Optimal Trial Design for Investigating Drugs Designed to Slow the Course of Alzheimer's Disease

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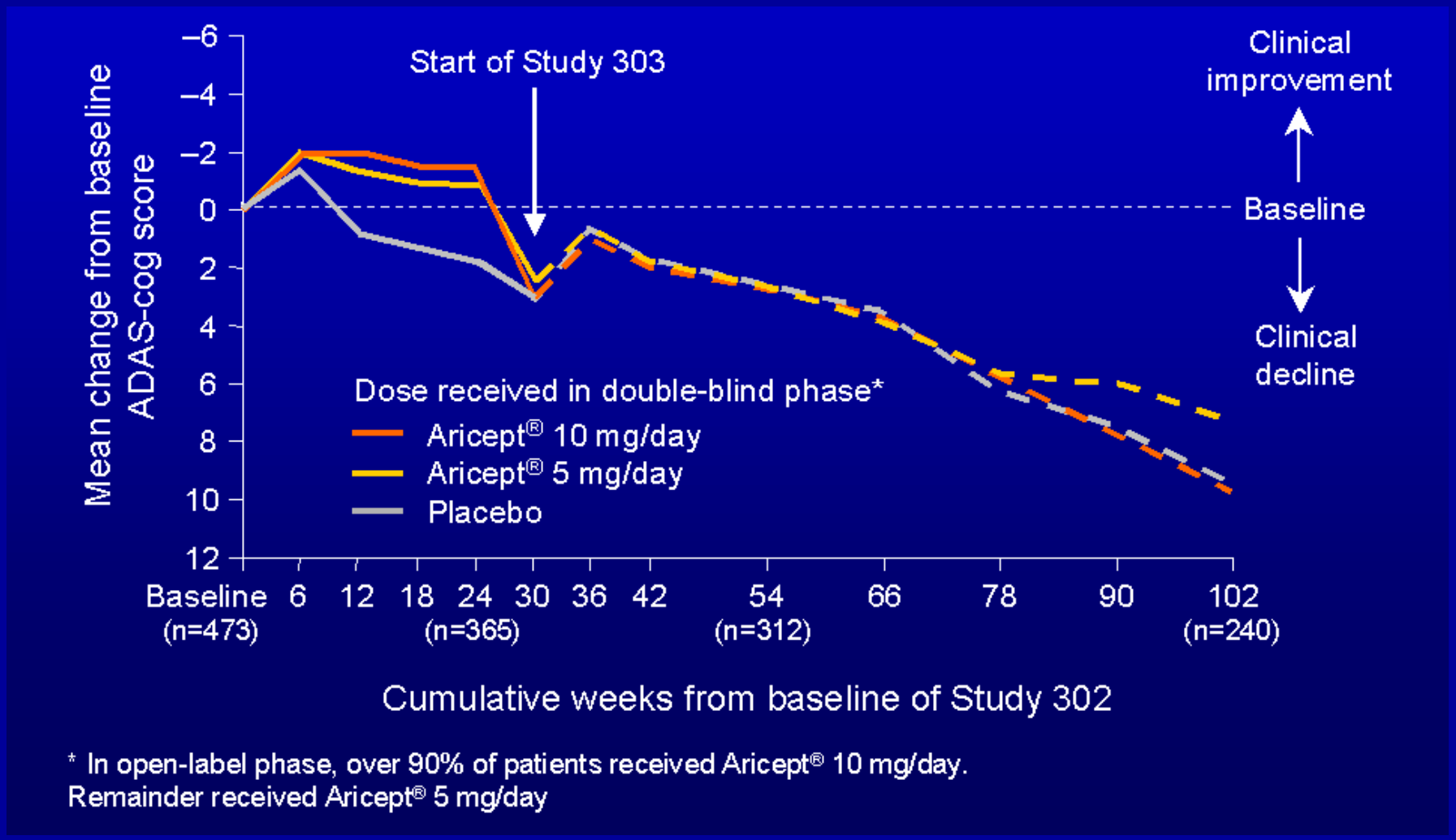
Topics Covered at the Roundtable Meeting Held November 23-24, 2005

- Lessons from Other Therapeutic Areas
  - Multiple Sclerosis (Richard Rudick)
  - Rheumatoid Arthritis (Marc Hochberg)
  - Cardiovascular Disease (Gregg Larson)
  - Osteoporosis (Stuart Silverman)
- Clinical Data Requirements – Outcomes and Study Designs
- Ongoing Clinical Trials in Alzheimer's Disease
- Biomarkers
- Statistical and Regulatory Considerations

What's Special About "Disease Modifying" Drugs?

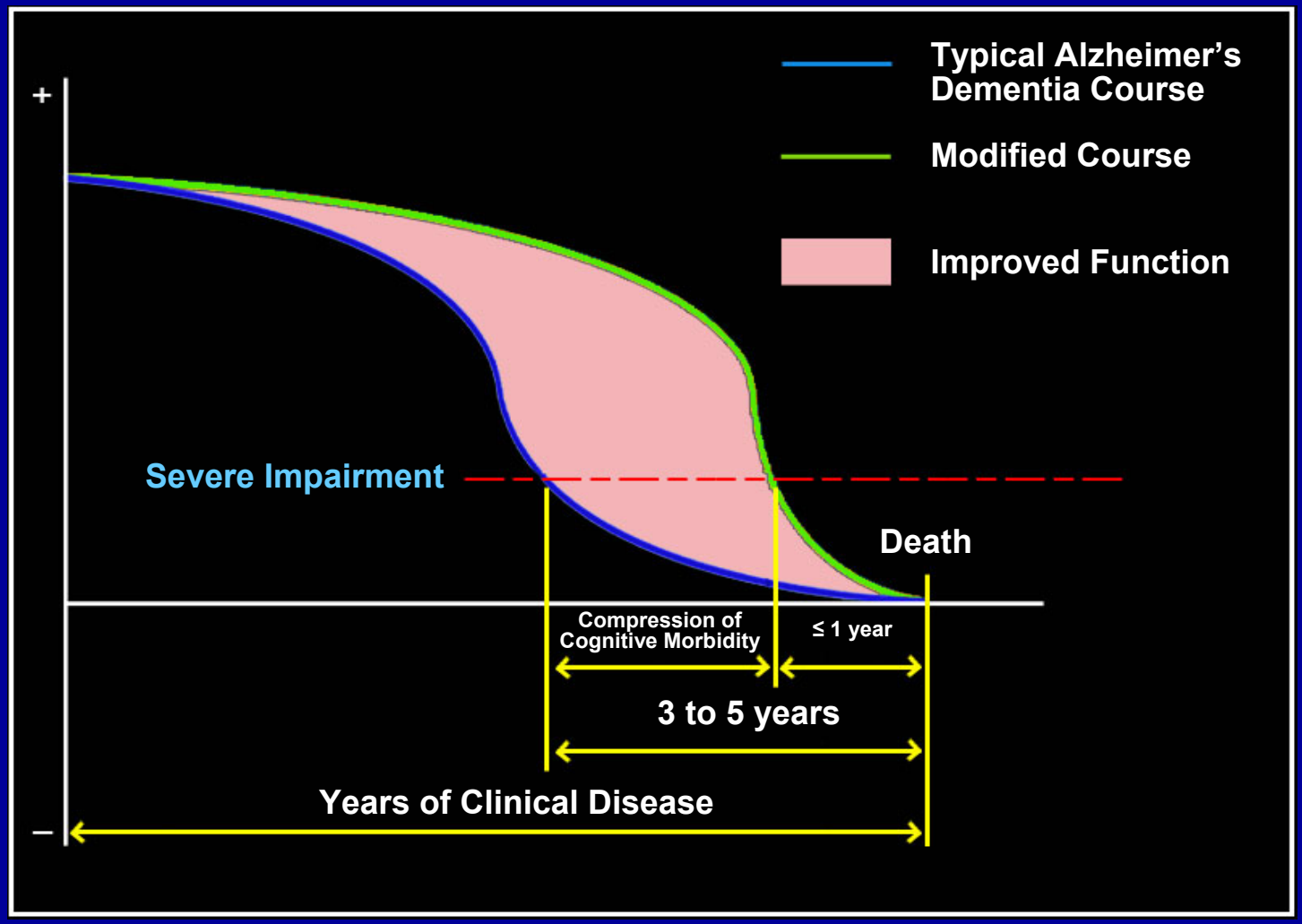
- Full clinical benefits emerge only with extended treatment.
- Clinical benefits may not disappear quickly when the drug is stopped.
- Effects on one or more aspects of disease pathology.
- Effects on pathology are correlated with clinical benefit.

Cognitive Performance: 302 Cohort



* In open-label phase, over 90% of patients received Aricept® 10 mg/day. Remainder received Aricept® 5 mg/day

Effects of Disease Modifying Drug on the Natural History of Alzheimer's Disease



Becker et al. *Am J Psychiat.* 2007;164:851

Potential Claims for RA

- Reduction in signs and symptoms of RA
- Major clinical response
- Complete clinical response
- Remission
- Prevention of disability
- Prevention of structural damage

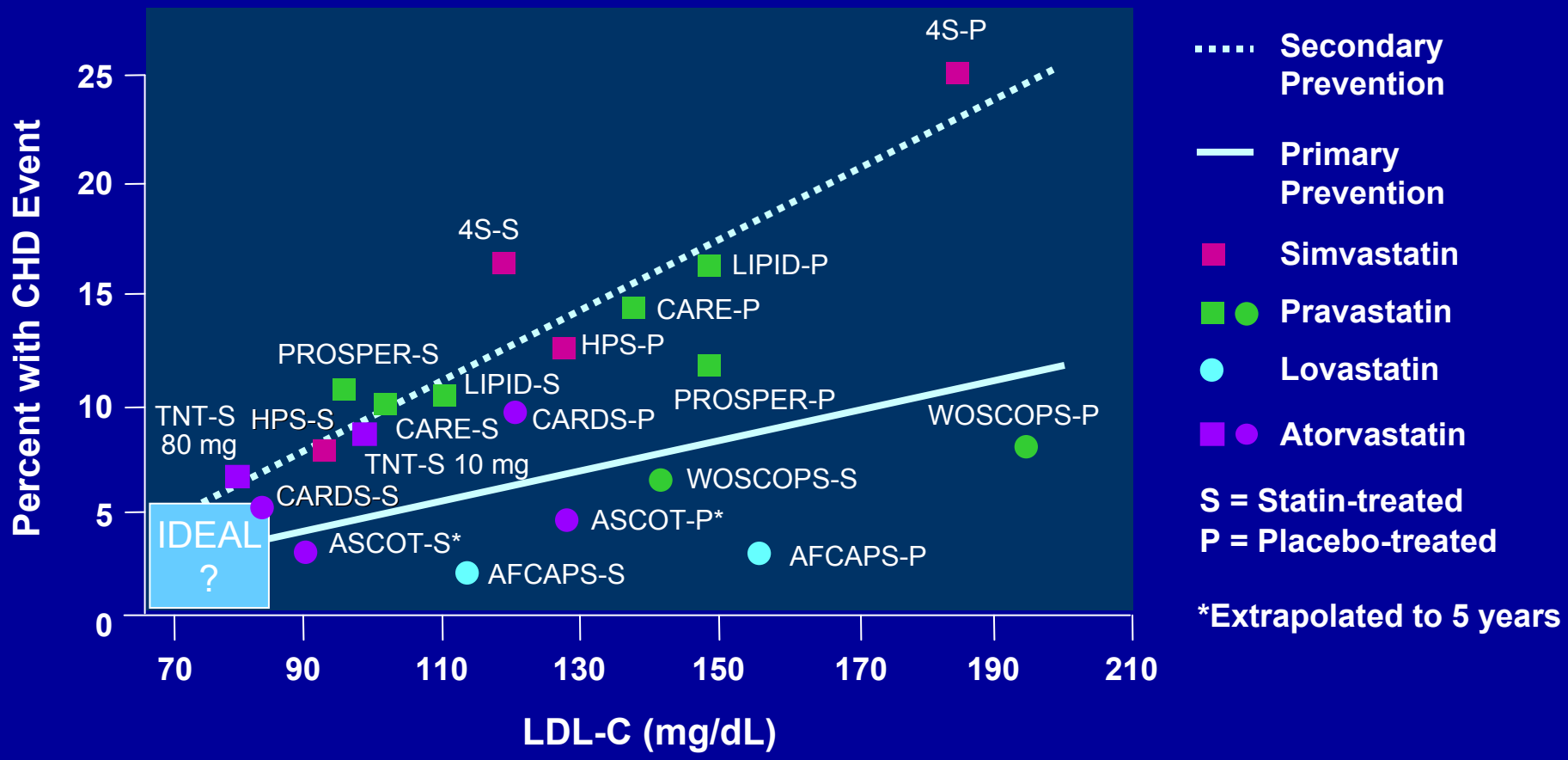
From: Marc Hochberg, M.D. AA Research Roundtable, November, 2005

Prevention of Structural Damage

- Slowing radiographic progression
  - Larsen or modified Sharp score
- Prevention of new radiographic erosions
- Trials should be at least 1 year in duration
- Considered a valid surrogate endpoint

From: Marc Hochberg, M.D. AA Research Roundtable, November, 2005

LDL-C Levels Versus Events in Landmark Statin Trials



Modified from: Kastelein JJP. *Atherosclerosis* 1999;143:S17-S21

Characteristics of the "New Approaches" to AD Therapy

- Most Targeted Toward Specific Biologic Target Thought to be Involved in Pathogenesis of AD (β Amyloid)
- New Approaches Provide Additional Benefit to Currently Approved Drugs
- Hypothesis is that Therapeutic Benefit is Cumulative with Greater Benefit Resulting From Continuous Treatment
- Benefits of Therapy Do Not Cease With Drug Discontinuation

How Should the Studies on these New Therapies Be Described?

- Aspects of the AD Syndrome Affected (Cognition, Function, Psychiatric Symptoms)
- Effects in Combination with Currently Approved Therapies (and Maybe Without)
- Onset and Duration of Effect Described
- Effects on Disease Biology
- Correlation of Biological and Clinical Effects