



**Problems with dementia
trial designs:
experience from AD2000***

**Richard Gray, University of Birmingham
Clinical Trials Unit**

***AD2000 Collaborative Group**

Lancet 2004; 363; 2105-15

www.bctu.bham.ac.uk

AD2000 findings on donepezil*

- Small but definite improvement in tests of mental ability (MMSE) as in previous trials
- Small but definite improvement in functional ability (sustained to two years)
- No measurable effect on behaviour, caregiver well-being, progress of disability, health resource usage or institutionalisation
- No predictors of better response identified

* AD2000, Lancet 2004; 363: 2010-15

AD2000 addressed the unanswered research needs identified by Cochrane reviews *

- trials of longer duration including:
- more typical clinical populations
- effects on ADLs and measures of problematic behaviour
- dependency and effects on carers
- caregiver burden linked to economic analyses

* Cochrane Library, Issue 2, 2002; see also www.nice.org.uk

AD2000: pragmatic, 'real life' trial assessing clinically relevant outcome measures

- **Function:**
 - Bristol Activities of Daily Living Scale (**BADLS**)
- **Behaviour/psychological symptoms:**
 - Neuropsychiatric Inventory (**NPI**)
- **Carer well-being:**
 - General Health Questionnaire-30 (**GHQ-30**)
- **Cognition:**
 - Mini-Mental State Examination (**MMSE**)
- **Carer time input and health resource usage**
- **Institutionalisation and Death**

Practical considerations

- Factorial design (donepezil and aspirin)
- Wide entry criteria
- Streamline procedures
- Maximise compliance and follow-up

Rationale for wide eligibility

- either the relative efficacy will turn out to be the same in different diagnostic subgroups, in which case the trial should include PPD, LBD and AD
- or it will be different, in which case it is particularly important to include all subgroups to allow examination of heterogeneity in treatment response
- for same reason include mild, moderate and severe dementias

Avoiding bias in assessing effectiveness of treatments for dementia

- Randomised treatment allocation to avoid 'selection bias'
- Placebo control to avoid 'ascertainment bias'
- Complete as possible follow-up to avoid 'drop-out' bias

Problems with some economic assessments in dementia

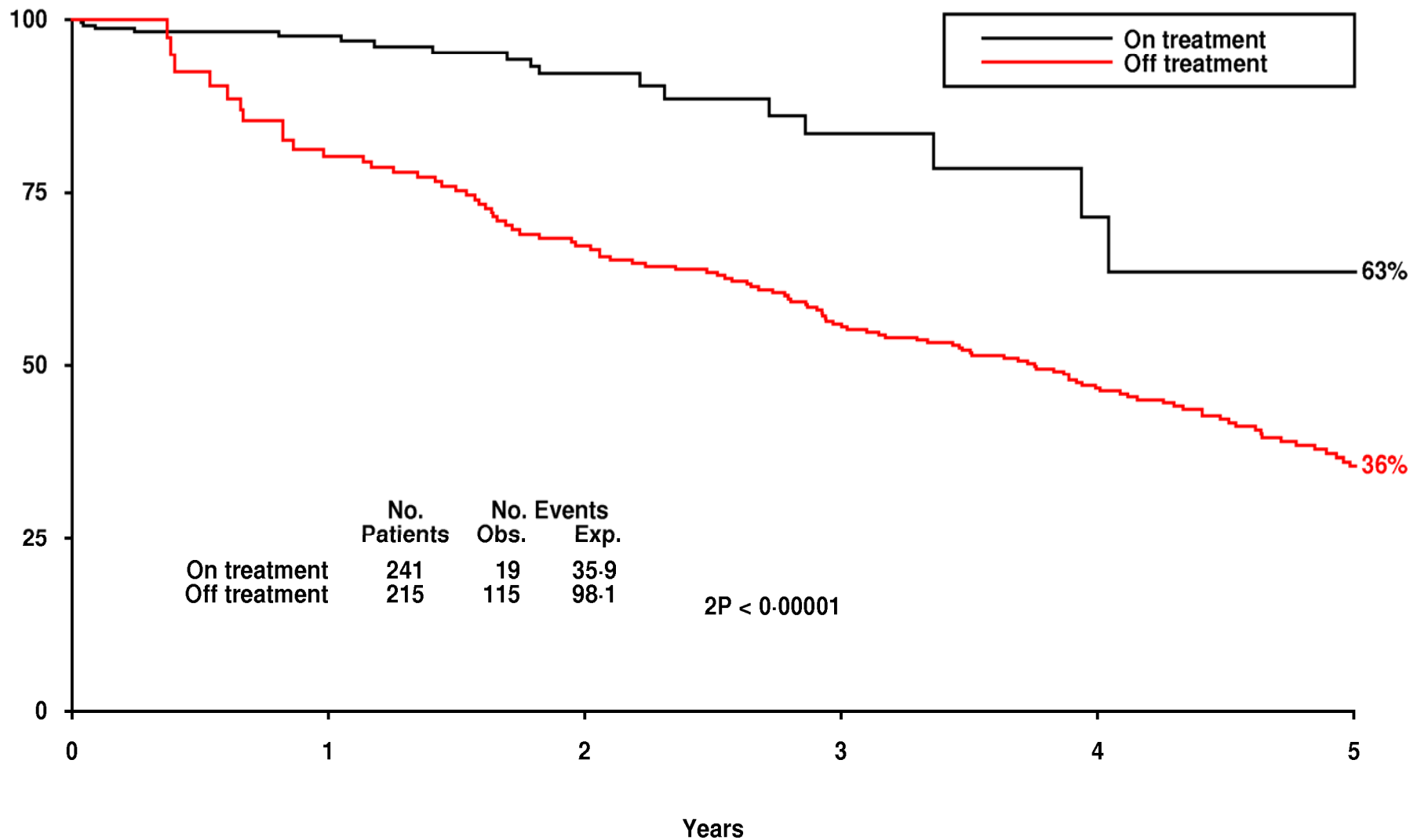
- **Some are based on non-randomised (i.e. unreliable) observational studies** (e.g. Geldmacher et al 2003)
- **Treatment efficacy may be exaggerated because of non-random drop-outs** (in 6 of 14 published studies, there were statistically significantly more active treatment than placebo drop-outs*)
- **Assuming that change in cognitive scores equates to lower costs** (it doesn't)

* Abstract 338, 8th Int Conf on AD, Stockholm 2002

Some are based on non-randomised (i.e. unreliable) observational studies

- Geldmacher et al (2003) reported that nursing home placement was delayed by 2 years in those who continued donepezil in an open label extension trial compared to those who did not
- This was due to 'selection bias' – those who opted to continue were healthier

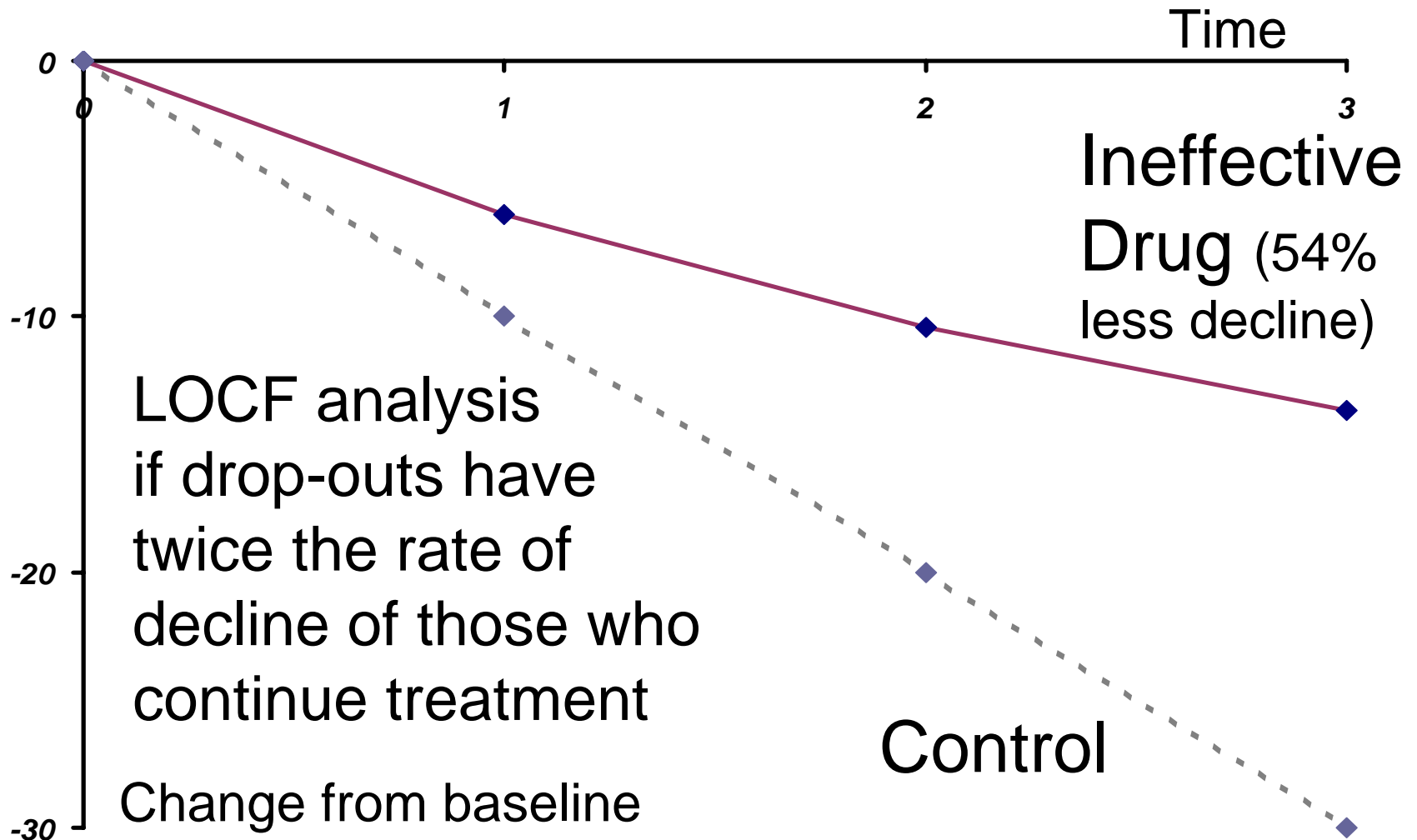
AD2000: Survival from 12 weeks on and off treatment (Mantel-Byar) Donepezil



Two types of non-random dropout in Alzheimer's studies:

- Treatment-related dropout (active treatment patients more likely to drop out for toxicity than placebo patients)**
- Outcome-related dropout (patients for whom treatment does not appear to be working more likely to drop out)**
- Both exaggerate treatment efficacy**

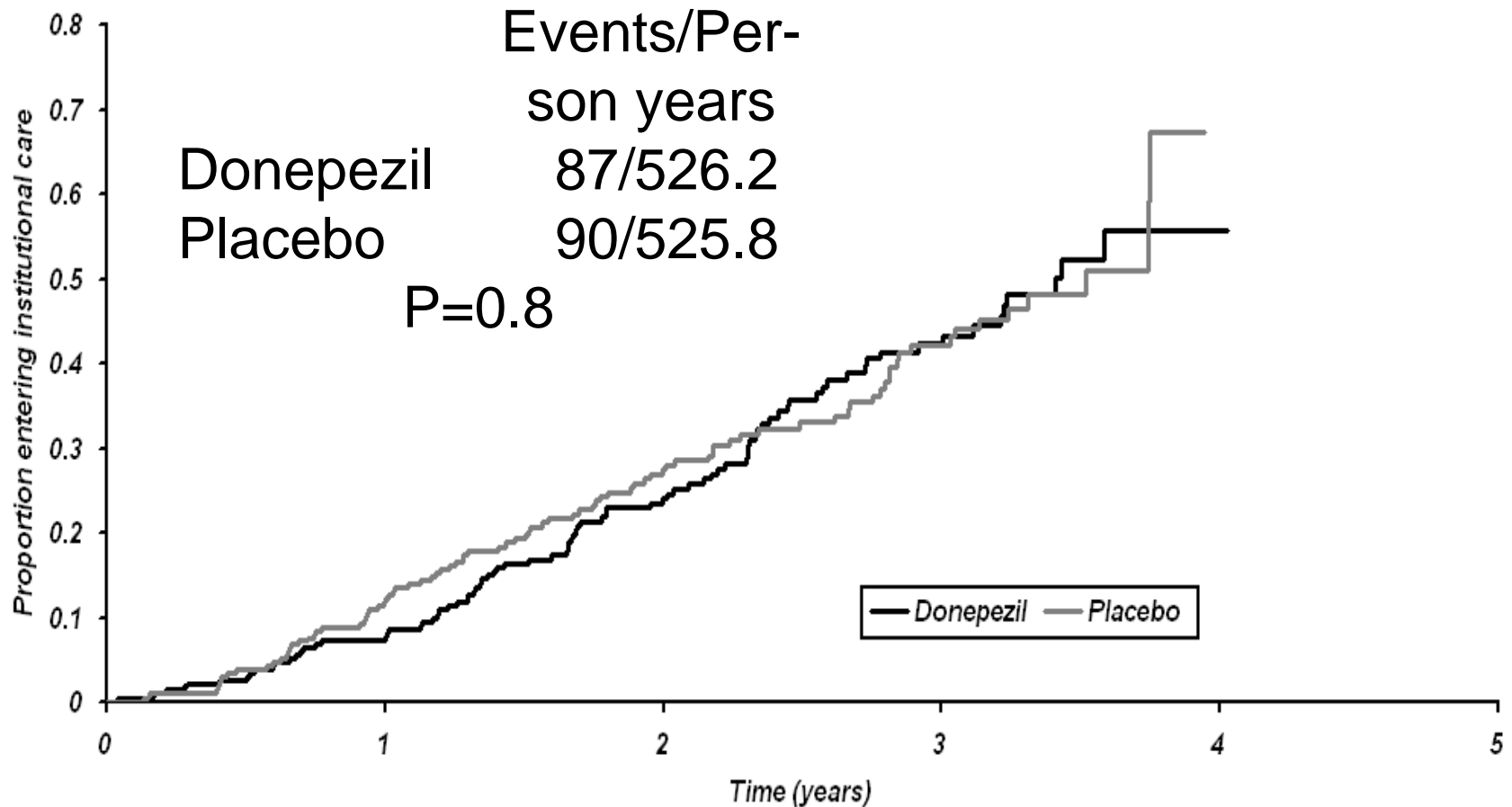
Bias is likely to be substantial given typical reported drop-out rates



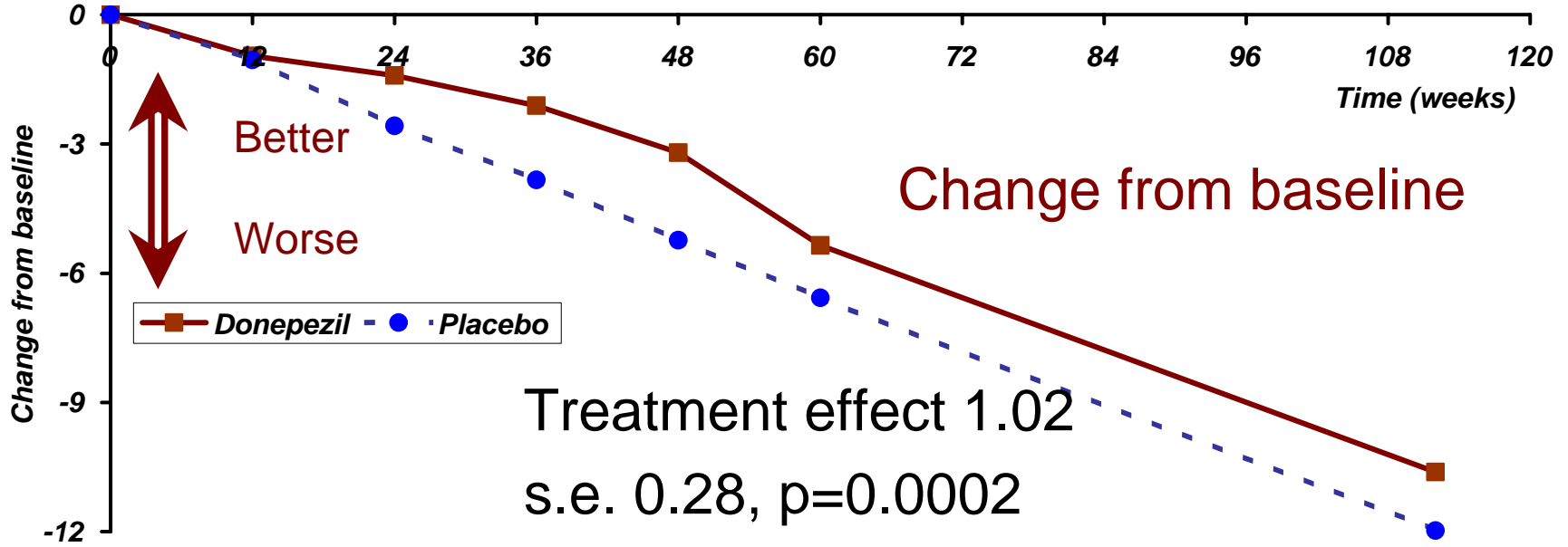
AD2000 trial design: randomised run-in to minimise potential for 'drop-out bias'

- 'Run-in' treatment is given for 12 weeks prior to the randomisation to long-term donepezil/placebo to screen out non-compliant patients.
- Follow-up of all patients irrespective of treatment compliance

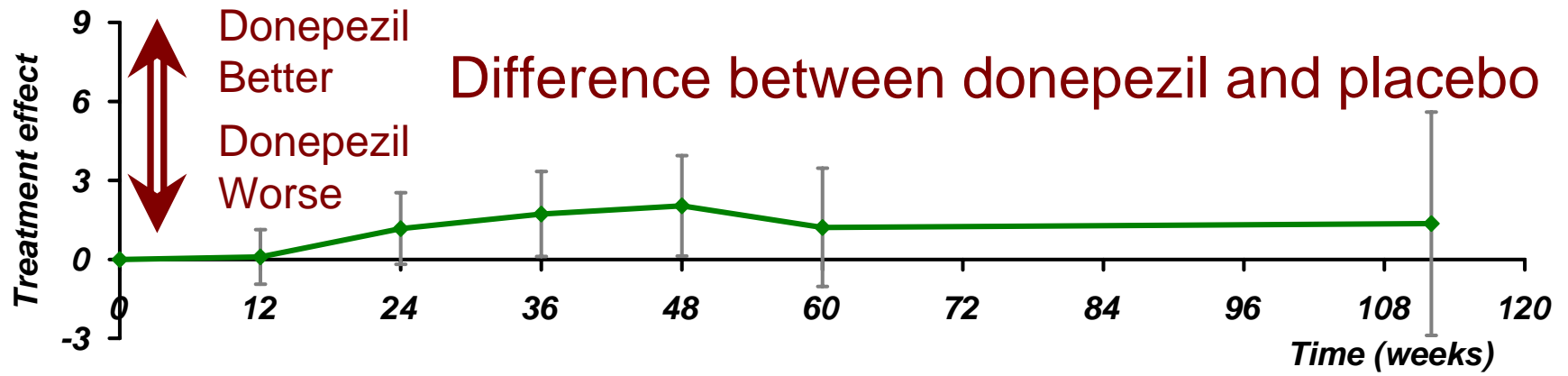
Entry to institutional care by allocated treatment



Effect of donepezil on functional ability (as measured by Bristol ADL Score)

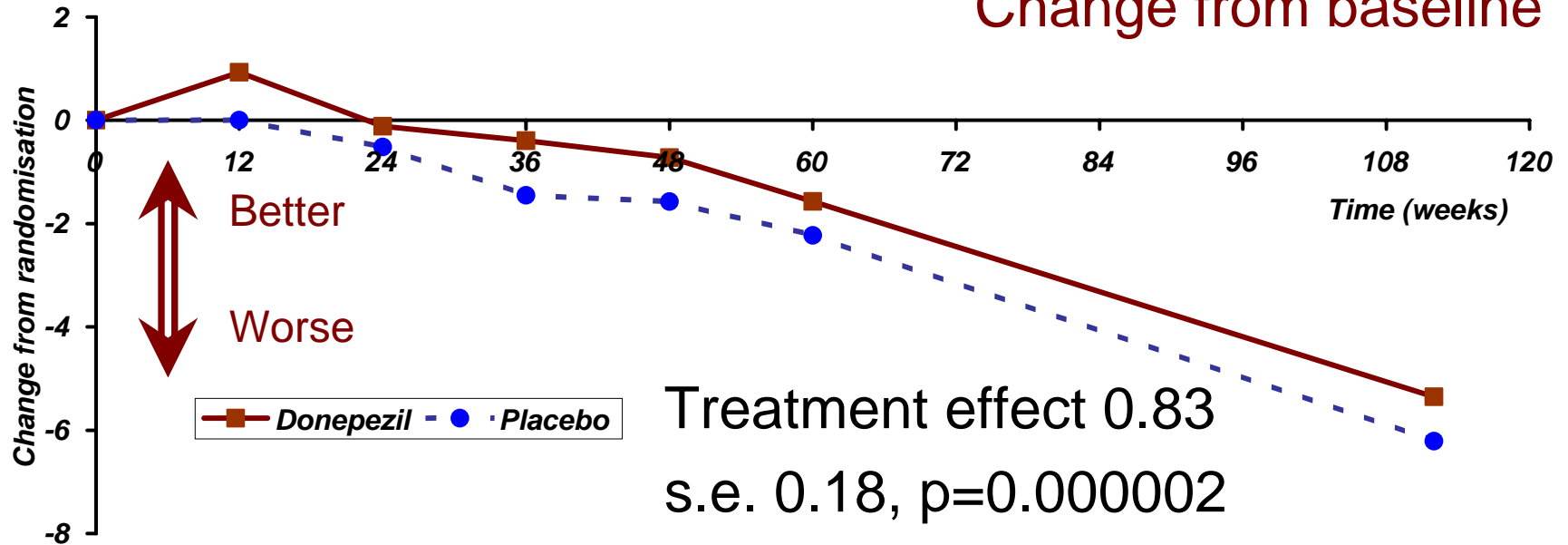


Don:	282	262	220	182	162	157	81
Plac:	283	269	230	185	162	150	74

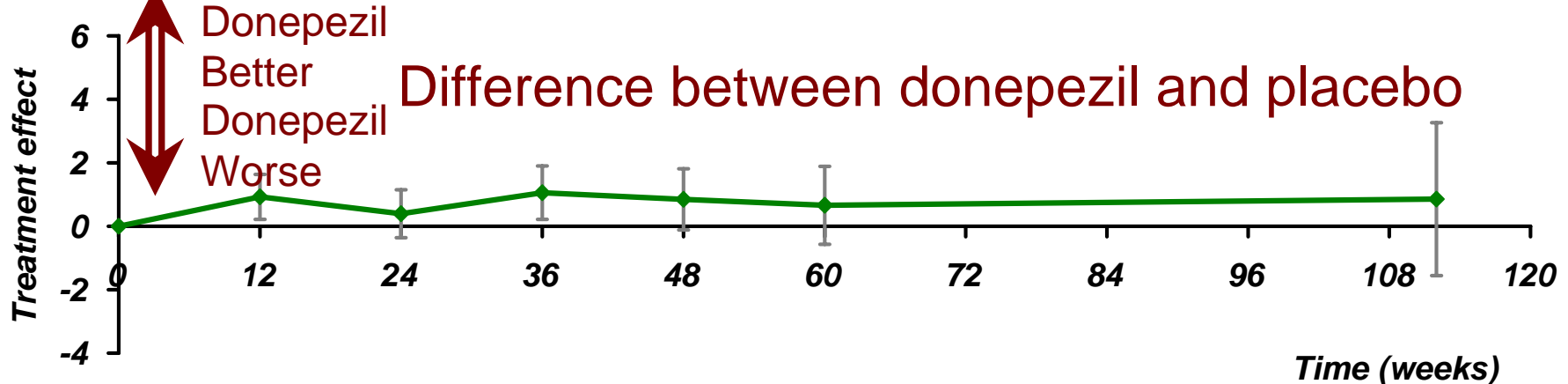


Effect of donepezil on test of mental ability (MMSE)

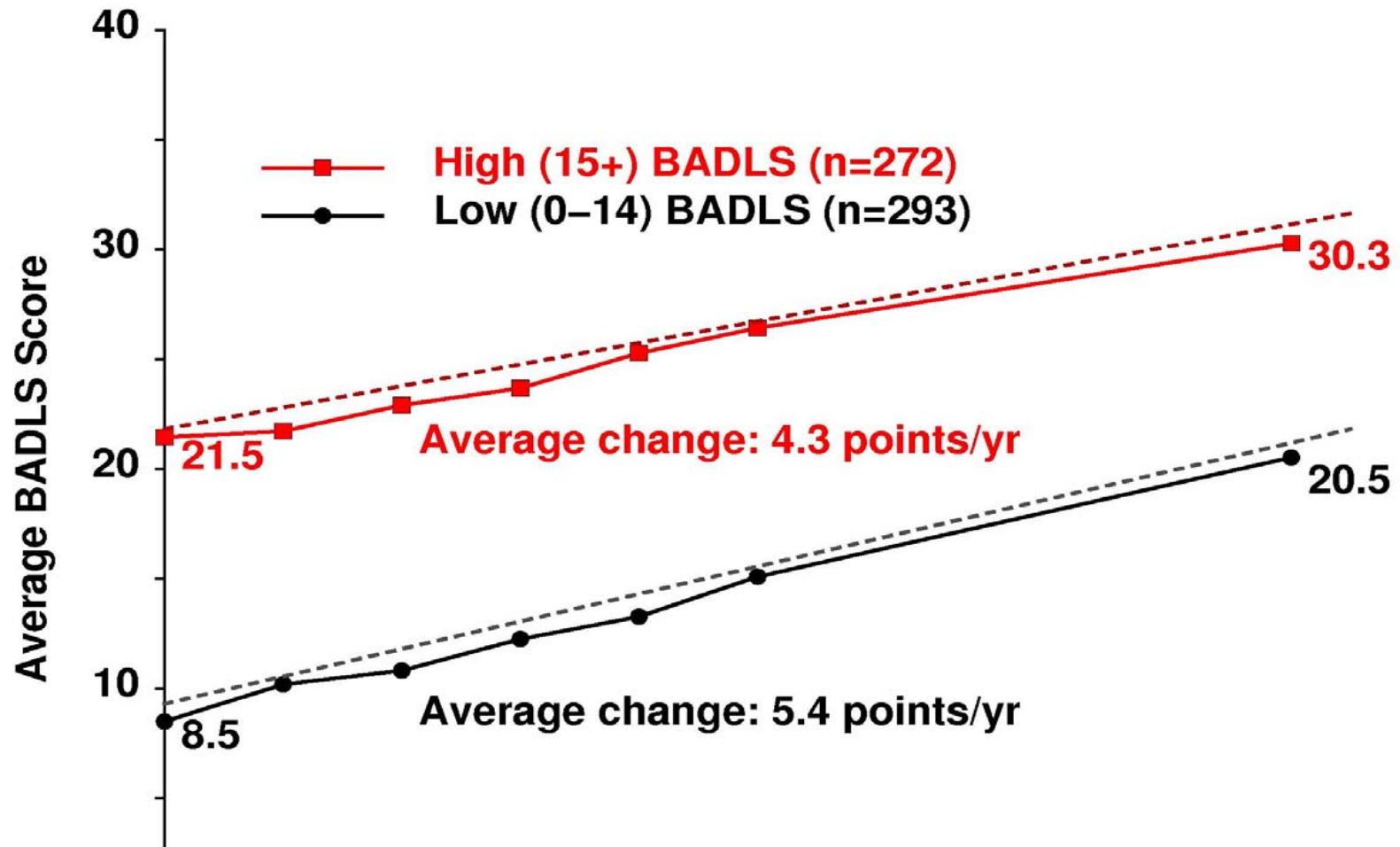
Change from baseline



Don:	281	245	212	186	165	153	93
Plac:	282	263	227	191	166	158	86



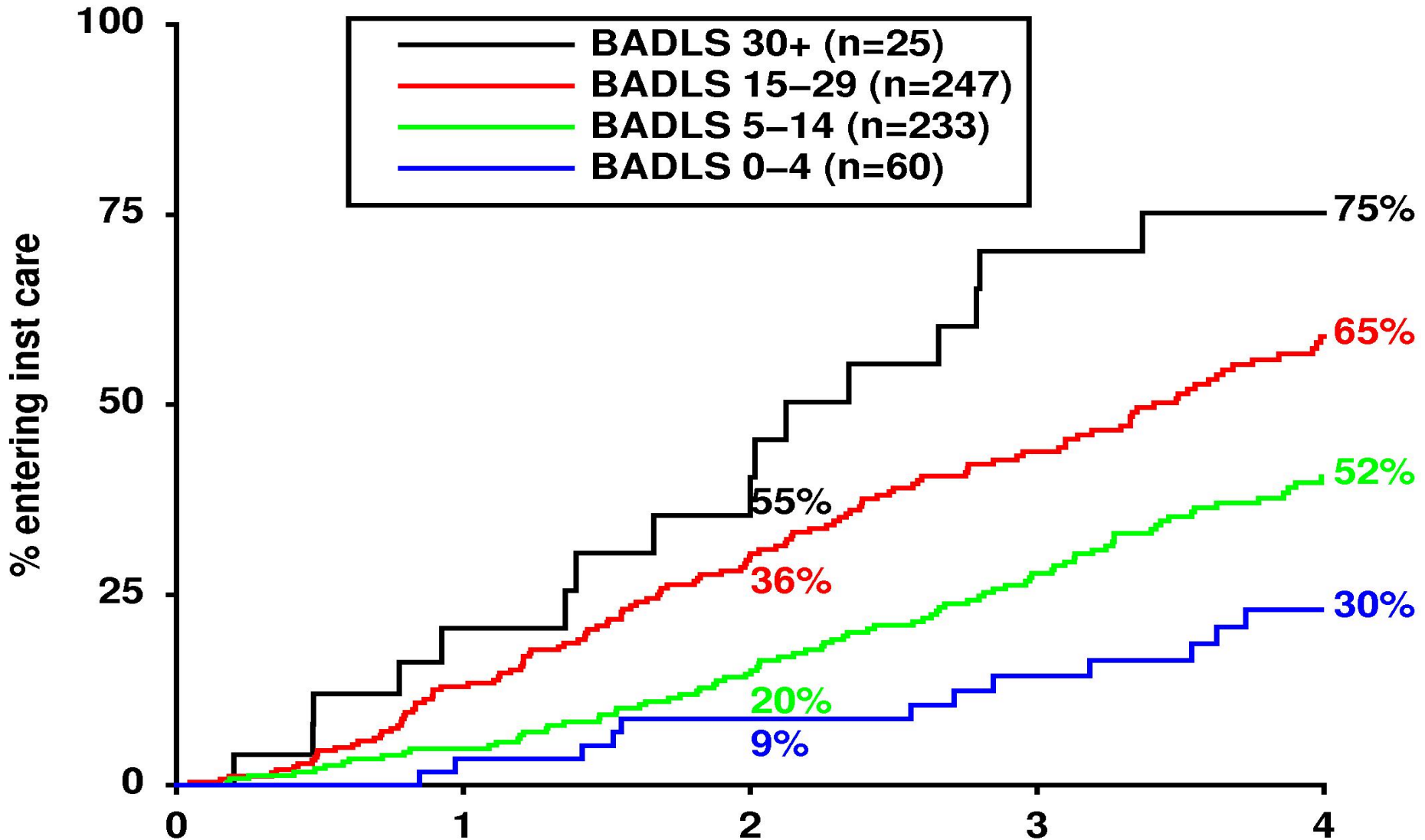
Change in Bristol ADL scores over first two years of follow-up for patients with high and low baseline levels of functional disability



What delay of institutionalisation is plausible given AD2000?

First step: identify main predictors of Institutionalisation:

(1) Activities of Daily Living

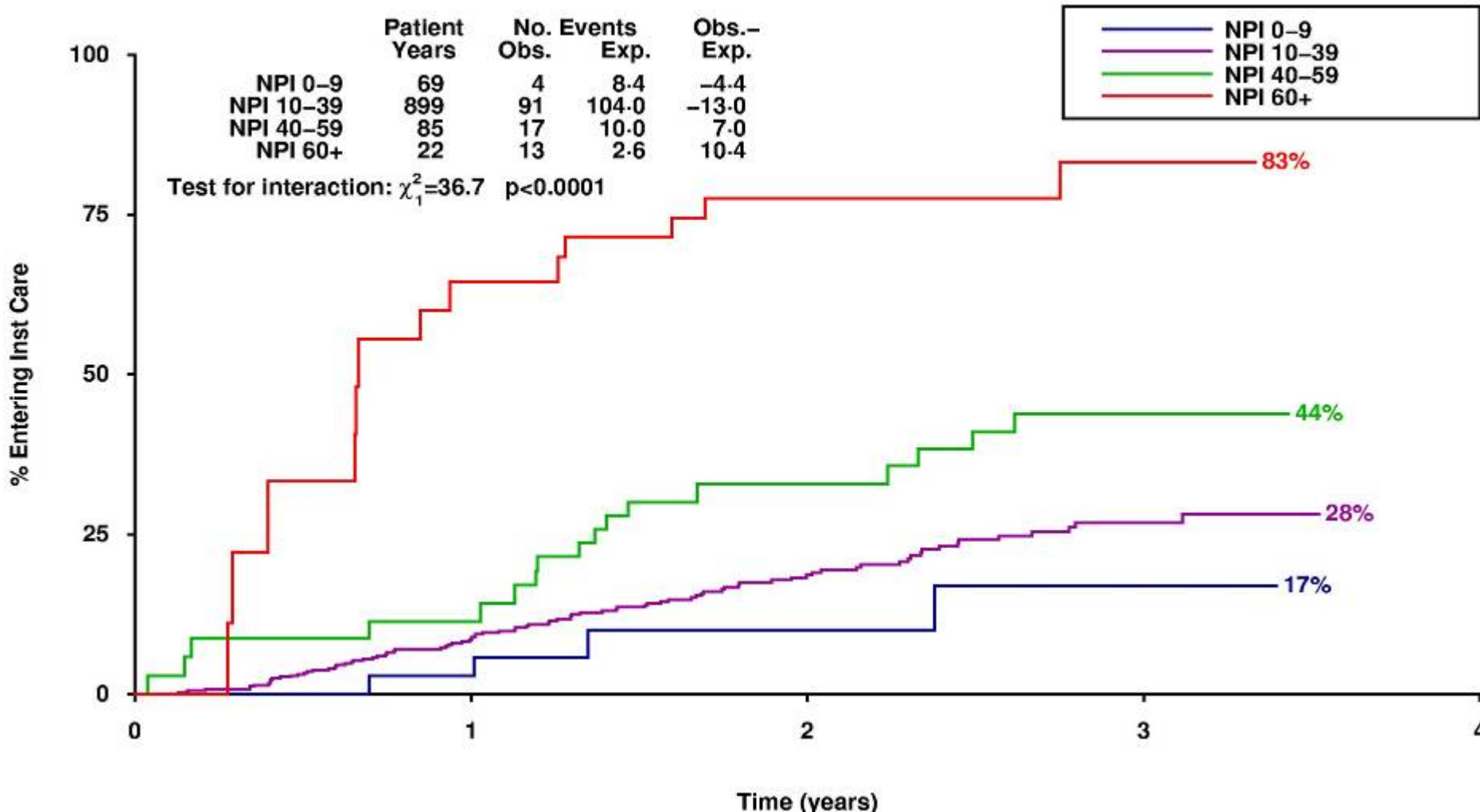


What delay of institutionalisation is plausible given AD2000?

First step: identify main predictors of Institutionalisation:

(2) behaviour/psychological symptoms

Time to institutionalisation by NPI Strata

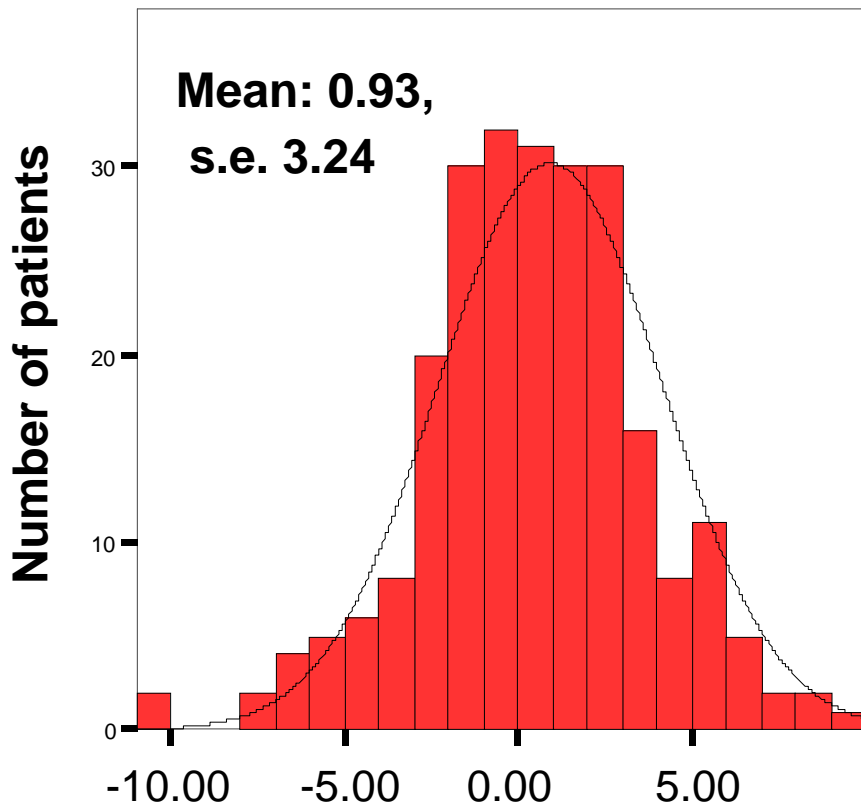


AD2000 cost-effectiveness study: conclusions

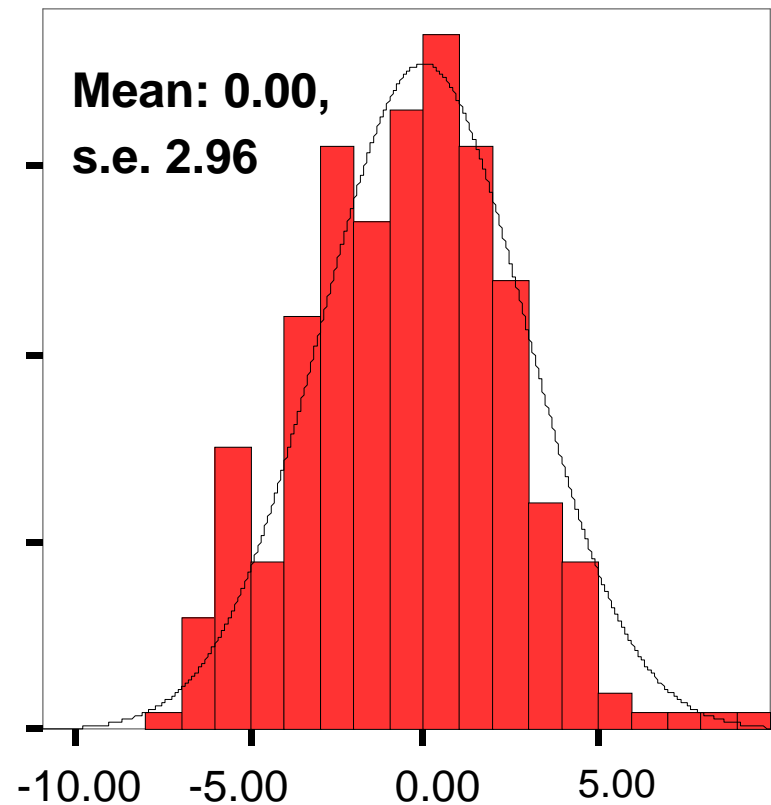
- No measurable reduction in health resource usage or delay in institutionalisation with donepezil but limited statistical power to detect small improvements
- Modelling indicates that behaviour and function – but not cognition – are strong predictors of institutional care
- The two to three point (maximum) improvement in BADLS seen with donepezil may reduce risk of inst care by about 5-15% (10%/year reduced to about 9%/year), i.e. an average of 1-3 days per patient/ year - no worthwhile cost savings

No predictors of response identified: improvement in MMSE weeks 0 -12

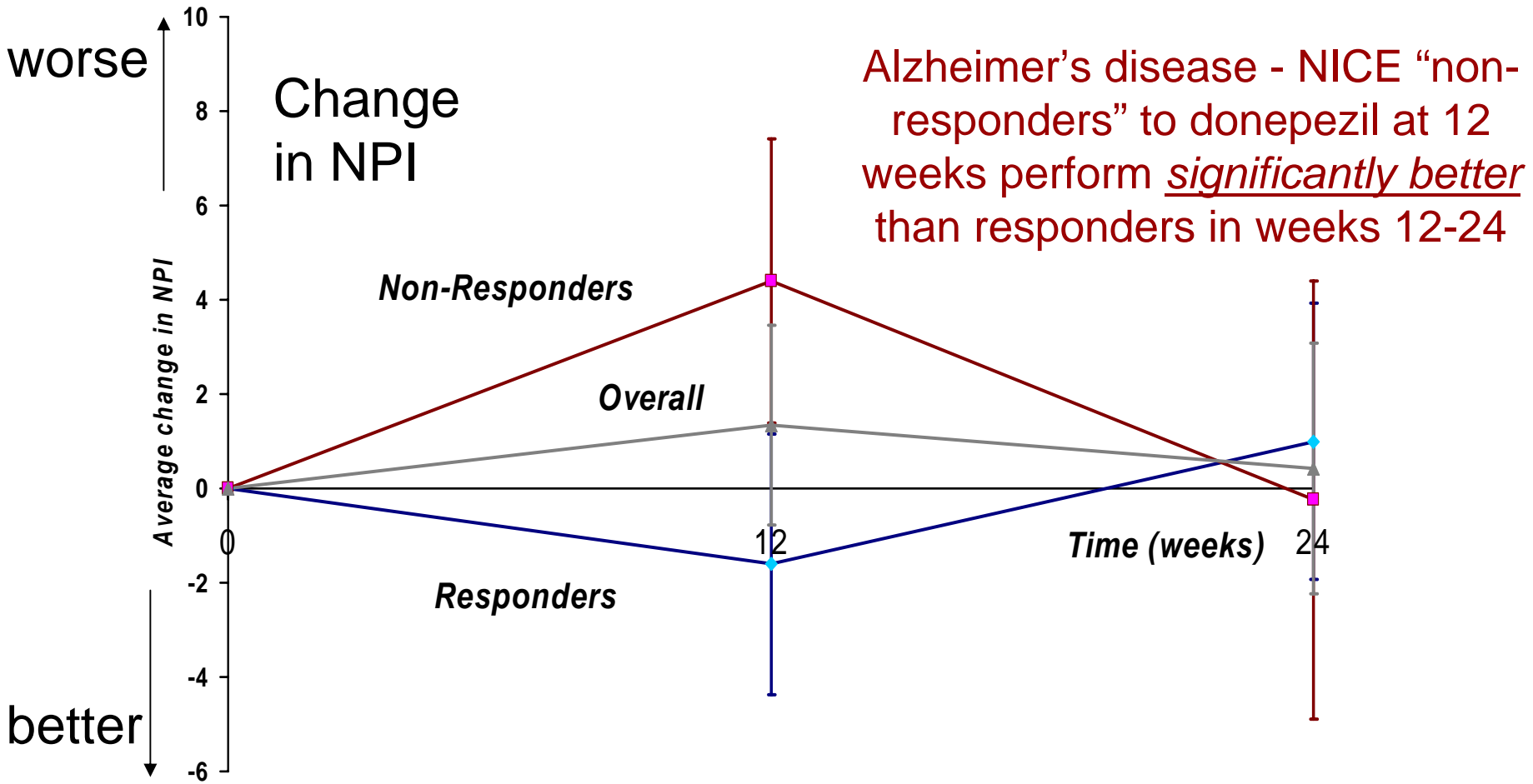
Donepezil



Placebo



NICE guidance: treat apparent 'responders'



NICE guidance (2001) on cholinesterase inhibitors

- Recommended treatment not clinically or cost-effective
- Most apparent responses are due to random fluctuations in disability
- Did NICE guidelines move treatment from postcode prescribing to a national lottery?!
- Better drugs, or combinations of drugs, are needed for Alzheimer's disease

AD2000: unreasonable criticisms*

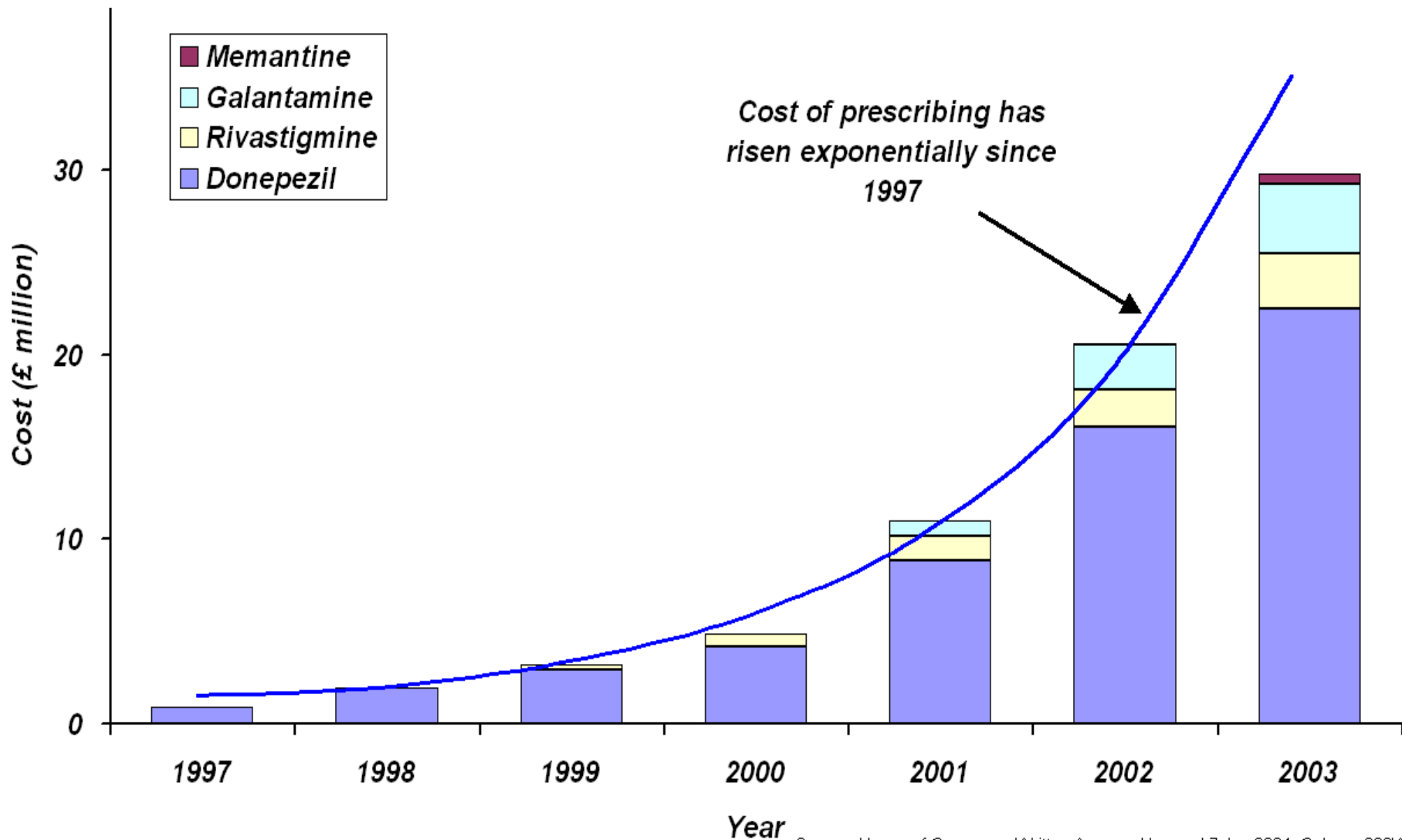
- Eligibility – doctors were uncertain whether patients would derive worthwhile benefit, not uncertain about diagnosis
- Attrition rates – lower than in any previous study
- Washout periods – full recovery on resuming treatment after washout

* See Lancet 2nd October 2004 for fuller details

Sample size

- Pragmatic recruitment target: *‘with widespread support, should be possible to randomise 3000 patients’*
- Because problems funding treatment and research support held back recruitment, target revised to 800, sufficient to confirm or refute cost neutrality
- Following NICE recommendation for cholinesterase inhibitors in 2001, recruitment closed early with 565 randomised

Cost of General Practice prescription of dementia drugs (England) NB Costs of hospital prescribing not reported



Why does cost matter?

- NICE estimate costs of prescribing cholinesterase inhibitors as £70 million per year (worldwide sales are over \$1 billion per year)
- £70 million would be enough to pay for 700 extra Old Age Psychiatrists/
Geriatricians or 3000 extra Psychiatric Nurses

Conclusions

- Neurodegenerative diseases poorly researched
- Many important questions
- Need for rigorous independent RCTs evaluating new drugs and non-medical treatments
- Need to make such trials easier