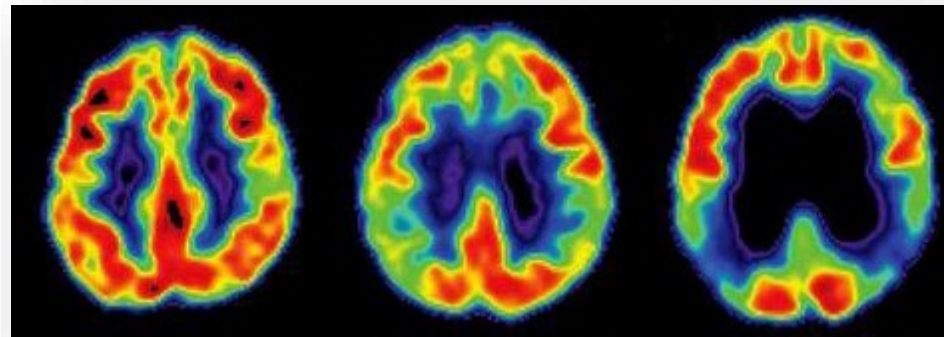


Treatment and Prevention of Alzheimer's Disease: Hope on the Horizon is Here Today!

Douglas Galasko, MD
Professor, Department of Neurosciences
Associate Director, Shiley-Marcos ADRC

SMADRC Annual Participant Appreciation Event
April 16, 2025



Disclosures

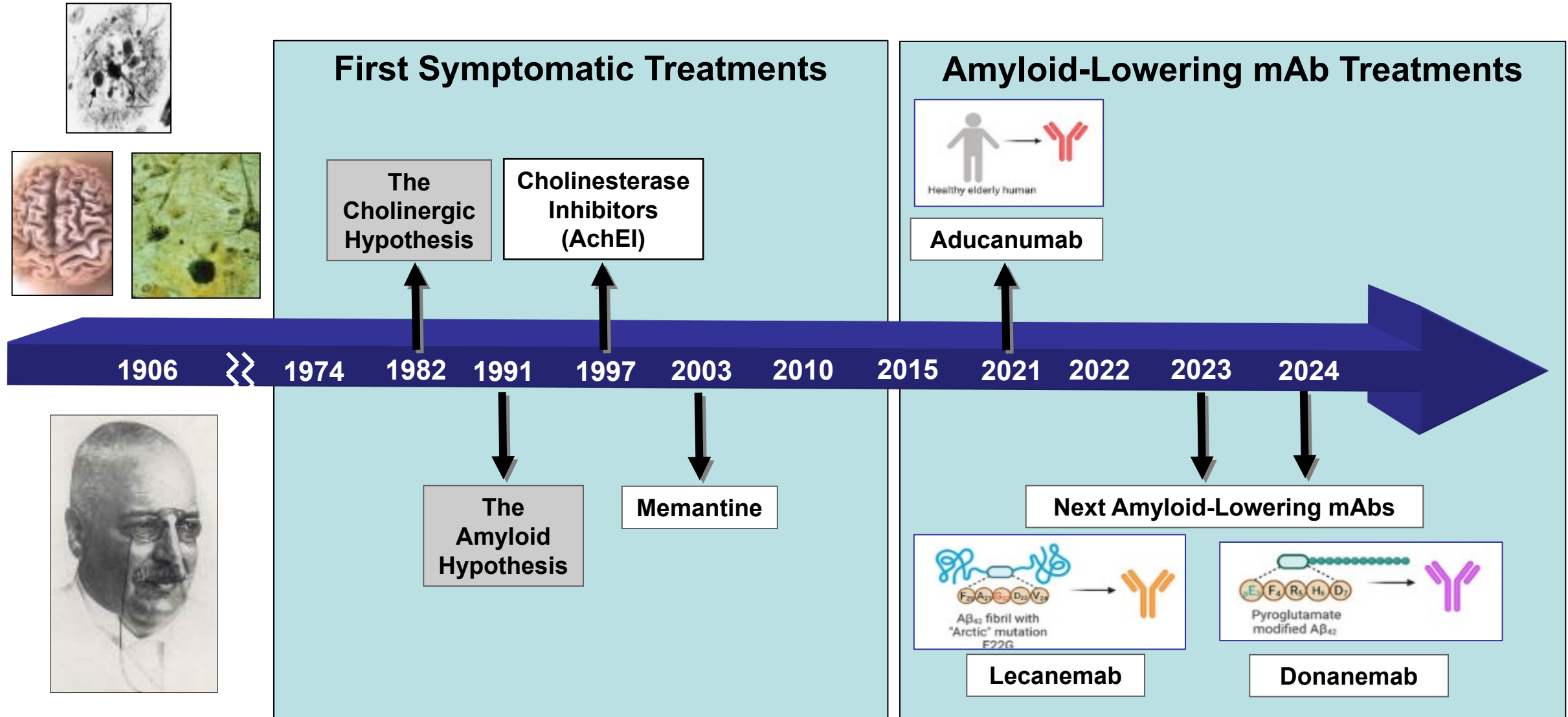
- Consultant for Eisai, GE Healthcare, Cognition Therapeutics, Artery Therapeutics

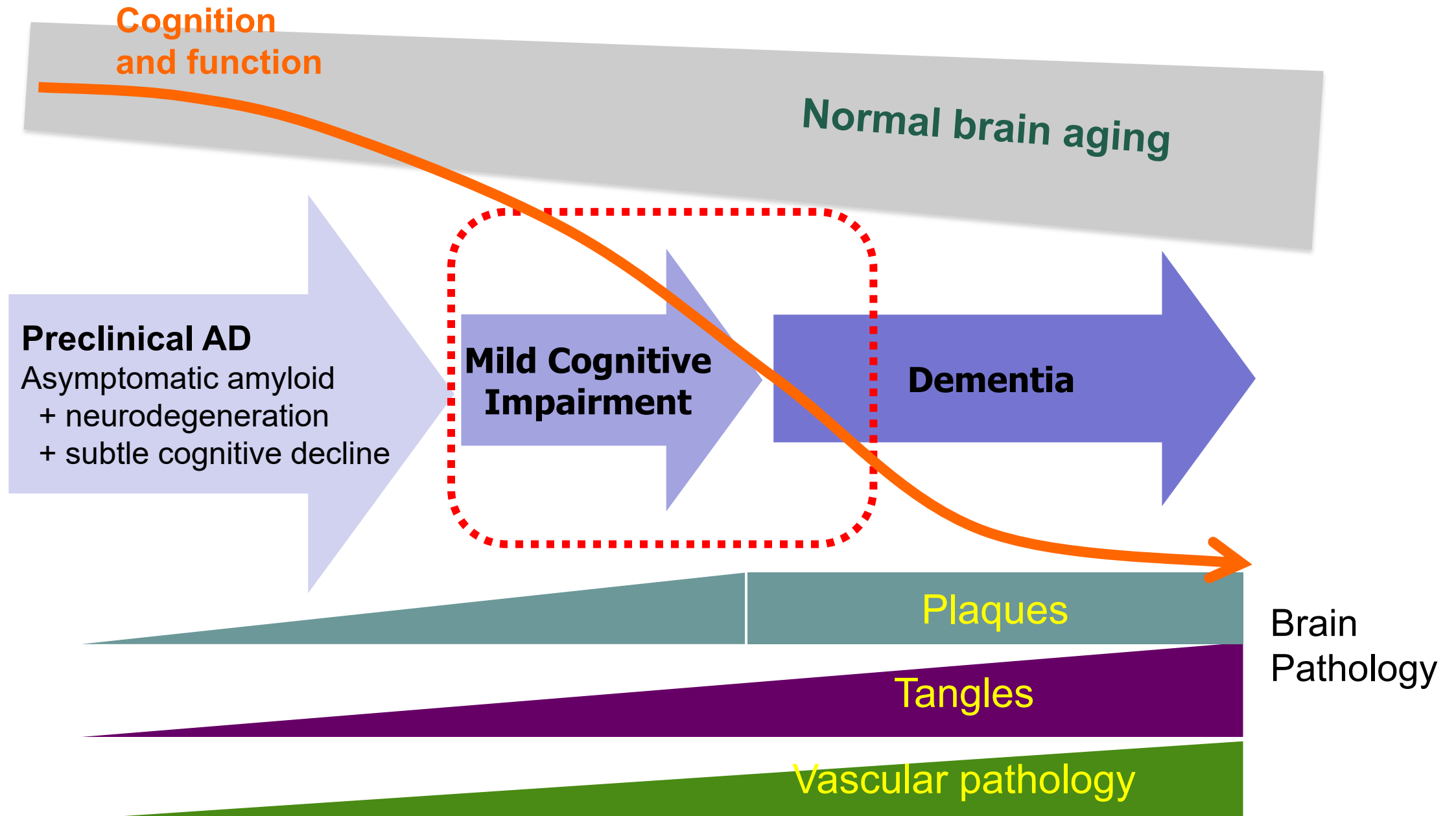
Review

- Treatments which are available today
 - Symptomatic medications
 - Anti-amyloid monoclonal antibodies (AAMAs) including:
 - Lecanemab (Leqembi™), Donanemab (Kisunla™)
- Clinical trials which will be reading out in 2025
 - evoke and evoke +: semaglutide (Ozempic™)
- Lifestyle interventions and their efficacy
 - Sprint Mind and EXERT

Treatments for Alzheimer's Disease
Available today.....! 🤗

FDA Approved Pharmaceutical Treatments

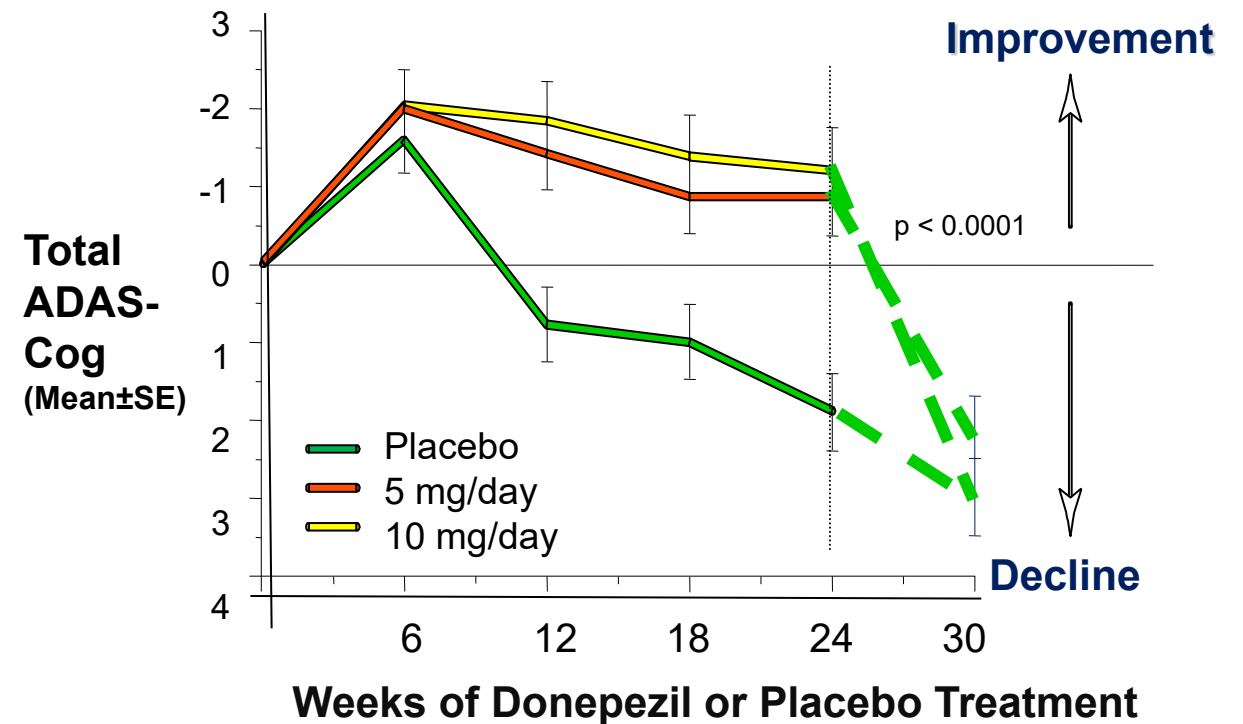




Acetylcholine (ACh) and Acetylcholinesterase Inhibitors AChEIs

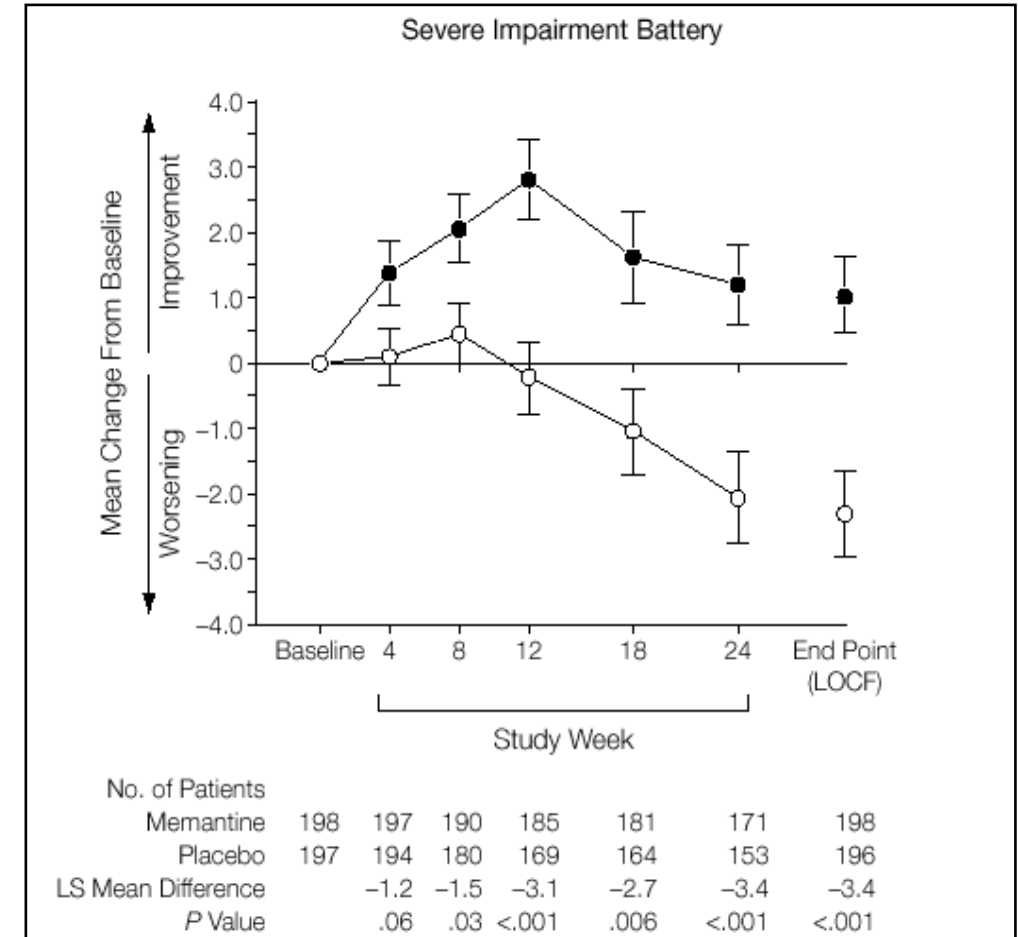
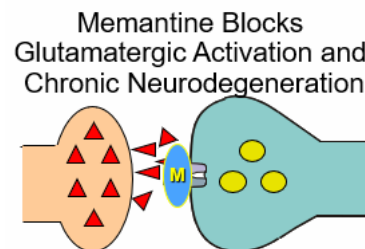
- ACh: Neurotransmitter and neuromodulator
- Involved in
 - Learning and memory
 - Regulation of arousal
 - Attention and motivation
- Deficient amounts and function in AD
- AChEIs ↑ ACh by inhibiting degradation
- Potential side effects
 - Cardiac slowing
 - Gastrointestinal
 - Cramping especially nighttime
 - Urinary symptoms

Donepezil and Cognition Mild to Moderate AD (MMSE 12-24)



Glutamate and Clinical Effects of Memantine

- Excitatory neurotransmitter
- Cell signaling in 90% of brain synapses
 - Supports synaptic function (plasticity)
- Involved in
 - Learning and memory
 - Attention, focus and decision making
 - Regulation of mood and sleep
- Memantine (Namenda)
 - Acts to modulate the receptors (NMDA) which transmit with glutamate



Severe Impairment Battery

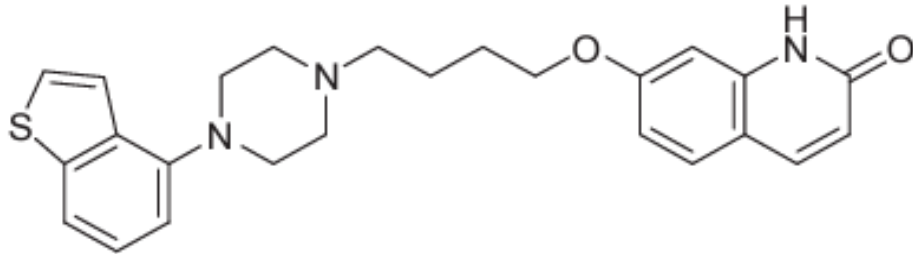
Brexpiprazole (Rexulti™)

Mechanism of Action

Efficacy and Safety of Brexpiprazole for the Treatment of Agitation in Alzheimer's Dementia: Two 12-Week, Randomized, Double-Blind, Placebo-Controlled Trials

George T. Grossberg, M.D., Eva Kobegyi, M.D., Victor Mergel, Ph.D., Mette Krog Josiassen, Ph.D., Didier Meulien, M.D., Mary Hobart, Ph.D., Mary Slomkowski, Pharm.D., Ross A. Baker, Ph.D., Robert D. McQuade, Ph.D., Jeffrey L. Cummings, M.D., Sc.D.

Figure 1 Structural Formula of Brexpiprazole



- Atypical antipsychotic FDA
- Newly approved for treatment of agitation in AD
- Mechanism of Action
 - Partial Agonist at 5-HT_{1A}, D₂ and D₃ receptors
 - Antagonist at 5-HT_{2A}, 2B, 5-HT₇, alpha 1-A, 1-D, Alpha 2C
- Range of dose
 - 0.25 -4 mg daily

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. REXULTI is not approved for the treatment of patients with dementia-related psychosis without agitation associated with dementia due to Alzheimer's disease. (5.1)

[FDA approval of Rexulti - May 11, 2023](#)

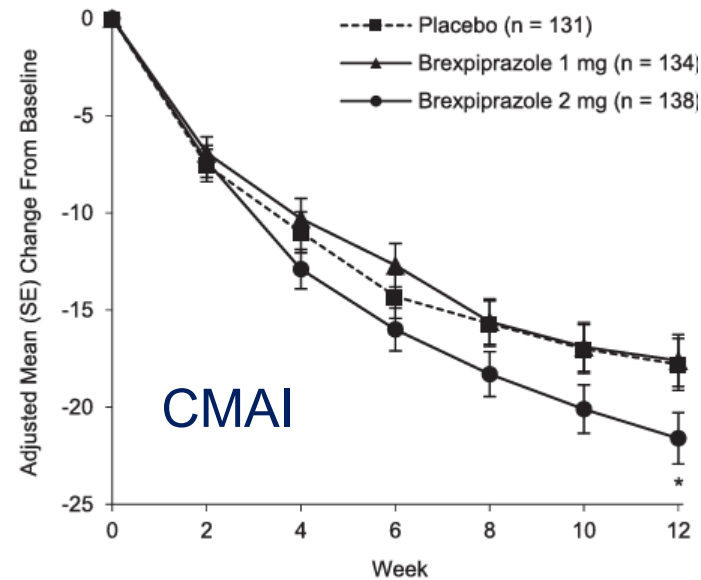
Eaves S, et al. P T. 2016 Jul;41(7):418-22. PMID: 27408517; PMCID: PMC4927015.

Grossberg GT, et al. Am J Geriatr Psychiatry. 2020. DOI: 10.1016/j.jagp.2019.09.009

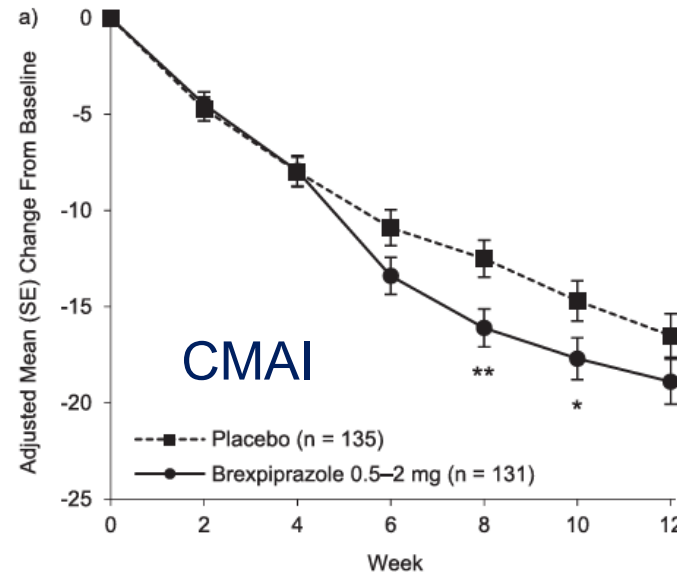
Effects of Brexpiprazole on Symptoms of Agitation

Cohen Mansfield
Agitation Inventory
Adjusted Mean Change
in Total Scores
12 weeks

Study 1

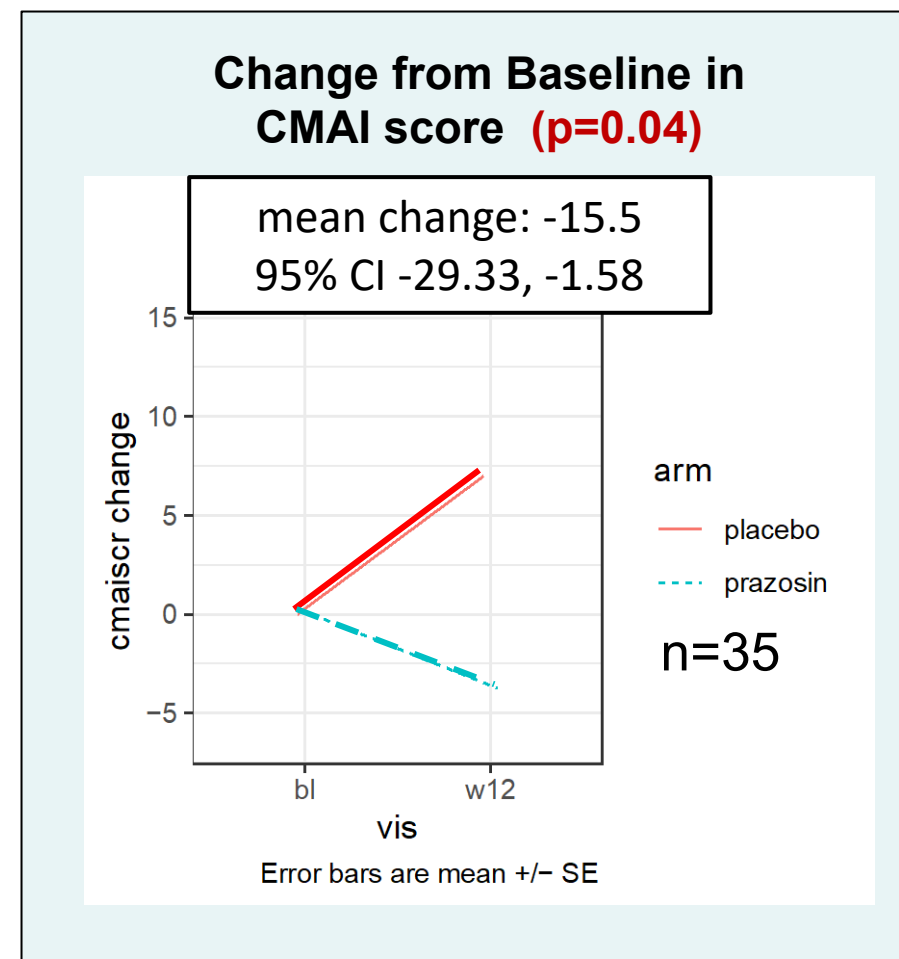


Study 2



Prazosin for the Treatment of Agitation in AD

- Prazosin is a CNS active alpha-1 AR antagonist
 - Blocks excessive noradrenergic stimulation
 - Available as generic medicine
- Design: multi-site placebo-controlled 12 week RCT trial
 - Prazosin or placebo titrated over 4 weeks to a maximum dose of 4 mg mid-morning and 6 mg at bedtime based on tolerability and persistent agitation
- Results: no significant differences in CGIC-A or total NPI scores
 - Significant benefit on CMAI favoring prazosin
 - Safety profile as anticipated with risks of low blood pressure and blackout

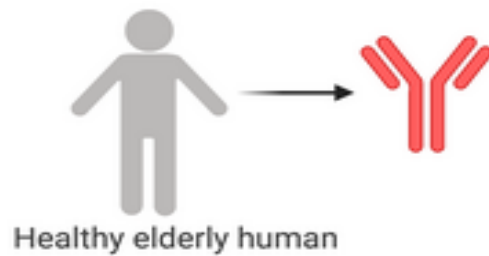


Peskind, E. *Alzheimer's & Dementia* (2023)

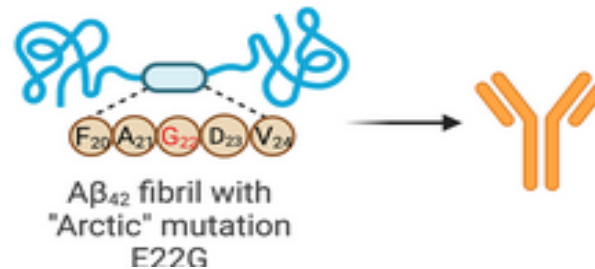
The Dawn of the Era of Amyloid-lowering Treatments of AD

The first disease modifying treatments.....ever !

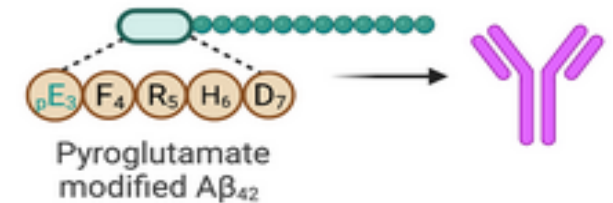
Aducanumab (Aduhelm)



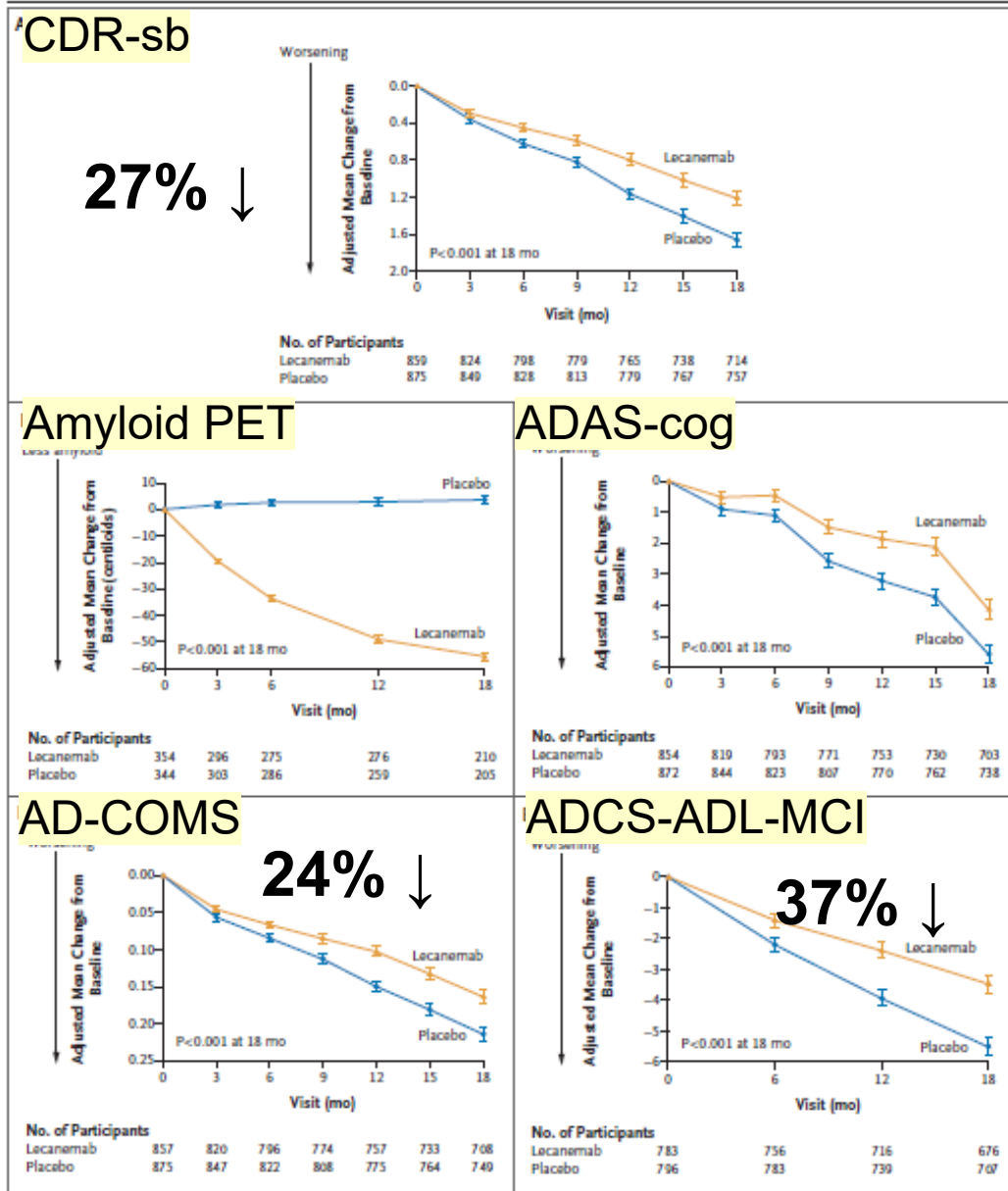
Lecanemab



Donanemab



Lecanemab lowers amyloid and shows consistent clinical slowing



Lecanemab 10 mg/kg vs placebo

- IV q2 weeks x 18 months
- N =1795 (898 Lecanemab & 897 placebo)
- Slowed clinical progression

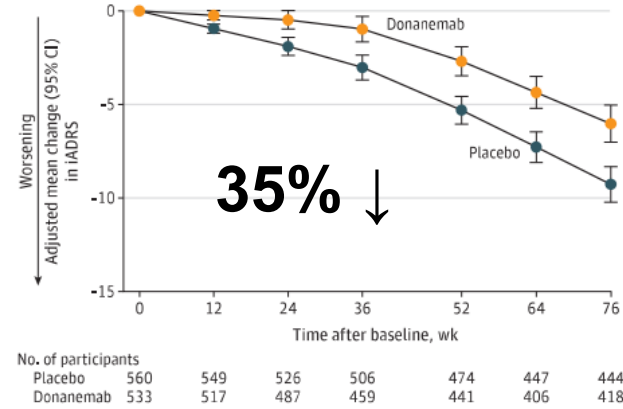
Consistent **group benefit** of treatment vs placebo across different ratings.

No clear if scores continue to diverge.

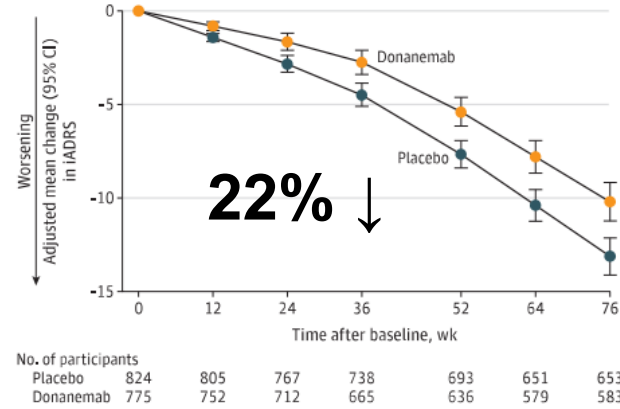
Van Dyck, C. H. et al.. *New Engl J Med* **388**, 9–21 (2022).

Donanemab lowers amyloid and shows consistent clinical slowing

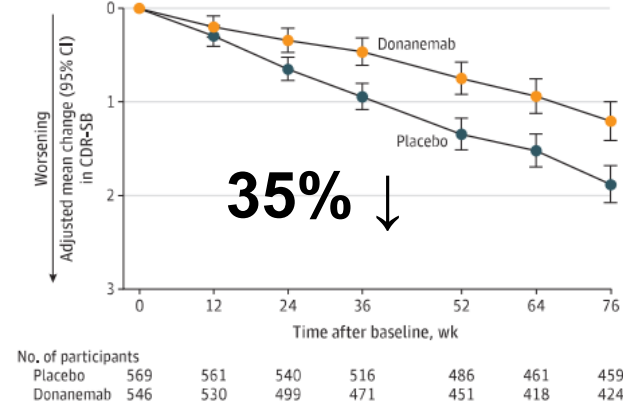
iADRS in low/medium Tau



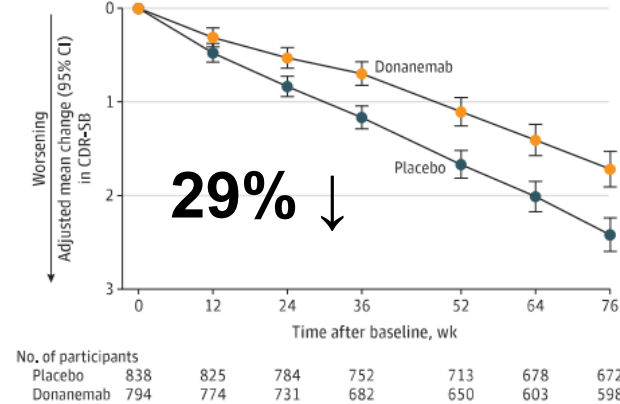
iADRS in entire trial population



CDRsb in low/medium Tau



CDRsb in entire trial population



- Phase 3 trial x 18 months
- Donanemab I-V every 4 weeks up to 76 weeks
- MCI/mild AD
- Cleared amyloid in 80% by 76 weeks
- Clinical benefits were stronger in people with low tau PET burden

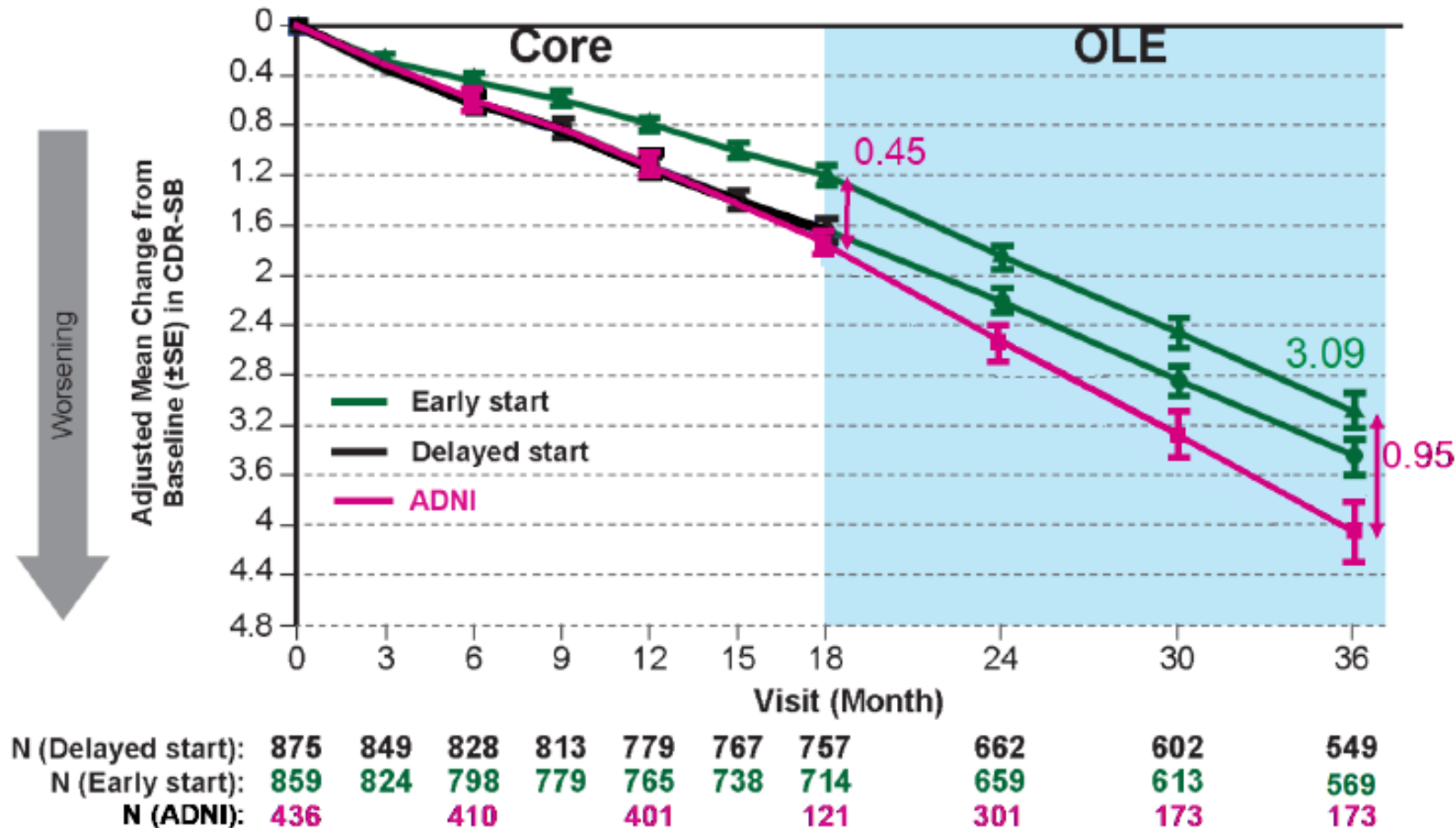
ARIA rates slightly higher than for lecanemab
1.6% rate of serious ARIA

Sims, J. R. *et al.* *JAMA* **330**, 512–527 (2023).

Long term effects of Lecanemab on CDR-sb

Treatment effect between lecanemab and ADNI cohort continues to expand from 18 through 36 months

Delayed start group also shows benefit in OLE relative to ADNI cohort

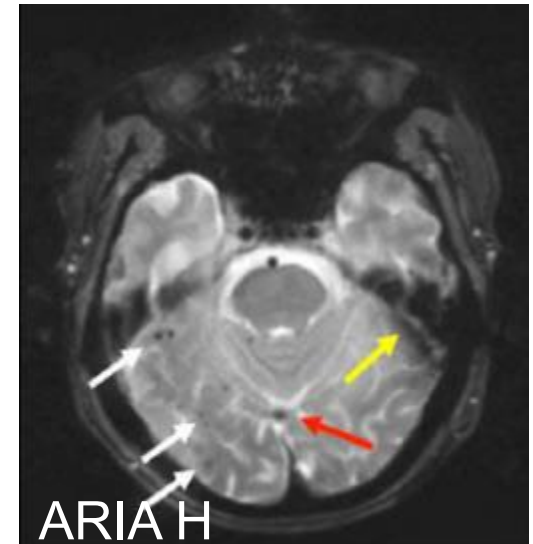
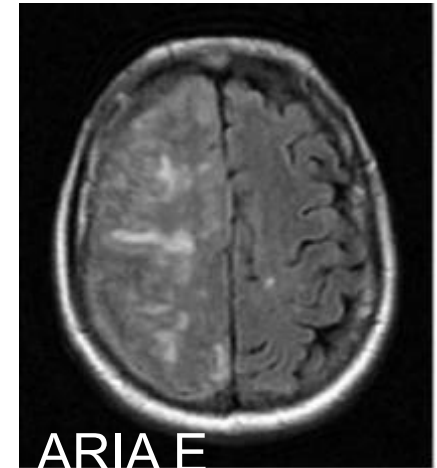


- ADNI observational cohort represents exact population of those in Clarity AD study
- Matched ADNI participants show similar degree of decline to placebo group out to 18 months













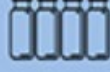
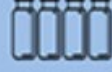
ARIA Side Effects of Lecanemab & Donanemab


Event	Lecanemab (N=898)	Placebo (N=897)	Donanemab (N=853)	Placebo (N=874)
Infusion Reactions	26.4%	7.4%	8.7%	0.5%
Amyloid Related Imaging Abnormalities (ARIA) – no. (%)				
ARIA-E	12.6%	1.7%	24.0%	2.1%
Symptomatic ARIA-E	2.8%	0%	6.1%	0.1%
ARIA-H	17.3%	9.0%	31.4%	13.6%
Symptomatic ARIA-H	0.7%	0.2%	N/A	N/A

Predicting ARIA: APOE4, CAA, higher dose, CVD, antithrombotic use, CMH
Potential preventive treatment: inhibiting complement cascade (C1Q antibodies)

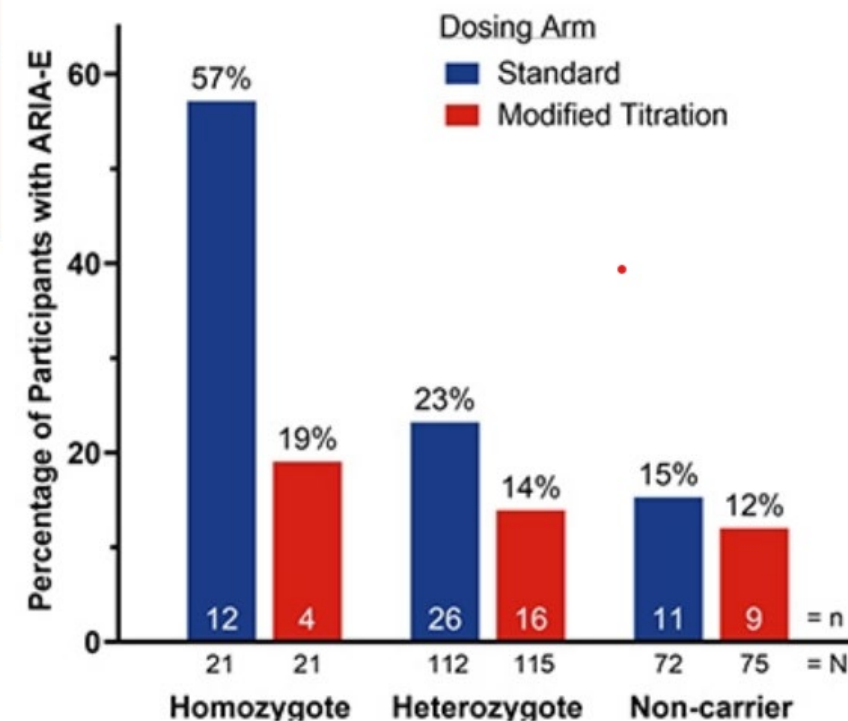


van Dyck CH, et al. N Engl J Med. 2023 Jan 5. DOI: 10.1056/NEJMoa2212948; Sperling RA et al Alz & Dementia 2011;
Sims JR, et al. JAMA. 2023;330(6):512–527. doi:10.1001/jama.2023.1323; Hampel H, Brain. 2023. doi: 10.1093/brain/awad188; Withington CG, Front Neurol. 2022 doi:
10.3389/fneur.2022.862369; Doran SJ, Front Neurosci. 2024 doi: 10.3389/fnins.2024.1326784; <https://www.alzforum.org/news/conference-coverage/aria-inflammatory-reaction-vascular-amyloid>

Dose	1	2	3	4	5	6	7
Study Week	0	4	8	12	16	20	24
Standard							
Modified Titration							

 = 350 mg

Trailblazer-ALZ 6 trial:
Slower titration reduced ARIA-E risk and had similar amyloid clearance outcomes



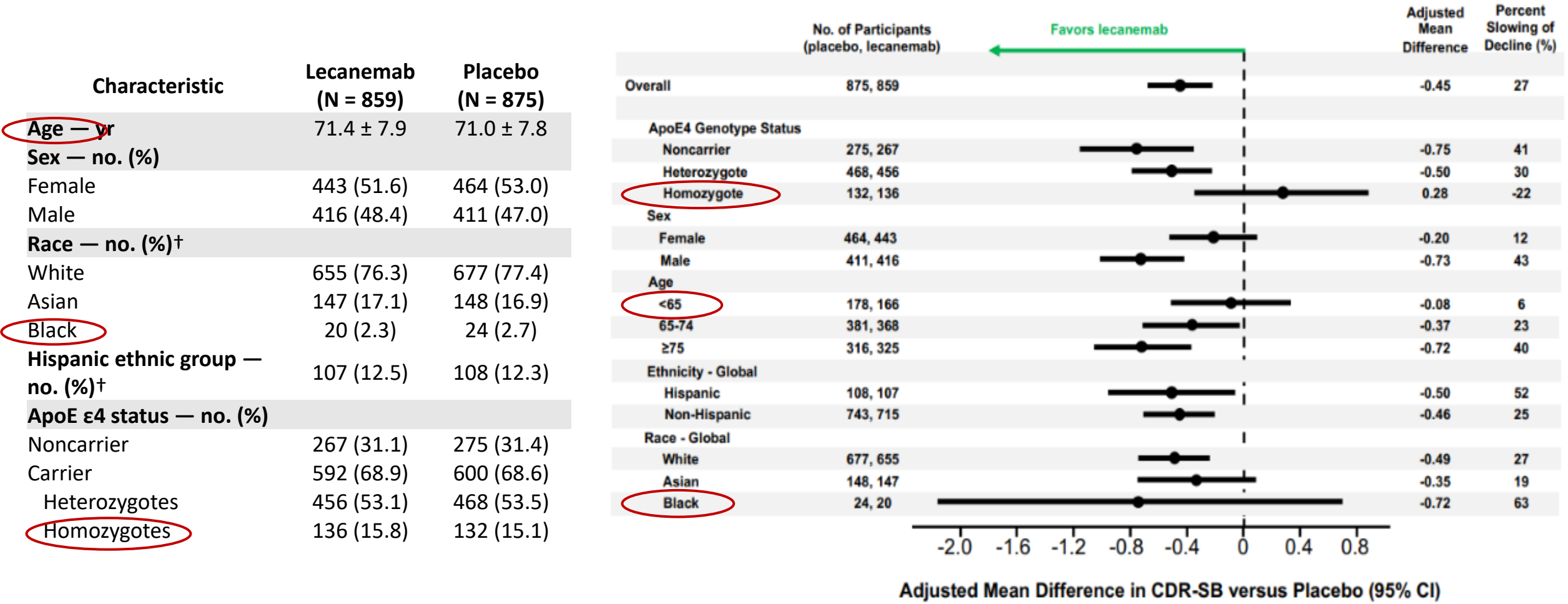
Further developments in Amyloid immunotherapy

- Subcutaneous Leqembi – allows home administration
- Prevention trials of lecanemab and donanemab
- Long term leqembi: once per month after 18 months
- “Son of donanemab”: remternetug: given every 3 months subQ, in phase 3 trials
- Combination of anti-amyloid and tau antibody Rx:
 - started in autosomal dominant AD (DIAN-TU)
- New anti-amyloid antibodies: Prothena, Acumen
- Active immunization: AC Immune, Vaxxinity, Prothena

Varying treatment responses to AAMAs

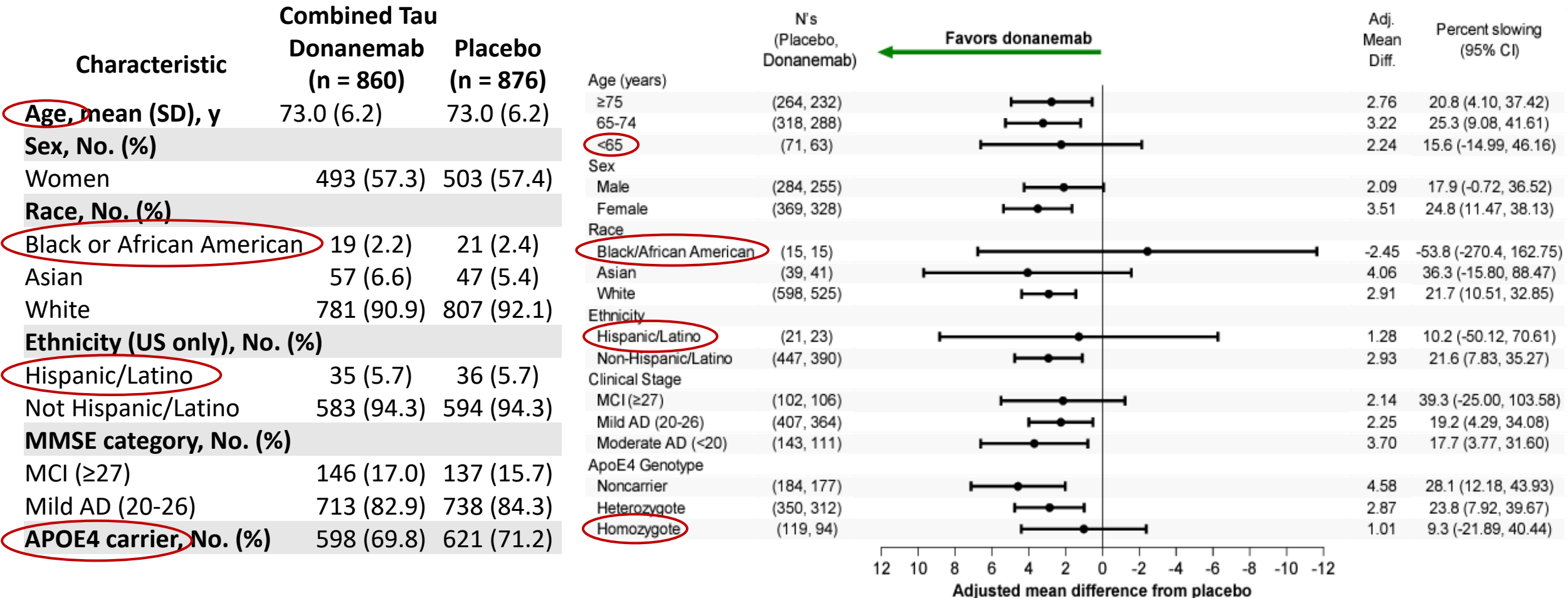
Lecanemab Treatment Effects on CDR-SB in Full Sample

Forest Plots of Treatment Outcomes by Subgroups



Donanemab Treatment Effects on iADRS in Full Sample

Forest Plots of Treatment Outcomes by Subgroups



Collecting Real World Experience with AAMAs

Site	Lecanemab	Donanemab
UC San Diego	50	9 (pending)
Washington University	300	13 + 10/month
Emory University		35
Barrow Neurological Institute		44
UT Southwestern		60

- At the UCSD Clinic: lecanemab use, first 50 patients
 - 8 patients have stopped treatment (16%), 16 have experienced side effects
- Decision-making between lecanemab and donanemab
 - **Donanemab** is more convenient, with monthly instead of 2x monthly infusions
 - Potential for stopping this treatment after 12-18 months
 - **Lecanemab**: offsetting considerations
 - Recent approval for monthly maintenance dosing
 - Potential approval for subcutaneous injections

Semaglutide/Ozempic™

Mechanism of Action of Glucagon Like Peptide Receptor Agonists (GLP1A)

- Enhances glucose dependent insulin secretion and decreases glucagon
- Slows gastric emptying
- Impacts appetite and satiety
- Treatment efficacy DM and obesity

Mechanism of Action in AD

- Effects on blood brain barrier
- Modulates neuroinflammation
- Decreases synaptic loss
- Acts outside CNS

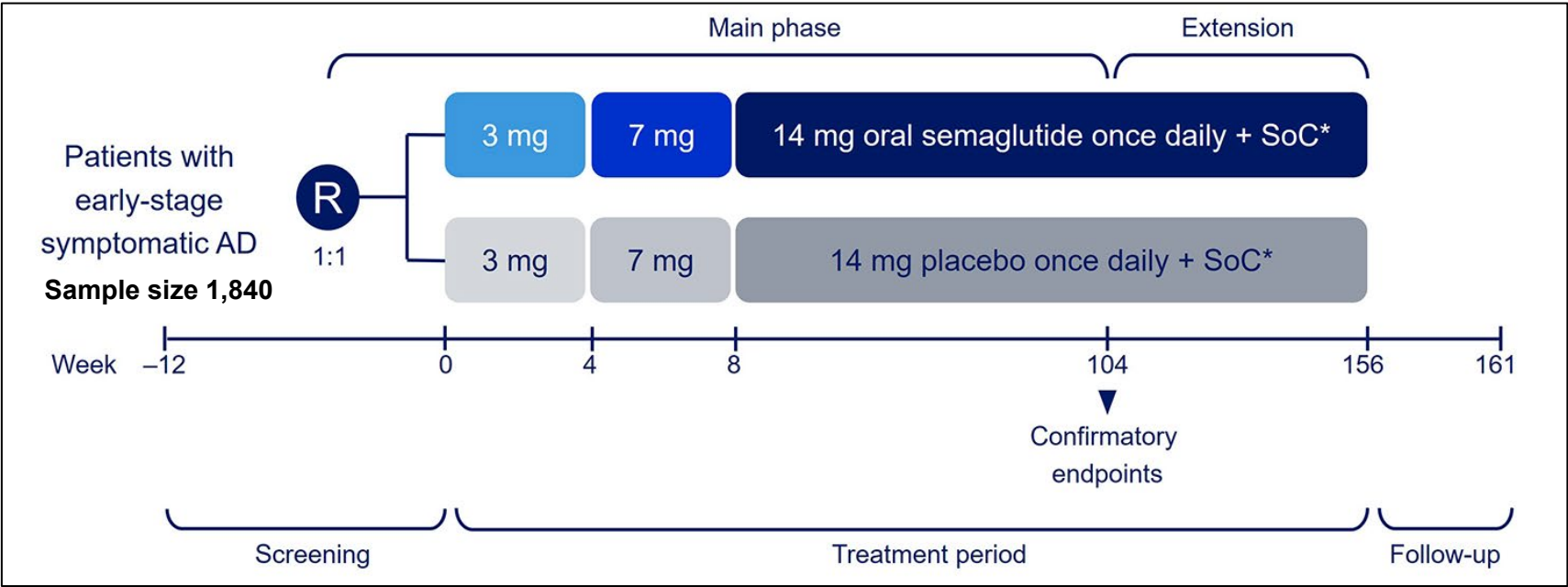
RESEARCH

Open Access



evoke and evoke+: design of two large-scale, double-blind, placebo-controlled, phase 3 studies evaluating efficacy, safety, and tolerability of semaglutide in early-stage symptomatic Alzheimer’s disease

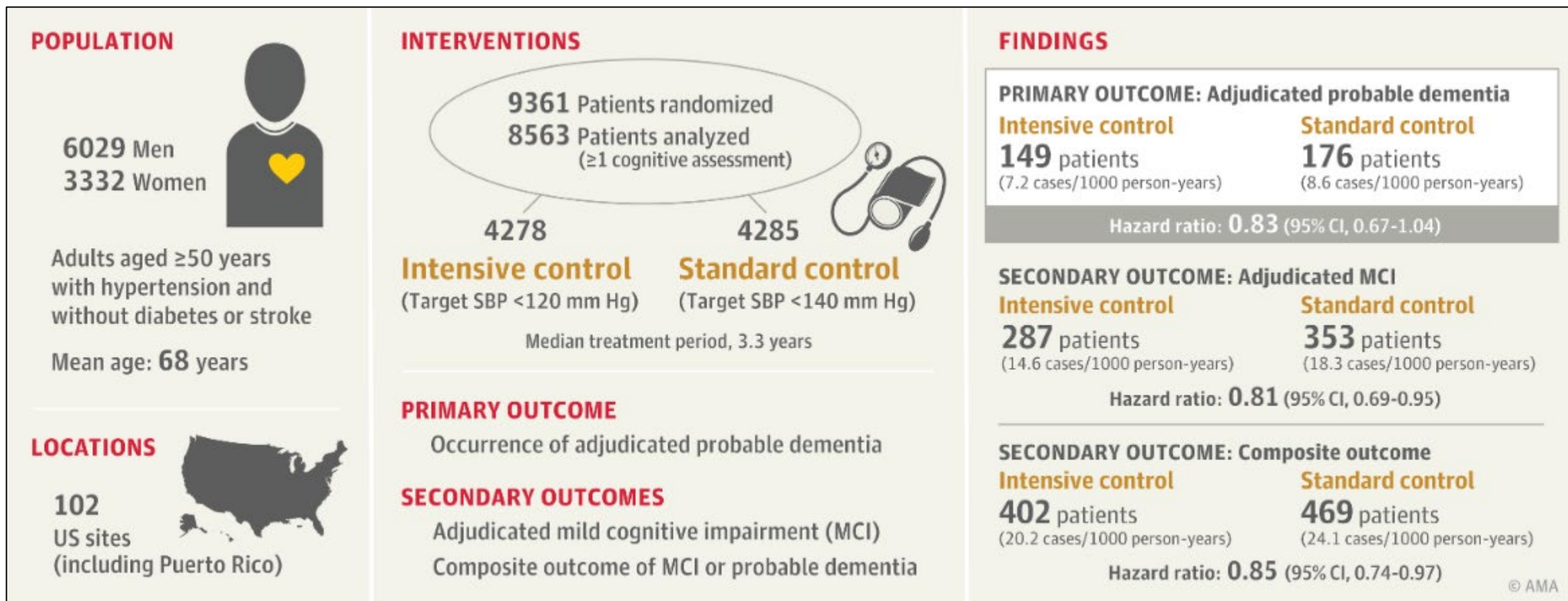
Jeffrey L. Cummings^{1,15*}, Alireza Atri^{2,3,4}, Howard H. Feldman⁵, Oskar Hansson^{6,7}, Mary Sano⁸, Filip K. Knop^{9,10,11,12}, Peter Johannsen¹², Teresa León¹² and Philip Scheltens^{13,14}



Lifestyle and risk factor interventions
Yes – it is worth it !

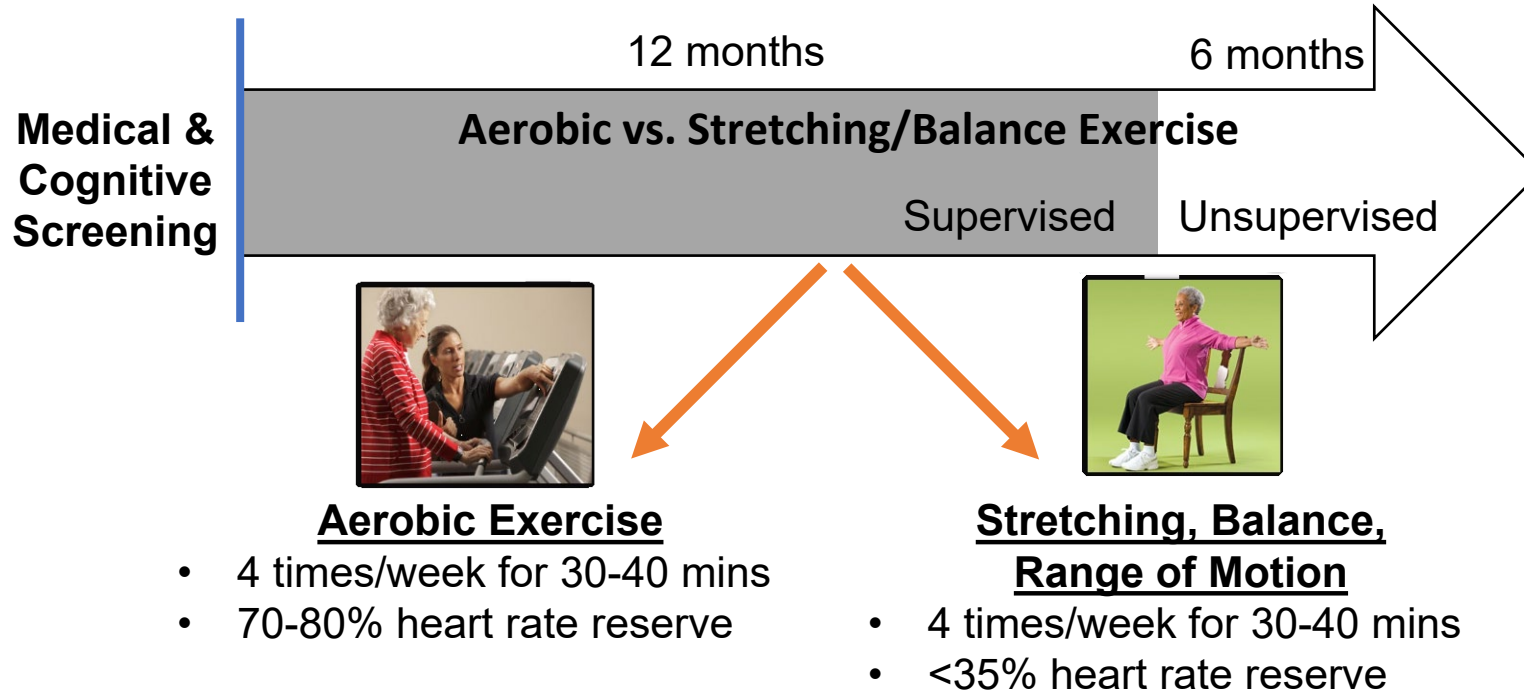
“SPRINT MIND” Prevention

Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia A Randomized Clinical Trial





Exercise for MCI

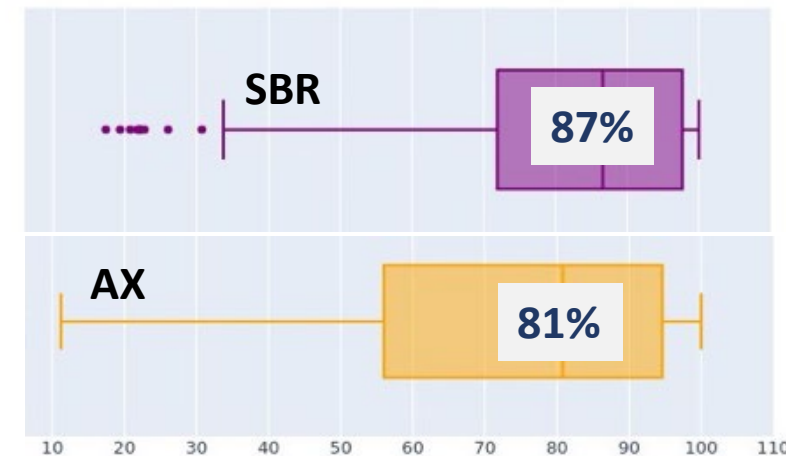


Intervention Oversight

- Supervision by YMCA Trainers
- Central oversight by exercise experts



median sessions completed



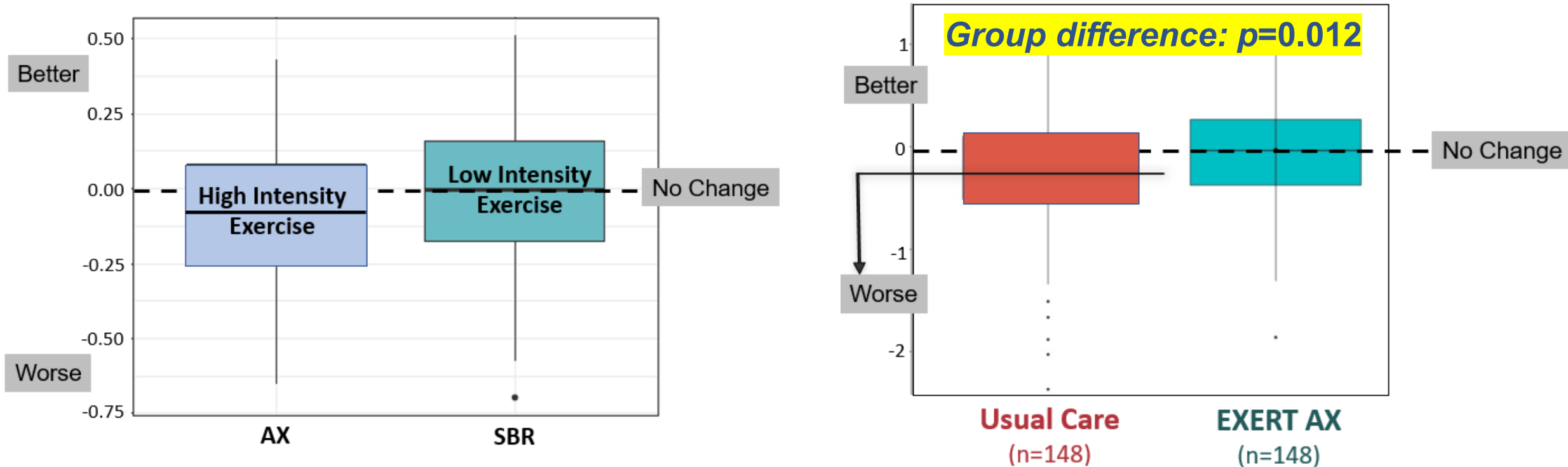
> 31,000 exercise sessions completed in 12 months



Results

ADAS-Cog-Exec

Treatment-related change from baseline (z-scores)



Online Brain Health & Risk Factor Modification Programs

■ Healthy Actions and Lifestyles to Avoid Dementia/Hispanos y el ALTo a la Demencia

- <https://www.haltad.ucsd.edu>
- <https://pubmed.ncbi.nlm.nih.gov/38440783/>



■ The Canadian Therapeutic Platform Trial for Multidomain Interventions to Prevent Dementia (CAN-THUMBS UP)

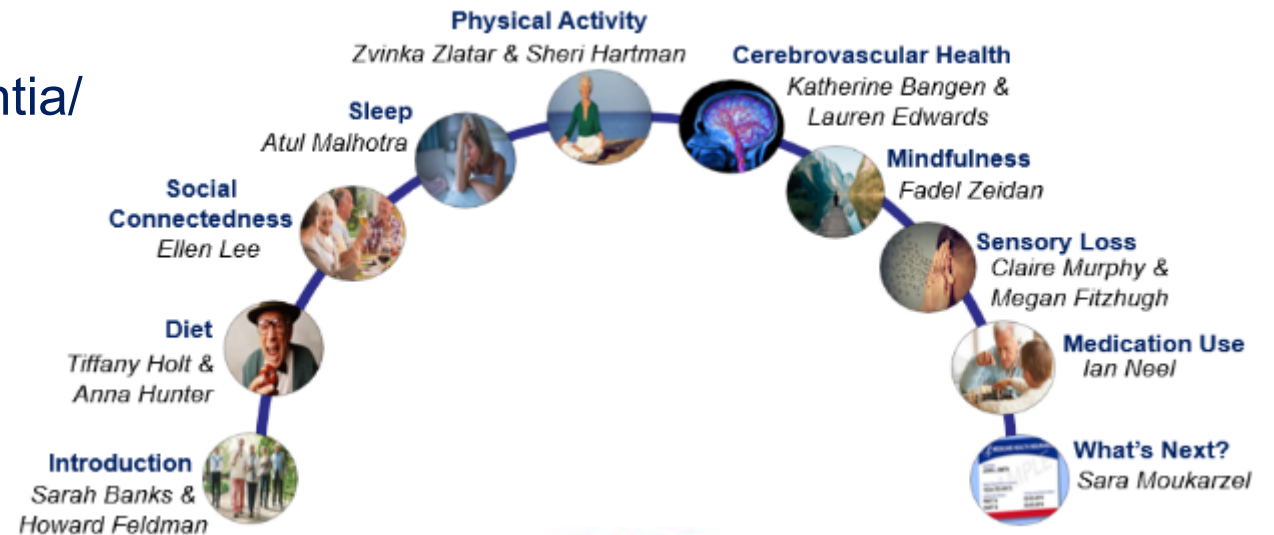
- <https://www.canthumbsup.ca/>
- <https://pubmed.ncbi.nlm.nih.gov/37874110/>



CCNA
Canadian Consortium
on Neurodegeneration
in Aging



CCNV
Consortium canadien en
neurodégénérescence
associée au vieillissement



Acknowledgements and Thank You!

■ NIH/NIA Funding

- R01AG061146-01 (Feldman)
- R01AG076634 (Gibson, Luchsinger, Feldman)
- U19AG079774-01 (Wang, Chui, Jung, Park)
- P30AG062429 (Brewer)

■ Canadian Institutes of Health Research (137794)

■ Epstein Family Alzheimer's Research Collaboration

■ Industry Funding

- Vivoryon Therapeutics
- Allyx Therapeutics

■ ADCS Site Network: Investigators and staff



QUESTIONS?