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Update on treatments for Alzheimer's disease

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COI and Grant Support

Conflict of Interest

- Consultant: Novo Nordisk, Eisai, Lundbeck, Biogen

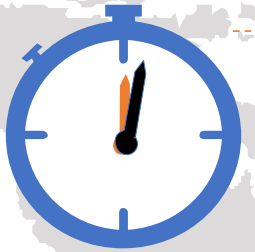
Current Grant support

- NIH:P30-AG066468; P01-AG025204; RF1-AG052525; U01-NS100610; U24-AG057437; U19-AG010483; U19-AG01048-24; R01-AG061848; U01-AG024904; U01-AG016976; R01-AG055389; R01-AG052510; R01-AG062531; R03-AG068413; R01-AG073267; R01-AG074971; R56-AG074951; R33-NS120245; RF1-AG080591; R01-AG083874.
- Foundations: Pittsburgh Foundation; Hillman Foundation; Aging Mind Foundation; Chuck Noll Foundation; Greater Houston Community Foundation.
- Other: NIDA; National Football League.

Epidemiology

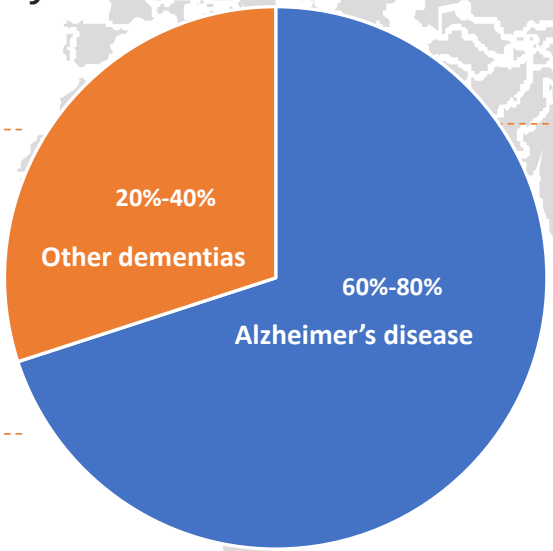
Global Statistics

The global number of people with dementia will increase from 50 in 2019 to **152 million** in 2050[4]



Someone is diagnosed with dementia every **3 seconds**[1]

~50 million people worldwide are currently living with dementia; this is around the population of South Korea or Spain[2]

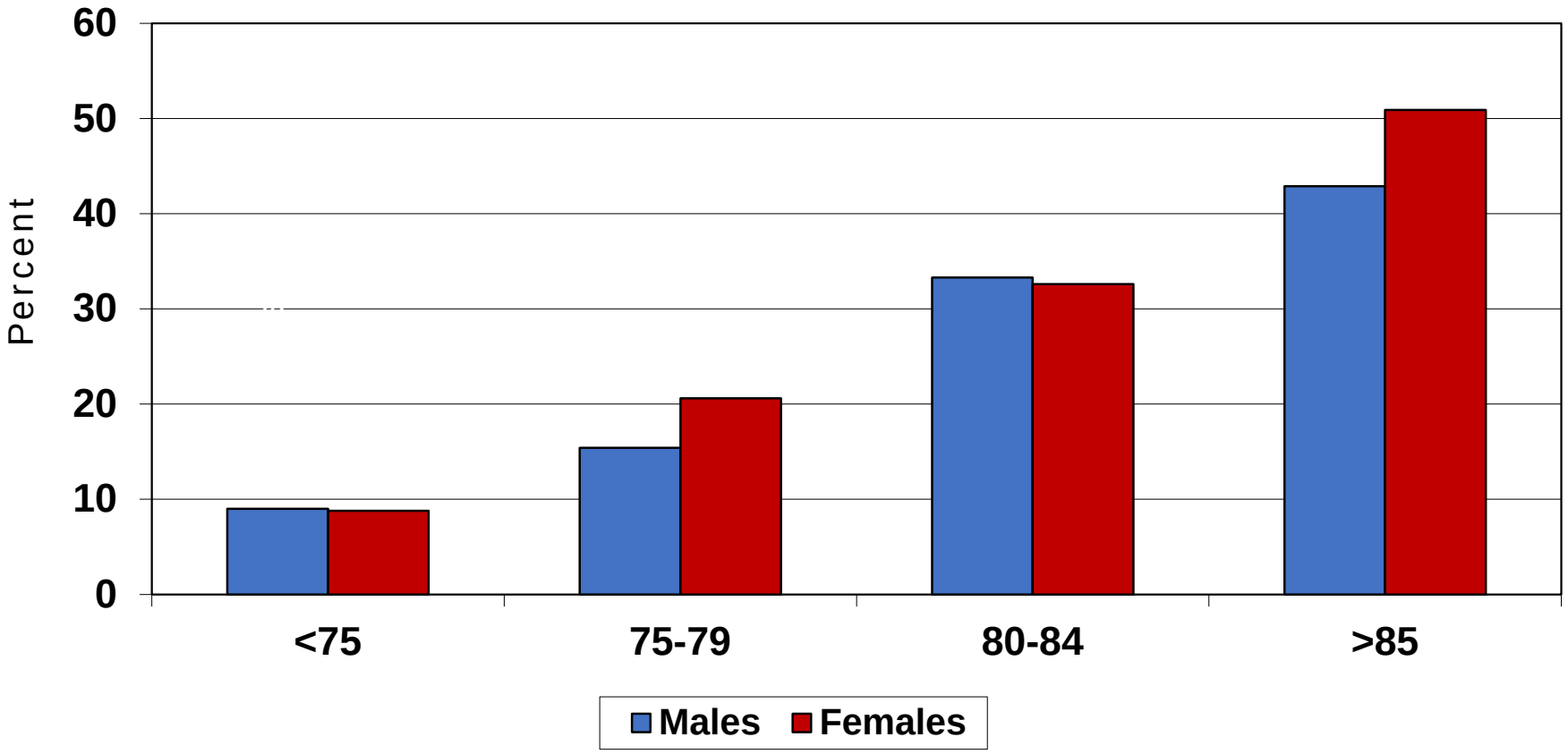


Alzheimer's disease is the most common cause of dementia, accounting for **60% to 80%** of cases worldwide[2,3]

There are **~10 million new cases** of dementia diagnosed **annually**[2]

1. World Health Organization. 10 facts on dementia. https://www.who.int/features/factfiles/dementia 2. World Health Organization. Dementia. Published September 21, 2020. 3. Alzheimer's Association. Alzheimer's Dement. 2021;17:327–406. 4. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the global burden of disease study 2019. GDB 2019. The Lancet Public Health 2022, January 6

Prevalence of dementia in the Cardiovascular Health Study (N=3,606, 490 with dementia)



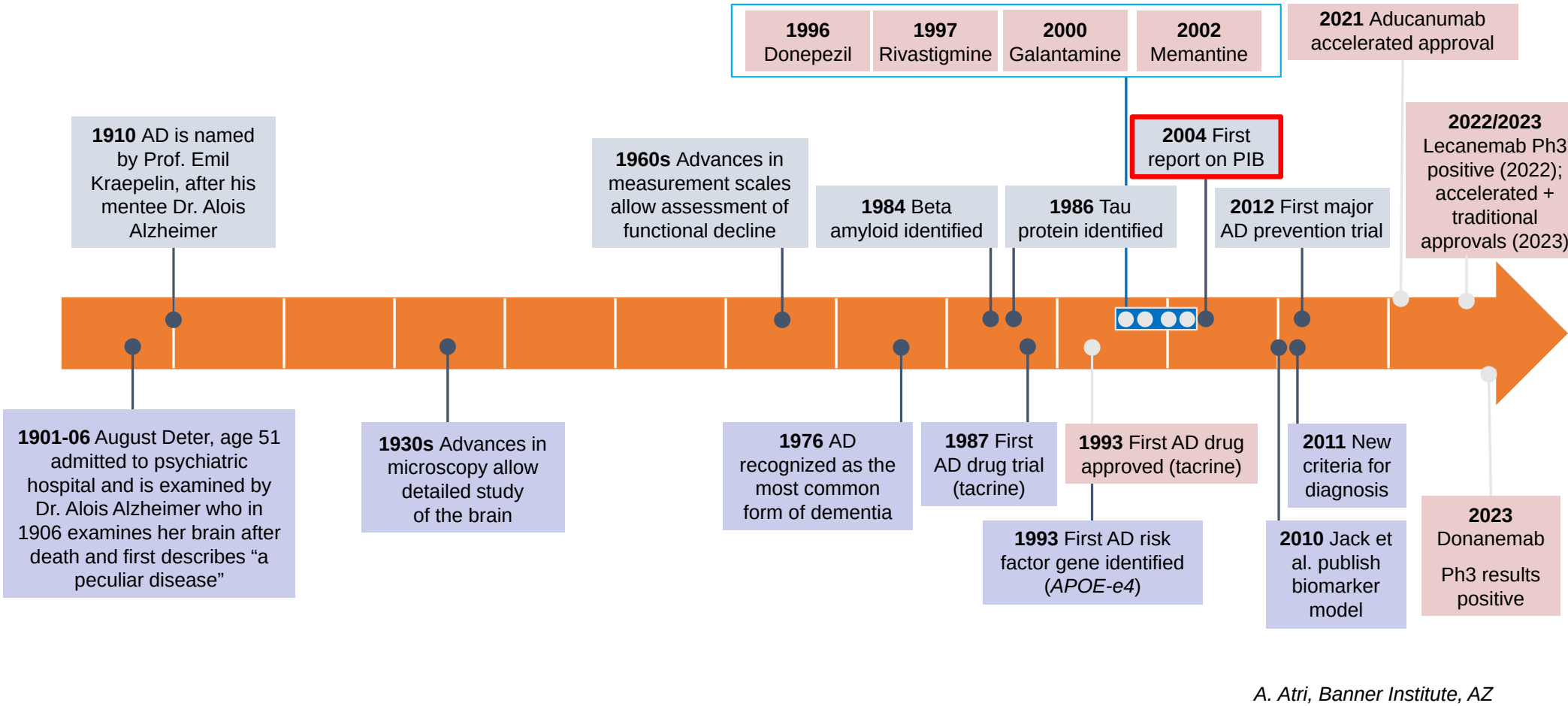
Fitzpatrick et al, JAGS 2004; 52: 195-204

Risk Factors for Alzheimer's Disease

Probable	• **Age** • APOE-4 allele
Possible	• Women • **Cerebrovascular disease** • **Cardiovascular risk factors (e.g., diabetes, hypertension)** • History of head trauma • Family history of dementia • Family history of Down's syndrome
"Protection"	• Moderate alcohol intake • Mediterranean diet • Physical activity • Cognitive activity

Lopez OL, et al. Journal of Alzheimer's Disease 2013 ***33****(1): S427-S438*

120 years of Alzheimer's disease (AD)

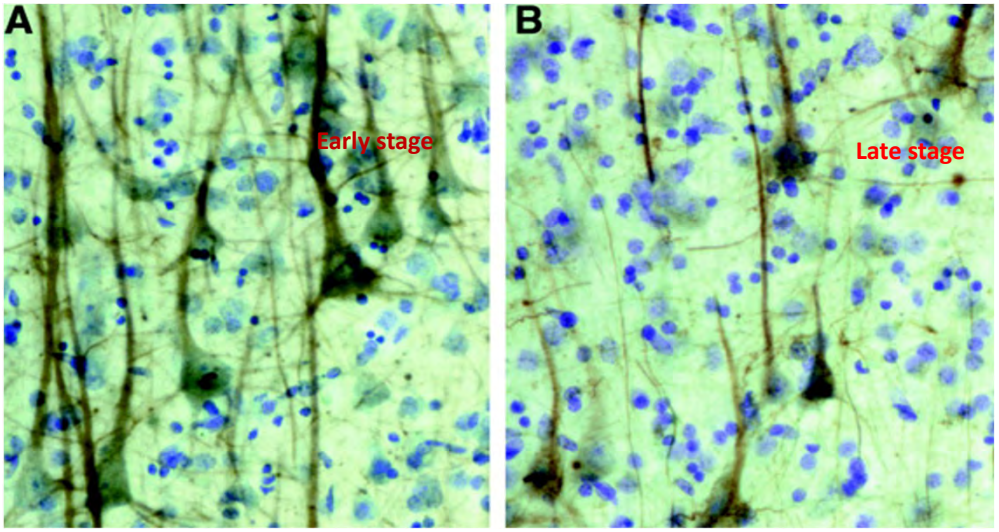


A. Atri, Banner Institute, AZ

Alzheimer's disease is a neurodegenerative process

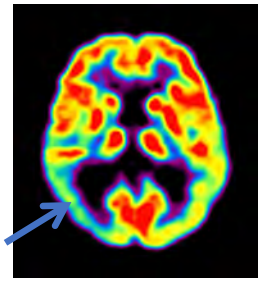
Neurodegeneration is a term used to describe the progressive loss of structure or function of neurons, including death of neurons.

Pyramidal Neuron Loss

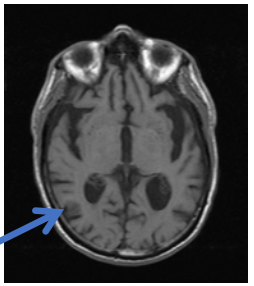


Examples of SMI-32 immunohistochemistry in layer IIIc of a CDR 0.5 case (A) and a CDR 3 case (B). *Bussière et al. J Comp Neurol.* 2003

N

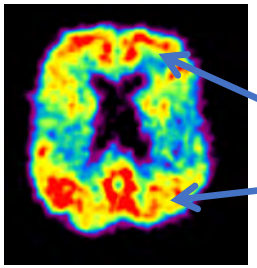


FDG-PET

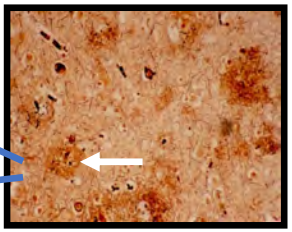


MRI

A



11CPiB-PET



Amyloid Plaques

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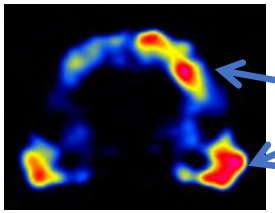
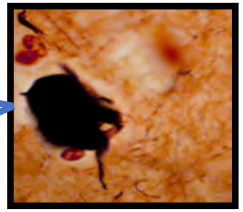
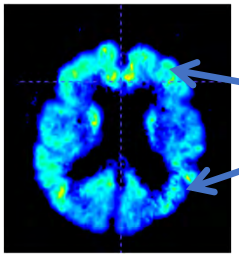


18F-flortaucipir

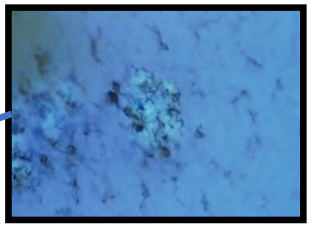


Neurofibrillary tangles

I

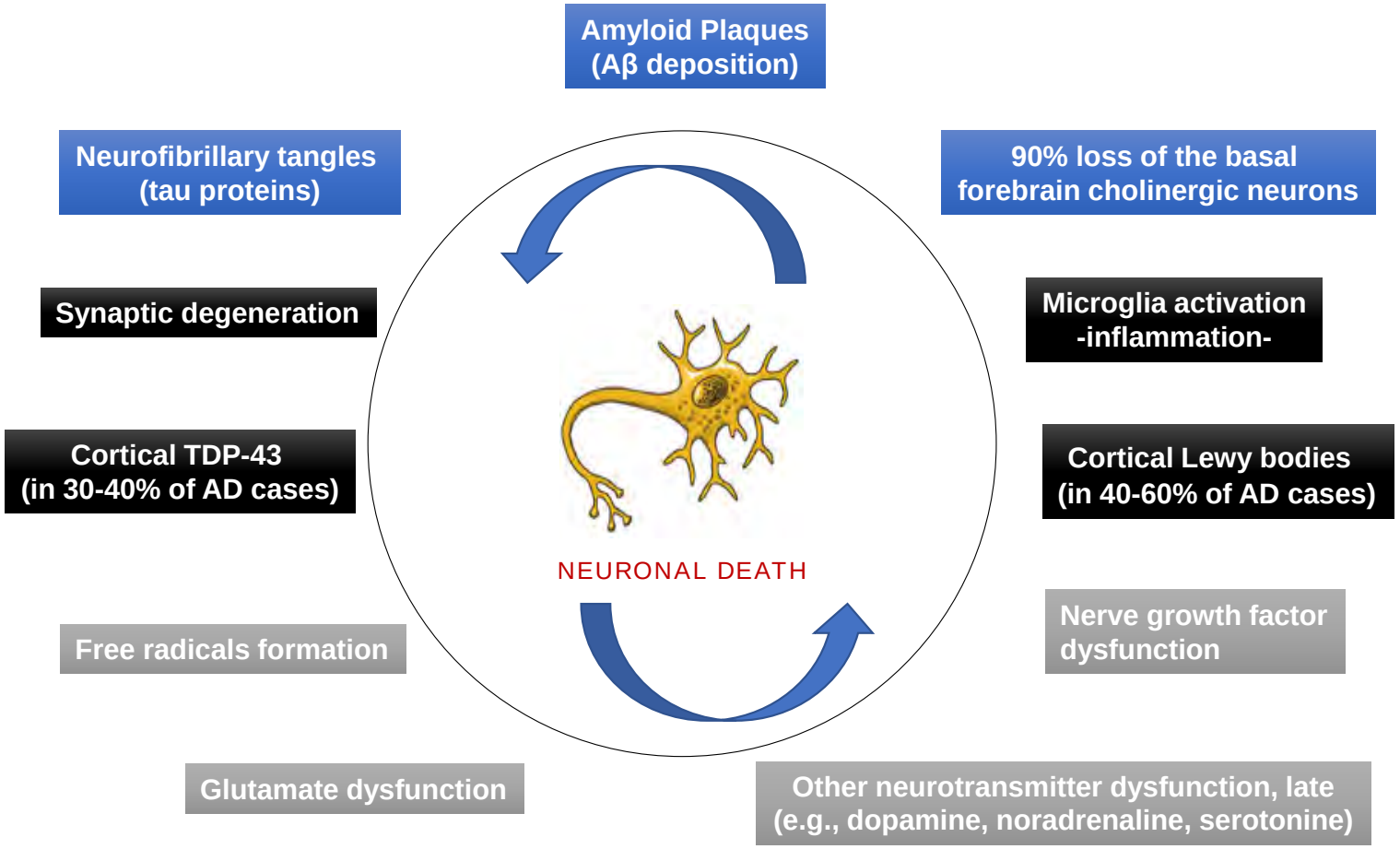


18F-SMBT-1



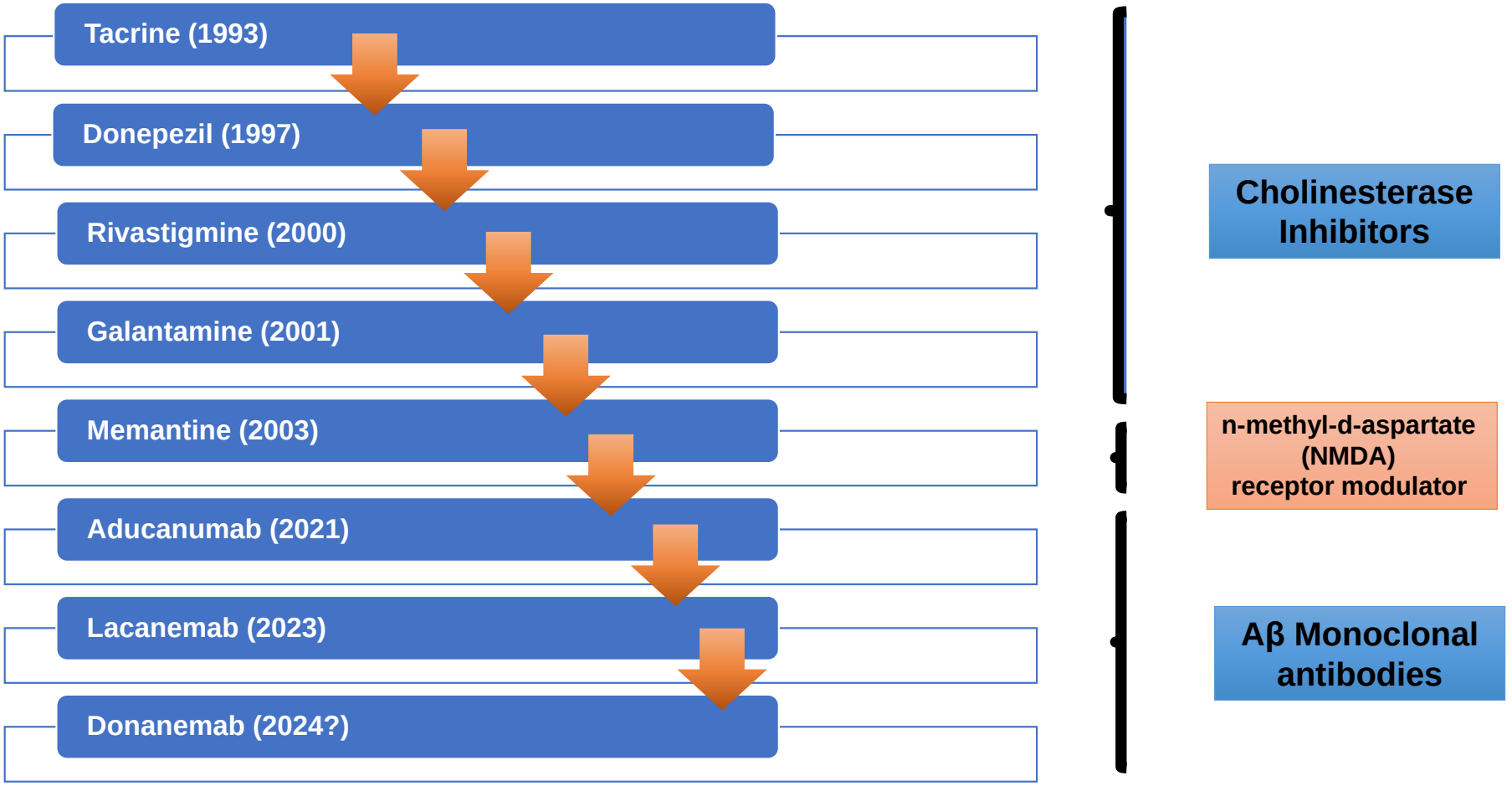
Inflammation

Structural Lesions and Biochemical Changes in AD



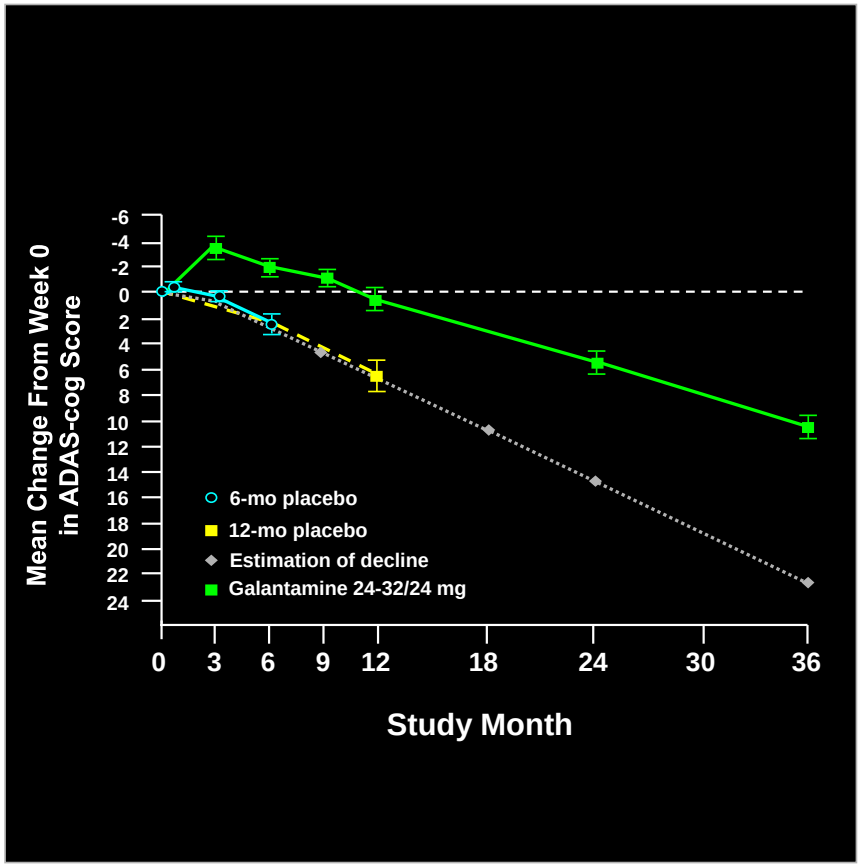
O.Lopez 2022

FDA Approved Medication for Alzheimer's disease

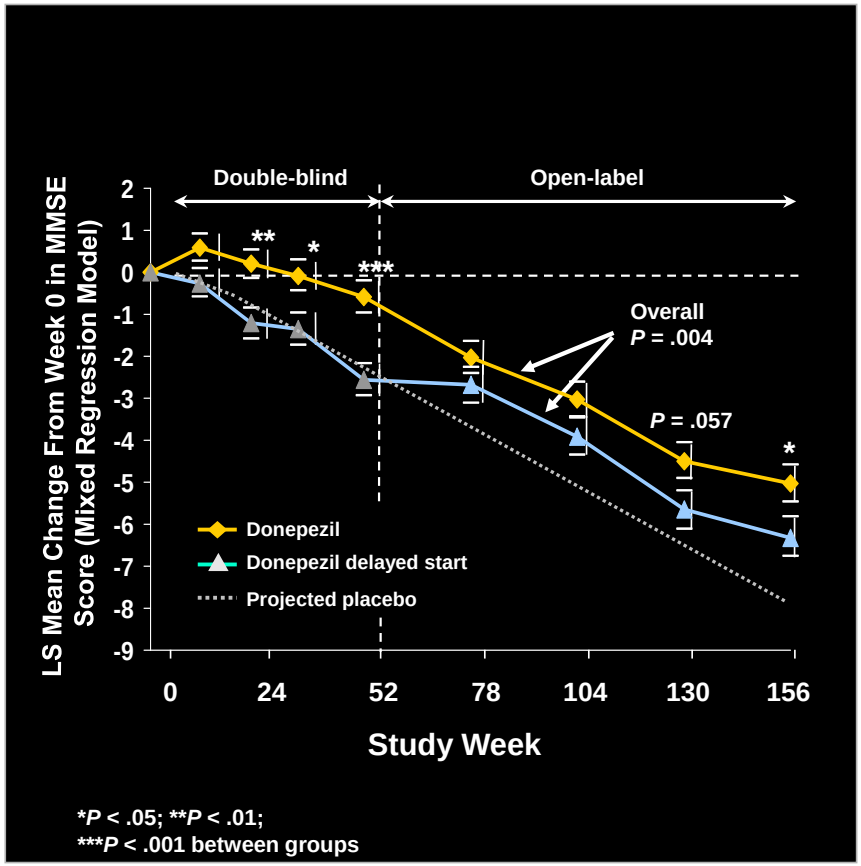


O.Lopez, 2021

Treatment With Cholinesterase inhibitors Over 3 Years

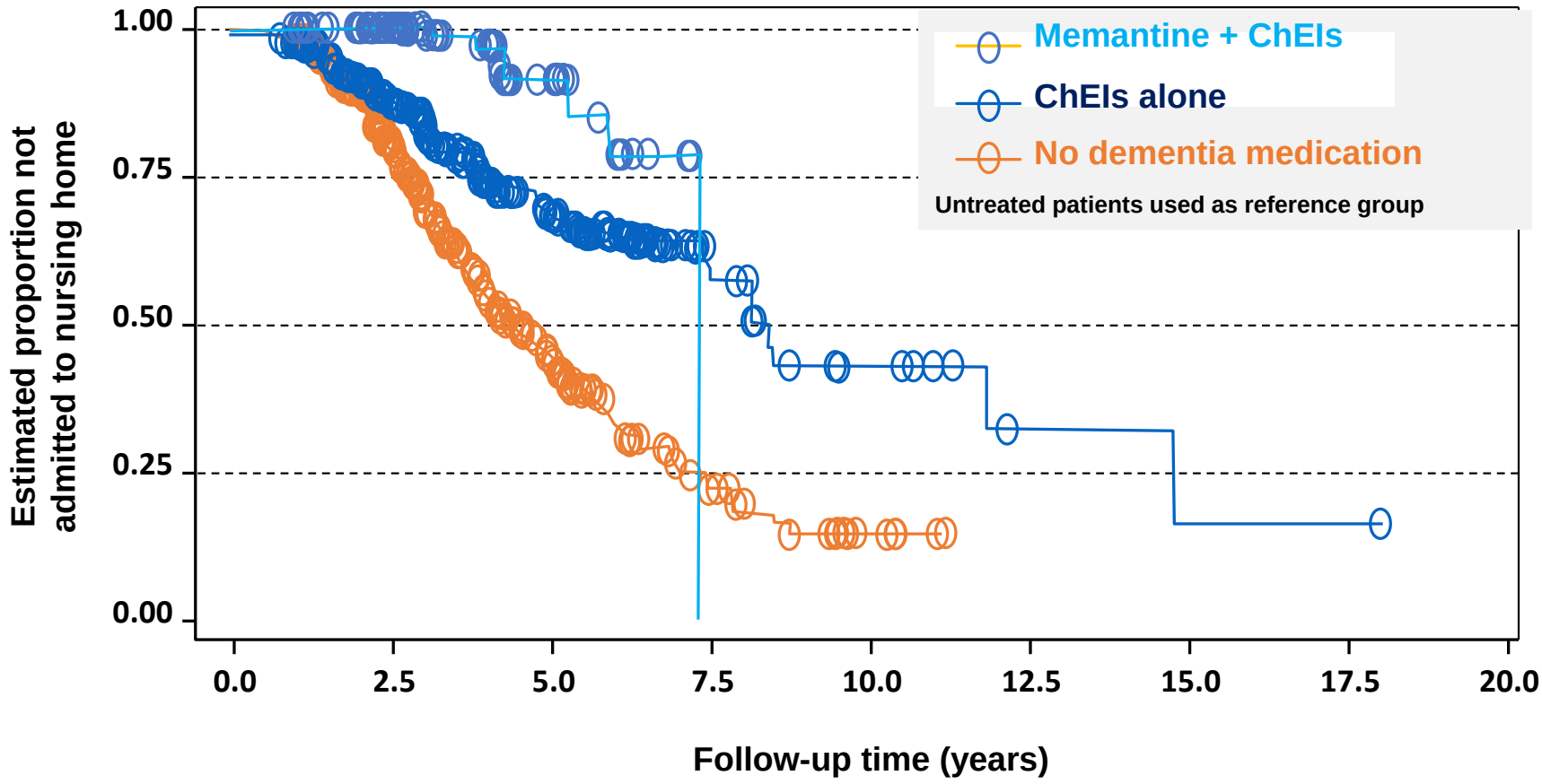


Raskind MA, et al. *Arch Neurol*. 2004.



Winblad B, et al. *Dement Geriatr Cogn Disord*. 2006.

Memantine in combination with Cholinesterase inhibitors delays nursing home admission (N= 943 Probable AD Patients)



Lopez et al. J Neurol Neurosurg Psychiatry 2009; 80: 600–607

There are currently 187 trials assessing 141 drugs for the treatment of AD

36 agents in phase 3

21 pathological pathways

More than 57,000 participants will be required to populated all currently registered trials

Cummings J, et al. Alzheimers & Dement 2023 Apr-Jun; 9(2): e12385

>230 treatment/intervention studies currently funded by the NIH for Alzheimer's disease

- **Early-Stage Clinical Drug Development (n= 39)**
- **Late-stage Clinical Drug Development (Phase II/III and III Clinical and Pragmatic Trials) (n= 9)**
- **Non-pharmacological interventions (n= 111)**
- **Clinical Therapy Development for the Neuropsychiatric Symptoms of Dementia (n= 9)**
- **Care and Caregiver Interventions (n= 65)**

NIA-Funded Active Alzheimer's and Related Dementias Clinical Trials and Studies | National Institute on Aging (nih.gov)

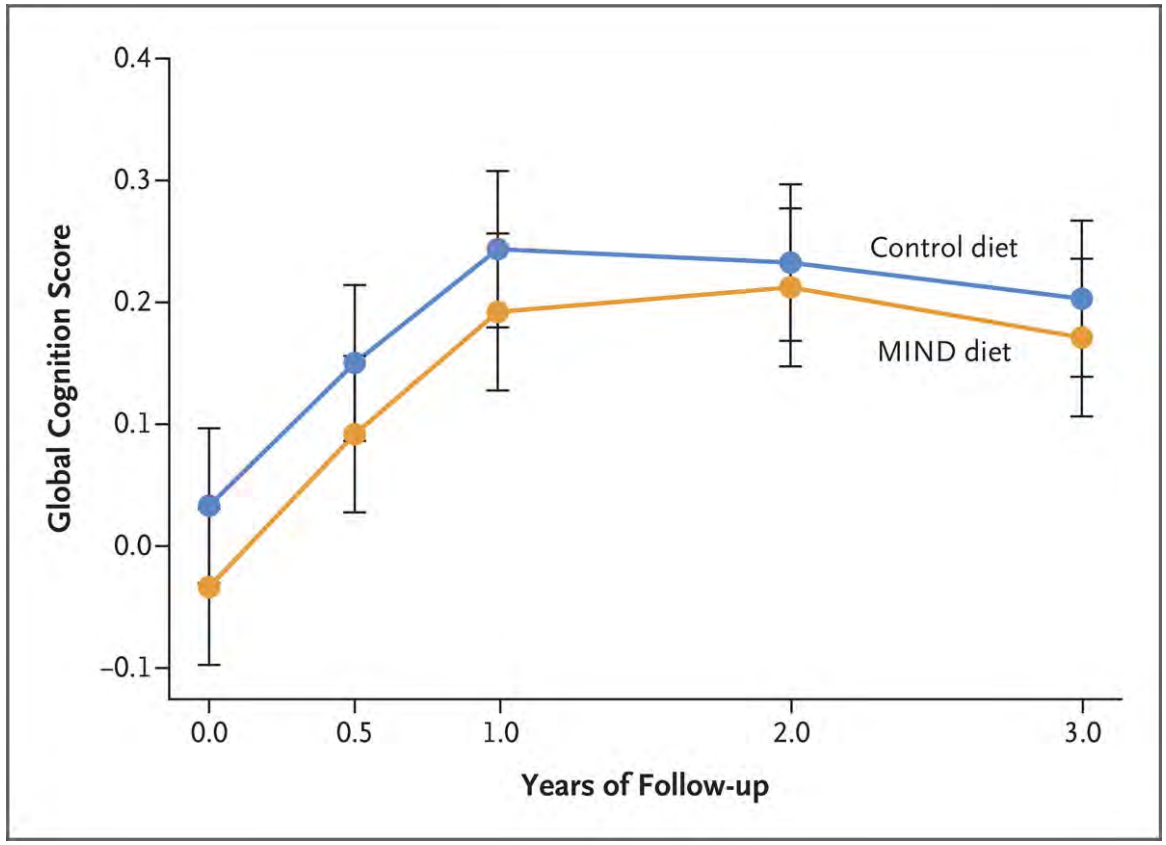
Current non-pharmacological interventions as prevention and treatment of cognitive disorders funded by the NIA.

Target	Number of studies	Method
Assisted technology and devices	13	e.g., Social activities instructed by a social robot; digital multidomain lifestyle intervention; in-home devices
Exercise	27	e.g., aerobic exercise, dancing,Tai Ji *Exert* Study *completed*: negative
Diet	7	e.g., Cocoa + MVI (*completed*), Ketogenic diet
Cognitive Training	18	e.g., Prevention of AD by cognitive training. Computerized training, smartphone
Combination therapy	11	e.g., aerobic exercise + cognitive training
Sleep	6	e.g., Cognitive behavioral therapy for insomnia
Neurostimulation	14	e.g., transcranial magnetic stimulation, photo-biomodulation
Other	14	e.g., internet-based conversation, hyperbaric oxygen therapy, mindfulness, conversation engagement, Light therapy

NIA-Funded Active Alzheimer's and Related Dementias Clinical Trials and Studies | National Institute on Aging (nih.gov)

Trial of the MIND Diet for Prevention of Cognitive Decline in Older Persons (N= 604, 3 years follow up)

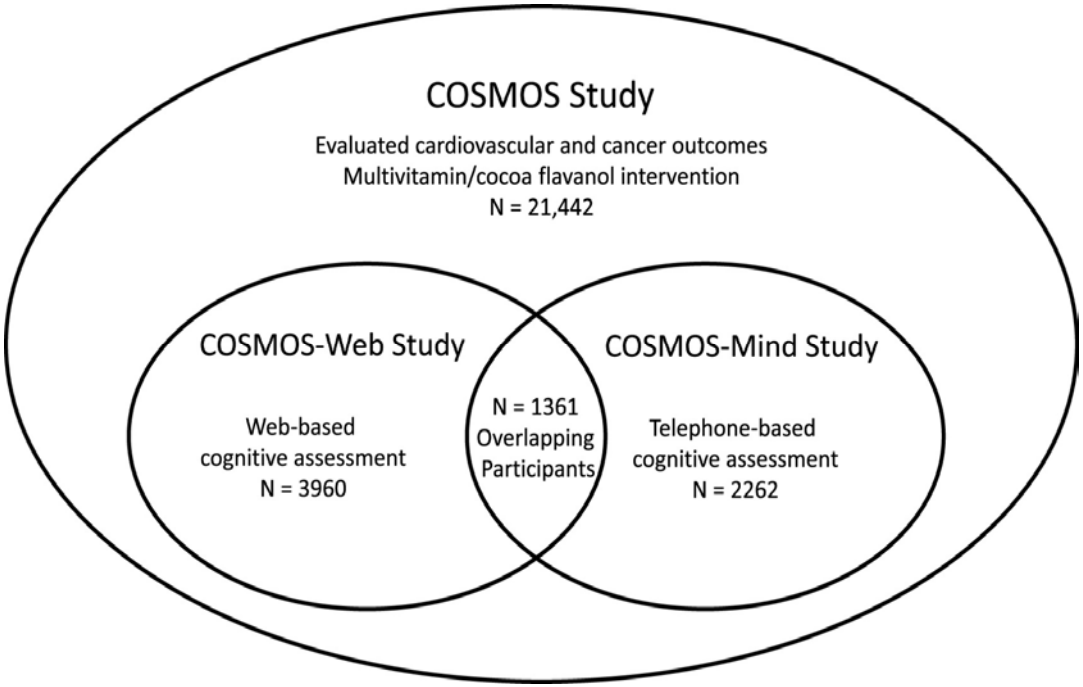
Among cognitively unimpaired participants with a family history of dementia, changes in cognition and brain MRI outcomes from baseline to year 3 did not differ significantly between those who followed the MIND diet and those who followed the control diet with mild caloric restriction.



MIND diet: Plant-based foods, fish, and olive oil.
Limits saturated fats and sugar

LL Barnes et al. N Engl J Med 2023;389:602-611.

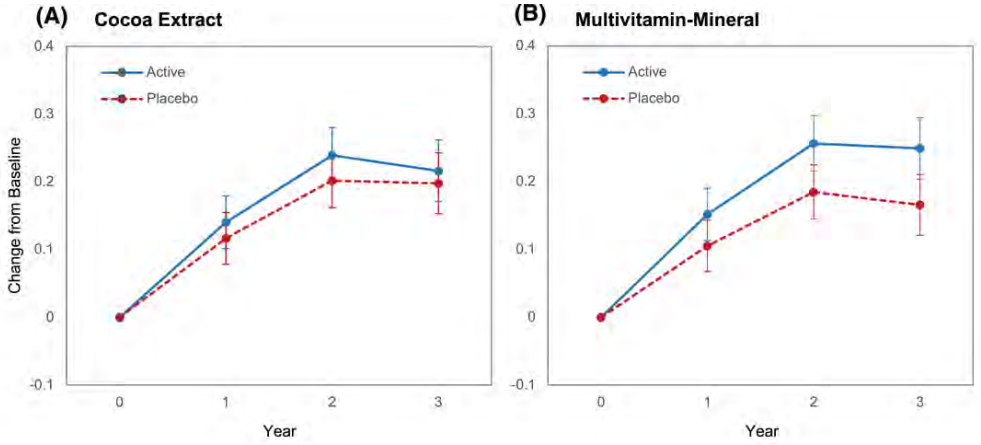
Effect of cocoa flavanol supplementation for the prevention of cardiovascular disease events: the COcoa Supplement and Multivitamin Outcomes Study (COSMOS) randomized clinical trial, and its ancillary studies (COSMOS-Mind)



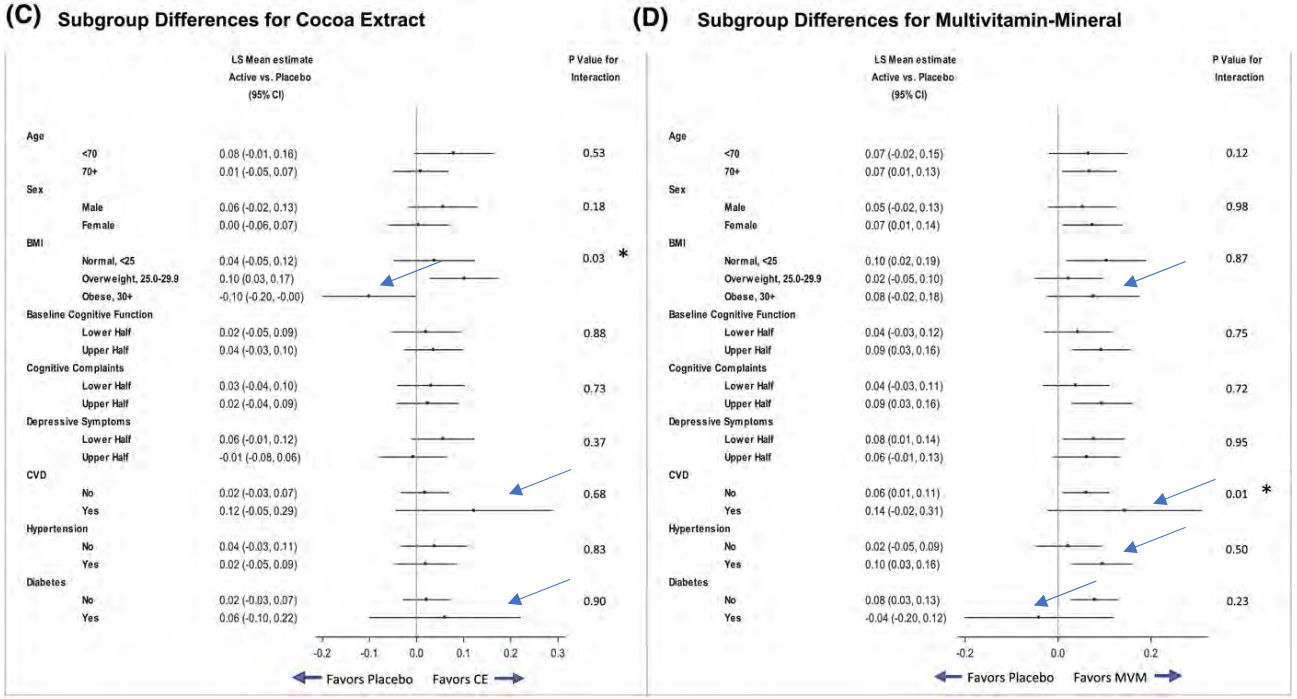
There was no effect on cardiovascular events, stroke, or death

Per-protocol analyses censoring follow-up at nonadherence supported a lower risk of total CVD events (HR: 0.85; 95% CI: 0.72, 0.99).

Yeung L., et al. The American Journal of Clinical Nutrition 2023; 118: 273-282
Sesso HD, et al. The American Journal of Clinical Nutrition 2022; 115: 1490-1500.



COSMOS-Mind Study: Effects of cocoa extract and a multivitamin on cognitive function: A randomized clinical trial



There was no cognitive benefit of daily cocoa extract administration.

Daily multivitamin-mineral (MVM) supplementation for 3 years improved global cognition, episodic memory, and executive function.

Neither cocoa nor MVM decreased the risk of incident MCI or dementia

Baker L, et al. Alzheimer's & Dementia 2022: 19: 1308-1319.
Sachs B, et al. Alzheimer's and Dementia 2023: 20: 1-9

Clinical Therapy Development for the Neuropsychiatric Symptoms of Dementia

Study	Compound/Intervention
Pharmacological	
Treatment of psychosis and agitation in AD	Lithium
Apathy in AD methylphenidate Trial II (ADMETII)	Methylphenidate
Escitalopram for agitation in Alzheimer's disease (S-CitAD)	Escitalopram
Trial of dronabinol adjunctive treatment of agitation in ADl(THC-AD)	Dronabinol
PEACE-AD Prazosin for Agitation in Alzheimer's disease	Prazosin (completed)
Night-time Agitation and restless legs syndrome with AD	Gabapentin Enacarbil
Life's end Benefits of CannaBidol and TetrahYdrocannabinol (LiBBY) Trial	THC and CBD oils
Non-pharmacological	
Reducing agitation in dementia patients at home: The customized Activity Trial	Patient customized activity
Problem adaption therapy for mild cognitive impairment with depression	Psychosocial therapy
Electroconvulsive therapy (ECT) for agitation in AD	ECT

ClinicalTrials.gov 2020-2021

Current and Recent Prevention Trials

Study	Drug	Subjects	Comments	Status/outcome
National Institute on Aging + Lilly –*The A4 Study*	Solaneuzumab	1,000 with subjective cognitive complaints	Positive amyloid PET scan	Negative (favored placebo)
National Institute on Aging + Eisai –*The AHEAD A3-A45 Study*	Lecanemab (BAN2401)	1,400 cognitively normal or with some complaints	-Preclinical AD with elevated amyloid deposition by PET scan (A45 Trial). -Early preclinical AD with intermediate amyloid deposition (A3 Trial).	**On going**
SKYLINE Trial (Roche)	Gantenerumab	1,200 cognitively normal or with some complaints	CSF/PET positive for amyloid	Stopped
Dominantly Inherited Alzheimer Network Trial (DIAN-TU) National Institute on Aging + Lilly + Roche	Solaneuzumab (phase 3) Gantenerumab (phase 2)	194 Cognitive normal (or with mild deficits) subjects with mutations in PSEN1, PSEN2, and APP genes	Cognitive end points were negative. Positive effect on biomarkers. Will reinitiate with other Mab.	Stopped
Autosomal Dominant Alzheimer's Disease (ADAD) Colombia Trial: National Institute on Aging + Genentech/Roche	Crenezumab	252 PSEN1 E280A mutation carriers who typically develop symptoms around age 45.	Conducted mainly in Antioquia, Colombia, with a US cohort.	Negative
GENERATION TRIAL: National Institute on Aging + Novartis	CAD106 + CNP520	480 Cognitively unimpaired individuals with two APOE4 genes		Negative
Metformin in Alzheimer's Dementia Prevention (MAP)	Metformin 500 mg to 2000 mg daily	370 early and late MCI without diabetes	Primary outcome: Free and Cued Selective Reminding Test	**On going**
Pragmatic Evaluation of Events and Benefits of Lipid-Lowering in older adults (PREVENTABLE)	Atorvastatin 40 mg daily	20,000 non-demented individuals, not taking lipid lowering drugs	End points: Incident MCI, dementia, CVD, mortality	**On going**
Presenilin 1 (PSEN1), presenilin 2 (PSEN2), and amyloid precursor protein (APP)				

Recent disease-modifying trials in Alzheimer's disease: Amyloid-targeted therapies

Author	Drug	N of patients	Outcome measures	p-value	% less decline
Doody et al. 2014	Solaneuzumab	1,396	ADAS-cog + ADCS-ADL	N.S.	
Doody et al. 2014	Solaneuzumab	1,306	ADAS-cog	**0.06**	
			ADCS-ADL	**0.08**	
Honig et al, 2018	Solaneuzumab	2,129	ADAS-cog	N.S.	
Salloway et al, 2014	Bapineuzumab	2,321	ADAS-cog + DAD	N.S.	
Egan et al, 2018	Verubecestat	1,958	ADAS-cog + ADCS-ADL	N.S.	
Egan et al, 2019	Verubecestat	1,454	CDR-SB	**0.01#**	
Henley et al. 2019	Atavesestat	557	PACC + RBANS	Stopped#	
Wessels et al. 2019	Lanabecestat	2218	ADAS-cog	N.S.	
Wessels et al. 2019	Lanabecestat	1177	ADAS-cog	N.S.	
Haeberlein et al. 2022	Aducanumab 301	1,647	CDR-sb + ADAS-cog	N.S.	
Haeberlein et al. 2022	Aducanumab 302	1,638	CDR-sb	**0.01**	**22%**
			ADAS-cog	**0.01**	**27%**
			ADCS-ADL	**0.001**	**40%**
Press release, 2022	Gantenerumab	1,965	CDR-sb	N.S.	
Ostrowitzki et al. 2022	Crenezumab	1,619	CDR-sb	N.S.	
Van Dyck et al. 2023	Lacanemab	1,795	CDR-sb	**0.001**	**27%**
			ADAS-Cog (secondary outcome)	**0.001**	**47%**
Sims et al. 2023	Donanemab	1736	iADRS	**0.001**	**35%**
			CDRsb (secondary outcome)	**0.001**	**36%**

#:favors placebo. ADAS-cog: Alzheimer's disease Assessment Scale-cognition; ADCS: Alzheimer's Disease Cooperative Study-Activities of daily living; DAD: Disability Assessment for Dementia. ADCS-CGIC: Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change, CDR-sb: Clinical Dementia Rating –sum of boxes. iADRS: integrated Alzheimer's Disease Rating Scale; PACC: Preclinical Alzheimer's Cognitive Composite; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) .

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Recent disease-modifying and symptomatic trials in Alzheimer's disease

Author	Drug	N of patients	Outcome measures	p-value	% less decline
tau-targeted therapies					
Florian et al, 2023	Tilavonemab	453	CDRsb	N.S.	
ClinicalTials.gov	Zagotenemab	360	iADRS	N.S.	
Teng et al. 2022	Semorinemab	422	CDRsb	N.S.	
Monteiro et al, 2023	Semorinemab	272	ADAS-Cog	p=0.0008	42%
			ADCS-ADL	N.S.	
			MMSE	N.S.	
			CDRsb	N.S.	
Other therapies					
Craft et al, 2020	Intranasal insulin	240	ADAS-cog	N.S.	
Atri et al, 2018	Idalopirdine	2,525	ADAS-cog	N.S.	
			ADCS-ADL	N.S.	
Boada et al. 2020	Plasma exchange	347	ADAS-cog	**0.06**	**66%**
			ADCS-ADL	**0.03**	**52%**
			CDR-sb	**0.002**	**71%**
			ADCS-CGIC	**<0.001**	**100%**

ADAS-cog: Alzheimer's disease Assessment Scale-cognition; ADCS: Alzheimer's Disease Cooperative Study-Activities of daily living; DAD: Disability Assessment for Dementia. ADCS-CGIC: Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change, CDR-sb: Clinical Dementia Rating –sum of boxes; iADRS: integrated Alzheimer's Disease Rating Scale.

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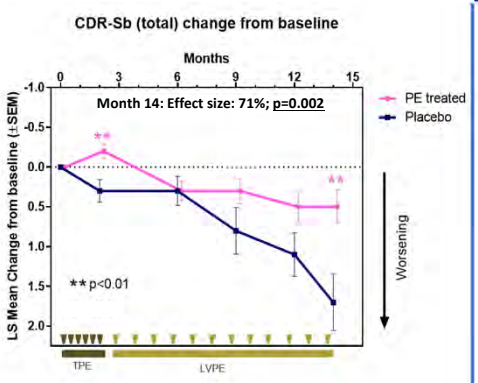
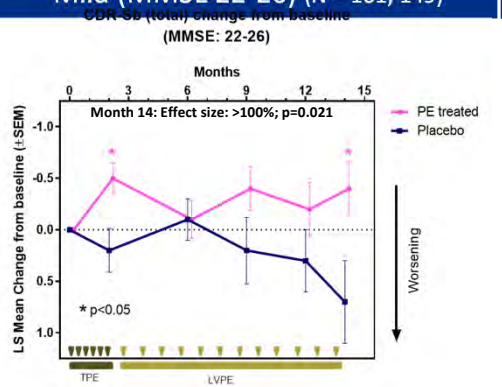
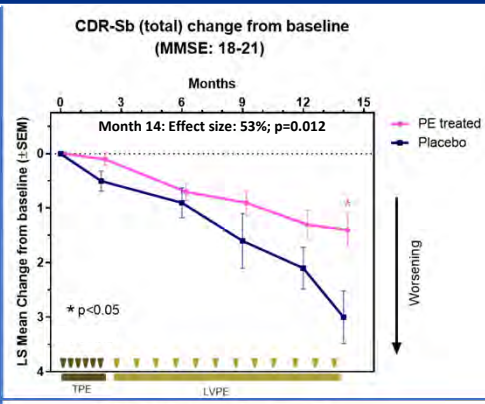
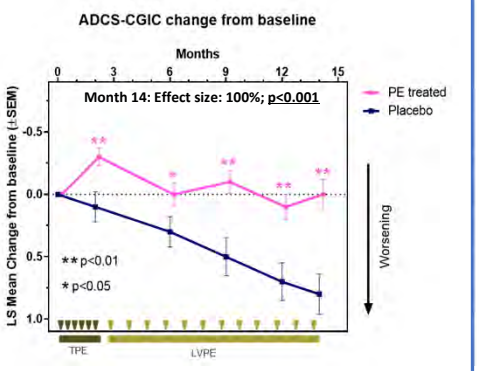
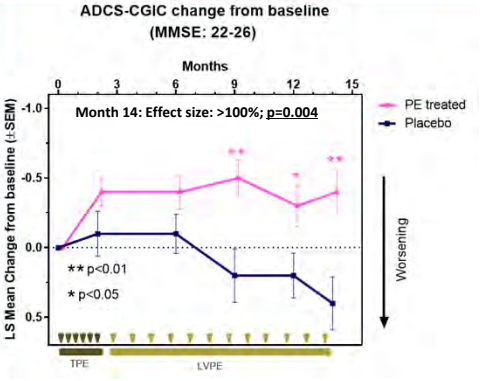
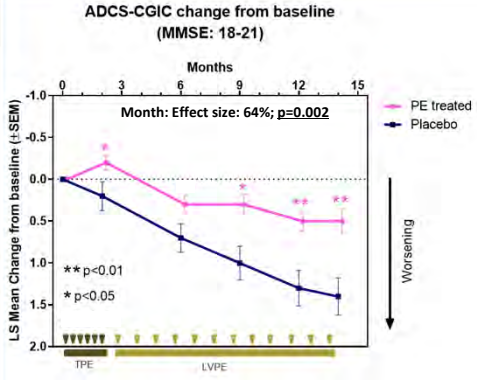
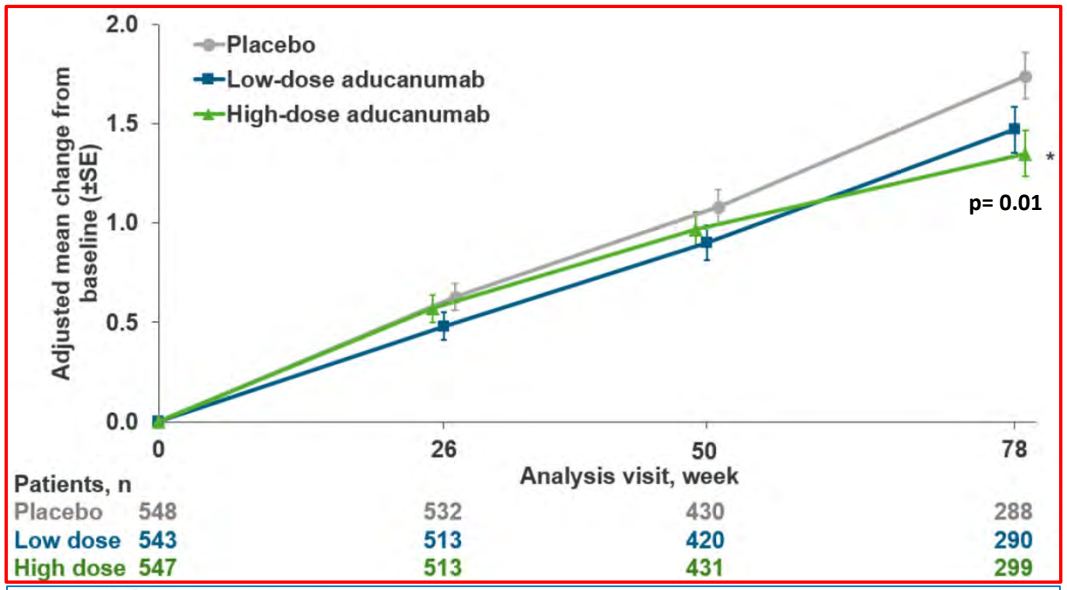
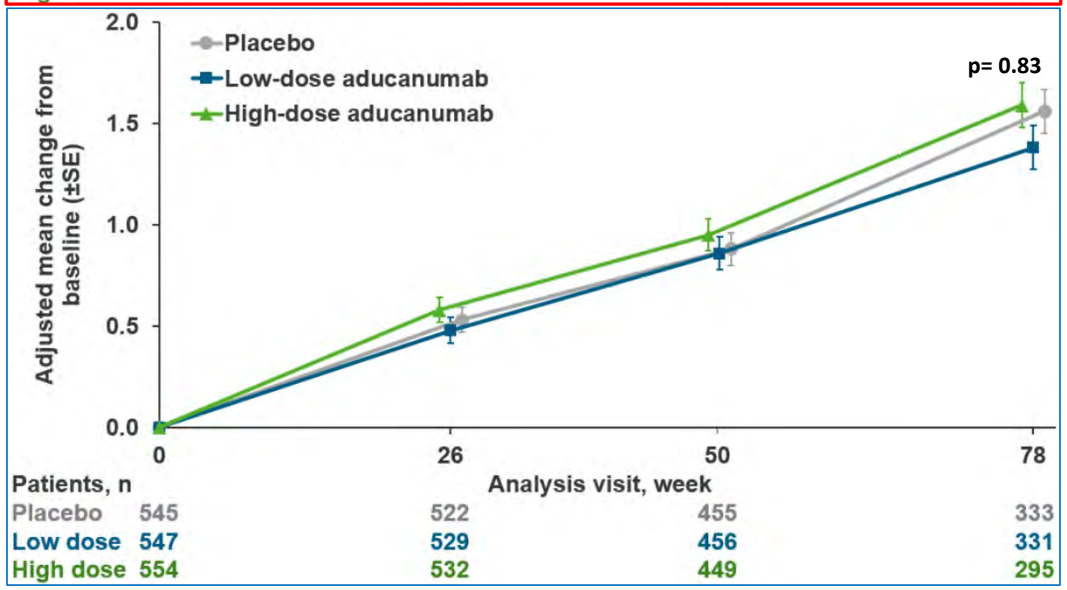
AMBAR: Global end-points: Cognition/function and physician's impression

	All Patients (N = 321; 299)	Mild (MMSE 22-26) (N = 161; 149)	Moderate (MMSE 18-21)(N=160;150)
CDR-Sb			
ADCS-CGIC			

CDR-Sb: Clinical Dementa Rating – Sum of Boxes
ADCS-CGIC: AD Cooperative Study- Clinical Global Impression of Change

Boada M, et al. Alzheimers & Dementia 2020 Oct;16(10):1412-1425.





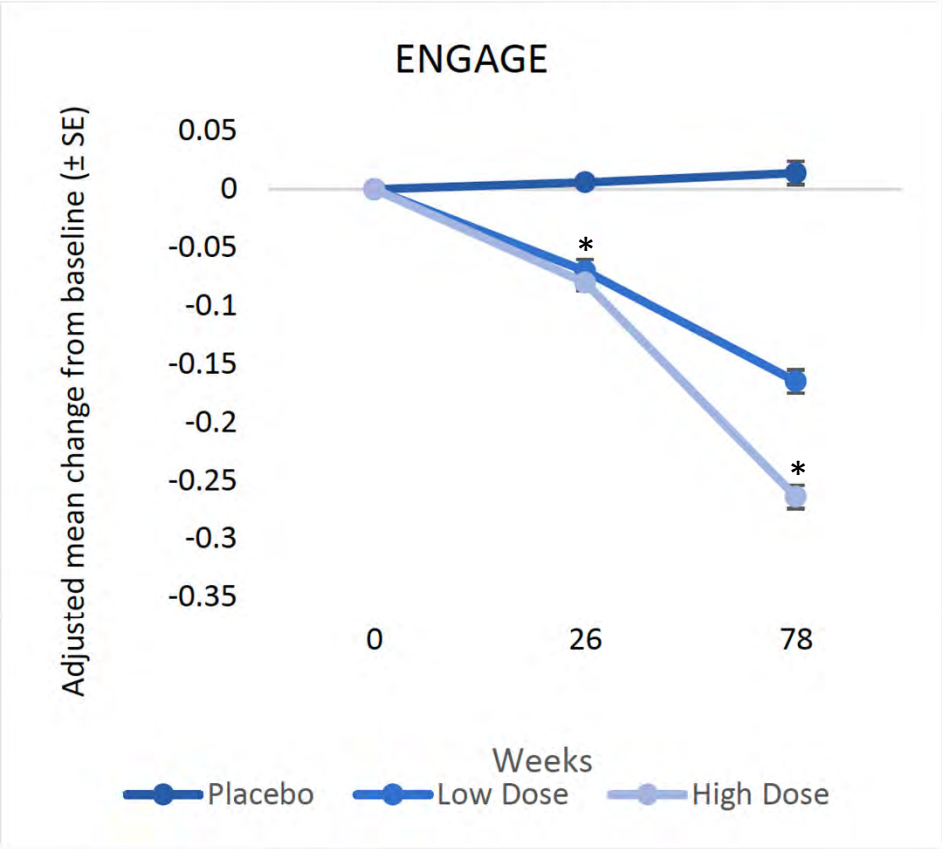
ADUCANUMAB

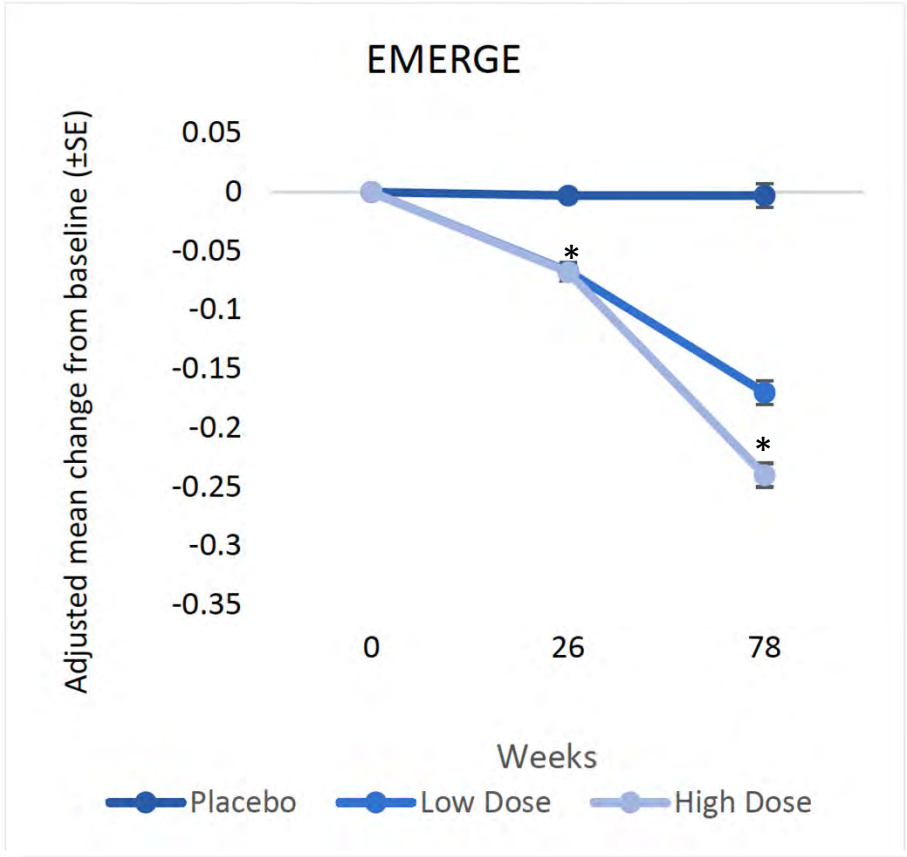
Change from baseline on the CDR-SB over time in Study 302 (EMERGE)
22% less decline

Change from baseline on the CDR-SB over time in Study 301 (ENGAGE)
2% increase

S. Budd Haeberlein, et al. J Prev Alz Dis 2022;2(9):197-210

Change from baseline in Aβ PET SUVR in EMERGE and ENGAGE

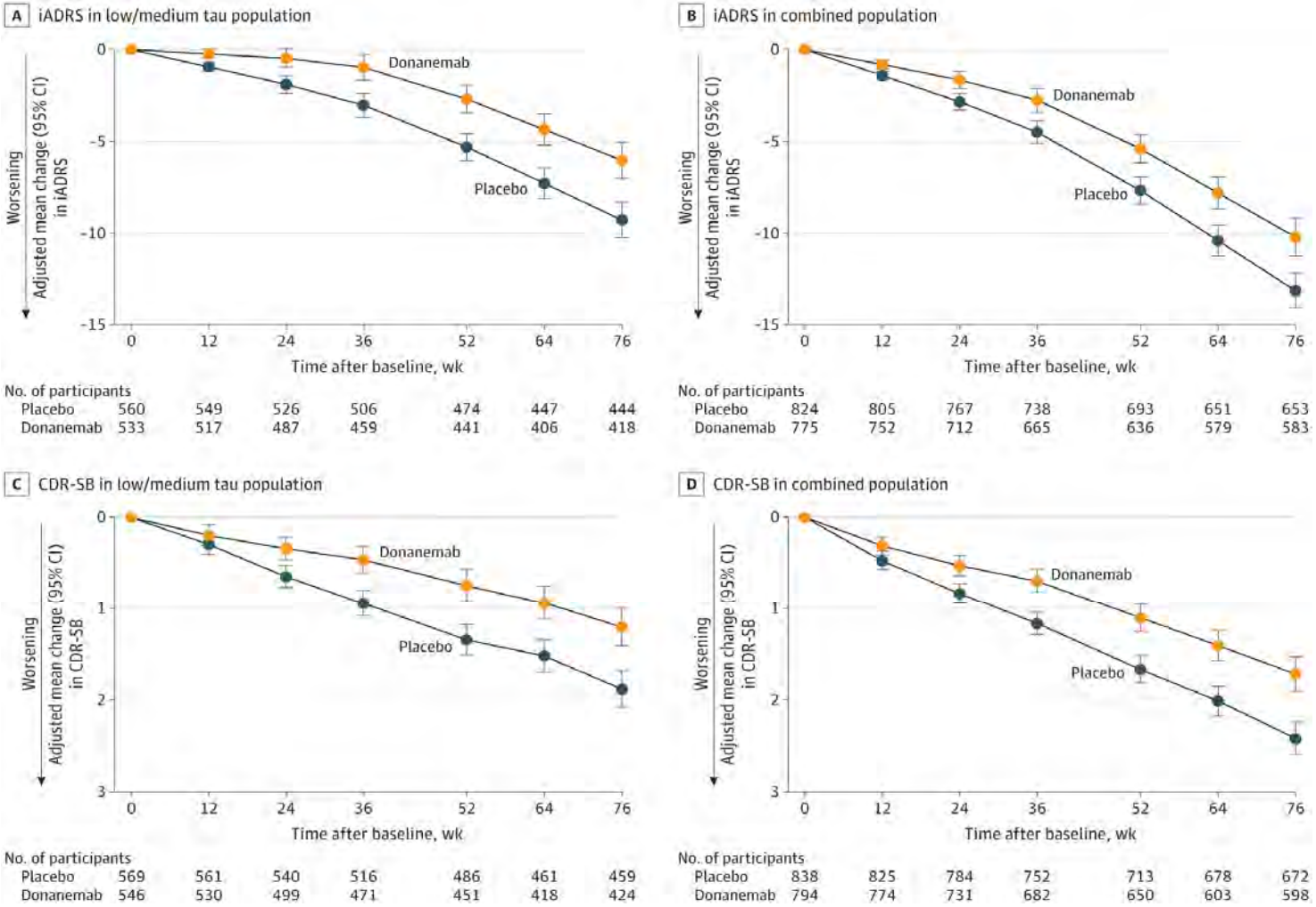




SE: standard error

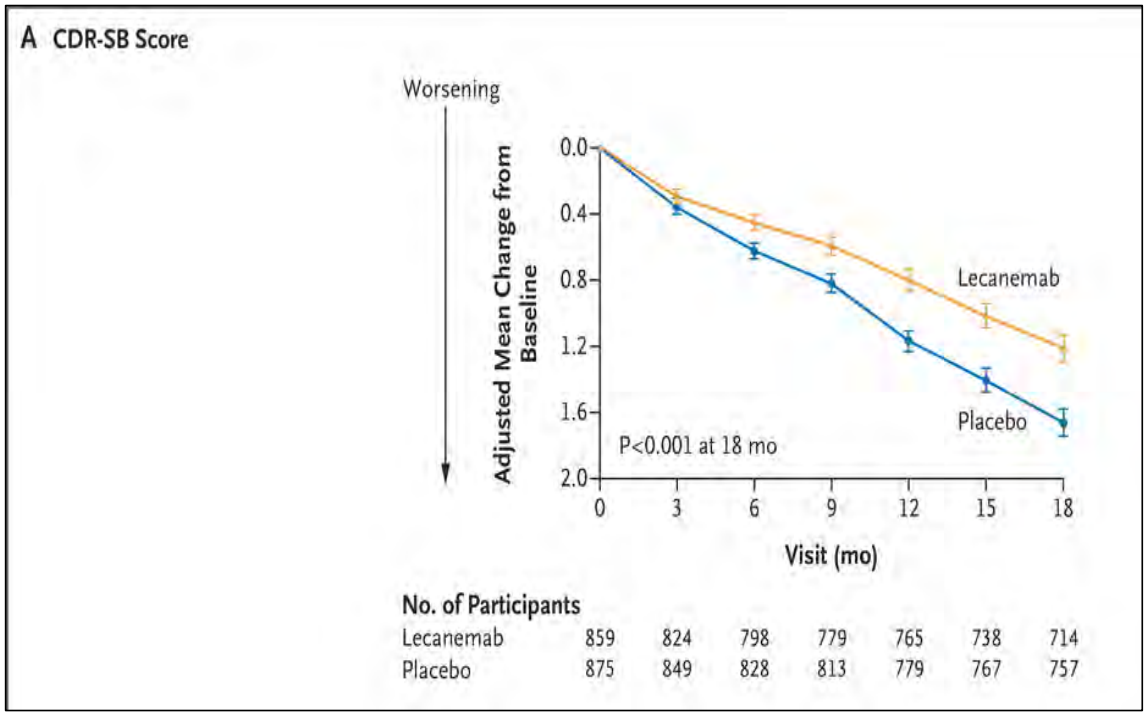
S. Budd Haeberlein, et al. J Prev Alz Dis 2022;2(9):197-210

Donamemab in early Alzheimer's disease: Integrated Alzheimer Disease Rating Scale (iADRS) and Sum of Boxes of the Clinical Dementia Rating Scale (CDR-SB).

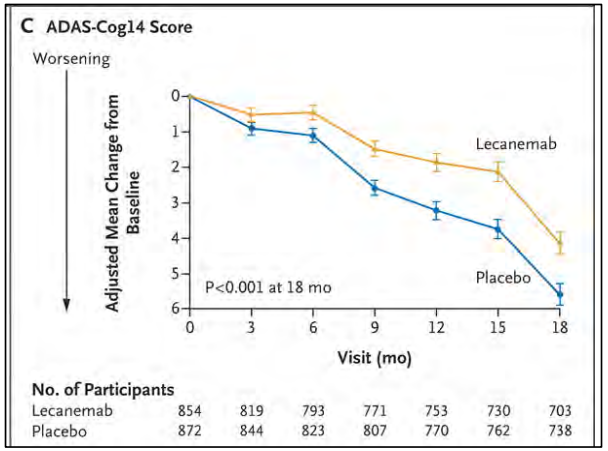


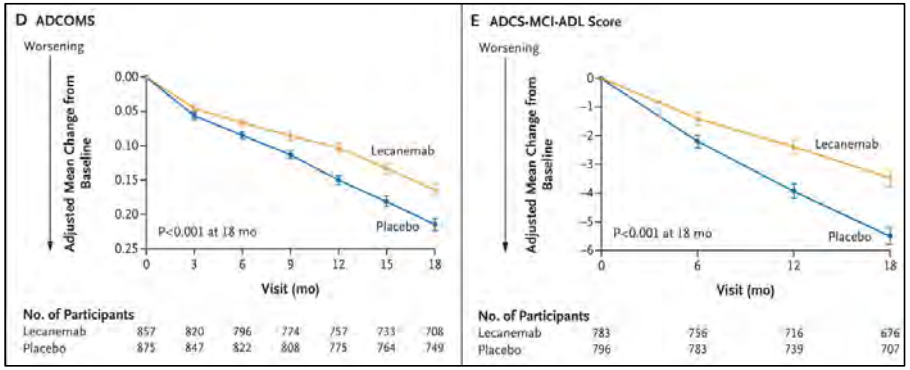
Sims, JR, et al. JAMA. 2023;330(6):512-527

Lecanemab in early Alzheimer's disease: Cognitive outcomes



Sum of Boxes of the Clinical Dementia Rating Scale (CDR-SB)

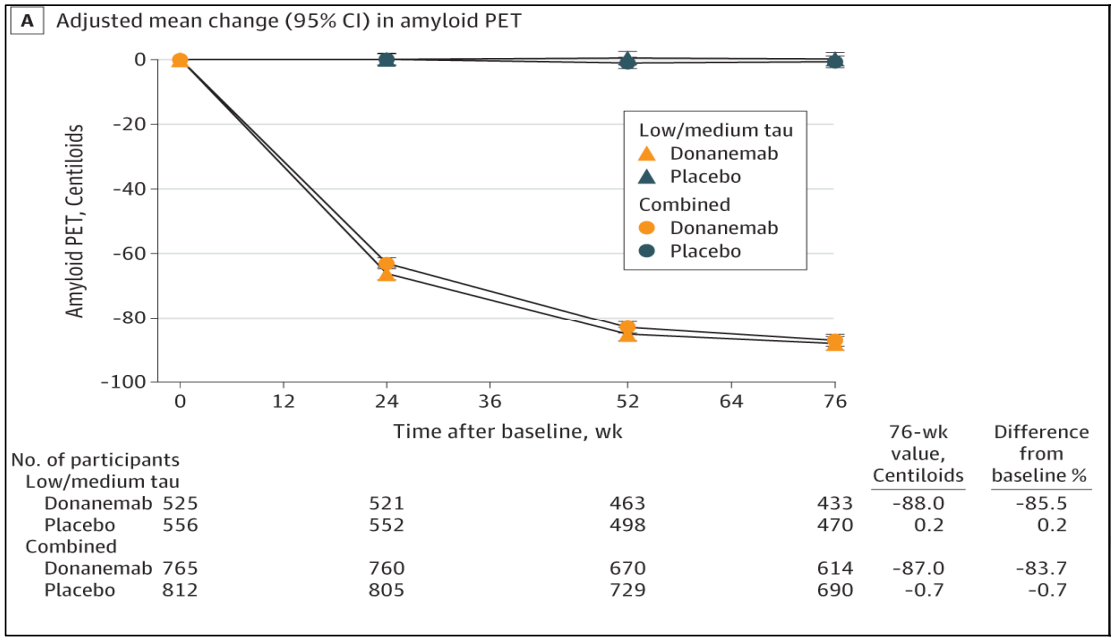




Van Dyke C, et al. N Engl J Med 2023; 388:9-21

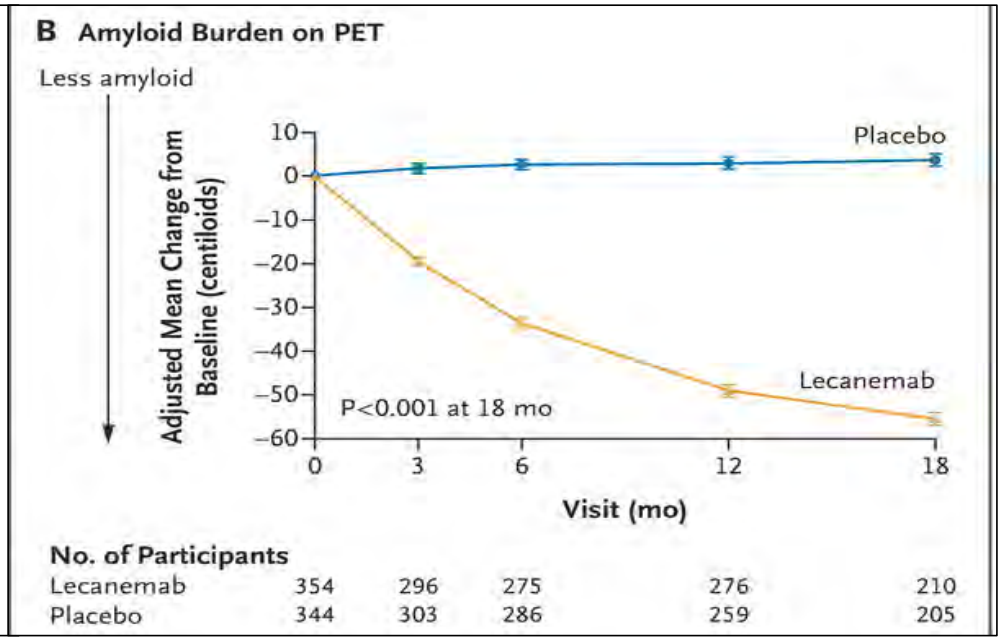
Amyloid removal with donanemab and lacanemab

Donanemab



No. of participants					76-wk value, Centiloids	Difference from baseline %
Low/medium tau						
Donanemab	525	521	463	433	-88.0	-85.5
Placebo	556	552	498	470	0.2	0.2
Combined						
Donanemab	765	760	670	614	-87.0	-83.7
Placebo	812	805	729	690	-0.7	-0.7

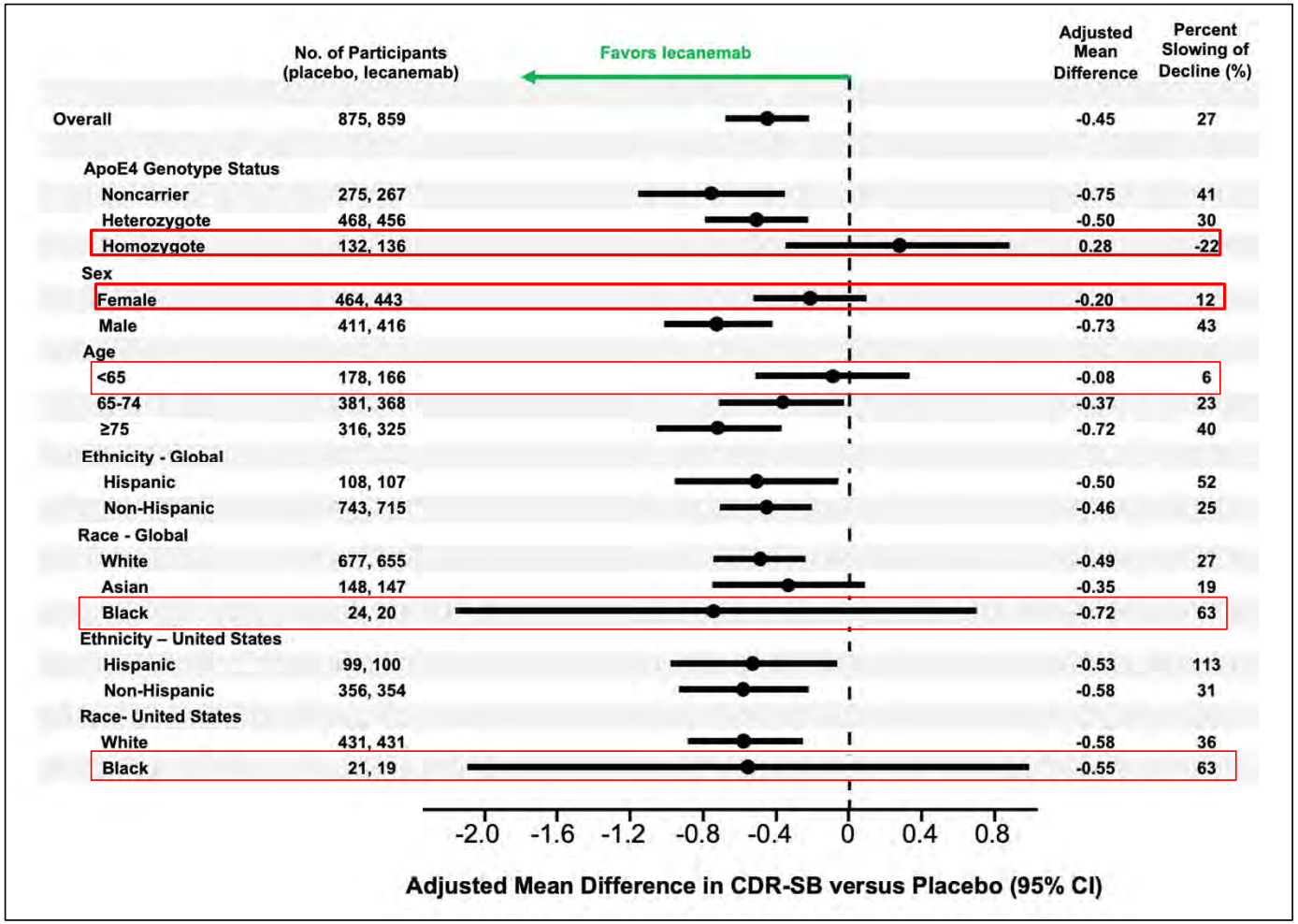
Lecanemab



No. of Participants					
Lecanemab	354	296	275	276	210
Placebo	344	303	286	259	205

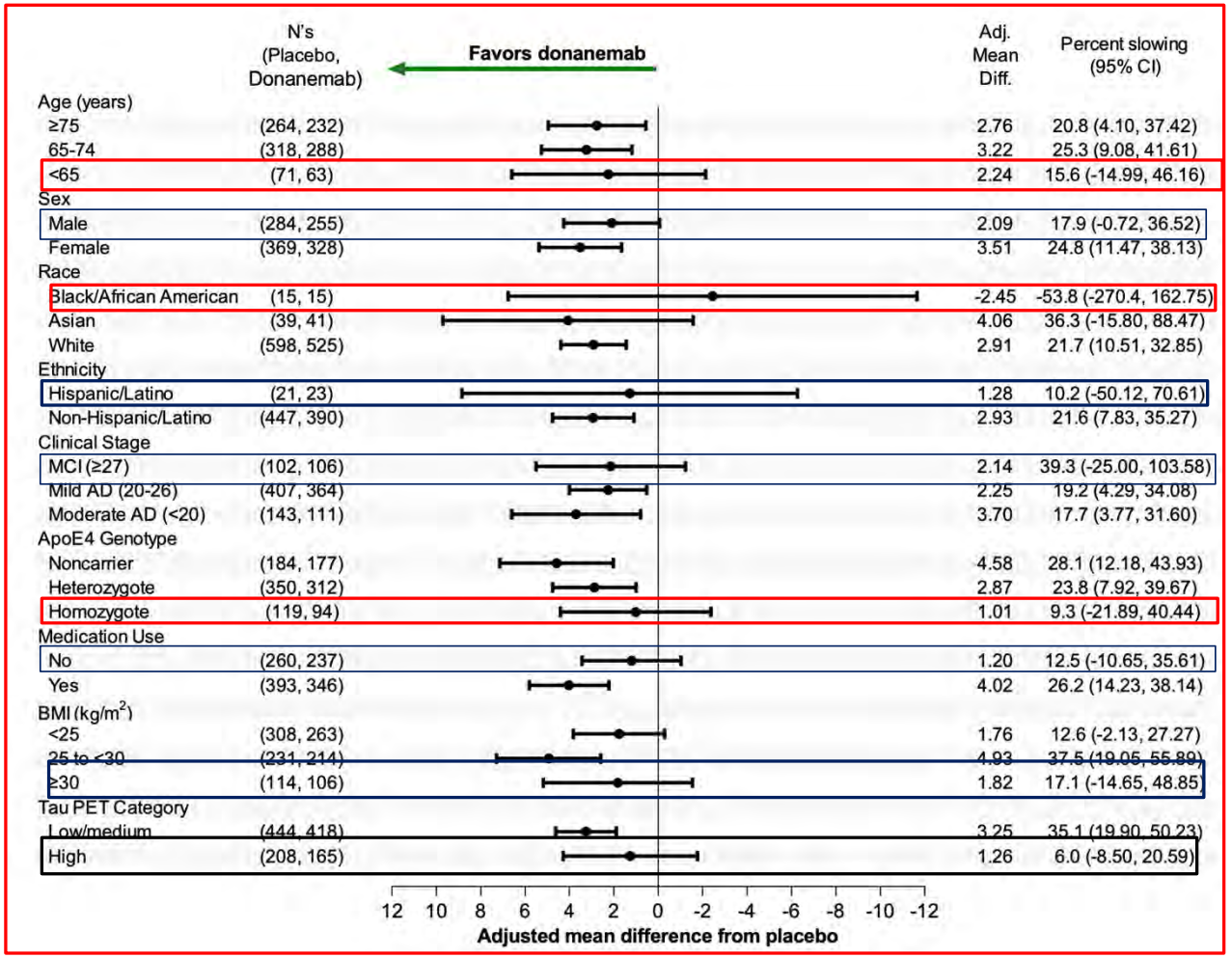
Sims, JR, et al. JAMA. 2023;330(6):512-527
Van Dyke C, et al. N Engl J Med 2023; 388:9-21

Lecanemab in early Alzheimer's disease: subgroup analysis of primary outcomes



van Dyck CH, et al. *N Engl J Med*. 2023;388(1):9-21

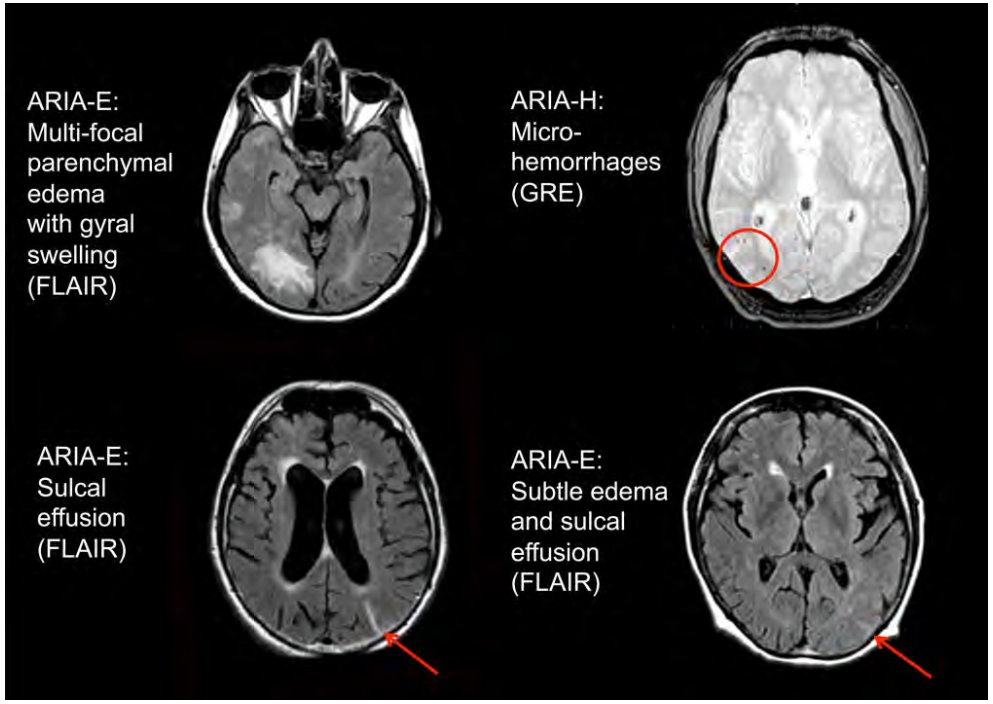
Donanemab in early Alzheimer's disease: subgroup analysis of primary outcomes



Sims, JR, et al. JAMA. 2023;330(6):512-527.

Amyloid-related imaging abnormalities (ARIA) in patients with Alzheimer's disease treated with anti-amyloid compounds

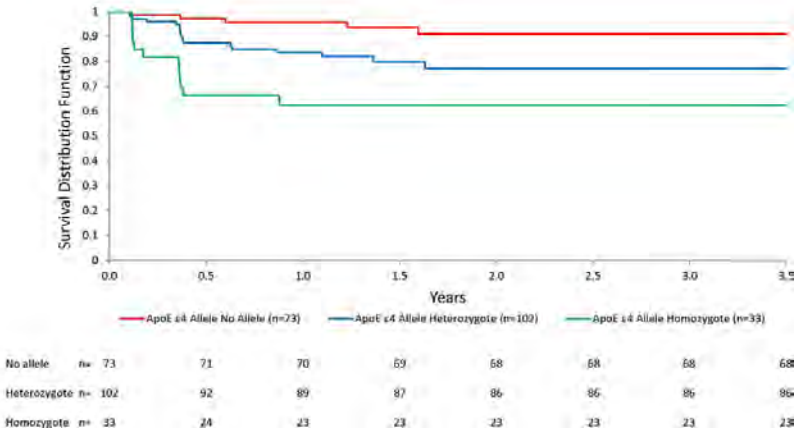
Bapineuzumab



ARIA-E	vasogenic edema and sulcal effusions
ARIA-H	microhemorrhages and hemosiderin deposits

Compound	% ARIA E and H
Bapineuzumab	16%
Aducanumab	35% - 41%
Gantenerumab	28% - 42%
Lacanemab	10% - 12%
Donenamab	36.4%

ARIA more frequent in APOE-4 allele carriers

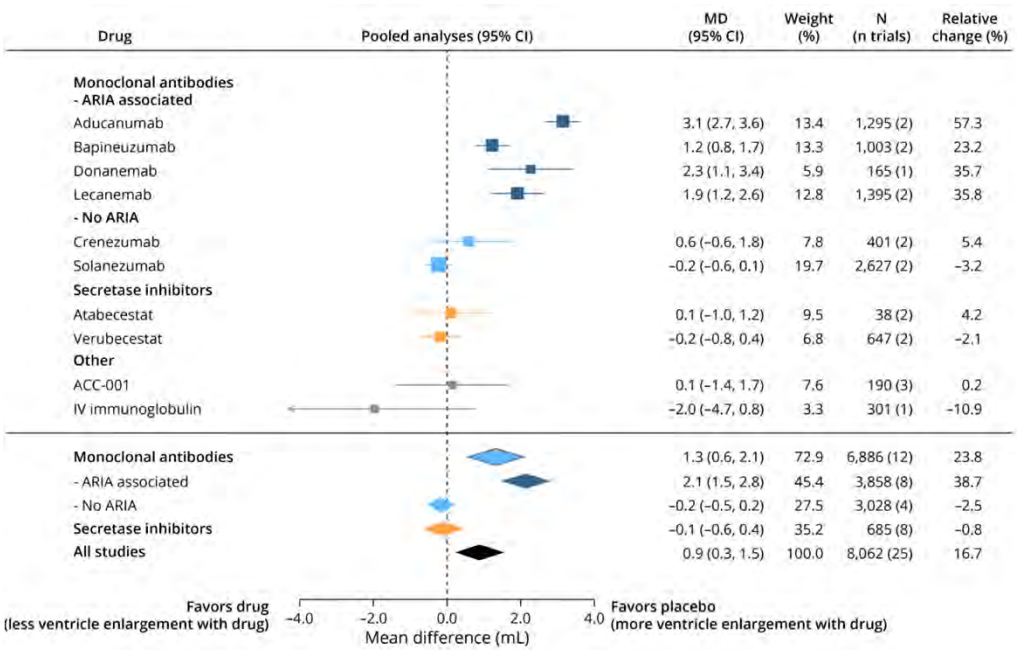


Lopez 2023

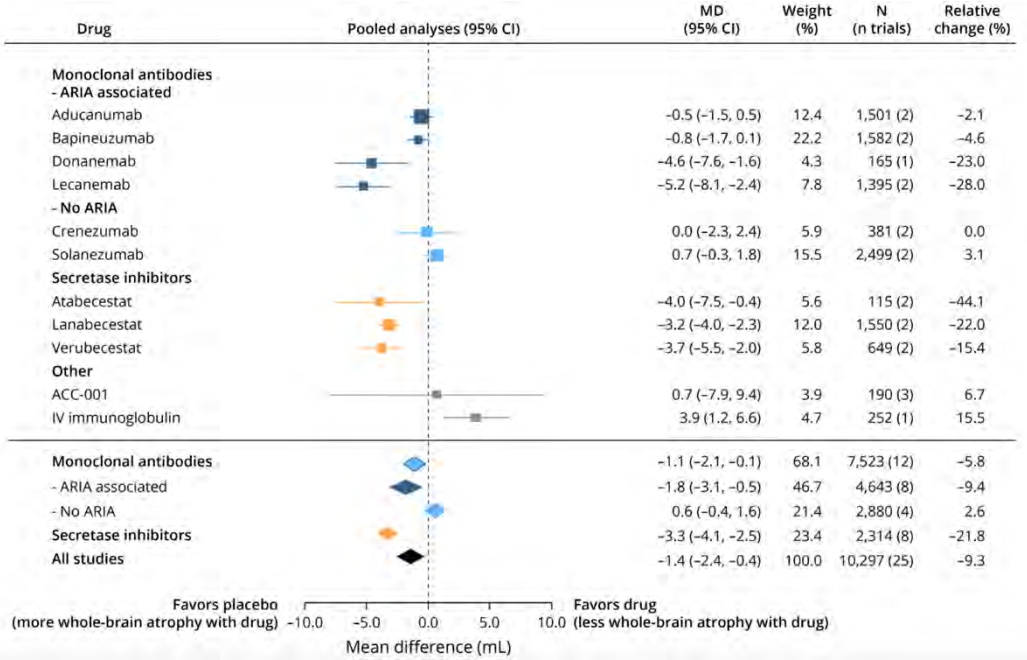
Sperling et al., Lancet-Neurology 2012; 11:241-49

Accelerated brain volume loss caused by anti-amyloid drugs –a Meta-analysis

Effect of anti-amyloid drugs on ventricular volume



Effect of anti-amyloid drugs on whole brain atrophy



MD: mean difference, CI 95% confidence interval
Relative change: the mean difference between volume changes in drug and placebo as a ratio to the change in placebo

Alves F, Kallinowski P, Ayton S. Neurology 2023

INCLUSION criteria in CLARITY-AD phase 3 trial, and VAMC and expert guidelines for the use of lacanemab

Clinical Trial	VAMC Criteria (2023)	Proposed Guidelines Cummings J, et. al., JPAD 2023
Mild cognitive impairment (MCI) due to AD or mild AD	MCI due to AD or mild AD	MCI due to AD and mild AD
Age 50 - 85	>65	Physician judgement
Objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler Memory Scale IV-Logical Memory (subscale) II (WMS-IV LMII), MMSE >22	MMSE ≥21; MoCA ≥16 Functional Assessment Staging Test score 2-4	MCI due to AD and mild AD MMSE 22-30 or other cognitive screening compatible with early AD
Positive PET scan for amyloid deposition	Positive PET scan for amyloid deposition, or CSF consistent with AD	Positive PET scan for amyloid deposition, or CSF indicative of AD
BMI index greater than 17 and less than 35 at screening	NS	Physician judgement
MRI of the brain in the past 12 months	MRI of the brain in the past 12 months	NS
Included APOE-4 homozygotes	Excluded APOE-4 homozygotes	NS
Receiving cholinesterase inhibitors or memantine on stable dose for 12 months	Receiving cholinesterase inhibitors or memantine on stable dose for 12 months	Receiving cholinesterase inhibitors or memantine on stable dose for 12 months
Up to 5 MRI of the brain	Neuroradiology available to review serial MRIs either at site or through teleradiology	NS
Have an identified study partner	NS	Have an identified study partner
Provide written informed consent	Provide written informed consent	Provide written informed consent
Treatment monitoring as per protocol	A process is in place before starting the therapy to ensure the provider and pharmacy are notified to hold the infusion until ordering physician can access the patient and decide whether to continue with treatment.	Monitoring and management of ARIA

Exclusion criteria in CLARITY-AD phase 3 trial, and VAMC and expert guidelines

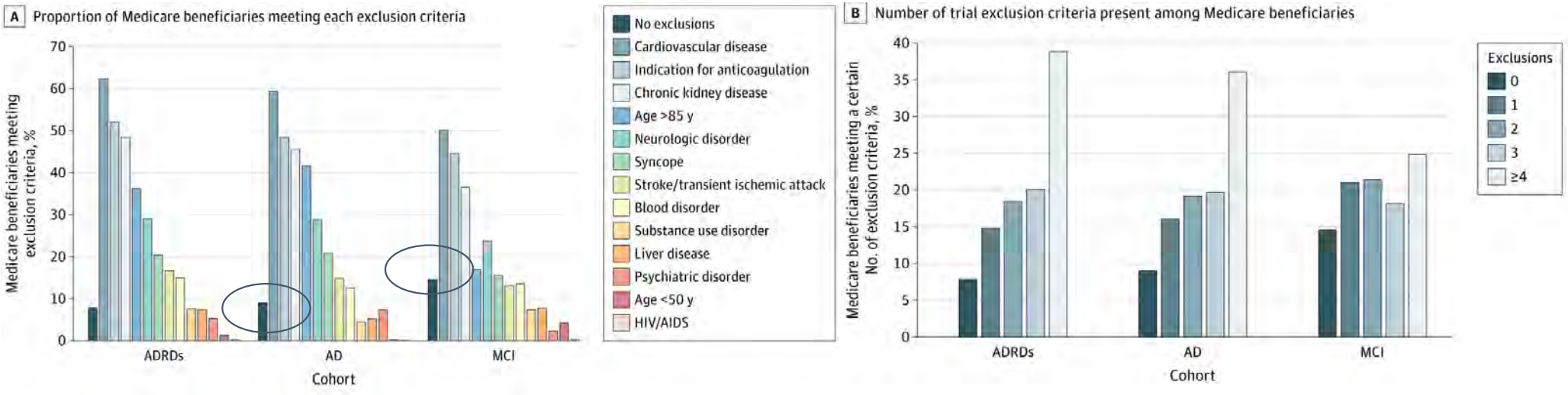
Clinical Trial	VAMC	Proposed Guidelines Cummings J, et. al., JPAD 2023
Contraindication to brain MRI	Contraindication to brain MRI	NS
Acute macro or micro-hemorrhages, more than 4 microhemorrhages <1cm, a single macro-hemorrhage >1 cm, superficial siderosis, vasogenic edema, multiple lacunar infarcts or strokes involving a major vascular territory, severe small vessel disease or other major intracranial pathology	More than 4 microhemorrhages; a single macro hemorrhage >1 cm at greatest diameter; an area of superficial siderosis; evidence of vasogenic edema; evidence of acute/subacute cerebral contusion, acute/subacute stroke, aneurysms, vascular malformations, or infective lesions; severe small vessel, or white matter disease; space occupying lesions; or intra-axial brain tumor	More than 4 microhemorrhages; a single macro hemorrhage >1 cm at greatest diameter; an area of superficial siderosis; evidence of vasogenic edema; evidence of acute/subacute cerebral contusion, acute/subacute stroke, aneurysms, vascular malformations, or infective lesions; severe WMHs (Fazekas score 3), ABRA, CAA-ri or other major pathology that may cause cognitive impairment.
Lesions on MRI at screening that could indicate a dementia diagnosis other than AD	Evidence of other clinically significant lesion on the brain MRI that indicate other cause of dementia	MRI evidence of non-AD dementia
History of transient ischemic attacks, stroke, or seizures within 12 months of screening	History of transient ischemic attacks, stroke, or any history of seizures in the past 12 months	History of transient ischemic attacks, stroke, or any history of seizures in the past 12 months
Any psychiatric diagnosis or symptoms (e.g., psychosis) that could interfere with the study procedures.	Patient must be stable psychiatrically; clinical decision can be exercised on the ability of the patient to participate safely with the therapeutic regimen.	Mental illness (e.g., psychosis) that interferes with comprehension of the requirements, potential benefits, and potential harms of treatment and are considered by the physician to render the patient unable to comply with management requirements
Geriatric depression scale score >8 at screening.	NS	Major depression that interferes the requirements, potential benefits, and potential harms of treatment and are considered by the physician to render the patient unable to comply with management requirements. Patient with less severe depression or whose treatment resolves may be treatment candidates
Excluded participants with suicidal ideation	Columbia-Suicide Severity Rating Scale suicidal ideation type 4 or 5.Hospitalized or treated for suicidal behavior within the past 5 years	NS
Excluded substance abuse individuals	Current substance use disorder or positive drug screen	NS

Exclusion criteria in CLARITY-AD phase 3 trial, and VAMC and expert guidelines

Clinical Trial	VAMC	Proposed Guidelines Cummings J, et. al., JPAD 2023
Any neurological condition that maybe contributing to cognitive impairment above and beyond that caused by the participant's AD	Any medical, neurological, or mental condition that maybe contributing/primary cause of cognitive impairment	Any medical, neurological, or mental condition that maybe contributing to the cognitive impairment or any non-AD MCI dementia
Low vitamin B12 level, high TSH level	Low vitamin B12 level, high TSH level, HIV positive	NS
Active cancer	Malignant neoplasm under active therapy	NS
Any other medical condition (e.g., cardiovascular disease) which are not stably and adequately controlled or which could affect the patient's safety or interfere with the study assessments	NS	Unstable medical conditions that may affect or be affected by lecanemab therapy
Any immunological disease that is not adequately controlled, or which requires treatment with immunoglobulins, systemic monoclonal antibodies, systemic immunosuppressants or plasmapheresis during the study	Any immunological disease which is not controlled, or which requires treatment with biological drugs	Any history of immunological disease, or systemic treatment with immunosuppressants or plasmapheresis during the study, or monoclonal antibodies or their derivatives
Participants with a bleeding disorder that is not under adequate control. (including , platelet count <50,000, or INR >1.5 for participants who are not on anticoagulant treatment.	Untreated bleeding disorder, platelet count <50,000, or INR >1.5.	Patients with a bleeding disorder that is not under adequate control. (including , platelet count <50,000, or INR >1.5 for participants who are not on anticoagulant treatment
Participants who are on anticoagulant therapy should have their anticoagulant status optimized and be on a stable dose before screening	NS (combined use of lecanemab with anti-platelets or and coagulants may increase the risk of cerebral macrohemorrhages)	Patients on anticoagulants (e.g., coumadin dabigatran, apixaban, heparin) should not receive lecanemab, tPA should not be administered to individuals on lecanemab.
Participation in a clinical study involving any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before screening unless it can be documented that the participant was randomized to placebo	N.S.	NS

Representativeness of participants eligible to be enrolled in clinical trials of Aducanumab for Alzheimer's disease compared with Medicare beneficiaries with Alzheimer's disease and Mild Cognitive Impairment (n= 27, 785, 076 Medicare beneficiaries)

Prevalence of Aducanumab Trial exclusion criteria among Medicare beneficiaries with Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI)



A total of 92.2% of patients with AD and Related Disorders (ADRDs), 91.0% with AD, and 85.5% with MCI met at least 1 trial exclusion criteria

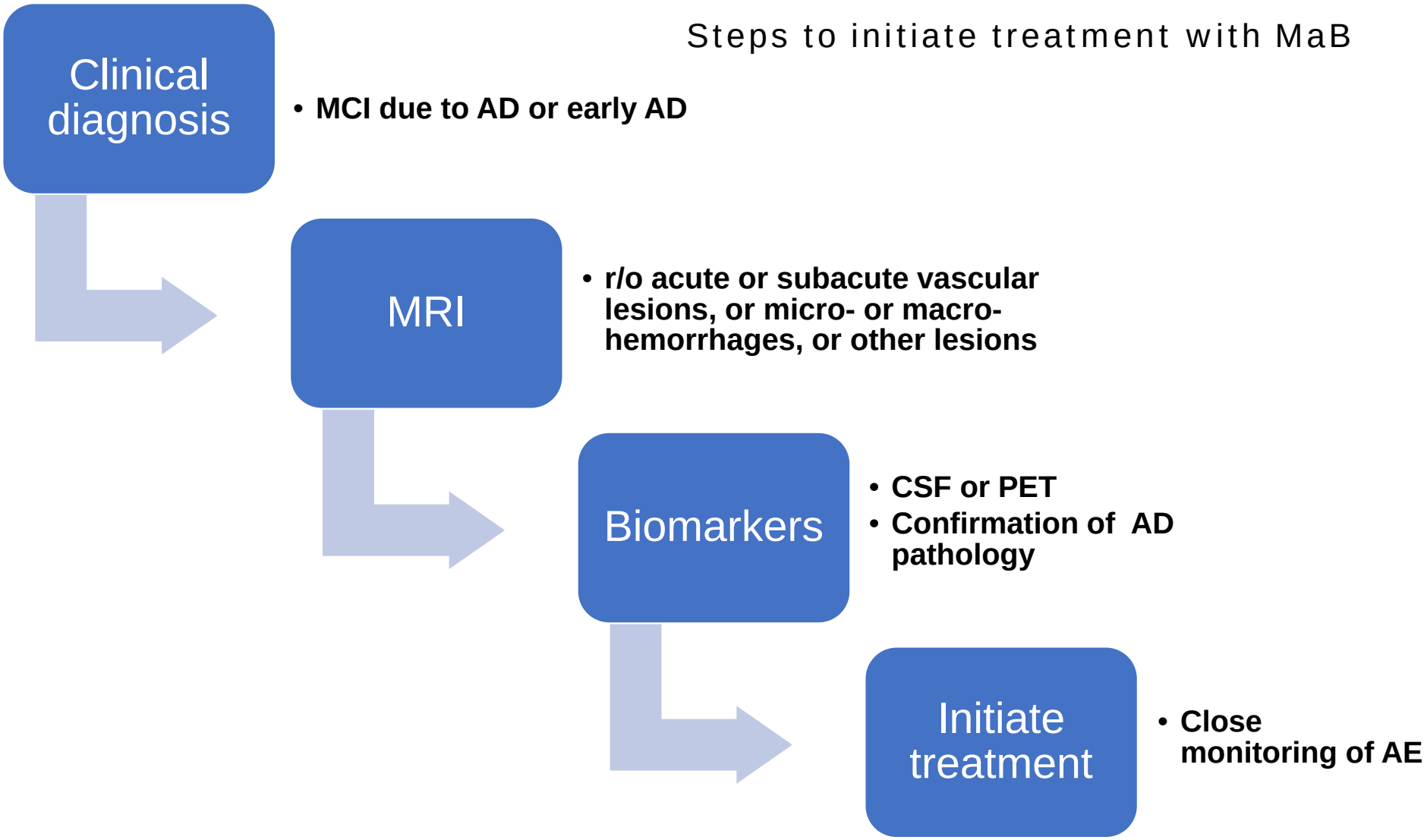
Most patients met multiple exclusion criteria, including 77.4% of patients with ADRDs and 64.4% with MCI

Anderson TS, JAMA September 9, 2021. doi:10.1001/jama.2021.15286

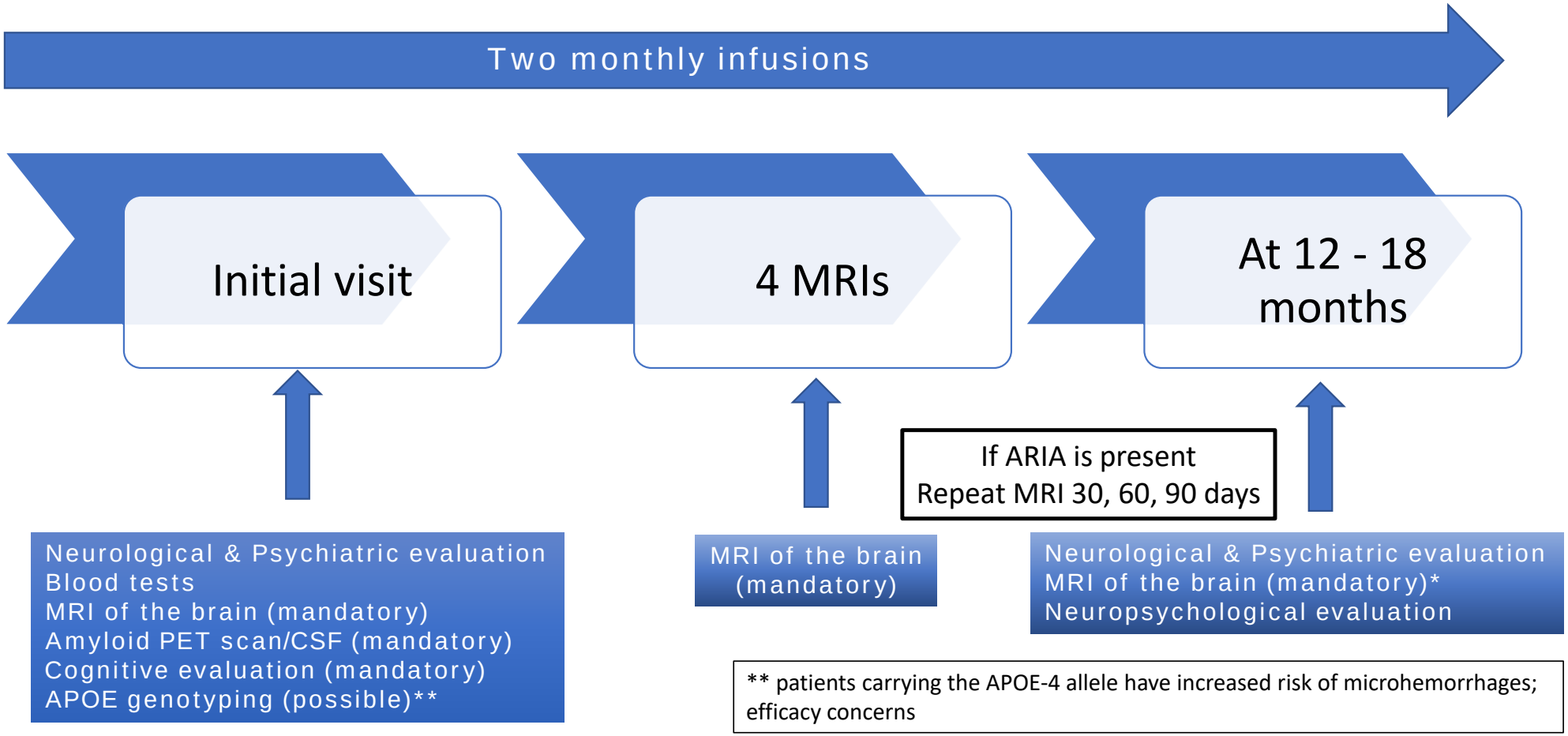
Who will have access to the treatment with MaB

- Patient has MCI due to AD or early AD by cognitive testing and functional scales.
- Cardiovascular and metabolic comorbidities under control
- Similar exclusion criteria described in the trial
- MRI scan free of acute or subacute vascular lesions, or of micro- or macro-hemorrhages
- Amyloid PET or CSF show the presence of AD.
- Neuroradiology expertise is available to review amyloid PET scans and MRIs
- A process is in place to manage AEs.
- Access to experts who can determine efficacy of the treatment.
- Exclude patients who cannot have MRIs
- Exclude those on antiplatelet or anticoagulant medications.
- Exclude those who are APOE-4 homozygotes (?)
- Age <65(?)

Steps to initiate treatment with MaB



Evaluation and management of patients treated with lacanemab



Comments

- We are entering in a new era of Alzheimer's disease treatment
- More anti-amyloid treatments are coming.
- Implementation of the treatments requires well-trained personnel.
- Increased role of blood and imaging biomarkers
- There will be combination of treatments
- Cholinesterase inhibitors and memantine will remain as symptomatic treatments for AD