bengt Winblad, Nikolaos Sfikas, Linda Mancione, Yunsheng He, Sibel Tekin, Alistair Burns, Jeffrey Cummings, Teodoro del Ser, Domenico Inzitari, Jean-Marc Orgogozo, Heinrich Sauer, Philip Scheltens, Elio Scarpini, Nathan Herrmann, Martin Farlow, Steven Potkin, H Cecil Charles, Nick C Fox, Roger Lane

Summary

Objective To assess the effect of rivastigmine in patients with mild cognitive impairment (MCI) on the time to clinical diagnosis of Alzheimer's disease (AD) and the rate of cognitive decline.

Methods The study was a double-blind, randomised, placebo-controlled trial of up to 48 months. All patients had MCI operationally defined by having cognitive symptoms, a global clinical dementia rating stage of 0·5, a score of less than 9 on the New York University delayed paragraph recall test, and by not meeting the diagnostic criteria for AD. Primary efficacy variables were time to clinical diagnosis of AD, and change in performance on a cognitive test battery. This study is registered with the US National Institutes of Health clinical trials database (ClinicalTrials.gov), number NCT00000174.

Findings Of 1018 study patients enrolled, 508 were randomly assigned to rivastigmine and 510 to placebo; 17·3% of patients on rivastigmine and 21·4% on placebo progressed to AD (hazard ratio 0·85 [95% CI 0·64–1·12]; p=0·225). There was no significant difference between the rivastigmine and placebo groups on the standardised *Z* score for the cognitive test battery measured as mean change from baseline to endpoint (–0·10 [95% CI –0·63 to 0·44], p=0·726). Serious adverse events were reported by 141 (27·9%) rivastigmine-treated patients and 155 (30·5%) patients on placebo; adverse events of all types were reported by 483 (95·6%) rivastigmine-treated patients and 472 (92·7%) placebo-treated patients. The predominant adverse events were cholinergic: the frequencies of nausea, vomiting, diarrhoea, and dizziness were two to four times higher in the rivastigmine group than in the placebo group.

Interpretation There was no significant benefit of rivastigmine on the progression rate to AD or on cognitive function over 4 years. The overall rate of progression from MCI to AD in this randomised clinical trial was much lower than predicted. Rivastigmine treatment was not associated with any significant safety concerns.

Lancet Neurol 2007; 6: 501–12

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See Reflection and Reaction page 473

See In Context page 482

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