JAMA Neurology | Original Investigation

Amyloid-Related Imaging Abnormalities With Donanemab in Early Symptomatic Alzheimer Disease

Secondary Analysis of the TRAILBLAZER-ALZ and ALZ 2 Randomized Clinical Trials

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IMPORTANCE Amyloid-related imaging abnormalities (ARIA) are the major adverse event associated with amyloid-targeting immunotherapy. Identifying clinical features and individual risk factors for ARIA could facilitate effective prediction and prevention strategies.

OBJECTIVE To characterize ARIA in participants treated with donanemab.

DESIGN, SETTING, AND PARTICIPANTS These prespecified and post hoc exploratory analyses use data from the placebo-controlled portions of the TRAILBLAZER-ALZ and ALZ 2 randomized clinical trials, conducted from December 2017 to December 2020 and from June 2020 to April 2023, respectively. Additional analyses are included from a stand-alone open-label addendum conducted from August 2021 through August 2023. Participants in the placebo-controlled trials and the open-label addendum aged 60 to 85 years with early symptomatic Alzheimer disease and elevated amyloid levels were included. The placebo-controlled trials, but not the addendum, had tau inclusion criteria.

INTERVENTIONS Placebo-controlled trial participants were randomized 1:1 to receive placebo or donanemab, and all open-label participants received donanemab. Donanemab was administered every 4 weeks for up to 72 weeks.

MAIN OUTCOMES AND MEASURES The primary outcomes were the frequency, radiographic severity, seriousness, symptoms, timing relative to donanemab treatment, and risk factors for ARIA.

RESULTS Across 3030 total participants (placebo-controlled trials: 999 placebo participants, 984 donanemab participants; open-label addendum: 1047 donanemab participants), mean (SD) age was approximately 73.7 (6.0) years and 1684 participants (55.6%) were female. Frequencies of ARIA–edema/effusions (ARIA-E) and ARIA–microhemorrhages and hemosiderin deposition (ARIA-H) were higher with donanemab (24.4% and 31.3% in placebo-controlled trials, respectively; 19.8% and 27.2% in open-label addendum, respectively) than with placebo (1.9% and 13.0%, respectively). ARIA-E was mostly mild or moderate in severity. Serious ARIA-E was reported in 1.5% and symptomatic ARIA-E in 5.8% of donanemab-treated participants in the placebo-controlled trials. Symptoms most frequently reported with ARIA-E were headache and confusional state. In 58.3% of donanemab-treated participants with ARIA-E, the first event occurred by the third infusion (approximately month 3). Risk analysis demonstrated independent associations between ARIA-E and 6 baseline variables, including increased risk with *APOE* ε4 allele number, greater number of microhemorrhages, presence of cortical superficial siderosis, higher amyloid plaque, and elevated mean arterial pressure, and decreased risk with antihypertensive use.

CONCLUSIONS AND RELEVANCE ARIA is an adverse event associated with donanemab treatment that requires safety monitoring. Individual ARIA risk can be assessed by *APOE* ε4 status and baseline imaging findings.

TRIAL REGISTRATIONS ClinicalTrials.gov Identifiers: NCT03367403 and NCT04437511

JAMA Neurol. 2025;82(5):461-469. doi:10.1001/jamaneurol.2025.0065
Published online March 10, 2025.

Supplemental content

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Amyloid-related imaging abnormalities (ARIA) are adverse events detected by magnetic resonance imaging (MRI) in patients with Alzheimer disease (AD). ARIA presents as 2 general types: (1) vasogenic cerebral edema or sulcal effusion (ARIA-E) and (2) microhemorrhages, hemosiderin deposits, and superficial siderosis (ARIA-H).[1] Macrohemorrhages (intracerebral hemorrhages ≥1 cm) are also adverse events of special interest. Although significantly associated with amyloid-targeting therapies (ATTs),[2-4] spontaneous ARIA-H can frequently occur and spontaneous ARIA-E can rarely occur as amyloid deposition increases in the cerebral vasculature.[1,5]

TRAILBLAZER-ALZ and ALZ 2 were phase 2 and 3 randomized clinical trials, respectively, designed to assess safety and efficacy of donanemab for early symptomatic AD (mild cognitive impairment or mild dementia). Donanemab demonstrated rapid and robust amyloid removal and significantly slowed cognitive decline compared with placebo.[2,3] Pooled data were analyzed from the placebo-controlled portions of these trials, as well as data from an open-label addendum to TRAILBLAZER-ALZ 2 to further characterize ARIA frequency, clinical presentation, and its independent predictors.

Key Points

Question How is donanemab treatment associated with amyloid-related imaging abnormalities (ARIA) in early symptomatic Alzheimer disease?

Findings In this secondary analysis of 2 placebo-controlled trials and 1 open-label study, donanemab increased ARIA risk over 76 weeks, with ARIA–edema/effusions occurring in 20% to 24% of donanemab-treated participants and ARIA–microhemorrhages and hemosiderin deposition occurring in 27% to 31% of donanemab-treated participants. ARIA was associated with *APOE* ε4 status and baseline imaging findings, and most events were mild to moderate, asymptomatic, and initially presented within the first 6 donanemab infusions, with most serious events occurring within the first 3 infusions.

Meaning Safety monitoring is necessary with donanemab treatment; identifying specific baseline characteristics may facilitate risk assessment.

Methods

Participants and Study Design

Participants were enrolled in TRAILBLAZER-ALZ (N = 257), conducted December 2017 to December 2020, TRAILBLAZER-ALZ 2 (N = 1736), conducted June 2020 to April 2023, or the stand-alone open-label addendum to TRAILBLAZER-ALZ 2 (N = 1053), conducted August 2021 to August 2023. For each study, an independent ethics committee or institutional review board at each site approved the study protocol, and participants and study partners provided written consent.

TRAILBLAZER-ALZ and ALZ 2 were multicenter, randomized, double-blind, placebo-controlled, 76-week registration studies of participants treated with donanemab with early symptomatic AD.[2,3] A TRAILBLAZER-ALZ 2 addendum collected open-label exposure and safety data over 76 weeks in previously donanemab-naive participants with early symptomatic AD who did not participate in the placebo-controlled trials. The open-label addendum allowed for observation of safety in a population with a lower baseline threshold of amyloid pathology (≥24.1 Centiloids [CL] vs ≥37 CL for placebo-controlled trials) and with no requirement for evidence of tau pathology.

Dosing regimens were previously described[2,3] and are detailed in the eMethods in Supplement 2. Placebo-controlled trial participants were randomly assigned 1:1 to receive placebo or donanemab intravenously every 4 weeks for up to 72 weeks; outcomes were assessed through 76 weeks. Addendum dosing was the same as that in TRAILBLAZER-ALZ 2, except that the addendum was open-label and all participants received donanemab. ARIA was managed as previously described, with TRAILBLAZER-ALZ 2 allowing for greater investigator discretion than TRAILBLAZER-ALZ for continued donanemab dosing once ARIA occurred (eFigure 1 in Supplement 2).[2,3]

ARIA frequency, radiographic severity, seriousness, symptoms, and timing were evaluated separately in the pooled placebo-controlled trials and the open-label addendum. Data from all 3 studies were integrated to evaluate onset, resolution, recurrence, and medications prescribed to treat ARIA-E, and risk factors associated with ARIA-E and ARIA-H. Unless otherwise noted, no statistical comparisons were conducted across groups.

Analyses include participant data from the first dose of randomized assignment of donanemab or placebo plus 57 days past the double-blind or open-label study period based on approximately 5 half-lives of donanemab. Data from the ongoing TRAILBLAZER-ALZ 2 long-term extension are not included in analyses, except as part of an integrated analysis to evaluate the effect of the 4-week MRI on risk of serious ARIA and symptomatic ARIA-E (eMethods in Supplement 2).

ARIA Characterization

ARIA and macrohemorrhage analyses were based on either centrally read MRI scans or by ARIA treatment-emergent adverse event (Medical Dictionary for Regulatory Activities Preferred Term) clusters. Analysis types are noted in the respective Table and Figure legends. Further details on MRI schedule, ARIA Preferred Term groupings, severity evaluation (eTable 1 in Supplement 2), and event definitions are available in the eMethods in Supplement 2.

Statistical Analysis

Key factors associated with ARIA-E in donanemab-treated participants were identified using a post hoc machine learning model with an initial set of 42 baseline variables (eTable 2 in Supplement 2). The least absolute shrinkage and selection operator (LASSO) model[6] selected the most informative subset of baseline predictors of ARIA-E, which were then incorporated into a multiple logistic regression model to predict ARIA-E events (yes/no). Odds ratios (ORs) were adjusted for all covariates and assessed using 2-sided hypothesis tests with a .05 significance level. R version 4.1.2 (The R Foundation) was used

Table 1. Baseline Demographic and Clinical Characteristics of Participants in the Placebo-Controlled Trials and Open-Label Addendum

Characteristic	Participants, No. (%)		
	Placebo-controlled trials		Open-label addendum, donanemab-treated participants (n = 1047)
	Placebo (n = 999)	Donanemab (n = 984)	
Age, mean (SD), y	73.3 (6.1)	73.2 (6.1)	74.6 (5.9)
Sex			
Female	565 (56.6)	556 (56.5)	563 (53.8)
Male	434 (43.4)	428 (43.5)	484 (46.2)
Race[a]			
American Indian or Alaska Native	0	4 (0.4)	2 (0.2)
Asian	49 (4.9)	58 (5.9)	64 (6.1)
Black or African American	23 (2.3)	24 (2.4)	36 (3.4)
Multiple	1 (0.1)	1 (0.1)	4 (0.4)
Missing	0	1 (0.1)	5 (0.5)
Native Hawaiian or Pacific Islander	0	0	1 (0.1)
White	926 (92.7)	896 (91.1)	935 (89.3)
Hispanic/Latino ethnicity[b]	38 (5.1)	40 (5.4)	99 (10.9)
APOE ε4 carrier status			
Noncarrier	282 (28.2)	291 (29.6)	391 (37.3)
Carrier	712 (71.3)	690 (70.1)	649 (62.0)
Heterozygous	538 (53.9)	522 (53.0)	535 (51.1)
Homozygous	174 (17.4)	168 (17.1)	114 (10.9)
Unknown	5 (0.5)	3 (0.3)	7 (0.7)
Screening amyloid pathology, mean (SD), Centiloids	101.5 (34.4)	103.9 (34.6)	82.5 (37.2)
Screening MMSE score by clinical category			
Mild cognitive impairment (>26)	159 (15.9)	171 (17.4)	345 (32.0)
Mild AD (20-26)	831 (83.2)	801 (81.4)	702 (67.0)
Moderate AD (<20)	4 (0.4)	7 (0.7)	0
No baseline/screening MMSE	5 (0.5)	5 (0.5)	0

Abbreviations: AD, Alzheimer disease; *APOE*, apolipoprotein E; MMSE, Mini-Mental State Examination.

[a] Race data were self-reported by participants within fixed categories (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White). Ethnicity was limited to participants in the US and Puerto Rico (Hispanic or Latino, Not Hispanic or Latino, Not Reported).

[b] Ethnicity data were not reported by all participants. The denominator used to calculate the percent was the number of participants with ethnicity reported.

to fit the final model, with glmnet and caret packages used for model training and 5-fold cross-validation.

Due to the common occurrence of ARIA-H, risk factors for ARIA-H could be assessed in both the placebo and donanemab populations. Baseline predictors were identified from variables in eTable 2 in Supplement 2 using the treatment-specific subgroup detection tool (TSDT),[7] which yielded a bias-adjusted estimate of the differential effect (donanemab vs placebo) for the identified predictors. TSDT R package version 1.0.7 was used for analysis.

Results

Trial Populations

Analyses included 984 donanemab-treated and 999 placebo-treated participants from the pooled, 76-week, placebo-controlled portions of TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 and 1047 donanemab-treated participants from a stand-alone 76-week addendum to TRAILBLAZER-ALZ 2 (eFigure 2 in Supplement 2). Across 3030 total participants, mean (SD) age was approximately 73.7 (6.0) years and 1684 participants (55.6%) were female.

Among donanemab-treated and placebo-treated participants in the placebo-controlled trials and donanemab-treated participants in the open-label addendum, 17.1% to 17.4% and 10.9% of participants, respectively, were apolipoprotein (*APOE*) ε4 homozygotes, mean baseline amyloid levels were 101.5 to 103.9 CL and 82.5. CL, respectively, and 15.9% to 17.4% and 32.0% of participants, respectively, had mild cognitive impairment per the Mini-Mental State Examination (**Table 1**).

ARIA Frequency

Frequency of ARIA (ARIA-E and/or ARIA-H) was higher in donanemab-treated participants (37.0% in placebo-controlled trials; 32.0% in open-label addendum) than in placebo-treated participants (14.2%; **Table 2**). In donanemab-treated participants from both populations and placebo-treated participants, ARIA-E occurred in 19.8% to 24.4% and 1.9% of participants, respectively, and ARIA-H occurred in 27.2% to 31.3% and 13.0% of participants, respectively. Across all groups, frequencies were similar for

Table 2. Amyloid-Related Imaging Abnormalities (ARIA) Frequency in the Placebo-Controlled Trials and Open-Label Addendum

Event	No. (%)		
	Placebo-controlled trials[a]		Open-label addendum, donanemab-treated participants (n = 1047)
	Placebo (n = 999)	Donanemab (n = 984)	
Any ARIA (E or H)[b]	142 (14.2)	364 (37.0)	335 (32.0)
Serious adverse events[c]	0	16 (1.6)	9 (0.9)
Treatment discontinuation[c]	8 (0.8)	52 (5.3)	27 (2.6)
ARIA-E[b]	19 (1.9)	240 (24.4)	207 (19.8)
APOE ε4 carrier status, No./total No. (%)			
Noncarrier	2/282 (0.7)	43/291 (14.8)	43/391 (11.0)
Heterozygote	10/538 (1.9)	126/522 (24.1)	115/535 (21.5)
Homozygote	6/174 (3.4)	70/168 (41.7)	48/114 (42.1)
Symptomatic[d]	1 (0.1)	57 (5.8)	42 (4.0)
APOE ε4 carrier status, No./total No. (%)			
Noncarrier	0/282	12/291 (4.1)	10/391 (2.6)
Heterozygote	0/538	32/522 (6.1)	24/535 (4.5)
Homozygote	1/174 (0.6)	13/168 (7.7)	7/114 (6.1)
Serious adverse events[c]	0	15 (1.5)	7 (0.7)
Treatment discontinuation[c]	4 (0.4)	28 (2.8)	14 (1.3)
ARIA-H[b]	130 (13.0)	308 (31.3)	285 (27.2)
APOE ε4 carrier status, No./total No. (%)			
Noncarrier	30/282 (10.6)	55/291 (18.9)	71/391 (18.2)
Heterozygote	66/538 (12.3)	162/522 (31.0)	156/535 (29.2)
Homozygote	34/174 (19.5)	90/168 (53.6)	57/114 (50.0)
Symptomatic	3 (0.3)	10 (1.0)	2 (0.2)
Serious adverse events[c]	0	4 (0.4)	3 (0.3)
Treatment discontinuation[c]	4 (0.4)	24 (2.4)	13 (1.2)
Macrohemorrhage[b]	2 (0.2)	3 (0.3)	4 (0.4)
Serious adverse events[c]	1 (0.1)	1 (0.1)	2 (0.2)
Treatment discontinuation[c]	1 (0.1)	2 (0.2)	3 (0.3)

Abbreviations: *APOE*, apolipoprotein E; ARIA-E, amyloid-related imaging abnormality–edema/effusions; ARIA-H, amyloid-related imaging abnormality–microhemorrhages and hemosiderin deposits.

[a] Reflects TRAILBLAZER-ALZ final data lock.

[b] Based on safety magnetic resonance imaging or treatment-emergent adverse event (TEAE) cluster.

[c] Based TEAE Medical Dictionary for Regulatory Activities cluster.

[d] Based on ARIA clinical report form.

isolated ARIA-H (11.7%-12.5%; eTable 3 in Supplement 2) and macrohemorrhage (0.2%-0.4%).

ARIA Severity

ARIA maximum radiographic severity was determined from centrally read MRI scans (eTable 3 in Supplement 2). Using a 3-point severity scale,[8] ARIA-E, ARIA-H microhemorrhage, and isolated ARIA-H were mostly mild or moderate in donanemab-treated participants in both the placebo-controlled trials and open-label addendum. Serious ARIA events (eg, events requiring hospitalization) occurred more with moderate to severe radiographic ARIA in both donanemab-treated populations. Symptomatic ARIA-E was more likely to be classified as radiographically severe than asymptomatic ARIA-E. Among donanemab-treated participants in the placebo-controlled trials and open-label addendum, severe ARIA-E was observed in 15 of 54 symptomatic cases (27.8%) and 9 of 42 symptomatic cases (21.4%), respectively, compared with 6 of 183 asymptomatic cases (3.3%) and 5 of 165 asymptomatic cases (3.0%), respectively.

ARIA Serious Adverse Events

Frequencies of serious adverse events of ARIA and macrohemorrhage are reported in Table 2. Serious adverse events associated with macrohemorrhage are detailed in eTable 4 in Supplement 2.

In both donanemab-treated populations, 18 of 25 serious ARIA cases (ARIA-E and/or ARIA-H) (72.0%) occurred within the time of the first 3 monthly donanemab infusions (**Figure 1**). This included 3 of 4 participants who had both serious ARIA-E and serious ARIA-H (Figure 1B).

Due to increased frequency of serious ARIA during initial infusions, a 4-week MRI scan was added to the TRAILBLAZER-ALZ 2 protocol (eMethods in Supplement 2). Approximately 16% of donanemab-treated participants in TRAILBLAZER-ALZ 2 had a 4-week MRI scan. Cox proportional hazards indicated the 4-week MRI reduced risk of symptomatic ARIA-E by 36.3% (hazard ratio [HR], 0.64; 95% CI, 0.41-0.98; P = .04). The 4-week MRI resulted in a statistically nonsignificant 23.9% risk reduction of serious ARIA (ARIA-E, ARIA-H, or macrohemorrhage) (HR, 0.76; 95% CI, 0.35-1.65; P = .49).

There were overall 17 deaths in the donanemab group and 12 deaths with placebo in the placebo-controlled trials (eTable 5 in Supplement 2). As discussed by Sims and colleagues,[3] 3 participants had serious ARIA and subsequently died during TRAILBLAZER-ALZ 2. One of these participants had large baseline superficial siderosis; 2 of the 3 deaths were among *APOE* ε4 heterozygotes and 1 was in a noncarrier.[3] Other than these ARIA-related deaths, no pattern or trend was reported in events that led to death in the placebo-controlled trials and open-label addendum. Beyond these studies, in the ongoing long-term extension of TRAILBLAZER-ALZ 2, an *APOE* ε4 heterozygote died due to ARIA-E after the fifth donanemab dose; corticosteroids were initiated 5 days after identification of ARIA-E. In addition, a death occurred following thrombolytic administration for potential acute strokelike symptoms, where MRI the same day showed severe ARIA-E; the patient subsequently died due to intracranial hemorrhage.

ARIA-E–Associated Symptoms

Among donanemab-treated participants with ARIA-E, 57 of 240 participants (23.8%) in the placebo-controlled trials and 42 of 207 participants (20.3%) in the open-label addendum reported symptoms (eTable 6 in Supplement 2). The most frequently reported symptoms were headache (10.4%-13.5%) and confusional state (3.9%-5.4%); approximately 80% of participants in the placebo-controlled trials and 90% in the open-label addendum had symptom resolution within the study period. Of 52 donanemab-treated participants with symptomatic ARIA-E in TRAILBLAZER-ALZ 2, where symptom severity was collected, 30 participants (57.7%) had mild symptoms, 12 (23.1%) had moderate symptoms, and 10 (19.2%) had severe symptoms.

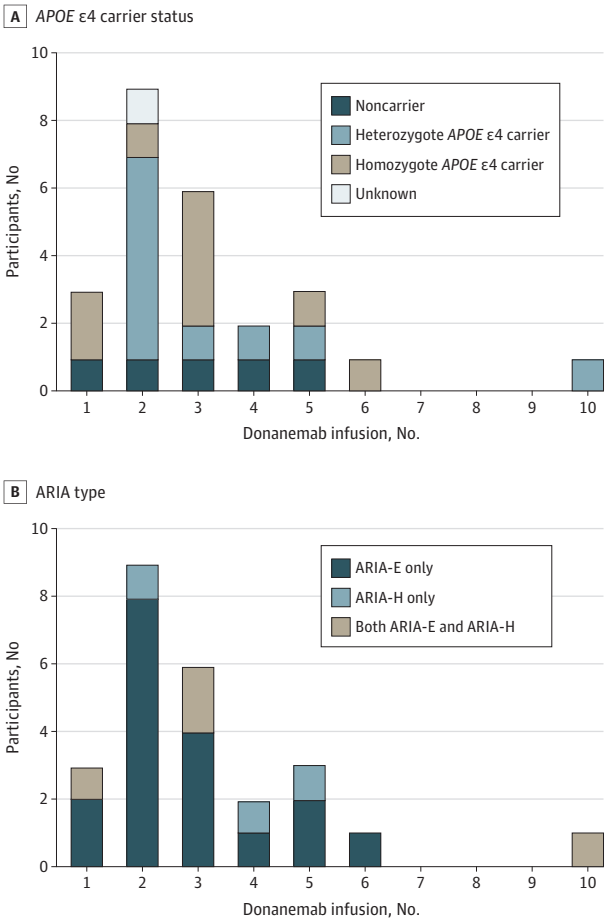
Medications Used to Treat ARIA-E

Medications prescribed to treat ARIA-E included corticosteroids, paracetamol, and ibuprofen. Guidance for corticosteroid dosage was provided (eTable 7 in Supplement 2), with treatment at the discretion of the investigator. Of 42 donanemab-treated participants in the placebo-controlled trials and open-label addendum who received medication to treat ARIA-E, 21 received corticosteroids for a median duration of 17 days (eTable 8 in Supplement 2). Given that corticosteroids were generally administered for more severe events and not in a controlled manner, these biases preclude conclusions of the effectiveness on symptom resolution.

APOE ε4 Status and Other Potential ARIA Risk Factors

The frequency or severity of ARIA varied by *APOE* ε4 status (Table 2; eTable 9 in Supplement 2). Among donanemab-treated patients in the placebo-controlled trials and open-label addendum, ARIA-E occurred in 41.7% to 42.1% of *APOE* ε4 homozygotes, 21.5% to 24.1% of heterozygotes, and 11.0% to 14.8% of noncarriers (Table 2). ARIA-H occurred in 50.0% to 53.6% of homozygotes, 29.2% to 31.0% of heterozygotes, and 18.2% to 18.9% of noncarriers. Across both donanemab-treated populations, frequencies of serious and severe ARIA-E and ARIA-H, as well as symptomatic ARIA-E, were highest in *APOE* ε4 homozygotes, although the increase in symptomatic ARIA-E in homozygotes was modest compared with the increase in overall ARIA (eTable 9 in Supplement 2). eTable 10 and eFigure 3 in Supplement 2 summarize ARIA frequencies by *APOE* ε4 status and baseline MRI findings.

Figure 1. Number of Infusions to First Serious Amyloid-Related Imaging Abnormalities (ARIA) Event in Donanemab-Treated Participants

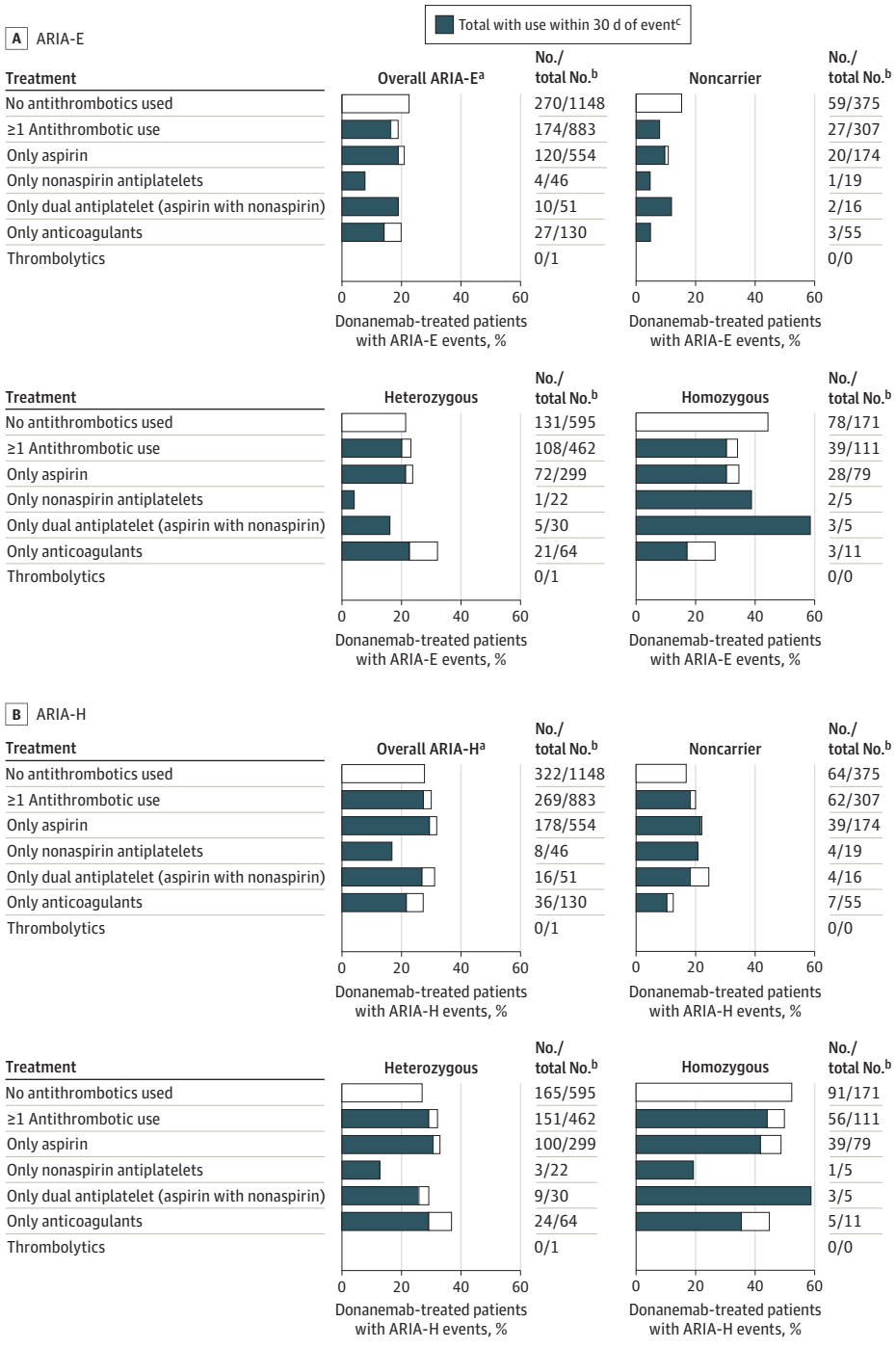


Number of infusions to first serious ARIA event in donanemab-treated participants in the integrated placebo-controlled trials and the open-label addendum by apolipoprotein E (*APOE*) *ε4* carrier status (A) and ARIA type (B). Infusions were administered approximately every 4 weeks. ARIA-E indicates amyloid-related imaging abnormality–edema/effusions; ARIA-H, amyloid-related imaging abnormality–hemorrhage/hemosiderin deposition.

Of 2031 donanemab-treated participants across studies, 883 participants (43.5%) used antithrombotics at any time, with 700 (34.5%) using aspirin and 232 (11.4%) using anticoagulants. Overall ARIA frequencies were similar with and without antithrombotic use, regardless of *APOE* ε4 status (**Figure 2**).

In donanemab-treated participants with (n = 883) and without antithrombotic use (n = 1148), ARIA-E occurred in 174 (19.7%) and 270 participants (23.5%), and ARIA-H occurred in 269 (30.5%) and 322 participants (28.0%), respectively (eTable 11 in Supplement 2). In both studies, approximately 6% of ARIA-E cases and approximately 11% of ARIA-H cases were severe with or without antithrombotic use. In donanemab-treated participants with ARIA-H superficial siderosis, 20 of 135 cases with antithrombotic use (14.8%) and 11 of 150 cases

Figure 2. Frequency of Amyloid-Related Imaging Abnormalities–Edema/Effusions (ARIA-E) and ARIA–Hemorrhage/Hemosiderin Deposition (ARIA-H) Based on Concomitant Antithrombotic Medication Use



Concomitant antithrombotic medication use, overall and by apolipoprotein E (*APOE*) ε4 status, in donanemab-treated participants in the integrated placebo-controlled trials and open-label addendum who experienced ARIA-E (A) or ARIA-H (B). The size of the bar indicates the percentage of participants with antithrombotic use at any time, and the shaded portion indicates use within 30 days prior to the ARIA event.

[a]Includes unknown *APOE* ε4 status.

[b]No. at any time in the trial, not necessarily prior to the ARIA event.

[c]For participants who experienced multiple ARIA events, ≥1 ARIA event had antithrombotic use within 30 days prior to the event.

without (7.3%) were severe. In placebo-treated participants, 5 of 16 ARIA-H superficial siderosis cases with antithrombotic use (31.3%) were moderate compared with 0 of 12 cases without antithrombotic use.

ARIA-E Onset and Resolution

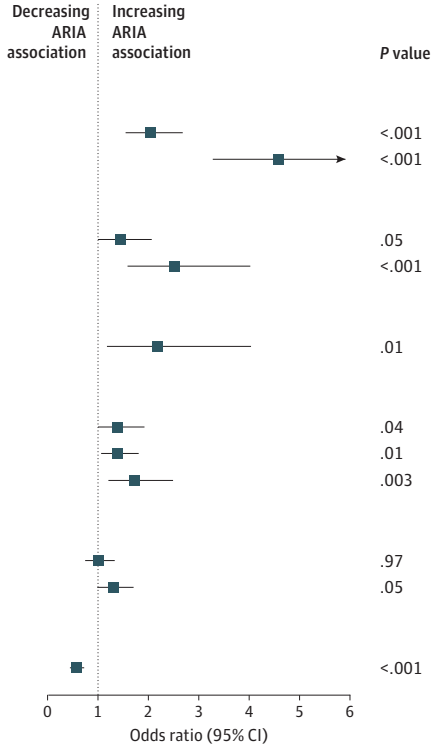
In 259 of 444 participants with at least 1 ARIA-E (58.3%), the first event occurred by the third donanemab infusion (approximately month 3; eFigure 4 in Supplement 2). Of 578 ARIA-E episodes documented on centrally reviewed MRI with donanemab, 555 episodes (96.0%) resolved radiographically, with a median (range) resolution time of 58 days (13-350).

Recurrence and Rechallenge

Following the first ARIA-E episode, 315 of 443 participants (71.1%) across all trials were rechallenged (received at least 1

Figure 3. Association of Baseline Risk Factors With Amyloid-Related Imaging Abnormalities–Edema/Effusions (ARIA-E)

Variable	Odds ratio (95% CI)	P value
APOE ε4 genotype	Reference	
Noncarrier	Reference	
Heterozygous	2.03 (1.55-2.67)	<.001
Homozygous	4.57 (3.27-6.39)	<.001
Microhemorrhages		
0	Reference	
1	1.44 (1.01-2.06)	.05
2,3, or 4	2.53 (1.59-4.02)	<.001
Superficial siderosis		
No	Reference	
Yes	2.18 (1.18-4.04)	.01
Mean arterial pressure[a]		
<93 mm Hg	Reference	
93-<97 mm Hg	1.39 (1.01-1.91)	.04
97-<107 mm Hg	1.39 (1.07-1.81)	.01
≥107 mm Hg	1.73 (1.21-2.48)	.003
Amyloid PET burden[b]		
<74 CL	Reference	
74-<108 CL	1.01 (0.76-1.33)	.97
≥108 CL	1.31 (1.00-1.71)	.05
Antihypertensive use		
No	Reference	
Yes	0.58 (0.47-0.73)	<.001



Analysis includes donanemab-treated participants in the integrated placebo-controlled trials and the open-label addendum. Forest plot of independent associations with ARIA-E identified in a post hoc analysis using machine learning approaches. Ranked from top, with the highest odds ratio for ARIA-E, to bottom, with lowest odds ratio. Odds ratios were obtained from a multiple logistic regression model adjusted for multiple covariates. This approach enables a thorough multivariable-adjusted evaluation of the association between the 6 key risk factors and ARIA-E events. *APOE* indicates apolipoprotein E; CL, Centiloids; PET, positron imaging tomography.

[a]Mean arterial pressure was estimated from systolic and diastolic blood pressure.

[b]Cerebellum used as reference region.

donanemab dose after resolution of the first ARIA-E episode); 216 of 315 rechallenged participants (68.6%) did not have ARIA-E recurrence. The maximum severity of the second ARIA-E episode in rechallenged participants is provided in eTable 12 in Supplement 2, and recurrence by *APOE* ε4 status is summarized in eTable 13 in Supplement 2. The maximum number of ARIA-E events occurring in a participant was 5.

Modeling ARIA Risk Factors

Univariate associations between 42 baseline variables and ARIA-E events in donanemab-treated participants are presented in eTable 14 in Supplement 2. LASSO analysis identified 6 independent baseline predictors that were then applied into a single multiple logistic regression model (**Figure 3**). All identified variables were significantly associated with increased ARIA-E risk except antihypertensive medication use, which was associated with decreased risk compared with no use (OR, 0.58; 95% CI, 0.47-0.73; $P < .001$). *APOE* ε4 status showed the strongest association with ARIA-E, with both homozygotes and heterozygotes having higher odds of ARIA-E than noncarriers (homozygotes: OR, 4.57; 95% CI, 3.27-6.39; $P < .001$; heterozygotes: OR, 2.03; 95% CI, 1.55-2.67; $P < .001$). ARIA-E risk increased with number of microhemorrhages at baseline (2-4 vs 0 microhemorrhages: OR, 2.53; 95% CI, 1.59-4.02; $P < .001$) and presence vs absence of superficial siderosis at baseline (OR, 2.18; 95% CI, 1.18-4.04; $P = .01$). ARIA-E risk also increased with higher categories of mean arterial pressure (MAP)[9] (≥107 mm Hg vs <93 mm Hg: OR, 1.73; 95% CI, 1.21-2.48; $P = .003$) and with greater baseline amyloid plaque imaging burden (≥108 CL vs <74 CL: OR, 1.31; 95% CI, 1.00-1.71; $P = .05$).

TSDT identified *APOE* ε4 and superficial siderosis as the strongest baseline predictors for ARIA-H events for both donanemab-treated and placebo-treated participants. In the placebo-controlled trials, the differential occurrence rates of ARIA-H between the donanemab and placebo groups were 34.6% for *APOE* ε4 homozygotes vs 8.3% in noncarriers and 52.9% in participants with superficial siderosis at baseline vs 18.1% without (eTable 15 in Supplement 2).

Discussion

Analyses of ARIA from the TRAILBLAZER-ALZ program demonstrate the frequency, severity, and factors associated with ARIA and macrohemorrhage across 2031 participants treated with donanemab.

Several baseline factors were associated with ARIA risk, including *APOE* ε4 status (eTable 9 in Supplement 2) and MRI findings (eTable 10 in Supplement 2), and these results were further supported by findings from risk factor regression analysis (Figure 3). The highest frequency of ARIA was observed in *APOE* ε4 homozygotes. *APOE* ε4 status has previously been identified as the main risk factor for ARIA among several ATTs.[10-13] This is hypothesized to be due to higher parenchymal and vascular amyloid burden in carriers than in noncar-

riers, which is subsequently removed via microglial activation induced by ATTs.[14,15] Present data also indicated that ARIA risk increased with greater numbers of microhemorrhages (restricted to the range of 0-4 by study exclusion criteria) and presence of superficial siderosis (restricted to no more than 1 focus).[4,16-18] Findings here further support the hypothesis that underlying cerebral amyloid angiopathy (CAA) is linked with ARIA emergence during ATT.[19] Microhemorrhages and cortical superficial siderosis play a role in diagnoses of probable or possible CAA per the Boston 2.0 Criteria,[20] and *APOE* ε4 has been previously linked to increased risk of CAA.[21] One donanemab-treated participant with a large area of baseline superficial siderosis developed fatal ARIA-H with cerebral hemorrhage. Another participant with severe ARIA-E and numerous concurrent microhemorrhages, which resolved and stabilized, respectively, subsequently died following rechallenge with donanemab that resulted in serious ARIA-E and ARIA-H. These results collectively suggest that *APOE* ε4 status and baseline imaging findings help inform a patient's risk of developing ARIA with ATTs, and both factors should be reevaluated throughout the course of treatment and prior to rechallenge.

In post hoc analysis, blood pressure was the only variable identified that may be a modifiable ARIA risk factor, with elevated MAP increasing ARIA-E risk and antihypertensive use decreasing risk. Analysis also suggested increased ARIA-E risk with higher amyloid burden prior to initiation of donanemab treatment. These previously undetected associations will require replication in additional samples of treated patients.

Although clinical efficacy was not assessed in the open-label population, these data allowed for observing safety in a population of amyloid-positive participants with no requirement for evidence of tau pathology. ARIA findings were generally similar between donanemab-treated study populations, but overall ARIA frequencies were numerically lower in the open-label addendum (32.0%) than in the placebo-controlled trials (37.0%), possibly due to differences in baseline characteristics identified in the ARIA-E risk analysis. In particular, among donanemab-treated participants, there were more *APOE* ε4 carriers in the placebo-controlled trials (70.1%) than in the addendum (62.0%), and mean screening amyloid level was higher in the placebo-controlled trials (103.9 CL) than in the addendum (82.5 CL). This finding offers support for reduced ARIA risk when treatment is initiated earlier in the progression of amyloid pathology.

Concomitant antiplatelet or anticoagulant use was not associated with increased ARIA frequency in donanemab-treated patients in this study (Figure 2). However, this study was not powered to characterize the impact of antithrombotics on infrequently occurring events, including macrohemorrhage. The most frequently used antithrombotic was aspirin, followed by anticoagulants, nonaspirin antiplatelets, and dual (aspirin and nonaspirin) antiplatelet usage. One participant with ARIA-E treated with a thrombolytic for strokelike symptoms had a fatal intracranial hemorrhage. Caution is advised for use of thrombolytic therapy, as symptoms of ARIA may be similar to those of stroke.

As noted in the eMethods in Supplement 2, serious ARIA-E frequency decreased after amendment of TRAILBLAZER-ALZ 2 protocol to include dose titration (700 mg for the first 3 infusions and 1400 mg thereafter). Lower ARIA-E rates were also observed with modified titration in 24-week findings from TRAILBLAZER-ALZ 6 (NCT05738486), in which participants received 350 mg, 700 mg, and 1050 mg doses, respectively, for the first 3 monthly infusions and 1400 mg thereafter.[22] Consistent with previous studies that indicate ARIA is more likely to first occur closer to treatment initiation,[4,23] the present study shows that most serious ARIA-E and ARIA-H events occurred within the time of the first 3 donanemab infusions (Figure 1). Although the sample size is small, initial analyses on inclusion of the 4-week MRI suggest that early monitoring may decrease the risk of serious ARIA and symptomatic ARIA-E. Given these results, enhanced clinical vigilance and increased frequency of monitoring for ARIA should be performed early in donanemab treatment.

Limitations

The impact of race and ethnicity on ARIA was limited in these analyses due to underrepresentation of racial and ethnic minority populations. When evaluating ARIA-E risk, interaction terms among the identified 6 key factors were omitted from the regression model due to insufficient power. Additional data may further guide management of serious and symptomatic events. Present data reflect outcomes over 76 weeks; longer-term data are needed on individuals who experienced ARIA during the trials. The TRAILBLAZER-ALZ 2 long-term extension and the TRAILBLAZER-ALZ 6 study aim to further characterize ARIA risk factors and provide additional imaging-related insights.

Conclusions

In these randomized clinical trials and open-label addendum, donanemab treatment increased ARIA risk compared with placebo. While ARIA-E events were typically transient and asymptomatic, ARIA can be serious, life threatening, or fatal; therefore, safety monitoring is necessary with donanemab as with other ATTs used in slowing disease progression in early symptomatic AD. Identification of independent baseline risks for ARIA supports efforts to predict or prevent this adverse event.

ARTICLE INFORMATION

Accepted for Publication: December 31, 2024.

Published Online: March 10, 2025. doi:10.1001/jamaneurol.2025.0065

Author Contributions: Dr Sims had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Wang, Lauzon, Nery, Battioui, Engle, Biffi, Sims. *Critical review of the manuscript for important intellectual content*: All authors. *Statistical analysis*: Ardayfio, Wang, Lu, Sparks, Andersen, Lauzon, Battioui. *Obtained funding*: Sperling, Mintun, Brooks. *Administrative, technical, or material support:* Ardayfio, Evans, Otero Svaldi, Mintun. *Supervision:* Biffi, Sperling, Mintun, Brooks, Sims.

Conflict of Interest Disclosures: Drs Zimmer, Ardayfio, Wang, Khanna, Evans, Lu, Sparks, Andersen, Lauzon, Nery, Battioui, Engle, Biffi, Svaldi, Mintun, Brooks, and Sims were employees of and shareholders in Eli Lilly and Company during the conduct of the study. Dr Salloway reported grants from Biogen, Eisai, Genentech, Janssen, Lilly, Novartis, and Roche; consulting fees from AbbVie, Acumen, Biogen, Bristol Myers Squibb, Eisai, Genentech, Kisbee, LabCorp, Lilly, Neurophet, Prothena, and Roche; and nonfinancial travel support from Lilly and Neurophet outside the submitted work. Dr Greenberg reported consultant fees from Eli Lilly during the conduct of the study and personal fees from Washington University for service on the Safety Monitoring Committee outside the submitted work. Dr Sperling reported grants from Eli Lily during the conduct of the study; consultant fees from AbbVie, AC Immune, Acumen, Alector, Apellis, Biohaven, Bristol Myers Squibb, Genentech, Ionis, Janssen, Nervgen, Oligomerix, Prothena, Roche, Vigil Neuroscience, and Vaxxinity; and grants from Eisai and the US National Institutes of Health/National Institute on Aging outside the submitted work. No other disclosures were reported.

Funding/Support: This work was sponsored by Eli Lilly and Company.

Role of the Funder/Sponsor: Eli Lilly and Company was responsible for design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

Additional Contributions: Eli Lilly and Company would like to thank the clinical trial participants and their caregivers, without whom this work would not be possible. The authors would like to thank Amy K. Ellinwood, PhD (Eli Lilly and Company), for writing and editorial support, as well as the late Barbara Lightfoot for her writing contributions to donanemab safety documents. Both individuals were salaried employees of Eli Lilly and Company and received no additional compensation.

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