Clinically Important Benefits and Harms of Monoclonal Antibodies Targeting Amyloid for the Treatment of Alzheimer Disease: A Systematic Review and Meta-Analysis

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ABSTRACT

PURPOSE We conducted a meta-analysis to evaluate clinically meaningful benefits and harms of monoclonal antibodies targeting amyloid in patients with Alzheimer dementia.

METHODS We searched PubMed, Cochrane CENTRAL, and 5 trial registries, as well as the reference lists of identified studies. We included randomized controlled trials comparing a monoclonal antibody with placebo at a dose consistent with that used in phase 3 trials or for Food and Drug Administration approval. Studies had to report at least 1 clinically relevant benefit or harm. Data were extracted independently by at least 2 researchers for random effects meta-analysis. Changes in cognitive and functional scales were compared between groups, and each difference was assessed to determine if it met the minimal clinically important difference (MCID).

RESULTS We identified 19 publications with 23,202 total participants that evaluated 8 anti-amyloid antibodies. There were small improvements over placebo in the Alzheimer's Disease Assessment Scale (ADAS)-Cog-11 to -14 score (standardized mean difference = −0.07; 95% CI, −0.10 to −0.04), Mini Mental State Examination score (0.32 points; 95% CI, 0.13 to 0.50), and Clinical Dementia Rating–Sum of Boxes scale score (mean difference = −0.18 points; 95% CI, −0.34 to −0.03), and the combined functional scores (standardized mean difference = 0.09; 95% CI, 0.05 to 0.13). None of the changes, including those for lecanemab, aducanumab, and donanemab, exceeded the MCID. Harms included significantly increased risks of amyloid-related imaging abnormalities (ARIA)-edema (relative risk [RR] = 10.29; number needed to harm [NNH] = 9), ARIA-hemorrhage (RR = 1.74; NNH = 13), and symptomatic ARIA-edema (RR = 24.3; NNH = 86).

CONCLUSIONS Although monoclonal antibodies targeting amyloid provide small benefits on cognitive and functional scales in patients with Alzheimer dementia, these improvements are far below the MCID for each outcome and are accompanied by clinically meaningful harms.

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INTRODUCTION

The hypothesis that amyloid deposition is part of the causal pathway in the pathogenesis of Alzheimer dementia has led to the development of monoclonal antibodies to reduce this deposition.[1,2] In fact, the primary justification for approval of these drugs by the Food and Drug Administration (FDA) is reduced amyloid deposition in the brain.[3,4] Their approval despite their failure to provide a clinically significant improvement in cognitive and functional outcomes has resulted in substantial controversy,[3-6] including charges of research misconduct in some of the original studies.[7]

Surrogate outcomes often do not correspond to improvements in patient-oriented outcomes such as reduced mortality or morbidity. For example, 3 large trials in patients with diabetes found that a lower glycated hemoglobin target of 6.5% either did not reduce or increased mortality compared with standard targets of 7.0% to 8.0%.[8-10] A clear focus on patient-oriented benefits and harms is thus central to evidence-based practice.[11,12] A recent systematic review concluded that patients with dementia most value quality of life, self-efficacy, and avoidance of depression.[13]

Previous systematic reviews have evaluated the efficacy and harms of monoclonal antibodies targeting amyloid.[14-16] These reviews were, however, unable to include several recent studies that were critical to drug approval. The reviews also

in some cases included phase 1 and 2 trials that used different doses from those used in later trials, and did not interpret the findings in the context of the minimal clinically important difference (MCID) for each outcome.

Recently, the monoclonal antibodies lecanemab and aducanumab were studied in large randomized controlled trials that found substantial reductions in amyloid deposition but only modest improvements in cognition and function.[1,17,18] Significant harms were observed, including symptomatic amyloid-related imaging abnormalities of edema (ARIA-E) and hemorrhage (ARIA-H). We set out to perform a meta-analysis of all randomized controlled trials comparing an anti-amyloid monoclonal antibody with placebo. Our sole focus was on patient-oriented outcomes, which we defined as improved cognition and/or function attaining at least the MCID for each scale, and potentially serious harms such as cerebral edema, hemorrhage, serious adverse events, and mortality.

METHODS

Our protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) as protocol CRD42023392698. The review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 statement for reporting systematic reviews (Supplemental Appendix 1).

Inclusion and Exclusion Criteria

We included randomized controlled trials that compared a monoclonal antibody intended to decrease the amount of brain amyloid with placebo. All trials had to enroll adults with cognitive impairment, Alzheimer disease of any severity, or high risk for Alzheimer disease, and had to report at least 1 patient-oriented benefit or harm after a minimum of 1 year. There were no limits by year or language. We excluded trials reporting the results of only a single infusion and phase 1 trials, as well as trials or trial arms using doses lower than those used in phase 3 trials or ultimately approved by the FDA.

Search Strategy

Our PubMed search strategy included terms for each monoclonal antibody identified through a preliminary search of the literature as well as general free text and Medical Subject Heading (MeSH) terms for monoclonal antibodies (Supplemental Appendix 2). We also searched the Cochrane CENTRAL Trials Register, ClinicalTrials.gov, and 4 other clinical trial registries (www.vivli.org, www.clinicalstudydatarequest.com, www.isrctn.com, and yoda.yale.edu). The reference lists of identified studies were also reviewed.

Data Abstraction and Quality Assessment

Titles and abstracts were reviewed in parallel by 2 researchers, at least 1 of whom was a physician. Any study identified as potentially relevant by at least 1 researcher was selected for full text review. Full text review was performed in parallel, again with at least 1 physician researcher for each study, to identify studies meeting our inclusion and exclusion criteria.

Abstraction of study characteristics, assessment of study quality, and abstraction of outcome data were done in parallel by 2 researchers, 1 of whom was a physician. The second physician helped resolve any discrepancies between the first 2 reviewers. The quality assessment used the Cochrane Risk of Bias Tool.[19] Details regarding the data preparation for 2 studies requiring slight modifications are given in Supplemental Appendix 2.

Analysis

We performed a random effects meta-analysis of each outcome using the metan procedure in Stata version 17 (StataCorp LLC). For dichotomous outcomes, we calculated relative risks (RRs), 95% CIs, and where relevant, the number needed to treat (NNT) or number needed to harm (NNH). For continuous outcomes, we calculated the mean difference (MD) or when combining similar continuous scales but with different ranges (eg, the Alzheimer's Disease Assessment Scale Cognitive Subscale-11 items through -14 items [ADAS-Cog-11 through ADAS-Cog-14]), we used the Cohen procedure for calculating summary estimates of the standardized mean difference (SMD).

Forest plots were created for each outcome. Heterogeneity was measured using the I^2 statistic.[20] Publication bias was assessed using funnel plots for key outcomes using all available studies.

MCID Determination

The MCID is the smallest change in a scale measuring cognition or function that is noticeable by the patient or their caregiver. Jaeschke and colleagues[21] estimate that for a 7-point scale, a change of 0.5 points (7% of the range) represents the MCID, with changes of 11.5% to 13.7% representing a moderate effect and 12.3% to 21.0% representing a large change. We determined from the literature the MCID for each scale used in 2 or more studies. Where there was no published MCID, we used 7% of the full range of the scale, for example, a change of at least 1.4 points on a 20-point scale. For SMDs, previous research has concluded that a standardized difference of 0.5 should be considered the MCID.[22,23] The range and MCID for each scale are shown in Table 1.

RESULTS

Search Results

The results of our literature search are summarized in Supplemental Figure 1 and Supplemental Table 1. We identified 87 studies from PubMed and 71 from other sources, of which 16 were duplicates. A total of 142 records were screened and 41 underwent full text review. We excluded some studies that initially appeared promising but used

subtherapeutic doses,[34] studied an anti-Tau antibody,[35] or were phase 1 studies.[36-40] Two studies reported data regarding ARIA-E outcomes for the same pair of phase 3 trials[29,41]; we used the information from the more detailed report.[41] Just before submitting the revised manuscript we added 2 recently published studies that met our criteria.[42,43] Ultimately, we included 19 studies with 23,202 participants evaluating 8 anti-amyloid antibodies.

Study Characteristics

Characteristics of the 19 included studies are summarized in Table 2. All studies were industry-funded, placebo-controlled randomized trials. Most were 18 to 19 months in duration, and enrolled patients with mild cognitive impairment or with mild or moderate Alzheimer disease.

Risk of Bias Assessment

The risk of bias assessment for each study is summarized in Table 3. Twelve studies were at high risk for bias because of a lack of complete outcome data (>10% missing). Four studies were at unclear risk for bias because of uncertainty about allocation concealment. The remaining 3 studies were at low risk for bias.

Potential Benefits

Forest plots of the summary estimates of the SMD for the combined ADAS-Cog-11 through -14 cognitive scores are shown in Figure 1 (individual forest plots for each scale are shown in Supplemental Figures 2-5). The overall improvement with anti-amyloid antibodies over placebo was small (SMD = −0.07; 95% CI, −0.10 to −0.04). Statistically significant improvements in one of these cognitive scores were seen for solanezumab (SMD = 0.07; 95% CI, −0.12 to −0.02), aducanumab (SMD = −0.11; 95% CI, −0.19 to −0.02), and lecanemab (SMD = −0.11; 95% CI, −0.19 to −0.02). For the 2 FDA-approved antibodies, the MD for lecanemab (−1.8 points; 95% CI, −3.1 to −0.52 points) did not exceed the MCID of 4 to 5 points for the ADAS-Cog-14 and the MD for aducanumab (−0.98 points; 95% CI, −1.77 to −0.18 points) did not exceed the MCID for the ADAS-Cog-13 of 3.75 points.[24] For donanemab, which is pending FDA approval, the unstandardized MD for change in the ADAS-Cog-13 score was −1.41 points (95% CI, −2.11 to −0.70).

Results for the Mini Mental State Examination (MMSE) cognitive score are shown in Figure 2. The score was improved relative to placebo for all of the anti-amyloid antibodies combined by 0.32 points (95% CI, 0.13 to 0.50). The MMSE was improved by a statistically significant extent but not by a clinically significant extent for solanezumab (MD = 0.53 points; 95% CI, 0.15 to 0.80). For the FDA-approved drugs, the MMSE was not significantly better with aducanumab (MD = 0.25 points; 95% CI, −0.44 to 0.93), while there was a statistically significant benefit for donanemab (MD = 0.49 points; 95% CI, 0.14 to 0.83). None of these improvements exceeded the MCID for the MMSE of 1 to 3 points, however.[30]

The Clinical Dementia Rating–Sum of Boxes scale (CDR-SB) is a combined cognitive and functional scale with an MCID of 1 to 2 points (Figure 3). Overall, the CDR-SB was improved slightly with the anti-amyloid antibodies compared with placebo (MD = −0.18 points; 95% CI, −0.34 to −0.03). The only individual antibodies with a statistically significant improvement in the CDR-SB were lecanemab (MD = −0.43 points; 95% CI, −0.78 to −0.07) and donanemab (MD = −0.59 points; 95% CI, −0.86 to −0.33). Neither of these differences exceeded the MCID for the CDR-SB of 1 to 2 points, however.[30]

A forest plot of the summary estimates of the SMDs for the 3 functional scales—the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) scale, the Alzheimer's Disease Cooperative Study–Activities of Daily Living scale for patients with Mild Cognitive Impairment

Table 1. Cognitive Scoring Tools and Their MCIDs

Scoring Tool	Range, Points	MCID, Points	Interpretation
Cognitive assessments			
ADAS-Cog-11	0 to 70[24]	3[24]	Lower is better
ADAS-Cog-12	0 to 80[25]	3.5[a]	Lower is better
ADAS-Cog-13	0 to 85[26]	3.75[a]	Lower is better
ADAS-Cog-14	0 to 90[27]	4[a]	Lower is better
ADCOMS-overall	0 to 1.97[28]	0.14[b]	Lower is better
Neuropsychological test battery	Z scale[29]	0.5 SD	Higher is better
MMSE	0 to 30[30]	1 to 3[30]	Higher is better
Functional assessments			
ADCS-ADL	0 to 78	5.5[b]	Higher is better
ADCS-ADL-MCI	0 to 53[17]	3.7[b]	Higher is better
DAD	0 to 100[c31]	7[b,c]	Higher is better
Behavioral disturbance			
NPI-Question	0 to 36[32]	8[32]	Lower is better
Combined or global assessments			
CDR-SB	0 to 18[30]	1 to 2[30]	Lower is better
iADRS	0 to 146	8.8[b]	Higher is better
Dependence scale	0 to 15[33]	1.5 to 2[33]	Lower is better

ADAS-Cog-11 = Alzheimer's Disease Assessment Scale–Cognitive Subscale-11 items; ADAS-Cog-12 = Alzheimer's Disease Assessment Scale–Cognitive Subscale-12 items; ADAS-Cog-13 = Alzheimer's Disease Assessment Scale–Cognitive Subscale-13 items; ADAS-Cog-14 = Alzheimer's Disease Assessment Scale–Cognitive Subscale-14 items; ADCOMS = Alzheimer's Disease Composite Score; ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living; ADCS-ADL-MCI = ADCS-ADL for patients with Mild Cognitive Impairment; CDR-SB = Clinical Dementia Rating–Sum of Boxes scale; DAD = Disability Assessment for Dementia; iADRS = integrated Alzheimer's Disease Rating Scale; MCID = minimal clinically important difference; MMSE = Mini Mental State Examination; NPI = neuropsychological inventory; SD = standardized difference.

[a] By extension from study of the ADAS-Cog-11.
[b] Estimated as 7% of the total range for the score.
[c] Percentages (not points).

Table 2. Characteristics of the 19 Included Studies

Study and Year	Substudy[a]	Drug and Dosing	Duration, Mos	Disease Severity	Treatment Group, No.	Placebo Group, No.	Age, Mean, Y
Budd Haeberlein et al,[1] 2022	ENGAGE and EMERGE	Aducanumab 3 mg/kg q 4 wks	18	MCI or mild AD (MMSE score ≥24)	1,082	1,076	70.4
		Aducanumab 6 mg/kg q 4 wks			1,096	1,076	
Salloway et al,[25] 2009		Bapineuzumab 0.15 mg/kg q 3 mos	18	Mild to moderate AD (MMSE score 16-26)	31	26	69.1
		Bapineuzumab 0.5 mg/kg q 3 mos			33	28	
		Bapineuzumab 1.0 mg/kg q 3 mos			29	26	
		Bapineuzumab 2.0 mg/kg q 3 mos			29	27	
Salloway et al,[29] 2014	Study 301 APOE(–)	Bapineuzumab 0.5 mg/kg q 3 mos	18	Mild to moderate AD (MMSE score 16-26)	314	493	72.5
		Bapineuzumab 1.0 mg/kg q 3 mos			307	493	
		Bapineuzumab 2.0 mg/kg q 3 mos			141	493	
	Study 302 APOE(+)	Bapineuzumab 0.5 mg/kg q 3 mos			658	432	
Lacey et al,[44] 2015	Study 301 APOE(–)	Bapineuzumab 0.5 or 1.0 mg/kg q 3 mos	18	Mild to moderate AD (MMSE score 16-26)	621	493	72.5
	Study 302 APOE(+)	Bapineuzumab 0.5 mg/kg q 3 mos			658	432	72.2
Vandenberghe et al,[45] 2016	APOE(–)	Bapineuzumab 0.5 mg/kg q 3 mos	18	Mild to moderate AD (MMSE score 16-26)	267	344	70.5
		Bapineuzumab 1.0 mg/kg q 3 mos			263	344	
	APOE(+)	Bapineuzumab 0.5 mg/kg q 3 mos	18	Mild to moderate AD (MMSE score 16-26)	654	439	
Brashear et al,[41] 2018	Study 301 APOE(–)	Bapineuzumab, 0.5 mg/kg q 3 mos	19	Mild to moderate AD (MMSE score 16-26)	337	524	72-74
		Bapineuzumab, 1 mg/kg q 3 mos			329	524	
		Bapineuzumab, 2 mg/kg q 3 mos			141	524	
	Study 302 APOE(+)	Bapineuzumab, 0.5 mg/kg q 3 mos			673	448	
Cummings et al,[46] 2018		Crenezumab 15 mg/kg q 4 wks	17	Mild to moderate AD (MMSE score 18-26)	165	82	70.6
		Crenezumab 300 mg q 2 wks			122	62	
Ostrowitzki et al,[26] 2022	CREAD and CREAD2	Crenezumab 60 mg/kg q 4 wks	24	Prodromal or mild AD (MMSE score ≥22)	808	803	70.7
Mintun et al,[47] 2021	TRAILBLAZER-ALZ	Donanemab 700 mg × 3 then 1,400 mg q 4 wks	19	Early or mild AD	131	126	75.2
Sims et al,[42] 2023	TRAILBLAZER-ALZ 2	Donanemab 700 mg × 3 then 1,400 mg q 4 wks	18	MCI or mild AD	860	876	74

continues

AD = Alzheimer disease; APOE = apolipoprotein E; APOE(+) = carriers of the ApoE mutation; APOE(–) = noncarriers of the ApoE mutation; MCI = mild cognitive impairment; MMSE = Mini Mental State Examination (score range is 0-30); NR = not reported.

[a] Shown where a study had an identifiable name or subgroup other than by dose.
[b] Median.

Table 2. Characteristics of the 19 Included Studies *(continued)*

Study and Year	Substudy[a]	Drug and Dosing	Duration, Mos	Disease Severity	Treatment Group, No.	Placebo Group, No.	Age, Mean, Y
Ostrowitzki et al,[48] 2017		Gantenerumab 105 mg q 4 wks	24	Mild AD (MMSE score ≥24)	271	266	70.4
		Gantenerumab 225 mg q 4 wks			260	266	
Salloway et al,[49] 2021		Gantenerumab 225 mg then 1,200 mg q 4 wks	24	Normal but at elevated risk or early AD	52	40	43.8
Swanson et al,[18] 2021		Lecanemab 10 mg/kg biweekly	18	MCI or mild AD	152	237	72[b]
		Lecanemab 10 mg/kg monthly			253	245	
Van Dyck et al,[17] 2023		Lecanemab 10 mg/kg biweekly	18	MCI or mild AD	859	875	71.2
Landen et al, [50] 2017	Cohort M	Ponezumab 10 mg/kg then 7.5 mg/kg q month	18	Probable AD	12	6	67.8
	Cohort Q	Ponezumab 10 mg/kg q 3 mos			12	6	
Doody et al,[27] 2014	EXPEDITION 1	Solanezumab 400 mg q 4 wks	18	Mild to moderate AD (MMSE score 16-26)	506	506	74.7
	EXPEDITION 2	Solanezumab 400 mg q 4 wks			521	519	72.5
Farlow et al,[36] 2012		Solanezumab 100 mg q 4 wks	12	Mild to moderate AD (MMSE score 15-26)	10	10	NR
		Solanezumab 100 mg weekly			11	10	
		Solanezumab 400 mg q 4 wks			10	10	
		Solanezumab 400 mg weekly			11	10	
Honig et al,[51] 2018		Solanezumab 400 mg q 4 wks	18	Mild AD (MMSE score 20-26)	1,057	1,072	73.0
Sperling et al,[43] 2023		Solanezumab 1,600 mg q 4 wks	54	Normal cognition with amyloid deposition	564	583	72

AD = Alzheimer disease; APOE = apolipoprotein E; APOE(+) = carriers of the ApoE mutation; APOE(–) = noncarriers of the ApoE mutation; MCI = mild cognitive impairment; MMSE = Mini Mental State Examination (score range is 0-30); NR = not reported.

[a] Shown where a study had an identifiable name or subgroup other than by dose.
[b] Median.

(ADCS-ADL-MCI) scale, and the Disability Assessment for Dementia (DAD)—is shown in Supplemental Figure 6 (forest plots for each scale separately are shown in Supplemental Figures 7-9). Overall, there was a statistically significant improvement in the combined functional scores with the anti-amyloid antibodies compared with placebo (SMD = 0.09; 95% CI, 0.05 to 0.13). Scores were also improved for aducanumab (SMD = 0.14; 95% CI, 0.06 to 0.23) and lecanemab (SMD = 0.19; 95% CI, 0.09 to 0.28) individually. None of these changes exceeded the MCID of 0.5 standardized differences, however.[22,23] Forest plots of the summary estimates of the SMDs for the Dependence Scale and for the Neuropsychological Test Battery scale are shown in Supplemental Figure 10 and Supplemental Figure 11, respectively.

None of the studies reported other clinically important outcomes such as functional dependence, placement in memory care units or nursing homes, caregiver burden, or development of aggressive behaviors.

Potential Harms

Overall, there was no significant difference between treatment and control groups with regard to all-cause mortality, as shown in Supplemental Figure 12 (RR = 1.15; 95% CI, 0.85 to 1.56). One drug, bapineuzumab, was associated with a significant increase in mortality (RR = 1.76; 95% CI, 1.03 to 3.00; NNH = 102). There was no significant difference between treatment and control groups in serious adverse events, shown in Supplemental Figure 13 (RR = 1.02; 95% CI, 0.92 to 1.12).

Table 3. Study Quality Assessment Using the Cochrane Risk of Bias Tool[19]

Study and Year	Sequence Generation	Allocation Concealment	Blinding of Personnel and Patients	Blinding of Outcome Assessors	Incomplete Outcome Data (% Missing)	Selective Outcome Reporting	Other Sources of Bias	Overall Risk of Bias
Brashear et al,[41] 2018	Low	Low	Low	Low	Low (0.4)	Low	Low	Low
Budd Haeberlein et al,[1] 2022	Low	Low	Low	Low	Low (0.6)	Low	Low	Low
Cummings et al,[46] 2018	Low	Low	Low	Low	High (26)	Low	Low	High
Doody et al,[27] 2014	Low	Low	Low	Low	High (24.7)	Low	Low	High
Farlow et al,[36] 2012	Low	Unclear	Low	Low	Low (4)	Low	Low	Unclear
Honig et al,[51] 2018	Low	Unclear	Low	Low	High (14)	Low	Low	High
Lacey et al,[44] 2015	Low	Low	Low	Low	High (29)	Low	Low	High
Landen et al,[50] 2017	Low	Unclear	Low	Low	Low (5.5)	Low	Low	Unclear
Mintun et al,[47] 2021	Low	Low	Low	Low	High (32)	Low	Low	High
Ostrowitzki et al,[48] 2017	Low	Low	Low	Low	High (53.8)	Low	Low	High
Ostrowitzki et al,[26] 2022	Low	Low	Low	Low	Low (7)	Low	Low	Low
Salloway et al,[25] 2009	Low	Low	Low	Low	High (23.5)	Low	Low	High
Salloway et al,[29] 2014	Low	Low	Low	Low	High (29)	Low	Low	High
Salloway et al,[49] 2021	Low	Unclear	Low	Low	Low (6)	Low	Low	Unclear
Sims et al,[42] 2023	Low	Low	Low	Low	High (24)	Low	Low	High
Sperling et al,[43] 2023	Low	Low	Low	Low	High (28)	Low	Low	High
Swanson et al,[18] 2021	Low	Unclear	Low	Low	Low (6.5)	Low	Low	Unclear
Van Dyck et al,[17] 2023	Low	Low	Low	Low	High (17)	Low	Low	High
Vandenberghe et al,[45] 2016	Low	Low	Low	Low	High (49)	Low	Low	High

The most frequently reported harms were ARIA-E, symptomatic ARIA-E, and ARIA-H. Those are summarized in the forest plot in Figure 4 (forest plots stratified by drug for each harm are shown in Supplemental Figures 14-16).

Development of any ARIA-H was significantly more common overall in patients given an anti-amyloid antibody (RR = 1.74; 95% CI, 1.24 to 2.44; NNH = 13). This outcome was also significantly more likely for the 2 FDA-approved drugs, lecanemab (RR = 2.33; 95% CI, 1.44 to 3.77; NNH = 9) and aducanumab (RR = 2.94; 95% CI, 2.27 to 3.79; NNH = 8), as well as for donanemab (RR = 2.31; 95% CI, 1.90 to 2.80), than for the other antibodies.

Any ARIA-E was also significantly more common overall in treated patients (RR = 10.29; 95% CI, 7.40 to 14.3; NNH = 9). This was also true for the 2 FDA-approved drugs, aducanumab (RR = 13.1; 95% CI, 9.0 to 18.9; NNH = 3) and lecanemab (RR = 8.1; 95% CI, 4.92 to 13.3; NNH = 9), as well as for donanemab (RR = 6.5; 95% CI, 1.98 to 21.4; NNH = 7).

Finally, symptomatic ARIA-E was distinguished from any ARIA-E in some studies. Although the overall RR was significantly increased for the 3 drugs for which this outcome was reported, the absolute increase was modest (RR = 24.3; 95% CI, 9.9 to 59.9; NNH = 86). It was significantly increased for the FDA-approved drug lecanemab (RR = 52; 95% CI, 3.2 to 852; NNH = 34) and for donanemab (RR = 20.7; 95% CI, 3.1 to 138; NNH = 25), although with broad CIs.

Assessment of Heterogeneity and Publication Bias

Heterogeneity across the studies was generally low, with a few exceptions. The 2 studies of aducanumab had substantial heterogeneity for CDR-SB scores (I^2 = 71%) and MMSE scores (I^2 = 63%), as well as for ADCS-ADL-MCI functional scale scores (I^2 = 56%). Lecanemab had moderate heterogeneity with respect to the ADAS-Cog-14 score (I^2 = 47%). Overall there was significant heterogeneity for the outcome of ARIA-H (I^2 = 89%), with summary estimates of the relative risk for different drugs ranging from 0.82 (ponezumab) to 2.94 (aducanumab).

Funnel plots for key benefit outcomes (ADAS-Cog-11 to -14, CDR-SB, and MMSE scores) and harm outcomes

(ARIA-E and ARIA-H) are shown in Supplemental Figures 17-21. These plots show no evidence of publication bias.

DISCUSSION

We identified 19 reports of 24 studies of monoclonal antibodies targeting amyloid depositions in patients who largely had mild cognitive impairment and mild Alzheimer disease. In no case did the results of any single study, of all combined studies for an individual drug, or of all combined studies overall find a change in cognition or function that exceeded the MCID for that scale. This was also true for lecanemab and aducanumab, the only 2 FDA-approved drugs, and for donanemab, which is pending approval. For their primary outcome of the CDR-SB (MCID = 1 to 2 points),[30] the studies found an improvement over placebo of only 0.43 points for lecanemab, 0.18 points for aducanumab, and 0.59 points for donanemab after 18 months of treatment.

We did find, however, that these drugs consistently cause statistically significant and potentially clinically significant increases in harms. The NNH was 13 for any ARIA-H, 9 for any ARIA-E, and 86 for symptomatic ARIA-E. The cost of these drugs is also substantial ($26,500 to $28,200 per year), and the requirement for regular magnetic resonance imaging monitoring adds considerable cost and inconvenience.

Some might argue that a longer study would find a clinically meaningful difference, but the changes we documented were so much lower than the MCIDs that this seems unlikely. For example, the improvement over placebo for the CDR-SB with lecanemab was 0.43 points after 18 months. The MCID for this scale is 1 to 2 points, so assuming a linear improvement in CDR-SB over time, it would take 3 years to get to 0.86 points and 6 years to reach 1.72 points. For aducanumab, with its improvement of only 0.18 points, it would take more than 5 years to reach even a 1-point change, again assuming linearity of effect.

It is possible that treatment earlier in the course of disease would be more beneficial. Indeed, all of the drugs approved or pending approval (lecanemab, aducanumab, and donanemab) were primarily studied in patients with mild cognitive impairment or mild Alzheimer disease, whereas most other drugs were studied in patients with mild to moderate dementia. As noted above, though, none of these drugs achieved the MCID for any benefit outcome. Also, a recent 4.5-year randomized trial of solanezumab in patients even earlier in the clinical pathway (having amyloid deposition but normal cognition) found no benefit at all.[43]

The FDA has previously argued that decisions about drug approvals should be based on the MCID. Lecanemab and aducanumab, however, were both approved based primarily on their effect on imaging and biomarkers, without any meaningful improvement in clinical outcomes. We feel that this is inappropriate and sets a bad precedent for the agency, not only for Alzheimer disease but also for other conditions wherein intermediate markers are easily measured but may not reliably predict clinical outcomes.

Our analysis had several limitations. All studies enrolled participants who underwent positron emission tomography scanning and/or cerebrospinal fluid analyses for amyloid, studies that are not typically done in current routine clinical practice. The included studies reported average changes on standard cognitive and functional scales, but did not report the percentage of participants achieving clinically meaningful differences in cognition or function from baseline. Such data would be more interpretable for clinicians and patients. Finally, studies had different inclusion criteria for severity of disease at baseline, which is a source of potential heterogeneity.

At best, anti-amyloid monoclonal antibodies, including those approved by the FDA, slightly slow the rate of progression of the dementia. Cognitive enhancers (donepezil, rivastigmine, galantamine, and memantine) also slow the rate of cognitive decline.[52,53] Although these older drugs, as monotherapy, do not provide a benefit that exceeds the MCID, at least their safety and cost are much better than those of the newer agents. To our knowledge, no head-to-head comparisons exist, and a search of ClinicalTrials.gov performed February 2, 2023 failed to identify any planned clinical trials comparing cholinesterase inhibitors and anti-amyloid antibodies in adults with dementia.

CONCLUSION

Alzheimer disease causes tremendous suffering in those afflicted, serious burdens to their families and caregivers, and enormous costs to the health care system. Each of these groups hope for effective tools to alleviate these burdens and to extend the time of meaningful life. But our meta-analysis shows that monoclonal antibodies targeting amyloid do not provide a clinically meaningful benefit, are associated with significant harms, and come at a high cost.

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Key words: aducanumab; aged; Alzheimer dementia; Alzheimer disease; amyloid; antibodies, monoclonal; ARIA; biological therapy; cerebral edema; cerebral hemorrhage; chronic disease; dementia; donanemab; drug approval; lecanemab; meta-analysis; risks and benefits; systematic review

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Data sharing statement: The authors will make the spreadsheet containing the primary data, along with a data dictionary, available to other researchers who request it. Anyone using the data for further publications should involve the authors in that publication.

Supplemental materials

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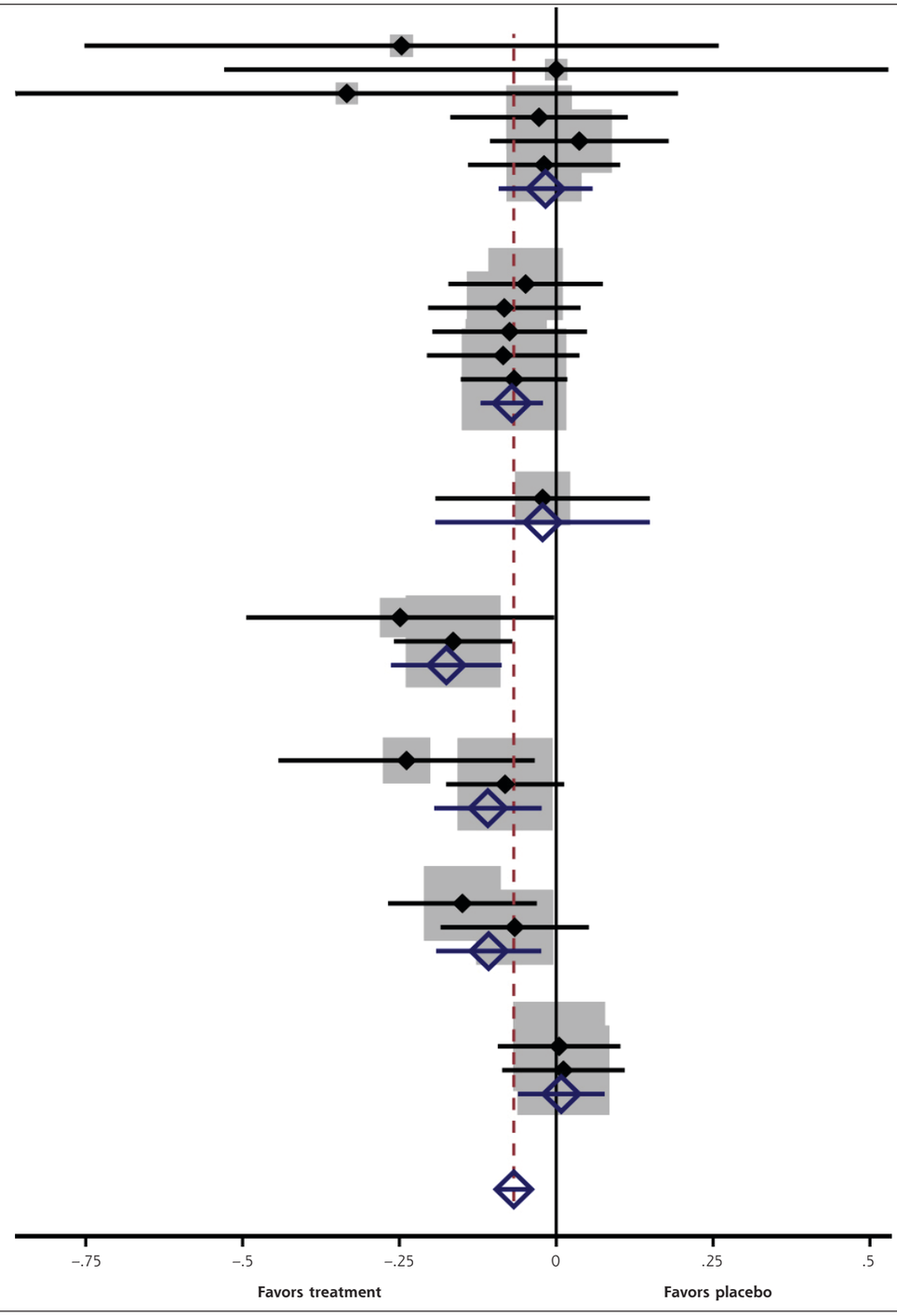
Figure 1. Forest plot for the standardized mean differences in ADAS-Cog-11 through ADAS-Cog-14 scores.

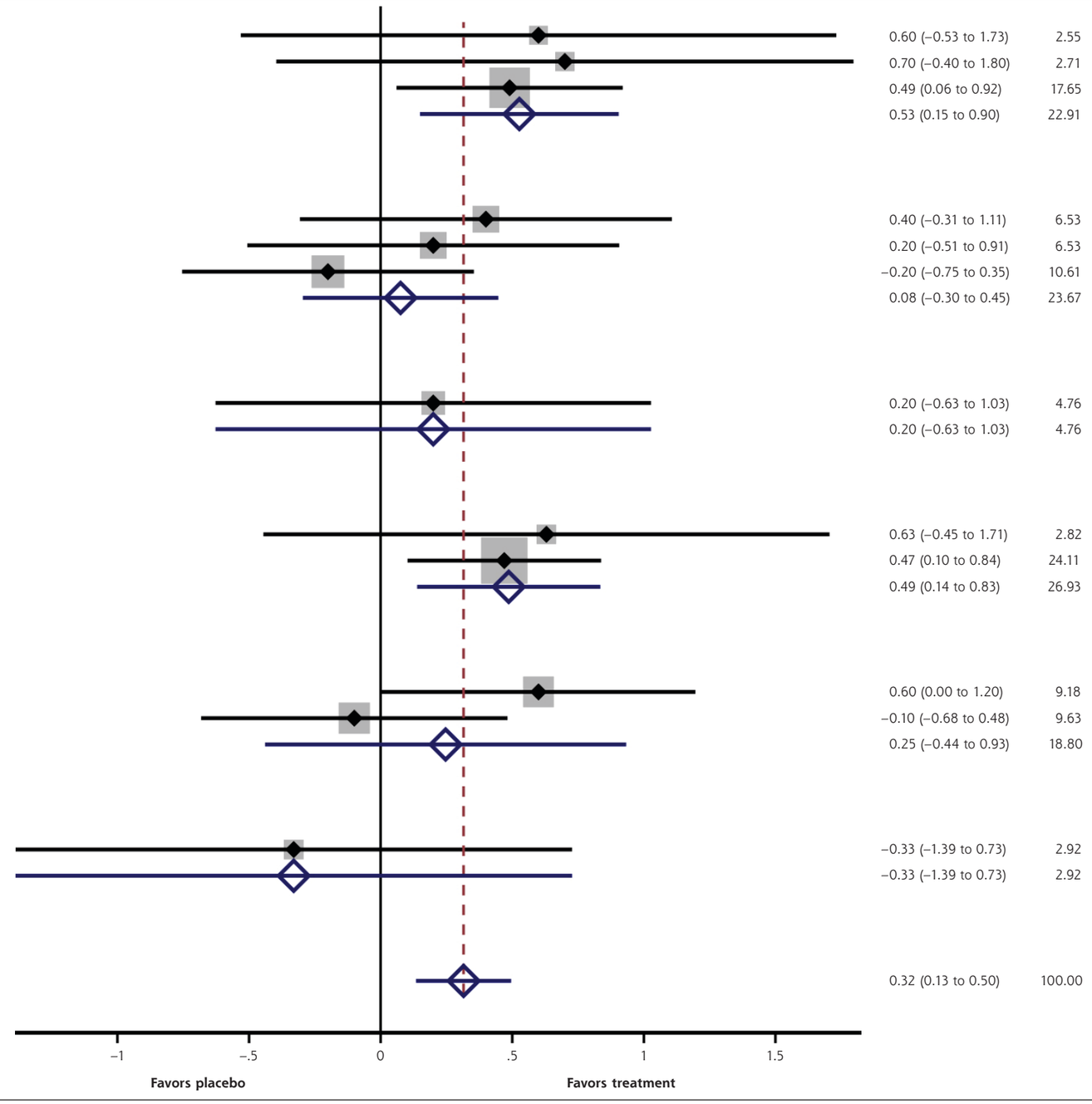
Drug, ADAS-Cog Tool, and Study Details	Treatment Group No.	Treatment Group Change in Score, Mean (SD)	Control Group No.	Control Group Change in Score, Mean (SD)	Effect (95% CI)	% Weight
Bapineuzumab						
ADAS-Cog-12: Salloway et al,[25] 2009: 0.5 mg/kg q 3 mos; mild-moderate	33	7.00 (13.21)	28	10.20 (12.70)	−0.25 (−0.75 to 0.26)	0.32
ADAS-Cog-12: Salloway et al, [25] 2009: 1.0 mg/kg q 3 mos; mild-moderate	29	6.00 (9.69)	26	6.00 (8.67)	0.00 (−0.53 to 0.53)	0.29
ADAS-Cog-12: Salloway et al, [25] 2009: 2.0 mg/kg q 3 mos; mild-moderate	29	2.60 (8.08)	27	5.60 (9.87)	−0.33 (−0.86 to 0.19)	0.29
ADAS-Cog-11: Salloway et al,[29] 2014 APOE(–): 0.5 mg/kg q 3 mos; mild-moderate	314	7.10 (10.63)	493	7.40 (11.10)	−0.03 (−0.17 to 0.11)	4.04
ADAS-Cog-11: Salloway et al,[29] 2014 APOE(–): 1.0 mg/kg q 3 mos; mild-moderate	307	7.80 (10.51)	493	7.40 (11.10)	0.04 (−0.11 to 0.18)	3.99
ADAS-Cog-11: Salloway et al,[29] 2014 APOE(+): 0.5 mg/kg q 3 mos; mild-moderate	658	8.50 (10.26)	432	8.70 (10.39)	−0.02 (−0.14 to 0.10)	5.50
Subgroup, IV	1,370		1,499		−0.02 (−0.09 to 0.06)	14.42
(I^2 = 0.0%, P = .74)						
Solanezumab						
ADAS-Cog-11: Doody et al,[27] 2014: 400 mg q 4 wks; mild-moderate	506	3.80 (14.35)	506	4.50 (14.35)	−0.05 (−0.17 to 0.07)	5.33
ADAS-Cog-11: Doody et al,[27] 2014: 400 mg q 4 wks; mild-moderate	521	5.30 (15.72)	519	6.60 (15.69)	−0.08 (−0.20 to 0.04)	5.47
ADAS-Cog-14: Doody et al,[27] 2014: 400 mg q 4 wks; mild-moderate	506	4.50 (17.79)	506	5.80 (17.22)	−0.07 (−0.20 to 0.05)	5.33
ADAS-Cog-14: Doody et al,[27] 2014: 400 mg q 4 wks; mild-moderate	521	5.90 (18.63)	519	7.50 (19.18)	−0.08 (−0.21 to 0.04)	5.47
ADAS-Cog-14: Honig et al,[51] 2018: 400 mg q 4 wks; mild	1,057	6.65 (11.70)	1,072	7.44 (11.79)	−0.07 (−0.15 to 0.02)	11.21
Subgroup, IV	3,111		3,122		−0.07 (−0.12 to −0.02)	32.82
(I^2 = 0.0%, P = .99)						
Gantenerumab						
ADAS-Cog-13: Ostrowitzki et al,[48] 2017: 225 mg q 4 wks; mild	260	5.54 (10.94)	266	5.77 (10.19)	−0.02 (−0.19 to 0.15)	2.77
Subgroup, IV	260		266		−0.02 (−0.19 to 0.15)	2.77
(I^2 = 0.0%)						
Donanemab						
ADAS-Cog-13: Mintun et al,[47] 2021: 700 mg x 3 then 1,400 mg q 4 wks; MCI-mild	131	2.91 (7.54)	126	4.77 (7.41)	−0.25 (−0.49 to −0.00)	1.34
ADAS-Cog-13: Sims et al,[42] 2023: 700 mg x 3 then 1,400 mg q 4 wks; mild	853	5.46 (8.20)	874	6.79 (7.99)	−0.16 (−0.26 to −0.07)	9.07
Subgroup, IV	984		1,000		−0.18 (−0.26 to −0.09)	10.41
(I^2 = 0.0%, P = .53)						
Lecanemab						
ADAS-Cog-14: Swanson et al,[18] 2021: 10 mg/kg biweekly; MCI-mild	152	2.59 (10.00)	237	4.90 (9.50)	−0.24 (−0.44 to −0.03)	1.94
ADAS-Cog-14: Van Dyck et al,[17] 2023: 10 mg/kg biweekly; MCI-mild	859	4.14 (17.59)	875	5.58 (17.75)	−0.08 (−0.18 to 0.01)	9.13
Subgroup, IV	1,011		1,112		−0.11 (−0.19 to −0.02)	11.07
(I^2 = 46.6%, P = .17)						
Aducanumab						
ADAS-Cog-13: Budd Haeberlein et al,[1] 2022: 6 mg/kg q 4 wks; MCI-mild	547	3.76 (9.36)	548	5.16 (9.36)	−0.15 (−0.27 to −0.03)	5.75
ADAS-Cog-13: Budd Haeberlein et al,[1] 2022: 6 mg/kg q 4 wks; MCI-mild	555	4.55 (8.95)	545	5.14 (8.87)	−0.07 (−0.18 to 0.05)	5.79
Subgroup, IV	1,102		1,093		−0.11 (−0.19 to −0.02)	11.54
(I^2 = 0.0%, P = .33)						
Crenezumab						
ADAS-Cog-11: Ostrowitzki et al,[26] 2022: 60 mg/kg q 4 wks; MCI-mild	808	8.53 (22.04)	803	8.43 (21.54)	0.00 (−0.09 to 0.10)	8.49
ADAS-Cog-13: Ostrowitzki et al,[26] 2022: 60 mg/kg q 4 wks; MCI-mild	808	9.82 (24.00)	803	9.55 (23.35)	0.01 (−0.09 to 0.11)	8.49
Subgroup, IV	1,616		1,606		0.01 (−0.06 to 0.08)	16.97
(I^2 = 0.0%, P = .92)						
Heterogeneity between groups: P = .03						
Overall, IV	9,454		9,698		−0.07 (−0.10 to −0.04)	100.00
(I^2 = 6.6%, P = .37)						



ADAS-Cog-11 = Alzheimer's Disease Assessment Scale–Cognitive Subscale-11 items; ADAS-Cog-12 = Alzheimer's Disease Assessment Scale–Cognitive Subscale-12 items; ADAS-Cog-13 = Alzheimer's Disease Assessment Scale–Cognitive Subscale-13 items; ADAS-Cog-14 = Alzheimer's Disease Assessment Scale–Cognitive Subscale-14 items; IV = interstudy variance; MCI = mild cognitive impairment.

Figure 2. Forest plot for the mean differences in Mini Mental State Examination scores.

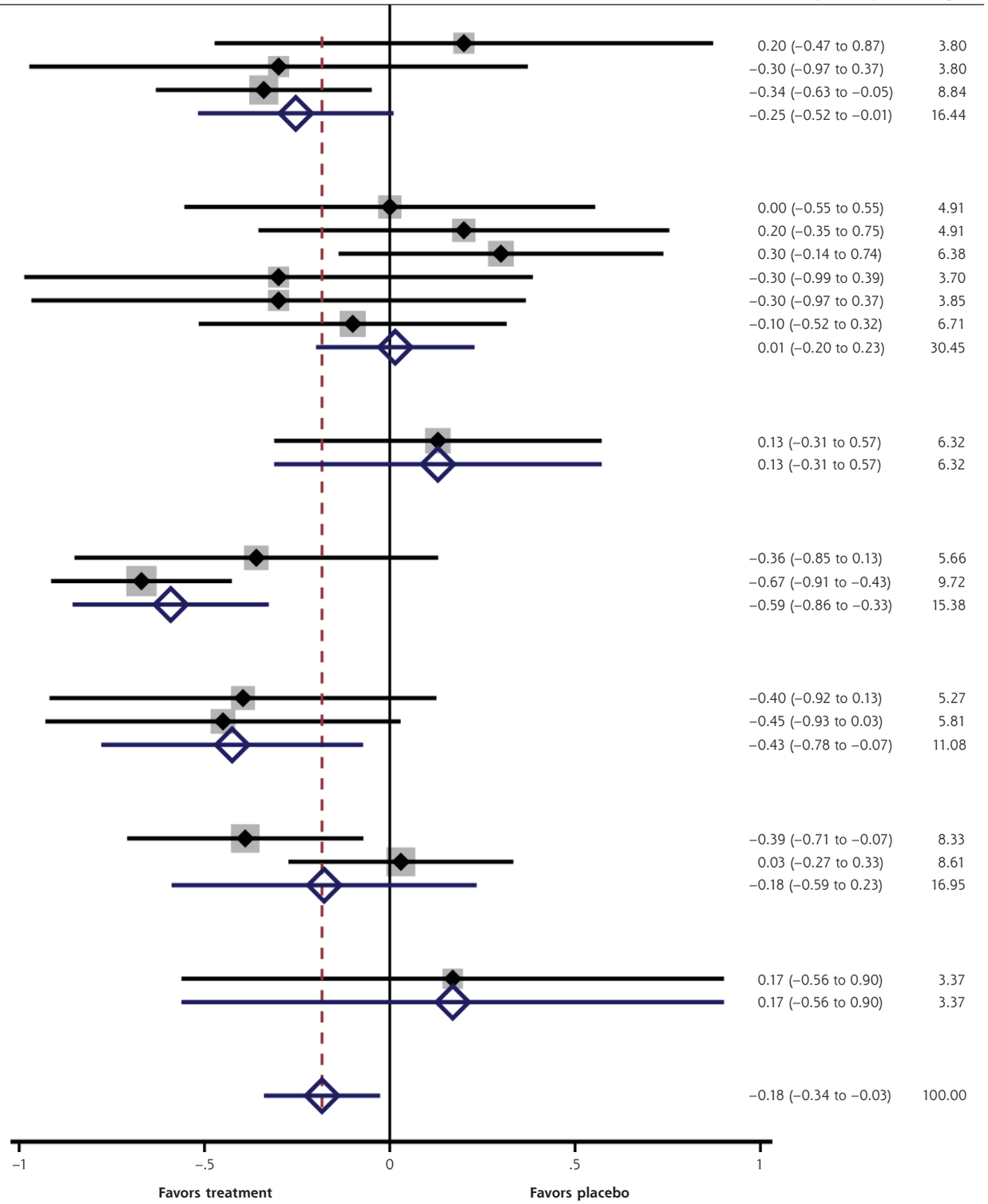
Drug and Study Details	Treatment Group No.	Treatment Group MMSE Score Change, Mean (SD)	Control Group No.	Control Group MMSE Score Change, Mean (SD)	Effect (95% CI)	% Weight
Solanezumab						
Doody et al,[27] 2014: 400 mg q 4 wks; mild-moderate	506	−1.40 (9.18))	506	−2.00 (9.18)	0.60 (−0.53 to 1.73)	2.55
Doody et al,[27] 2014: 400 mg q 4 wks; mild-moderate	521	−2.10 (8.73)	519	−2.80 (9.30)	0.70 (−0.40 to 1.80)	2.71
Honig et al,[51] 2018: 400 mg q 4 wks; mild	1,057	−3.17 (4.88)	1,072	−3.66 (5.24)	0.49 (0.06 to 0.92)	17.65
Subgroup, DL (I^2 = 0.0%, P = .93)	2,084		2,097		0.53 (0.15 to 0.90)	22.91
Bapineuzemab						
Salloway et al,[29] 2014 APOE(−): 0.5 mg/kg q 3 mos; mild-moderate	314	−3.50 (5.32)	493	−3.90 (4.44)	0.40 (−0.31 to 1.11)	6.53
Salloway et al,[29] 2014 APOE(−): 1.0 mg/kg q 3 mos; mild-moderate	307	−3.70 (5.26)	493	−3.90 (4.44)	0.20 (−0.51 to 0.91)	6.53
Salloway et al,[29] 2014 APOE(+): 0.5 mg/kg q 3 mos; mild-moderate	658	−4.70 (5.13)	432	−4.50 (4.16)	−0.20 (−0.75 to 0.35)	10.61
Subgroup, DL (I^2 = 0.0%, P = .39)	1,279		1,418		0.08 (−0.30 to 0.45)	23.67
Gantenerumab						
Ostrowitzki et al,[48] 2017: 225 mg q 4 wks; mild	260	−2.73 (4.89)	266	−2.93 (4.78)	0.20 (−0.63 to 1.03)	4.76
Subgroup, DL (I^2 = 0.0%)	260		266		0.20 (−0.63 to 1.03)	4.76
Donanemab						
Mintun et al,[47] 2021: 700 mg × 3 then 1,400 mg q 4 wks; MCI-mild	131	−2.35 (4.42)	126	−2.98 (4.38)	0.63 (−0.45 to 1.71)	2.82
Sims et al,[42] 2023: 700 mg × 3 then 1,400 mg q 4 wks; mild	853	−2.47 (3.95)	874	−2.94 (3.85)	0.47 (0.10 to 0.84)	24.11
Subgroup, DL (I^2 = 0.0%, P = .78)	984		1,000		0.49 (0.14 to 0.83)	26.93
Aducanumab						
Budd Haeberlein et al,[1] 2022: 6 mg/kg q 4 wks; MCI-mild	547	−2.70 (4.91)	548	−3.30 (5.15)	0.60 (0.00 to 1.20)	9.18
Budd Haeberlein et al,[1] 2022: 6 mg/kg q 4 wks; MCI-mild	555	−3.60 (4.95)	545	−3.50 (4.90)	−0.10 (−0.68 to 0.48)	9.63
Subgroup, DL (I^2 = 63.1%, P = .10)	1,102		1,093		0.25 (−0.44 to 0.93)	18.80
Crenezumab						
Ostrowitzki et al,[26] 2022: 60 mg/kg q 4 wks; MCI-mild	808	−4.96 (10.95)	803	−4.63 (10.70)	−0.33 (−1.39 to 0.73)	2.92
Subgroup, IV (I^2 = 0.0%)	808		803		−0.33 (−1.39 to 0.73)	2.92
Heterogeneity between groups: P = .38						
Overall, DL (I^2 = 0.0%, P = .52)	6,517		6,677		0.32 (0.13 to 0.50)	100.00



APOE = apolipoprotein E; DL = DerSimonian-Laird; MCI = mild cognitive impairment; MMSE = Mini Mental State Examination.

Figure 3. Forest plot for the mean differences in the Clinical Dementia Rating–Sum of Boxes scale.

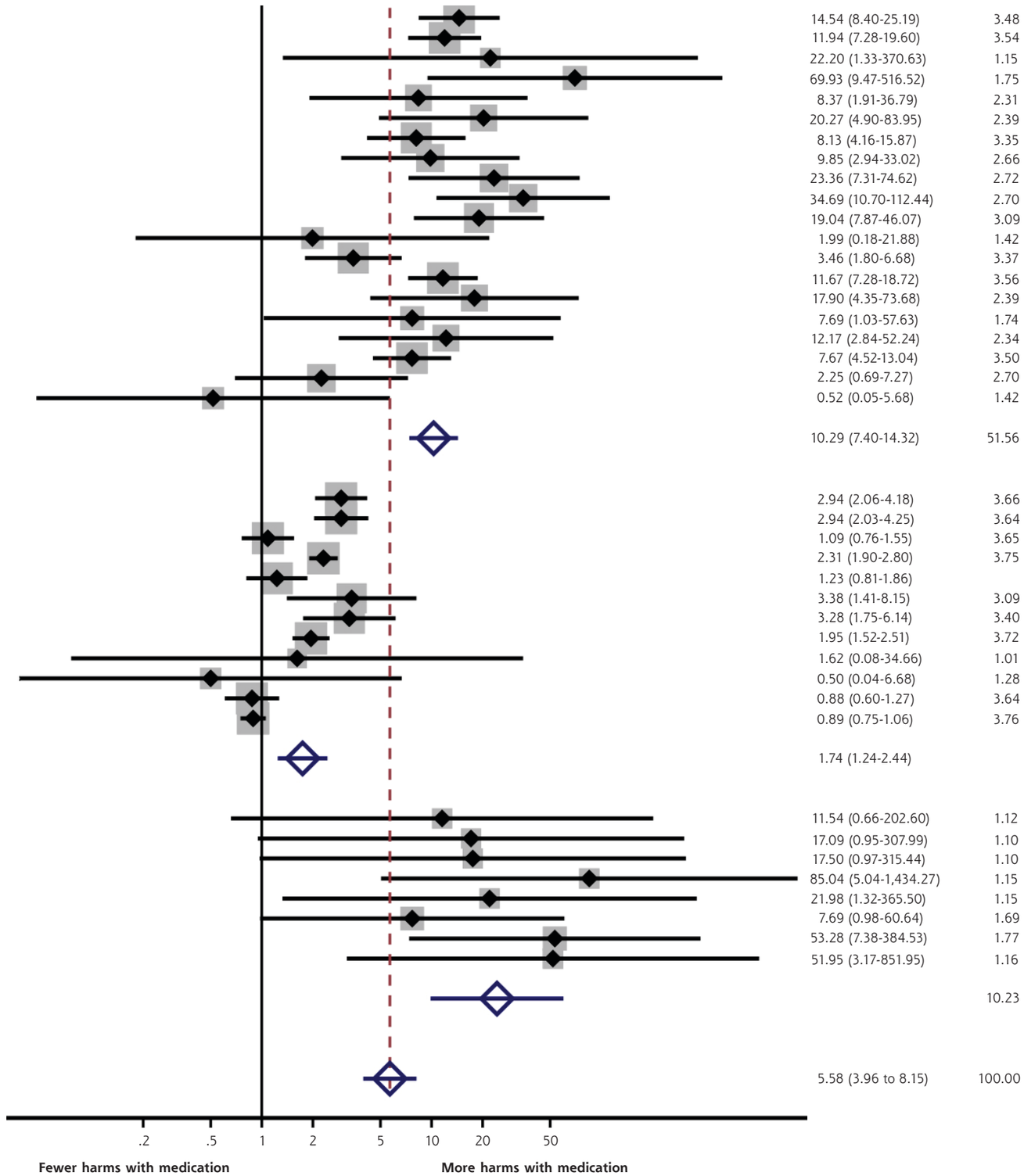
Drug and Study Details	Treatment Group No.	Treatment Group CDR-SB Score Change, Mean (SD)	Control Group No.	Control Group CDR-SB Score Change, Mean (SD)	Effect (95% CI)	% Weight
Solanezumab						
Doody et al,[27] 2014: 400 mg q 4 wks; mild-moderate	506	2.00 (5.16)	506	1.80 (5.74)	0.20 (−0.47 to 0.87)	3.80
Doody et al,[27] 2014: 400 mg q 4 wks; mild-moderate	521	1.60 (5.24)	519	1.90 (5.81)	−0.30 (−0.97 to 0.37)	3.80
Honig et al,[51] 2018: 400 mg q 4 wks; mild	1,057	1.87 (3.25)	1,072	2.21 (3.60)	−0.34 (−0.63 to −0.05)	8.84
Subgroup, DL	2,084		2,097		−0.25 (−0.52 to −0.01)	16.44
(I^2 = 4.7%, P = .35)						
Bapineuzumab						
Salloway et al,[29] 2014 APOE(−): 0.5 mg/kg q 3 mos; mild-moderate	314	2.60 (3.54)	493	2.60 (4.44)	0.00 (−0.55 to 0.55)	4.91
Salloway et al,[29] 2014 APOE(−): 1.0 mg/kg q 3 mos; mild-moderate	307	2.80 (3.50)	493	2.60 (4.44)	0.20 (−0.35 to 0.75)	4.91
Salloway et al,[29] 2014 APOE(+): 0.5 mg/kg q 3 mos; mild-moderate	658	3.30 (2.57)	432	3.00 (4.16)	0.30 (−0.14 to 0.74)	6.38
Vandenberghe et al,[45] 2016 APOE(−): 0.5 mg/kg q 3 mos; mild-moderate	115	2.20 (2.80)	144	2.50 (2.80)	−0.30 (−0.99 to 0.39)	3.70
Vandenberghe et al,[45] 2016 APOE(−): 1.0 mg/kg q 3 mos; mild-moderate	110	2.20 (2.60)	144	2.50 (2.80)	−0.30 (−0.97 to 0.37)	3.85
Vandenberghe et al,[45] 2016 APOE(+): 0.5 mg/kg q 3 mos; mild-moderate	427	2.30 (2.90)	310	2.40 (2.80)	−0.10 (−0.52 to 0.32)	6.71
Subgroup, DL	1,931		2,016		0.01 (−0.20 to 0.23)	30.45
(I^2 = 0.0%, P = .55)						
Gantenerumab						
Ostrowitzki et al,[48] 2017: 225 mg q 4 wks; mild	260	1.73 (2.55)	266	1.60 (2.62)	0.13 (−0.31 to 0.57)	6.32
Subgroup, DL	260		266		0.13 (−0.31 to 0.57)	6.32
(I^2 = 0.0%)						
Donanemab						
Mintun et al,[47] 2021: 700 mg x 3 then 1,400 mg q 4 wks; MCI-mild	131	1.22 (2.01)	126	1.58 (2.00)	−0.36 (−0.85 to 0.13)	5.66
Sims et al,[42] 2023: 700 mg x 3 then 1,400 mg q 4 wks; mild	853	1.66 (2.61)	874	2.33 (2.56)	−0.67 (−0.91 to −0.43)	9.72
Subgroup, DL	984		1,000		−0.59 (−0.86 to −0.33)	15.38
(I^2 = 18.7%, P = .26)						
Lecanemab						
Swanson et al,[18] 2021: 10 mg/kg biweekly; MCI-mild	152	1.10 (2.63)	238	1.50 (2.47)	−0.40 (−0.92 to 0.13)	5.27
Van Dyck et al,[17] 2023: 10 mg/kg biweekly; MCI-mild	859	1.21 (4.69)	875	1.66 (5.47)	−0.45 (−0.93 to 0.03)	5.81
Subgroup, DL	1,011		1,113		−0.43 (−0.78 to −0.07)	11.08
(I^2 = 0.0%, P = .88)						
Aducanumab						
Budd Haeberlein et al,[1] 2022: 6 mg/kg q 4 wks; MCI-mild	547	1.35 (2.69)	548	1.74 (2.69)	−0.39 (−0.71 to −0.07)	8.33
Budd Haeberlein et al,[1] 2022: 6 mg/kg q 4 wks; MCI-mild	555	1.59 (2.61)	545	1.56 (2.52)	0.03 (−0.27 to 0.33)	8.61
Subgroup, DL	1,102		1,093		−0.18 (−0.59 to 0.23)	16.95
(I^2 = 71.4%, P = .61)						
Crenezumab						
Ostrowitzki et al,[26] 2022: 60 mg/kg q 4 wks; MCI-mild	808	3.59 (7.54)	803	3.42 (7.45)	0.17 (−0.56 to 0.90)	3.37
Subgroup, DL	808		1,606		0.17 (−0.56 to 0.90)	3.37
(I^2 = 0.0%)						
Heterogeneity between groups: P = .009						
Overall, DL	8,180		8,388		−0.18 (−0.34 to −0.03)	100.00
(I^2 = 51.0%, P = .008)						



APOE = apolipoprotein E; CDR-SB = Clinical Dementia Rating–Sum of Boxes scale; DL = DerSimonian-Laird; MCI = mild cognitive impairment.

Figure 4. Forest plot for differences in any ARIA-E, any ARIA-H, and symptomatic ARIA-E.

Outcome and Study Details	Treatment Group, No. Affected/Total	Control Group, No. Affected/Total	Relative Risk (95% CI)	% Weight
Any ARIA-E				
Budd Haeberlein et al,[1] 2022: 6 mg/kg q 4 wks; MCI-mild	188/541	13/544	14.54 (8.40-25.19)	3.48
Budd Haeberlein et al,[1] 2022: 6 mg/kg q 4 wks; MCI-mild	199/554	16/532	11.94 (7.28-19.60)	3.54
Salloway et al, [25] 2009: any dose q 3 mos; mild-moderate	12/124	0/110	22.20 (1.33-370.63)	1.15
Salloway et al,[29] 2014 APOE(–): 2.0 mg/kg q 3 mos; mild-moderate	20/141	1/493	69.93 (9.47-516.52)	1.75
Vandenberghe et al,[45] 2016 APOE(–): 0.5 mg/kg q 3 mos; mild-moderate	13/267	2/344	8.37 (1.91-36.79)	2.31
Vandenberghe et al,[45] 2016 APOE(–): 1.0 mg/kg q 3 mos; mild-moderate	31/263	2/344	20.27 (4.90-83.95)	2.39
Vandenberghe et al,[45] 2016 APOE(+): 0.5 mg/kg q 3 mos; mild-moderate	109/654	9/439	8.13 (4.16-15.87)	3.35
Brashear et al,[41] 2018 APOE(–): 0.5 mg/kg q 3 mos; mild-moderate	19/337	3/524	9.85 (2.94-33.02)	2.66
Brashear et al,[41] 2018 APOE(–): 1 mg/kg q 3 mos; mild-moderate	44/329	3/524	23.36 (7.31-74.62)	2.72
Brashear et al,[41] 2018 APOE(–): 2 mg/kg q 3 mos; mild-moderate	28/141	3/524	34.69 (10.70-112.44)	2.70
Brashear et al,[41] 2018 APOE(+): 0.5 mg/kg q 3 mos; mild-moderate	143/673	5/448	19.04 (7.87-46.07)	3.09
Ostrowitzki et al,[26] 2022: 60 mg/kg q 4 wks; MCI-mild	2/808	1/803	1.99 (0.18-21.88)	1.42
Mintun et al,[47] 2021: 700 mg x 3 then 1,400 mg q 4 wks; MCI-mild	36/131	10/126	3.46 (1.80-6.68)	3.37
Sims et al,[42] 2023: 700 mg x 3 then 1,400 mg q 4 wks; mild	205/853	18/874	11.67 (7.28-18.72)	3.56
Ostrowitzki et al,[48] 2017: 225 mg q 4 wks; mild	35/260	2/266	17.90 (4.35-73.68)	2.39
Salloway et al,[49] 2021: 225 mg then 1,200 q 4 wks; at risk or MCI	10/52	1/40	7.69 (1.03-57.63)	1.74
Swanson et al,[18] 2021: 10 mg/kg biweekly; MCI-mild	16/161	2/245	12.17 (2.84-52.24)	2.34
Van Dyck et al,[17] 2023: 10 mg/kg biweekly; MCI-mild	113/859	15/875	7.67 (4.52-13.04)	3.50
Doody et al,[27] 2014: 400 mg q 4 wks; mild-moderate	9/1,027	4/1,025	2.25 (0.69-7.27)	2.70
Sperling et al,[43] 2023: 1,600 mg q 4 wks; normal	1/572	2/591	0.52 (0.05-5.68)	1.42
Subgroup, DL	1,233/8,747	112/9,671	10.29 (7.40-14.32)	51.56
(I^2 = 54.7%, P = .002)				
Any ARIA-H				
Budd Haeberlein et al,[1] 2022: 6 mg/kg q 4 wks; MCI-mild	108/541	37/544	2.94 (2.06-4.18)	3.66
Budd Haeberlein et al,[1] 2022: 6 mg/kg q 4 wks; MCI-mild	104/554	34/532	2.94 (2.03-4.25)	3.64
Ostrowitzki et al,[26] 2022: 60 mg/kg q 4 wks; MCI-mild	59/808	54/803	1.09 (0.76-1.55)	3.65
Sims et al,[42] 2023: 700 mg x 3 then 1,400 mg q 4 wks; mild	268/853	119/874	2.31 (1.90-2.80)	3.75
Ostrowitzki et al,[48] 2017: 225 mg q 4 wks; mild	42/260	35/266	1.23 (0.81-1.86)	
Salloway et al,[49] 2021: 225 mg then 1,200 q 4 wks: at risk or MCI	22/152	5/40	3.38 (1.41-8.15)	3.09
Swanson et al,[18] 2021: 10 mg/kg biweekly; MCI-mild	28/161	13/245	3.28 (1.75-6.14)	3.40
Van Dyck et al,[17] 2023: 10 mg/kg biweekly; MCI-mild	155/859	81/875	1.95 (1.52-2.51)	3.72
Landen et al,[50] 2017: 10 mg/kg q 3 mos; mild-moderate	1/12	0/6	1.62 (0.08-34.66)	1.01
Landen et al,[50] 2017: 10 mg/kg then 7.5 mg/kg q mo: mild-moderate	1/12	1/6	0.50 (0.04-6.68)	1.28
Doody et al,[27] 2014: 400 mg q 4 wks; mild-moderate	50/1,027	57/1,025	0.88 (0.60-1.27)	3.64
Sperling et al,[43] 2023: 1,600 mg q 4 wks; normal	167/572	194/591	0.89 (0.75-1.06)	3.76
Subgroup, DL	1,005/5,711	630/5,807	1.74 (1.24-2.44)	
(I^2 = 89.7%, P = .000)				
Symptomatic ARIA-E				
Salloway et al, [25] 2009: any dose q 3 mos; mild-moderate	6/124	0/110	11.54 (0.66-202.60)	1.12
Brashear et al,[41] 2018 APOE(–): 0.5 mg/kg q 3 mos; mild-moderate	5/337	0/524	17.09 (0.95-307.99)	1.10
Brashear et al,[41] 2018 APOE(–): 1 mg/kg q 3 mos; mild-moderate	5/329	0/524	17.50 (0.97-315.44)	1.10
Brashear et al,[41] 2018 APOE(–): 2 mg/kg q 3 mos; mild-moderate	11/141	0/524	85.04 (5.04-1,434.27)	1.15
Brashear et al,[41] 2018 APOE(+): 0.5 mg/kg q 3 mos; mild-moderate	16/673	0/448	21.98 (1.32-365.50)	1.15
Mintun et al,[47] 2021: 700 mg x 3 then 1,400 mg q 4 wks; MCI-mild	8/131	1/126	7.69 (0.98-60.64)	1.69
Sims et al,[42] 2023: 700 mg x 3 then 1,400 mg q 4 wks; mild	52/853	1/874	53.28 (7.38-384.53)	1.77
Van Dyck et al,[17] 2023: 10 mg/kg biweekly; MCI-mild	25/859	0/875	51.95 (3.17-851.95)	1.16
Subgroup, DL	128/3,447	2/4,005		10.23
(I^2 = 0.0%, P = .87)				
Heterogeneity between groups: P = .000				
Overall, DL	2,366/17,905	744/19,483	5.58 (3.96 to 8.15)	100.00
(I^2 = 91.8%, P = .000)				



APOE = apolipoprotein E; ARIA-E = amyloid-related imaging abnormalities of edema; ARIA-H = amyloid-related imaging abnormalities of hemorrhage; DL = DerSimonian-Laird; MCI = mild cognitive impairment.

Note: Separate plots stratified by drug are given in **Supplemental Figures 14-16**.