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Low-Dose vs Standard-Dose Alteplase in Acute Lacunar Ischemic Stroke

The ENCHANTED Trial

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Neurology® 2021;96:e1512-e1526. doi:10.1212/WNL.0000000000011598

Abstract

Objective

To determine any differential efficacy and safety of low- vs standard-dose IV alteplase for lacunar vs nonlacunar acute ischemic stroke (AIS), we performed post hoc analyzes from the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) alteplase dose arm.

Methods

In a cohort of 3,297 ENCHANTED participants, we identified those with lacunar or nonlacunar AIS with different levels of confidence (definite/according to prespecified definitions based on clinical and adjudicated imaging findings. Logistic regression models were used to determine associations of lacunar AIS with 90-day outcomes (primary, modified Rankin Scale [mRS] scores 2–6; secondary, other mRS scores, intracerebral hemorrhage [ICH], and early neurologic deterioration or death) and treatment effects of low- vs standard-dose alteplase across lacunar and nonlacunar AIS with adjustment for baseline covariables.

Results

Of 2,588 participants with available imaging and clinical data, we classified cases as definite/probable lacunar (n = 490) or nonlacunar AIS (n = 2,098) for primary analyses. Regardless of alteplase dose received, lacunar AIS participants had favorable functional (mRS 2–6, adjusted odds ratio [95% confidence interval] 0.60 [0.47–0.77]) and other clinical or safety outcomes compared to participants with nonlacunar AIS. Low-dose alteplase (versus standard) had no differential effect on functional outcomes (mRS 2–6, 1.04 [0.87–1.24]) but reduced the risk of symptomatic ICH in all included participants. There were no differential treatment effects of low- vs standard-dose alteplase on all outcomes across lacunar and nonlacunar AIS (all $p_{\text{interaction}} \geq 0.07$).

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Glossary

AIS = acute ischemic stroke; **BP** = blood pressure; **CI** = confidence interval; **CSVD** = cerebral small vessel disease; **CTA** = CT angiography; **DICOM** = Digital Imaging and Communications in Medicine; **ECASS** = European–Australian Cooperative Acute Stroke Study; **ENCHANTED** = Enhanced Control of Hypertension and Thrombolysis Stroke Study; **END** = early neurologic deterioration; **ICH** = intracerebral hemorrhage; **IST-3** = the third International Stroke Trial; **LVO** = large vessel occlusion; **MRA** = magnetic resonance angiography; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **NINDS** = National Institutes of Neurological Diseases and Stroke; **OCSP** = Oxfordshire Community Stroke Project; **OR** = odds ratio; **sICH** = symptomatic intracerebral hemorrhage; **SITS-MOST** = the Safe Implementation of Thrombolysis in Stroke–Monitoring Study; **TICI** = Thrombolysis in Cerebral Infarction; **TOAST** = Trial of Org 10172 in Acute Stroke Treatment classification; **WAKE-UP** = Efficacy and Safety of MRI-based Thrombolysis in Wake-Up Stroke trial.

Conclusions

We found no evidence from the ENCHANTED trial that low-dose alteplase had any advantages over standard dose for definite/probable lacunar AIS.

Classification of Evidence

This study provides Class II evidence that for patients with lacunar AIS, low-dose alteplase had no additional benefit or safety over standard-dose alteplase.

Clinical Trial Registration

Clinicaltrials.gov identifier NCT01422616.

In routine clinical practice, patients with lacunar acute ischemic stroke (AIS) are eligible to receive IV thrombolysis, given comparable favorable outcomes to other common AIS pathologic subtypes.[1–3] These results were confirmed in a recent subgroup analysis of the Efficacy and Safety of Magnetic Resonance Imaging–Based Thrombolysis in Wake-Up Stroke (WAKE-UP) trial, where the safety and efficacy of standard-dose IV alteplase were comparable between lacunar and nonlacunar subtypes defined on baseline MRI.[4] Similar consistency of effect of IV alteplase between lacunar and nonlacunar AIS, defined by the Oxfordshire Community Stroke Project (OCSP) syndromic classification, was found in the third International Stroke Trial (IST-3).[5] Despite this evidence, some clinical concern persists over whether the modest risk of thrombolysis-related intracerebral hemorrhage (ICH) could offset the modest benefits of IV thrombolysis for lacunar AIS, where the natural course is generally more benign compared to other AIS subtypes[6] from there being no or small thrombotic lytic target on the presumption of a single penetrating artery occlusion.[7,8]

In the alteplase-dose arm of the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED),[9] a lower dose (0.6 mg/kg) of IV alteplase was shown to have a lower risk of ICH compared to standard dose (0.9 mg/kg) in thrombolysis-eligible patients with AIS. Whether it is the same for lacunar AIS is unclear. Herein, we report further analyses of the efficacy and safety of low- vs standard-dose IV alteplase in the ENCHANTED participants with lacunar (versus nonlacunar) AIS who were identified by the combination of clinical and adjudicated imaging findings.

Methods

Primary Research Question and Evidence Level

Is there are any differential efficacy and safety of low- vs standard-dose IV alteplase between participants with lacunar and nonlacunar AIS in the alteplase dose arm of the ENCHANTED trial? This study provides Class II evidence that for patients with lacunar AIS, low-dose alteplase has no additional benefit or safety over standard-dose alteplase.

Design and Participants

ENCHANTED was an international, multicenter, 2 × 2 quasifactorial, prospective, randomized, open-label, blinded-endpoint trial that assessed the effectiveness of low-dose (0.6 mg/kg; 15% as bolus, 85% as infusion during 1 hour) vs standard-dose (0.9 mg/kg; 10% as bolus, 90% as infusion during 1 hour) IV alteplase, and more intensive vs guideline-recommended control of blood pressure (BP) in adult participants with AIS. The study design, participant characteristics, and main results of the alteplase-dose arm have been reported[9–11] for 3,310 patients with AIS recruited from 111 centers in 13 countries. Key demographic and clinical characteristics were recorded at the time of enrollment, with clinical severity defined according to the NIH Stroke Scale (NIHSS) at baseline, 24 hours, and at day 7 (or on discharge from hospital if earlier). A final clinical diagnosis of AIS subtypes based upon the opinion of site investigations, generally according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system,[12] was made at day 7, postrandomization (or on discharge from hospital, if earlier).

Standard Protocol Approvals, Registrations, and Participant Consents

The study protocol was approved by the appropriate ethics committee at each participating center and written informed consent was obtained from participants or an appropriate legal surrogate according to the Declaration of Helsinki. The ENCHANTED trial was registered at ClinicalTrials.gov (Unique identifier: NCT01422616).

Imaging Analysis

Uncompressed digital images of all baseline and follow-up digital CT, MRI, and angiographic images were uploaded into the study brain imaging database in Digital Imaging and Communications in Medicine (DICOM) format identified only by the participant's unique study identification number. Images were analyzed centrally for any ICH by a trial adjudication panel, blind to clinical data, treatment, date, and sequence of scan. Assessors graded any identified symptomatic ICH (sICH) using a range of standard definitions from the Safe Implementation of Thrombolysis in Stroke–Monitoring Study (SITS-MOST), National Institute of Neurologic Disease and Stroke (NINDS), the European–Australian Cooperative Acute Stroke Study II (ECASS), ECASS III, and IST-3 (additional Methods I, doi.org/10.5061/dryad.t1g1jwt0s).

The ENCHANTED Imaging Analysis Project was established in August 2016, with the aim of defining the presence, extent, and severity of, and swelling from, acute ischemic changes (including arterial territory, border zone, small subcortical and brainstem/cerebellar infarcts), coexisting old vascular lesions and their subtypes, white matter lesions, and brain volume loss on all collected images by an imaging analysis team of trained individuals, blind to all clinical data, using an electronic scoring system modified from IST-3.[13] All observed infarct lesions on baseline (prerandomization) CT or MRI were coded according to the IST-3 criteria for infarct site and size. Separately and subsequent to primary scan reads, a neuroradiologist (Z.Z.) and neurosurgeon (X.C.) sought the ischemic lesion on 24-hour follow-up images while viewing the baseline images for those with no infarct lesion identified at baseline. They also assessed large vessel occlusion (LVO) on baseline CT angiography (CTA) or magnetic resonance angiography (MRA) according to a modified Thrombolysis in Cerebral Infarction (TICI) score for an abnormal artery in IST-3.[14] All the imaging data were cross-checked (Z.Z.) and a final rating made before unmasking the clinical data and randomization code for analyses.

Definitions of Lacunar and Nonlacunar AIS

Different levels of confidence (definite/probable/possible) were used around the definitions of lacunar and nonlacunar AIS based on adjudicated imaging findings, clinical severity, and clinical diagnosis (additional Methods II, doi.org/10.5061/dryad.t1g1jwt0s). In brief, definite lacunar AIS was defined when all 4 criteria were met: (1) the presence of acute infarct lesion (maximum diameter ≤20 mm) in the territory of penetrating arteries, with a rounded, ovoid, or tubular shape on axial CT or diffusion-weighted imaging/apparent diffusion coefficient map (typical examples are shown in figure 1)[15]; (2) no LVO adjudicated centrally (on CTA/MRA) or reported by site investigators (on CTA/MRA/digital subtraction angiography); (3) the final diagnosis was reported as "small vessel or perforating vessel 'lacunar' disease" according to the TOAST criteria that involved any of the standard clinical lacunar syndromes with the lack of large vessel atheroma or cerebral cortical dysfunction; and (4) infarct side on images is consistent with that reported by site investigators. Definite nonlacunar AIS was defined as having acute infarct lesion with maximum diameter >20 mm or LVO on angiography. Participants were classified as nonlacunar if they had lacunar and nonlacunar infarcts.

Given that the clinical diagnosis of lacunar syndrome plus baseline NIHSS score <7 had a high specificity to predict imaging-confirmed lacunar stroke in IST-3,[16] probable lacunar and nonlacunar AIS were discriminated mainly by baseline NIHSS scores and final diagnosis in the situation that there was no acute infarct lesion identified on images or the images were not collected from the sites. For those with conflicting clinical and adjudicated imaging information that compromised the confidence of discrimination, we classified as possible lacunar or nonlacunar AIS according to the clinical diagnosis and LVO status.

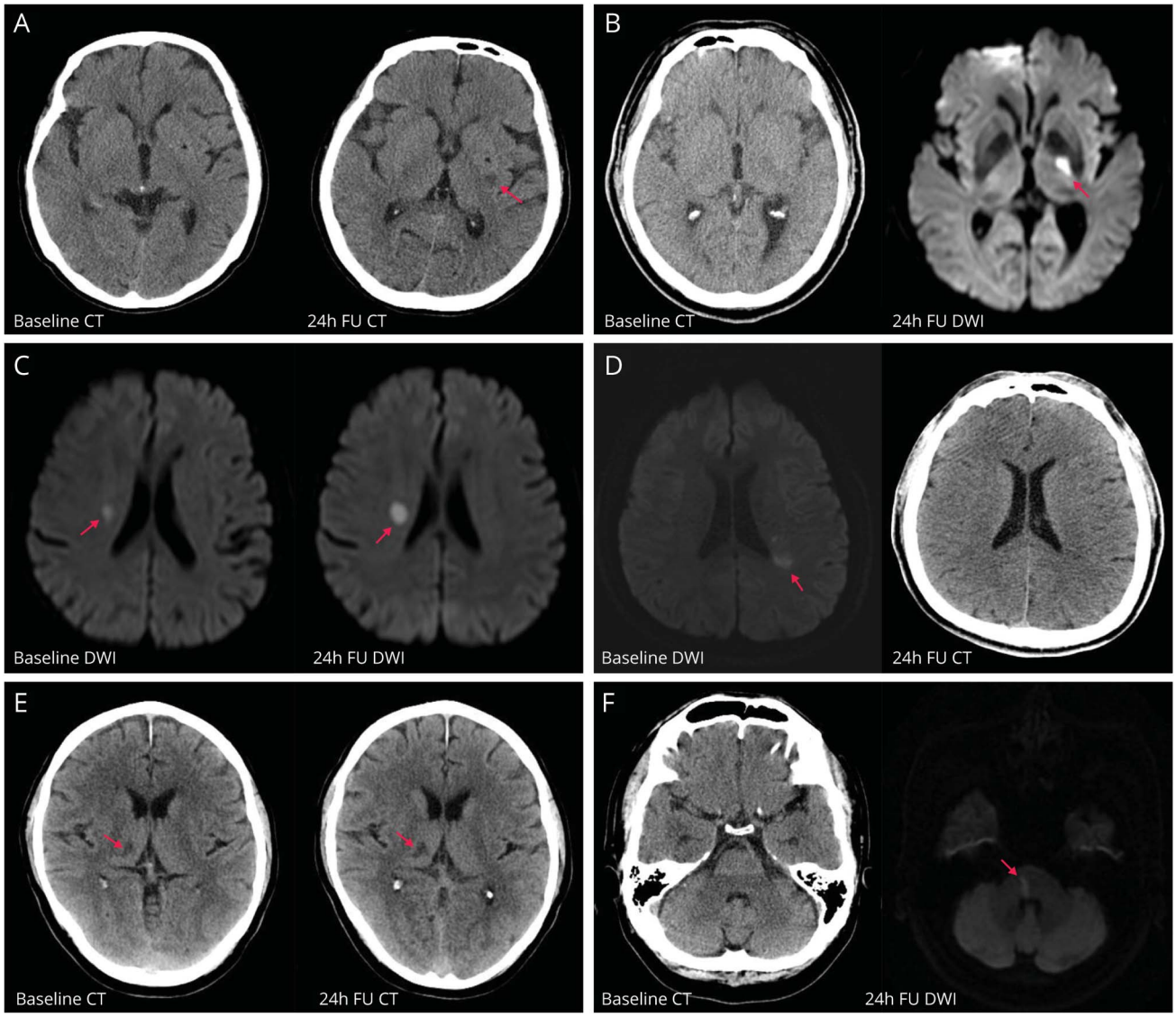
Outcomes

The primary outcome of these analyses was the composite endpoint of disability or death (modified Rankin Scale [mRS] scores 2–6) at 90 days postrandomization. Secondary efficacy outcomes included major disability or death (mRS 3–6), death (mRS 6), and ordinal shift of the full range of mRS scores at 90 days. Secondary safety outcomes were sICH defined according to several criteria from other studies, fatal ICH within 7 days, ICH identified by central adjudicators, and any ICH adjudicated centrally or reported by site investigators. Other clinical outcomes included early neurologic deterioration (END) (≥4-point increase in NIHSS scores) or death within 24 hours or 7 days.

Statistical Analysis

Continuous or categorical variables at baseline were presented as mean (SD), median (interquartile range), or number (percentage). Baseline differences between participants with lacunar and nonlacunar AIS were evaluated using analysis of variance, χ^2 test, or Wilcoxon signed-rank test, as appropriate. Associations of lacunar AIS with 90-day function, safety, and other secondary outcomes were estimated in logistic regression models with adjustment for randomized treatment and key prognostic covariates (age, sex, ethnicity, baseline NIHSS score, time from symptom onset to randomization, premorbid function [mRS score 0 or 1], prior use of antithrombotic agents, history of diabetes or cardiovascular disease, and assigned to intensive blood pressure–lowering group). The treatment effect of low- vs standard-dose alteplase was determined in logistic regression models and the heterogeneity of alteplase dose effect across participants with lacunar and

Figure 1 Examples of Lacunar Ischemic Stroke at Different Locations From ENCHANTED



Lacunar stroke at (A) left lentiform (red arrow) identified on 24-hour follow-up CT; (B) left internal capsule (red arrow) identified on 24-hour follow-up MRI; (C) right centrum semiovale (red arrow) identified on baseline and 24-hour follow-up MRI; (D) left internal border zone (red arrow) identified on baseline MRI; (E) right thalamus (red arrow) identified on baseline and 24-hour follow-up CT; and (F) brainstem (red arrow) identified on 24-hour follow-up MRI. DWI = diffusion-weighted imaging; ENCHANTED = Enhanced Control of Hypertension and Thrombolysis Stroke Study.

nonlacunar AIS was estimated by adding an interaction term to statistical models. Proportional odds regression models were used to analyze ordinal mRS scores. The primary analyses pertain to participants with definite/probable lacunar and nonlacunar AIS after excluding those with a possible diagnostic classification. Sensitivity analyses of the treatment effects of low- vs standard-dose alteplase were performed in participants with definite lacunar/nonlacunar AIS and in all participants with possible lacunar/nonlacunar AIS. We also performed an exploratory analysis of the treatment effects in a subset of lacunar AIS identified at baseline (infarct size ≤15 mm and no adjudicated LVO). Data were reported as odds ratios (ORs) and 95% confidence intervals (CIs) and a 2-sided $p < 0.05$ was considered statistically significant. All analyses were performed using SAS version 7.1 and Stata version 12.0.

Data Availability

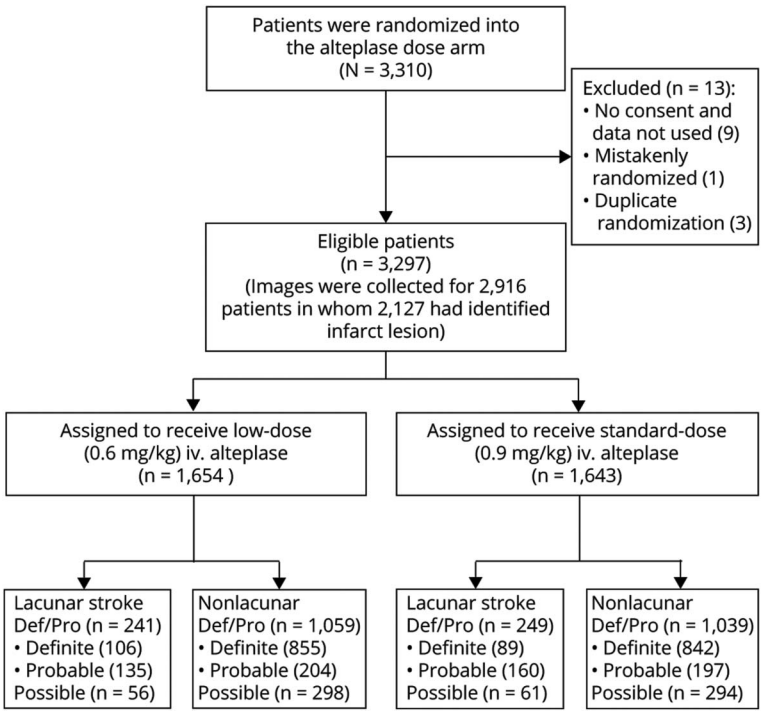
Additional methods (I and II) and data (supplementary tables 1–3) are available from Dryad (doi.org/10.5061/dryad.t1g1jwt0s). Individual de-identified participant data used in this analysis will be shared by request from any qualified investigator via the Research Office of The George Institute for Global Health.

Results

Baseline Characteristics

Among 3,297 AIS participants in the ENCHANTED alteplase dose arm, 2,588 (78.5%) were classifiable (definite lacunar, n = 195; probable lacunar, n = 295; definite nonlacunar, n = 1,697; and probable nonlacunar, n = 401 AIS) for inclusion in

Figure 2 Flowchart of Participants Included in Analyses



Def/Pro = definite or probable.

the primary analysis (figure 2). Compared to the 709 excluded participants, they were more likely to be older, have higher baseline NIHSS scores, be Asian, have a history of cardiovascular disease, and have a final diagnosis of LVO, but they also had shorter time interval from symptom onset to randomization (supplementary table 1, doi.org/10.5061/dryad.t1g1jwt0s). Table 1 shows that all the baseline clinical characteristics were significantly different between definite/probable lacunar and nonlacunar AIS except for sex, history of diabetes, and prior use of statin/other lipid-lowering agents. Participants with lacunar (versus nonlacunar) AIS were younger and had milder neurologic impairment, higher baseline BP, and a lower proportion with conventional cardiovascular risk factors except smoking. In keeping with the lacunar pattern of stroke, few participants had multiple lesions in both anterior and posterior circulation, but they were more likely to have a lesion only in the posterior circulation. They were also less likely to have brain atrophy or a hyperdense vessel sign on CT or hyperintense arteries on MRI.

Lacunar AIS and Outcomes

Compared to participants with definite/probable nonlacunar AIS, those with definite/probable lacunar AIS had better 90-day functional outcomes, whether defined by the outcome of mRS scores 2–6 (unadjusted OR 0.26, 95% CI 0.21–0.33), mRS scores 3–6 (0.20, 0.15–0.26), ordinal shift in the full range of scores (0.27, 0.23–0.33), or death alone (0.04, 0.01–0.12) (table 2). They were also less likely to have ICH and END or death after IV thrombolysis. The findings persisted with adjustment of baseline covariables and randomized alteplase dose.

Lacunar AIS and Alteplase Dose

The overall treatment effects of low- vs standard-dose alteplase on function, safety, and other outcomes in these 2,588 participants were comparable to the main results of the ENCHANTED trial, that low-dose vs standard-dose alteplase reduced the risk of sICH (SITS-MOST criteria, adjusted OR 0.39, 95% CI 0.21–0.73; NINDS criteria, 0.67, 0.50–0.89; ECASS II criteria, 0.56, 0.39–0.80; ECASS III criteria, 0.37, 0.21–0.67; IST-3 criteria, 0.54, 0.33–0.87) but with no difference in effect on functional outcomes (mRS 2–6, adjusted OR 1.04, 95% CI 0.87–1.24; mRS 3–6, 1.01, 0.85–1.21). There was no heterogeneity of treatment effects on all outcomes for definite/probable lacunar vs nonlacunar AIS after adjustment for baseline covariables (all $p_{\text{interaction}} \geq 0.07$) (figures 3 and 4). Similar results were seen in the sensitivity analyses for definite lacunar and nonlacunar AIS (all $p_{\text{interaction}} \geq 0.16$) (figures 4 and 5) and definite/probable/possible lacunar and nonlacunar AIS (all $p_{\text{interaction}} \geq 0.12$) (data available on request).

Specifically, in the definite subgroup of lacunar AIS, there were no significant differences on the primary efficacy outcome (mRS 2–6) (33.7% vs 32.9%, adjusted OR 0.96, 95% CI 0.49–1.87) or major disability or death (mRS 3–6) (20.2% vs 15.3%, adjusted OR 1.31, 95% CI 0.54–3.19) between low-dose and standard-dose alteplase groups (figure 5). There was one case of sICH (0.9%) meeting NINDS and IST-3 criteria in participants with definite lacunar AIS treated by low-dose alteplase, but no case of sICH was observed after use of standard-dose alteplase. In participants with definite lacunar

Table 1 Baseline Characteristics of Participants With Definite/Probable Lacunar and Nonlacunar Stroke

	Low-dose: LACS (n = 241), nonlacunar stroke (n = 1,059)	Standard-dose: LACS (n = 249), nonlacunar stroke (n = 1,039)	Total: LACS (n = 490), nonlacunar stroke (n = 2098)	*p* Value[a]
Age, y				
LACS	63.9 (12.8)	63.1 (12.5)	63.5 (12.7)	<0.001[b]
Nonlacunar stroke	67.8 (12.7)	67.8 (12.6)	67.8 (12.7)	
Female				
LACS	82 (34.0)	91 (36.5)	173 (35.3)	0.31
Nonlacunar stroke	402 (38.0)	390 (37.5)	792 (37.8)	
Asian ethnicity				
LACS	179 (74.3)	174 (69.9)	353 (72.0)	<0.001[b]
Nonlacunar stroke	675 (63.7)	663/1,038 (63.9)	1,338/2097 (63.8)	
Clinical features				
Systolic BP, mm Hg				
LACS	151.6 (17.8)	153.7 (19.4)	152.6 (18.7)	<0.001[b]
Nonlacunar stroke	148.0 (19.7)	148.3 (20.2)	148.2 (19.9)	
Diastolic BP, mm Hg				
LACS	86.6 (11.7)	86.7 (12.9)	86.6 (12.3)	<0.001[b]
Nonlacunar stroke	84.0 (13.2)	84.2 (13.0)	84.1 (13.1)	
Heart rate, beats per minute				
LACS	76.1 (11.7)	77.7 (12.7)	76.9 (12.2)	0.001[b]
Nonlacunar stroke	79.3 (16.6)	79.7 (16.3)	79.5 (16.5)	
NIHSS score[c]				
LACS	4 (3–6)	5 (4–6)	5 (3–6)	<0.001[b]
Nonlacunar stroke	11 (7–16)	11 (7–16)	11 (7–16)	
GCS score[d]				
LACS	15 (15–15)	15 (15–15)	15 (15–15)	<0.001[b]
Nonlacunar stroke	14 (12–15)	15 (12–15)	15 (12–15)	
Medical history				
Previous stroke				
LACS	39 (16.2)	30 (12.0)	69 (14.1)	0.03[b]
Nonlacunar stroke	185 (17.5)	197 (19.0)	382 (18.2)	
Hypertension				
LACS	142 (58.9)	148 (59.4)	290 (59.2)	0.03[b]
Nonlacunar stroke	671 (63.4)	678/1,038 (65.3)	1,349/2097 (64.3)	
Atrial fibrillation				
LACS	9 (3.7)	11 (4.4)	20 (4.1)	<0.001[b]
Nonlacunar stroke	288/1,056 (27.3)	259/1,038 (25.0)	547/2094 (26.1)	
Coronary artery disease				
LACS	23 (9.5)	16 (6.4)	39 (8.0)	<0.001[b]

Continued

Table 1 Baseline Characteristics of Participants With Definite/Probable Lacunar and Nonlacunar Stroke *(continued)*

	Low-dose: LACS (n = 241), nonlacunar stroke (n = 1,059)	Standard-dose: LACS (n = 249), nonlacunar stroke (n = 1,039)	Total: LACS (n = 490), nonlacunar stroke (n = 2098)	*p* Value[a]
Nonlacunar stroke	184 (17.4)	171/1,038 (16.5)	355/2097 (16.9)	
Valvular/other heart disease				
LACS	4 (1.7)	7 (2.8)	11 (2.2)	<0.001[b]
Nonlacunar stroke	92 (8.7)	95/1,038 (9.2)	187/2097 (8.9)	
Diabetes				
LACS	50 (20.7)	52 (20.9)	102 (20.8)	0.59
Nonlacunar stroke	203 (19.2)	211/1,038 (20.3)	414/2097 (19.7)	
Hypercholesterolemia				
LACS	34 (14.1)	32 (12.9)	66 (13.5)	0.04[b]
Nonlacunar stroke	194 (18.3)	171/1,038 (16.5)	365/2097 (17.4)	
Current smoker				
LACS	63 (26.1)	85 (34.1)	148 (30.2)	<0.001[b]
Nonlacunar stroke	222/1,057 (21.0)	233/1,037 (22.5)	455/2094 (21.7)	
Prestroke function without disability[e]				
LACS	36 (14.9)	33 (13.3)	69 (14.1)	0.005[b]
Nonlacunar stroke	194/1,058 (18.3)	216/1,037 (20.8)	410/2095 (19.6)	
Medication on admission				
Antihypertensive agents				
LACS	93 (38.6)	103 (41.4)	196 (40.0)	0.002[b]
Nonlacunar stroke	507 (47.9)	496/1,038 (47.8)	1,003/2097 (47.8)	
Warfarin anticoagulation				
LACS	1/240 (0.4)	1 (0.4)	2/489 (0.4)	<0.001[b]
Nonlacunar stroke	39 (3.7)	29/1,037 (2.8)	68/2096 (3.2)	
Aspirin/other antiplatelet agent				
LACS	46/240 (19.2)	47 (18.9)	93/489 (19.0)	0.01[b]
Nonlacunar stroke	287 (27.1)[f]	225/1,037 (21.7)[f]	512/2096 (24.4)	
Statin/other lipid-lowering agent				
LACS	40/240 (16.7)	38 (15.3)	78/489 (16.0)	0.11
Nonlacunar stroke	215/1,058 (20.3)	185/1,037 (17.8)	400/2095 (19.1)	
Time from stroke onset to CT/MRI scan, h				
LACS	1.8 (1.3–2.5)	1.9 (1.3–2.6)	1.8 (1.3–2.5)	<0.001[b]
Nonlacunar stroke	1.7 (1.1–2.3)	1.6 (1.1–2.3)	1.6 (1.1–2.3)	
Imaging features				
Infarct at left side				
LACS	78/153 (51.0)	78/150 (52.0)	156/303 (51.5)	0.14

Continued

Table 1 Baseline Characteristics of Participants With Definite/Probable Lacunar and Nonlacunar Stroke *(continued)*

	Low-dose: LACS (n = 241), nonlacunar stroke (n = 1,059)	Standard-dose: LACS (n = 249), nonlacunar stroke (n = 1,039)	Total: LACS (n = 490), nonlacunar stroke (n = 2098)	*p* Value[a]
Nonlacunar stroke	400/841 (47.6)	384/833 (46.1)	784/1,674 (46.8)	
Infarct at right side				
LACS	70/153 (45.8)	66/150 (44.0)	136/303 (44.9)	0.11
Nonlacunar stroke	407/841 (48.4)	428/833 (51.4)	835/1,674 (49.9)	
Infarct at midline or bilateral side				
LACS	5/153 (3.3)	6/150 (4.0)	11/303 (3.6)	0.76
Nonlacunar stroke	34/841 (4.0)	21/833 (2.5)	55/1,674 (3.3)	
Infarct in anterior circulation only				
LACS	117/153 (76.5)	114/150 (76.0)	231/303 (76.2)	0.09
Nonlacunar stroke	689/841 (81.9)	658/833 (79.0)	1,347/1,674 (80.5)	
Infarct in posterior circulation only				
LACS	35/153 (22.9)	36/150 (24.0)	71/303 (23.4)	<0.001[b]
Nonlacunar stroke	103/841 (12.2)	120/833 (14.4)	223/1,674 (13.3)	
Infarct in anterior and posterior circulation				
LACS	1/153 (0.7)	0/150 (0.0)	1/303 (0.3)	<0.001[b]
Nonlacunar stroke	49/841 (5.8)	55/833 (6.6)	104/1,674 (6.2)	
With FLAIR-HAs or hyperdense vessel sign				
LACS	3/151 (2.0)	5/156 (3.2)	8/307 (2.6)	<0.001[b]
Nonlacunar stroke	306/835 (36.6)	305/826 (36.9)	611/1,661 (36.8)	
With old vascular lesions				
LACS	70/153 (45.8)	59/150 (39.3)	129/303 (42.6)	0.83
Nonlacunar stroke	362/841 (43.0)	362/833 (43.5)	724/1,674 (43.2)	
With brain atrophy				
LACS	94/153 (61.4)	79/150 (52.7)	173/303 (57.1)	<0.001[b]
Nonlacunar stroke	574/841 (68.3)	589/833 (70.7)	1,163/1,674 (69.5)	
With white matter changes				
LACS	64/153 (41.8)[f]	46/150 (30.7)[f]	110/303 (36.3)	0.82
Nonlacunar stroke	301/841 (35.8)	318/833 (38.2)	619/1,674 (37.0)	
Site reported LVO or assessed centrally				
LACS	0 (0.0)	0 (0.0)	0 (0.0)	<0.001[b]
Nonlacunar stroke	270/1,041 (25.9)	262/1,027 (25.5)	532/2068 (25.7)	
Time from stroke onset to randomization, h				
LACS	3.0 (2.3–3.7)	2.8 (2.2–3.6)	2.9 (2.2–3.6)	<0.001[b]

Continued

Table 1 Baseline Characteristics of Participants With Definite/Probable Lacunar and Nonlacunar Stroke *(continued)*

	Low-dose: LACS (n = 241), nonlacunar stroke (n = 1,059)	Standard-dose: LACS (n = 249), nonlacunar stroke (n = 1,039)	Total: LACS (n = 490), nonlacunar stroke (n = 2098)	*p* Value[a]
Nonlacunar stroke	2.6 (1.9–3.3)	2.6 (1.9–3.4)	2.6 (1.9–3.4)	
Assigned to intensive BP lowering				
LACS	48 (19.9)	48 (19.3)	96 (19.6)	<0.001[b]
Nonlacunar stroke	127 (12.0)	139 (13.4)	266 (12.7)	
Assigned to standard BP lowering				
LACS	41 (17.0)	48 (19.3)	89 (18.2)	0.008[b]
Nonlacunar stroke	145 (13.7)	138 (13.3)	283 (13.5)	

Abbreviations: BP = blood pressure; FLAIR = fluid-attenuated inversion recovery; GCS = Glasgow Coma Scale; HAs = hyperintense arteries; LACS = lacunar stroke; LVO = large vessel occlusion; NIHSS = NIH Stroke Scale.
Data are n (%), mean (SD), or median (Q1, Q3). The *p* values are based on χ^2, analysis of variance, or Wilcoxon signed-rank test.
[a] Total lacunar stroke vs total nonlacunar stroke.
[b] Significant.
[c] Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurologic deficits.
[d] Scores on the GCS range from 15 (normal) to 3 (deep coma).
[e] mRS = 0.
[f] $p < 0.05$ by randomization treatment.

AIS who received low-dose alteplase, 3 (2.8%) had adjudicated ICH and 1 more had ICH reported by a site investigator, while any ICH occurred in 2 (2.2%) participants with definite lacunar AIS assigned to the standard-dose group. In a smaller subset of definite lacunar AIS identified at baseline with size <15 mm and no adjudicated LVO, 4 of the 9 participants (44.4%) in the low-dose group and 2 of the 7 participants (28.6%) in the standard-dose group had mRS 2–6 at 90 days postrandomization, and no ICH occurred in either treatment group (supplementary table 2, doi.org/10.5061/dryad.t1g1jwt0s).

Discussion

In these post hoc analyzes of the ENCHANTED trial, we did not identify any benefit, nor any harm, from the use of low-dose alteplase vs standard-dose alteplase to treat patients with lacunar AIS compared to those with other subtypes of AIS. As well as having a range of significantly different characteristics, the 90-day outcomes were better for those with lacunar than nonlacunar AIS, which provided some internal consistency for the classifications used in our study. However, given the low event rate of sICH, with fewer than 5 events in the primary analysis for definite or probable lacunar AIS, we are limited in the conclusions that can be drawn as to whether a lower dose of IV alteplase should be preferred because of the good prognosis for lacunar AIS.

Our results on thrombolysis outcomes for lacunar AIS are consistent with prior observational studies.[2,17–21] However, the net benefit of thrombolysis for lacunar AIS is still debated, mainly because the evidence is drawn from subgroup analyzes of trials, such as WAKE-UP[4] and IST-3,[5] where there is low statistical power. In addition, accurate identification of lacunar AIS is challenging, especially in the absence of an acute lesion on the initial CT, and even MRI (in nearly one third of patients with nondisabling stroke).[22] The pragmatic approach of applying a lacunar syndrome classification system in studies has moderate diagnostic sensitivity and specificity,[15] which may potentially mix patients with nonlacunar AIS with the target population of lacunar AIS, and nondifferentially bias results towards IV thrombolysis.

We were unable to confirm in ENCHANTED participants any benefit of low-dose over standard-dose alteplase in lacunar AIS. The fact that there were few cases of sICH in the low-dose alteplase group, and no sICH in the standard-dose group, highlights the potential for chance and imprecise estimates of treatment effects when there are few events. Even with current imaging techniques and clinical criteria, it is difficult to discriminate lacunar AIS due to occlusion of a deep penetrating arteriole presumed caused by progressive lipohyalinosis from thrombosis related to atherosclerosis or embolus. Platelet activation triggered by disintegration of the endothelium from intrinsic cerebral small vessel disease (CSVD) may also be relevant in this type of AIS.[8] It is possible, therefore, that IV thrombolysis may have a differential effect dependent on the cause of lacunar stroke, being more effective when there is underlying thromboembolism. In lacunar AIS, we noted a significant imbalance in the frequency of background white matter lesions between the low-dose and standard-dose alteplase groups (41.8% vs 30.7%), which could partly account for more ICH in the former (supplementary table 3, doi.org/10.5061/dryad.t1g1jwt0s).[23] Again, however, due to the few sICH events in patients with lacunar AIS, we cannot confirm whether the increase in sICH by low-dose alteplase was confounded by CSVD.

Table 2 Thrombolysis Outcomes in Definite/Probable Lacunar Versus Nonlacunar Stroke

			Lacunar vs nonlacunar stroke			
	Lacunar, n/N (%)	Nonlacunar, n/N (%)	OR (95% CI)[a]	*p* Value	aOR (95% CI)[a,b]	*p* Value
90-day functional outcomes						
mRS 2–6	147/481 (30.6)	1,284/2052 (62.6)	0.26 (0.21, 0.33)	<0.001[c]	0.60 (0.47, 0.77)	<0.001[c]
mRS 3–6	75/481 (15.6)	987/2052 (48.1)	0.20 (0.15, 0.26)	<0.001[c]	0.51 (0.38, 0.69)	<0.001[c]
mRS 6	3/490 (0.6)	282/2098 (13.4)	0.04 (0.01, 0.12)	<0.001[c]	0.13 (0.04, 0.43)	<0.001[c]
mRS 0	185/481 (38.5)	370/2052 (18.0)	0.27 (0.23, 0.33)	<0.001[c]	0.64 (0.52, 0.78)	<0.001[c]
1	149/481 (31.0)	398/2052 (19.4)				
2	72/481 (15.0)	297/2052 (14.5)				
3	47/481 (9.8)	278/2052 (13.5)				
4	21/481 (4.4)	265/2052 (12.9)				
5	4/481 (0.8)	162/2052 (7.9)				
6	3/481 (0.6)	282/2052 (13.7)				
Safety outcomes (sICH or ICH)						
SITS-MOST	1/490 (0.2)	48/2098 (2.3)	0.09 (0.01, 0.63)	0.02[c]	0.09 (0.01, 0.70)	0.02[c]
NINDS	4/490 (0.8)	211/2098 (10.1)	0.07 (0.03, 0.20)	<0.001[c]	0.10 (0.04, 0.27)	<0.001[c]
ECASS II	2/490 (0.4)	132/2098 (6.3)	0.06 (0.02, 0.25)	<0.001[c]	0.08 (0.02, 0.31)	<0.001[c]
ECASS III	1/490 (0.2)	57/2098 (2.7)	0.07 (0.01, 0.53)	0.01[c]	0.08 (0.01, 0.58)	0.01[c]
IST-3	2/490 (0.4)	74/2098 (3.5)	0.11 (0.03, 0.46)	0.002[c]	0.13 (0.03, 0.54)	0.005[c]
Fatal ICH	0/490 (0.0)	32/2098 (1.5)	—	—	—	—
Adjudicated any ICH	17/490 (3.5)	524/2098 (25.0)	0.11 (0.07, 0.18)	<0.001[c]	0.18 (0.11, 0.29)	<0.001[c]
Any ICH	18/490 (3.7)	582/2098 (27.7)	0.10 (0.06, 0.16)	<0.001[c]	0.16 (0.10, 0.27)	<0.001[c]
Other secondary outcomes						
END or death						
Within 24 h	20/490 (4.1)	216/2098 (10.3)	0.37 (0.23, 0.59)	<0.001[c]	0.30 (0.18, 0.50)	<0.001[c]
Within 7 d	27/490 (5.5)	336/2098 (16.0)	0.31 (0.20, 0.46)	<0.001[c]	0.36 (0.24, 0.56)	<0.001[c]

Abbreviations: aOR = adjusted odds ratio; CI = confidence interval; ECASS = European–Australian Cooperative Acute Stroke Study; END = early neurologic deterioration; ICH = intracerebral hemorrhage; IST-3 = third International Stroke Trial; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; NINDS = National Institutes of Neurologic Diseases and Stroke; OR = odds ratio; sICH = symptomatic intracerebral hemorrhage; SITS-MOST = Safe Implementation of Thrombolysis in Stroke–Monitoring Study.

[a] Refers to the effect of IV thrombolysis in definite/probable lacunar stroke vs nonlacunar stroke after pooling the 2 groups of randomized alteplase dose as one cohort.

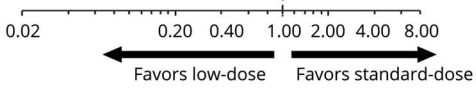
[b] Adjusted for key prognostic covariates (age, sex, ethnicity, baseline NIHSS score, time from stroke onset to randomization, premorbid function [mRS score 0 or 1], prior use of antithrombotic agents [aspirin, other antiplatelet agent, or warfarin], history of diabetes or cardiovascular disease [stroke, atrial fibrillation, coronary artery disease, valvular or other heart disease], assigned to intensive blood pressure–lowering group, and randomization to low-dose alteplase group) for functional outcomes. Adjusted for minimization and key prognostic covariates (age, baseline NIHSS score, time from stroke onset to randomization, assigned to intensive blood pressure–lowering group, and randomization to low-dose alteplase group) for safety outcomes and neurologic deterioration within 24 hours and 7 days.

[c] Significant.

Some strengths of our study include the large, prospective, multicenter cohort of patients with AIS who had systematic, complete, and high-quality data collected prospectively, where we were able to adjust for multiple covariables in statistical models. Furthermore, the imaging assessment was completed blind to clinical features and other data, using a rigorously defined approach developed for the IST-3 study. However, we acknowledge limitations that include insufficient statistical power and inevitable selection bias from the data being derived from a clinical trial where a large number of participants were from Asia and had mild to moderate stroke. Moreover, given the pragmatic nature of ENCHANTED, few participants had a baseline brain MRI, and the identification of lacunar AIS required analysis of follow-up images with comparison to those obtained at baseline. Whereas this approach may have altered the imaging appearances of acute ischemic lesions after use of IV thrombolysis[24] and

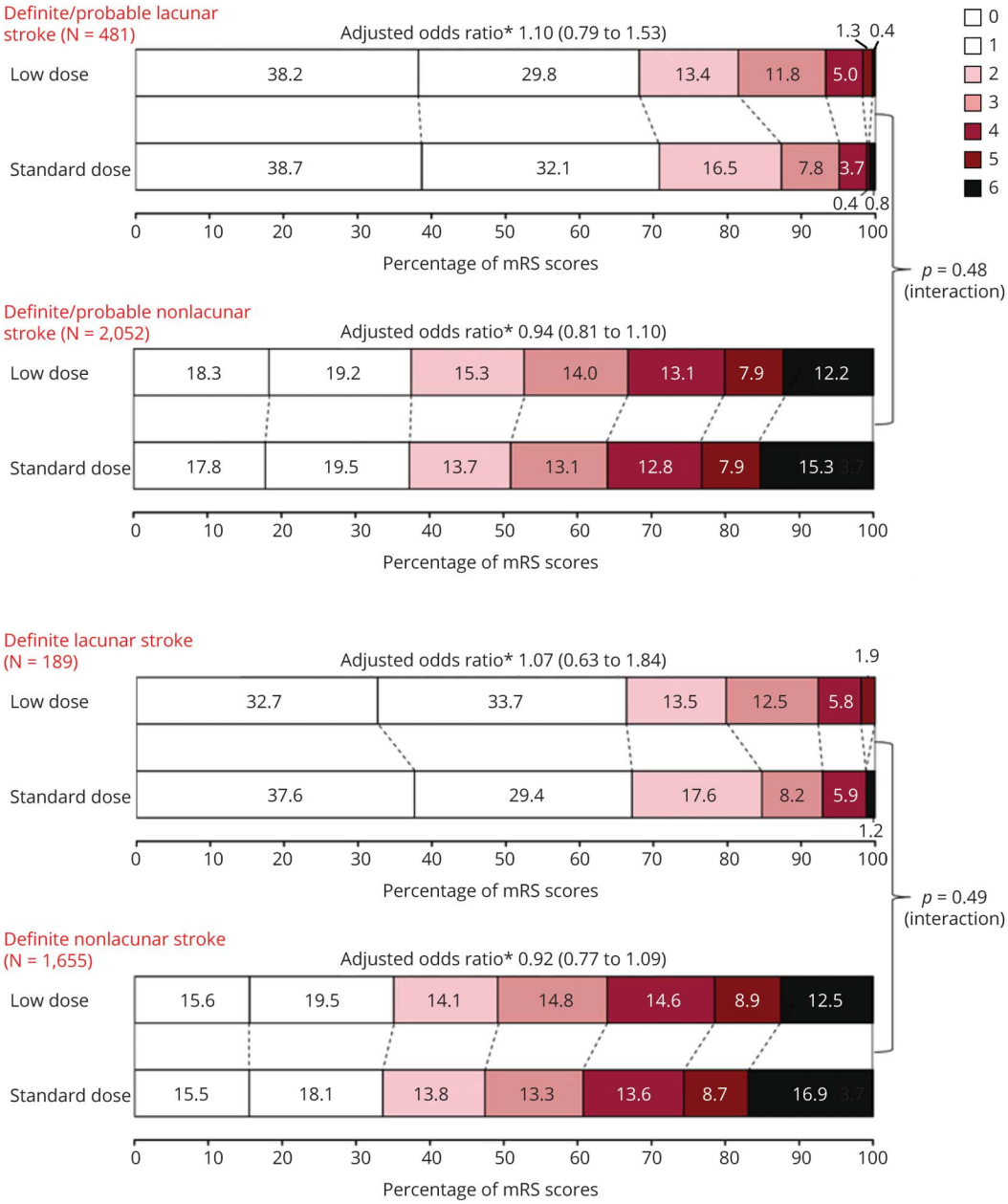
Figure 3 Thrombolysis Outcomes in Participants With Definite/Probable Lacunar and Nonlacunar Stroke by Randomized Treatment

Thrombolysis outcomes	Randomized alteplase, n/N (%)		Adjusted odds ratio* (95% CI)	*p* interaction
	Low-dose	Standard-dose		
mRS 2-6 (primary): overall	722/1,272 (56.8)	709/1,261 (56.2)	1.04 (0.87, 1.24)	
Lacunar stroke	76/238 (31.9)	71/243 (29.2)	1.18 (0.78, 1.78)	0.65
Nonlacunar stroke	646/1,034 (62.5)	638/1,018 (62.7)	1.02 (0.84, 1.24)	
mRS 3-6: overall	532/1,272 (41.8)	530/1,261 (42.0)	1.01 (0.85, 1.21)	
Lacunar stroke	44/238 (18.5)	31/243 (12.8)	1.66 (0.97, 2.85)	0.07
Nonlacunar stroke	488/1,034 (47.2)	499/1,018 (49.0)	0.95 (0.79, 1.15)	
mRS 6 (death): overall	127/1,300 (9.8)	158/1,288 (12.3)	0.79 (0.60, 1.03)	
Lacunar stroke	1/241 (0.4)	2/249 (0.8)	0.44 (0.03, 5.71)	0.73
Nonlacunar stroke	126/1,059 (11.9)	156/1,039 (15.0)	0.79 (0.60, 1.03)	
sICH (SITS-MOST): overall	14/1,300 (1.1)	35/1,288 (2.7)	0.39 (0.21, 0.73)	
Lacunar stroke	1/241 (0.4)	0/249 (0.0)	–	–
Nonlacunar stroke	13/1,059 (1.2)	35/1,039 (3.4)	0.36 (0.19, 0.68)	
sICH (NINDS): overall	88/1,300 (6.8)	127/1,288 (9.9)	0.67 (0.50, 0.89)	
Lacunar stroke	4/241 (1.7)	0/249 (0.0)	–	–
Nonlacunar stroke	84/ 1,059 (7.9)	127/1,039 (12.2)	0.63 (0.47, 0.84)	
sICH (ECASS2): overall	49/1,300 (3.8)	85/1,288 (6.6)	0.56 (0.39, 0.80)	
Lacunar stroke	2/241 (0.8)	0/249 (0.0)	–	–
Nonlacunar stroke	47/1,059 (4.4)	85/1,039 (8.2)	0.53 (0.36, 0.76)	
sICH (ECASS3): overall	16/1,300 (1.2)	42/1,288 (3.3)	0.37 (0.21, 0.67)	
Lacunar stroke	1/241 (0.4)	0/249 (0.0)	–	–
Nonlacunar stroke	15/1,059 (1.4)	42/1,039 (4.0)	0.34 (0.19, 0.62)	
sICH (IST-3): overall	27/1,300 (2.1)	49/1,288 (3.8)	0.54 (0.33, 0.87)	
Lacunar stroke	2/241 (0.8)	0/249 (0.0)	–	–
Nonlacunar stroke	25/1,059 (2.4)	49/1,039 (4.7)	0.49 (0.30, 0.80)	
Fatal ICH within 7 days: overall	8/1,300 (0.6)	24/1,288 (1.9)	0.32 (0.15, 0.73)	
Lacunar stroke	0/241 (0.0)	0/249 (0.0)	–	–
Nonlacunar stroke	8/1,059 (0.8)	24/1,039 (2.3)	0.32 (0.14, 0.72)	
Adjudicated any ICH: overall	260/1,300 (20.0)	281/1,288 (21.8)	0.90 (0.74, 1.10)	
Lacunar stroke	10/241 (4.1)	7/249 (2.8)	1.37 (0.50, 3.70)	0.28
Nonlacunar stroke	250/1,059 (23.6)	274/1,039 (26.4)	0.87 (0.71, 1.06)	
Any ICH⁺: overall	290/1,300 (22.3)	310/1,288 (24.1)	0.91 (0.75, 1.10)	
Lacunar stroke	11/241 (4.6)	7/249 (2.8)	1.50 (0.56, 3.99)	0.20
Nonlacunar stroke	279/1,059 (26.3)	303/1,039 (29.2)	0.87 (0.72, 1.06)	
END or death within 24 hrs: overall	108/1,300 (8.3)	128/1,288 (9.9)	0.83 (0.63, 1.08)	
Lacunar stroke	9/241 (3.7)	11/249 (4.4)	0.78 (0.31, 1.95)	0.99
Nonlacunar stroke	99/1,059 (9.3)	117/1,039 (11.3)	0.82 (0.62, 1.09)	
END or death within 7 hrs: overall	165/1,300 (12.7)	198/1,288 (15.4)	0.81 (0.65, 1.01)	
Lacunar stroke	13/241 (5.4)	14/249 (5.6)	0.89 (0.40, 1.95)	0.68
Nonlacunar stroke	152/1,059 (14.4)	184/1,039 (17.7)	0.79 (0.63, 1.00)	



*Adjusted for key prognostic covariates (age, sex, ethnicity, baseline NIH Stroke Scale [NIHSS] score, time from stroke onset to randomization, premorbid function [modified Rankin Scale (mRS) scores 0 or 1], prior use of antithrombotic agents [aspirin, other antiplatelet agent, or warfarin], history of diabetes or cardiovascular disease [stroke, atrial fibrillation, coronary artery disease, valvular or other heart disease], assigned to intensive blood pressure–lowering group) for functional outcomes. Adjusted for minimization and key prognostic covariates (age, baseline NIHSS score, time from stroke onset to randomization, and assigned to intensive blood pressure–lowering group) for safety outcomes and neurologic deterioration within 24 hours or 7 days.†Site reported or adjudicated centrally. CI = confidence interval; ECASS = European–Australian Cooperative Acute Stroke Study; END = early neurologic deterioration; ICH = intracerebral hemorrhage; IST-3 = third International Stroke Trial; NINDS = National Institutes of Neurologic Diseases and Stroke; sICH = symptomatic intracerebral hemorrhage; SITS-MOST = Safe Implementation of Thrombolysis in Stroke–Monitoring Study.

Figure 4 Randomized Treatment Effects on the Ordinal Modified Rankin Scale (mRS) Score by Lacunar and Nonlacunar Stroke



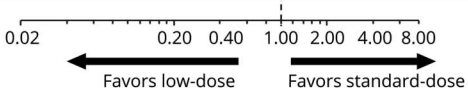
*Adjusted for key prognostic covariates (age, sex, ethnicity, baseline NIH Stroke Scale [NIHSS] score, time from stroke onset to randomization, premorbid function [mRS scores 0 or 1], prior use of antithrombotic agents [aspirin, other antiplatelet agent, or warfarin], history of diabetes or cardiovascular disease [stroke, atrial fibrillation, coronary artery disease, valvular or other heart disease], assigned to intensive blood pressure–lowering group).

limited the identification of all true lacunar AIS, our results are comparable with previous work showing that nearly one-third of patients with nondisabling AIS lack an infarct lesion on acute MRI (median 4 days poststroke).[22] In the ENCHANTED alteplase arm, 27.1% (789/2,916) of participants had no infarct lesion on either the baseline or 24-hour follow-up images. Thus, we had to use a combination of clinical and adjudicated imaging data to classify as many cases as possible into lacunar and nonlacunar AIS, which likely closely represents that used in routine practice. Relatively small samples in lacunar AIS compromised the power of a reliable assessment of any interaction, especially for sICH. Moreover, regarding the outcomes of major disability or death, a $p_{interaction}$ of 0.07 might have been due to chance rather than true differential treatment effects of low- vs standard-dose alteplase across definite/probable lacunar and nonlacunar AIS. Future research in systematic reviews and clinical registries may be required to confirm or refute these findings.

We found no clear evidence that low-dose IV alteplase was any better or safer than standard-dose alteplase in the

Figure 5 Thrombolysis Outcomes in Participants With Definite Lacunar and Nonlacunar Stroke by Randomized Treatment

Thrombolysis outcomes	Randomized alteplase, n/N(%)		Adjusted odds ratio* (95% CI)	*p* interaction
	Low-dose	Standard-dose		
mRS 2-6 (primary): overall	574/935 (61.4)	575/909 (63.3)	0.96 (0.78, 1.18)	
Lacunar stroke	35/104 (33.7)	28/85 (32.9)	0.96 (0.49, 1.87)	0.92
Nonlacunar stroke	539/831 (64.9)	547/824 (66.4)	0.96 (0.77, 1.20)	
mRS 3-6: overall	443/935 (47.4)	446/909 (49.1)	0.98 (0.80, 1.20)	
Lacunar stroke	21/104 (20.2)	13/85 (15.3)	1.31 (0.54, 3.19)	0.38
Nonlacunar stroke	422/831 (50.8)	433/824 (52.5)	0.96 (0.78, 1.19)	
mRS 6 (death): overall	104/961 (10.8)	140/931 (15.0)	0.70 (0.52, 0.94)	
Lacunar stroke	0/106 (0.0)	1/89 (1.1)	–	–
Nonlacunar stroke	104/855 (12.2)	139/842 (16.5)	0.71 (0.53, 0.96)	
sICH (SITS-MOST): overall	13/961 (1.4)	33/931 (3.5)	0.38 (0.20, 0.72)	
Lacunar stroke	0/106 (0.0)	0/89 (0.0)	–	–
Nonlacunar stroke	13/855 (1.5)	33/842 (3.9)	0.38 (0.20, 0.73)	
sICH (NINDS): overall	76/961 (7.9)	117/931 (12.6)	0.60 (0.44, 0.82)	
Lacunar stroke	1/106 (0.9)	0/89 (0.0)	–	–
Nonlacunar stroke	75/855 (8.8)	117/842 (13.9)	0.60 (0.44, 0.82)	
sICH (ECASS2): overall	43/961 (4.5)	80/931 (8.6)	0.50 (0.34, 0.74)	
Lacunar stroke	0/106 (0.0)	0/89 (0.0)	–	–
Nonlacunar stroke	43/855 (5.0)	80/842 (9.5)	0.51 (0.34, 0.74)	
sICH (ECASS3): overall	15/961 (1.6)	39/931 (4.2)	0.37 (0.20, 0.67)	
Lacunar stroke	0/106 (0.0)	0/89 (0.0)	–	–
Nonlacunar stroke	15/855 (1.8)	39/842 (4.6)	0.37 (0.20, 0.67)	
sICH (IST-3): overall	25/961 (2.6)	45/931 (4.8)	0.53 (0.32, 0.87)	
Lacunar stroke	1/106 (0.9)	0/89 (0.0)	–	–
Nonlacunar stroke	24/855 (2.8)	45/842 (5.3)	0.51 (0.31, 0.85)	
Fatal ICH within 7 days: overall	8/961 (0.8)	22/931 (2.4)	0.35 (0.16, 0.79)	
Lacunar stroke	0/106 (0.0)	0/89 (0.0)	–	–
Nonlacunar stroke	8/855 (0.9)	22/842 (2.6)	0.35 (0.16, 0.80)	
Adjudicated any ICH: overall	233/961 (24.2)	251/931 (27.0)	0.88 (0.71, 1.09)	
Lacunar stroke	3/106 (2.8)	2/89 (2.2)	1.19 (0.19, 7.46)	0.67
Nonlacunar stroke	230/855 (26.9)	249/842 (29.6)	0.88 (0.71, 1.09)	
Any ICH†: overall	258/961 (26.8)	274/931 (29.4)	0.89 (0.73, 1.10)	
Lacunar stroke	4/106 (3.8)	2/89 (2.2)	1.50 (0.26, 8.66)	0.44
Nonlacunar stroke	254/855 (29.7)	272/842 (32.3)	0.89 (0.72, 1.10)	
END or death within 24 hrs: overall	86/961 (8.9)	113/931 (12.1)	0.71 (0.53, 0.96)	
Lacunar stroke	1/106 (0.9)	5/89 (5.6)	0.10 (0.01, 0.94)	0.16
Nonlacunar stroke	85/855 (9.9)	108/842 (12.8)	0.75 (0.56, 1.02)	
END or death within 7 hrs: overall	131/961 (13.6)	173/931 (18.6)	0.70 (0.54, 0.90)	
Lacunar stroke	4/106 (3.8)	5/89 (5.6)	0.48 (0.12, 1.97)	0.90
Nonlacunar stroke	127/855 (14.9)	168/842 (20.0)	0.71 (0.55, 0.91)	



*Adjusted for key prognostic covariates (age, sex, ethnicity, baseline NIH Stroke Scale [NIHSS] score, time from stroke onset to randomization, premorbid function [modified Rankin Scale (mRS) scores 0 or 1], prior use of antithrombotic agents [aspirin, other antiplatelet agent, or warfarin], history of diabetes or cardiovascular disease [stroke, atrial fibrillation, coronary artery disease, valvular or other heart disease], assigned to intensive blood pressure–lowering group) for functional outcomes. Adjusted for minimization and key prognostic covariates (age, baseline NIHSS score, time from stroke onset to randomization, and assigned to intensive blood pressure–lowering group) for safety outcomes and neurologic deterioration within 24 hours or 7 days. †Site reported or adjudicated centrally. CI = confidence interval; ECASS = European–Australian Cooperative Acute Stroke Study; END = early neurologic deterioration; ICH = intracerebral hemorrhage; IST-3 = third International Stroke Trial; NINDS = National Institutes of Neurologic Diseases and Stroke; sICH = symptomatic intracerebral hemorrhage; SITS-MOST = Safe Implementation of Thrombolysis in Stroke–Monitoring Study.

ENCHANTED participants who had lacunar AIS. According to standard eligibility criteria, patients with lacunar AIS should receive standard dose IV alteplase as with other AIS subtypes.

Acknowledgment

The authors thank the investigators, study teams, and patients for participating in the ENCHANTED trial. The research team acknowledges the support of the National Institute for Health Research Clinical Research Network (NIHR CRN) for conduct of the trial in England. Z.Z. received overseas visiting funding from Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University (2016–2018) and a Scientia PhD Scholarship from the University of New South Wales, Sydney (2018–2022) during the conduct of the study. C.S.A. holds an NHMRC Senior Investigator Fellowship.

Study Funding

This study is supported by grants from the National Health and Medical Research Council (NHMRC) of Australia (project grant numbers 1020462 and 1101113), the Stroke Association of the UK (TSA 2012/01 and 2015/01), the Ministry of Health and the National Council for Scientific and Technological Development of Brazil (CNPQ: 467322/2014-7, 402388/2013-5), the Ministry for Health, Welfare and Family Affairs of the Republic of Korea (HI14C1985) (for the alteplase-dose arm), and a research grant from Takeda for conduct of the study in China.

Disclosure

Dr. Xia received a scholarship from China Scholarship Council (CSC). Prof. Hackett reports a fellowship and research grants from the National Health and Medical Research Council (NHMRC) of Australia. Prof. Woodward reports a National Health and Medical Research Council Investigator Grant (APP1174120) and Program Grant (APP1149987) and is a consultant to Amgen, Freeline, and Kyowa Hakko Kirin. Prof. Chalmers reports research grants and honoraria from Servier for the ADVANCE trial, outside the submitted work. Prof. Robinson reports grants from The Stroke Association, UK, and was a National Institute for Health Research (NIHR) Senior Investigator during the conduct of the study. Prof. Parsons reports personal fees from serving on Advisory Board for Boehringer Ingelheim (which markets alteplase outside of North America) during the conduct of the study. Prof. Demchuk reports personal fees from Medtronic, personal fees from Daiichi Sankyo, and a patent to Circle NVI issued outside the submitted work. Prof. Lindley reports grants from NHMRC of Australia during the conduct of the study. Dr. Mair reports grants from The Stroke Association, UK, during the conduct of the study. Prof. Wardlaw reports grants from The Stroke Association, UK, the Fondation Leducq, the British Heart Foundation, The European Union, the Row Fogo Charitable Trust, the Alzheimer's Society, Alzheimer's Research UK, and UK Medical Research Council during the conduct of the study. Prof. Anderson reports receiving honorarium from Takeda during the conduct of the study. Other authors have nothing to disclose for the present study. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* July 6, 2020. Accepted in final form December 7, 2020.

Appendix Authors

Name	Location	Contribution
Zien Zhou, MD	The George Institute for Global Health, Australia; and Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, China	Designed and conceptualized study, major role in the acquisition of data, analyzed the data, interpreted the data, drafted the manuscript for intellectual content, revised the manuscript for intellectual content
Candice Delcourt, MD, PhD	The George Institute for Global Health, Australia	Major role in the acquisition of data, interpreted the data, revised the manuscript for intellectual content
Chao Xia, MD	The George Institute for Global Health, Australia	Major role in the acquisition of data, interpreted the data, revised the manuscript for intellectual content
Sohei Yoshimura, MD, PhD	The George Institute for Global Health, Australia	Major role in the acquisition of data, revised the manuscript for intellectual content
Cheryl Carcel, MD, PhD	The George Institute for Global Health, Australia	Major role in the acquisition of data, revised the manuscript for intellectual content
Takako Torii-Yoshimura, MD	The George Institute for Global Health, Australia	Major role in the acquisition of data, revised the manuscript for intellectual content
Shoujiang You, MD, PhD	Second Affiliated Hospital of Soochow University, China	Major role in the acquisition of data, revised the manuscript for intellectual content
Alejandra Malavera, MD	The George Institute for Global Health, Australia	Major role in the acquisition of data, revised the manuscript for intellectual content
Xiaoying Chen, BPharm, BMgt	The George Institute for Global Health, Australia	Major role in the acquisition of data, revised the manuscript for intellectual content
Maree L. Hackett, PhD	The George Institute for Global Health, Australia	Interpreted the data, revised the manuscript for intellectual content
Mark Woodward, PhD	The George Institute for Global Health, Australia and UK	Interpreted the data, revised the manuscript for intellectual content
John Chalmers, MD, PhD	The George Institute for Global Health, Australia	Interpreted the data, revised the manuscript for intellectual content
Jianrong Xu, MD, PhD	Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, China	Designed and conceptualized study, interpreted the data, revised the manuscript for intellectual content

Continued

Appendix *(continued)*

Name	Location	Contribution
Thompson G. Robinson, MD	University of Leicester, UK	Designed and conceptualized study, interpreted the data, revised the manuscript for intellectual content
Mark W. Parsons, MD, PhD	University of New South Wales, Australia	Designed and conceptualized study, interpreted the data, revised the manuscript for intellectual content
Andrew M. Demchuk, MD	University of Calgary, Canada	Designed and conceptualized study, interpreted the data, revised the manuscript for intellectual content
Richard I. Lindley, MD	University of Sydney, Australia	Designed and conceptualized study, interpreted the data, revised the manuscript for intellectual content
Grant Mair, MD	University of Edinburgh, UK	Interpreted the data, revised the manuscript for intellectual content
Joanna M. Wardlaw, MD	University of Edinburgh, UK	Designed and conceptualized study, interpreted the data, revised the manuscript for intellectual content
Craig S. Anderson, MD, PhD	The George Institute for Global Health, Australia and China	Designed and conceptualized study, interpreted the data, drafted the manuscript for intellectual content, revised the manuscript for intellectual content

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Disputes & Debates: Editors' Choice

Editors' Note: CSF Biomarkers in Patients With COVID-19 and Neurologic Symptoms: A Case Series

In "CSF Biomarkers in Patients With COVID-19 and Neurologic Symptoms: A Case Series," Edén et al. describe CSF results in 6 patients with neurologic symptoms in the setting of COVID-19 infection. Three patients had a positive CSF SARS-CoV-2 PCR initially, although the cycle threshold was elevated (>35), indicating a low viral load. It is important that SARS-CoV-2 RNA was undetectable in all 3 samples when reanalyzed. All patients had elevated CSF neopterin and β2-microglobulin. Kumar and Lall comment that these findings are consistent with nonspecific inflammation and emphasize the fact that neuropathogenesis in COVID-19 is multifactorial because of systemic inflammation, hypoxemia, hypercoagulability, and potentially unidentifiable mechanisms. Brenner agrees that these findings suggest COVID-19 does not directly invade the CNS, but that it can cause an autoimmune or immune-mediated meningoencephalitis. He proposes that treatment with steroids, IVIG, and/or plasmapheresis may be considered. Edén agrees that a number of different mechanisms may contribute to the development of neurologic symptoms in patients with COVID-19 and reinforces the need for ongoing research to evaluate potential interventions.

Ariane Lewis, MD, and Steven Galetta, MD
Neurology® 2021;97:508. doi:10.1212/WNL.0000000000012526

Reader Response: CSF Biomarkers in Patients With COVID-19 and Neurologic Symptoms: A Case Series

Anand Kumar (Varanasi, India) and Neha Lall (Varanasi, India)
Neurology® 2021;97:508–509. doi:10.1212/WNL.0000000000012527

We read with interest the article by Edén et al.[1] assessing the CSF biomarkers of intrathecal inflammation (CSF white blood cell counts, neopterin, β2-microglobulin [β2M], and immunoglobulin G index), blood-brain barrier integrity (albumin ratio), and axonal injury (CSF neurofilament light chain protein [NfL]) in COVID-19 patients with neurologic symptoms. The results illustrate evidence of significant CSF inflammation with raised soluble markers without any cellular response, unlike other viral CNS infections. As far as intrathecal markers such as neopterin and β2M are concerned, these are nonspecific and are produced by macrophages during the activation of cell-mediated immune response. These are often found significantly raised in various conditions such as HIV infection,[2] relapsing-remitting or chronic progressive multiple sclerosis,[3] and head trauma,[4] putting forth questions about its value as a disease-specific marker.

NfL being a component of axonal and dendritic cytoskeleton, it is considered as a biomarker of axonal injury. It is raised in the CSF in diseases such as amyotrophic lateral sclerosis, Parkinson disease, multiple sclerosis, head trauma, and Alzheimer disease, making it a very low specific marker.[5]

Author disclosures are available upon request (journal@neurology.org).

Neuropathogenesis in COVID-19 is still unknown and is considered multifactorial. Systemic inflammation, hypoxemia, hypercoagulability, and some unidentifiable mechanisms may all contribute to specific neurologic condition, and this warrants further study.

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Reader Response: CSF Biomarkers in Patients With COVID-19 and Neurologic Symptoms: A Case Series

Steven R. Brenner (University City, MO)
Neurology® 2021;97:509. doi:10.1212/WNL.0000000000012529

I read the article by Edén et al. regarding COVID-19 patients with neurologic symptoms with interest.[1] It appears the adults with neurologic symptoms, primarily of encephalopathy, are similar to those of children with influenza experiencing encephalopathy—CSF neopterin elevation being a common feature, whereas CSF pleocytosis was only present in a third of patients.[2] Influenza-related encephalopathy is believed to primarily be mediated through inflammatory or immune-mediated mechanisms.[2]

CSF examination in a series of 6 patients with COVID-19, who were agitated or failed to regain consciousness after decrease in sedation following ventilation treatment of acute respiratory distress syndrome, revealed high protein, no pleocytosis, and negative PCR for SARS-CoV-2.[3] MRI findings appeared either normal or consistent with meningoencephalitis, indicating likely autoimmune encephalitis.[3] Plasmapheresis resulted in dramatic improvement—most patients regaining consciousness, with improvement in serum ferritin. In addition, MRI findings were reversible in those cases consistent with meningoencephalitis.

It appears likely COVID-19 triggers an autoimmune or immune-mediated meningoencephalitis, rather than direct viral invasion and infection. Immunomodulatory treatments such as corticosteroids,[2] IVIG,[2] and/or plasmapheresis[2,3] are considerations, having been used in these circumstances.

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Author disclosures are available upon request (journal@neurology.org).

Author Response: CSF Biomarkers in Patients With COVID-19 and Neurologic Symptoms: A Case Series

Arvid Edén (Gothenburg, Sweden)
Neurology® 2021;97:510. doi:10.1212/WNL.0000000000012530

We thank Dr. Brenner for his interest in our report[1] and for emphasizing CSF neopterin results. Indeed, marked CSF immune activation indicating microglial activation is a universal feature in all patients with neurologic manifestations that we have examined in our clinic during the acute phase of COVID-19. Of interest, other typical signs of CNS infections—CSF pleocytosis, blood-brain barrier injury, and intrathecal IgG synthesis—are usually mild or absent, and viral RNA is almost never detected. These features clearly distinguish COVID-19 from typical CNS-invasive infections but are similar to processes seen in other CNS encephalitides[2] and, as suggested, may well resemble influenza-encephalitis that is also a consequence of a respiratory viral infection.

Likely, the CNS pathology observed during COVID-19 is a consequence of several contributing factors, where direct viral interaction with olfactory mucosal cells, indirect effects of the systemic inflammatory response, and potentially viral interaction with cells of the vasculature can all contribute to the immune response observed within the CNS. Autoimmune mechanisms may well be triggered as part of the immune response, as is suggested in some early reports.[3] However, therapeutic efforts directed toward CNS manifestations are still anecdotal, and it is vital that proposed interventions are studied in properly designed, preferably controlled, clinical trials.

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Editors' Note: Dietary Antioxidants and the Risk of Parkinson Disease: The Swedish National March Cohort

In "Dietary Antioxidants and the Risk of Parkinson Disease: The Swedish National March Cohort," Hantikainen et al. surveyed dietary intake through a food frequency questionnaire from 1997 to 2016 and found that higher dietary vitamin E and vitamin C were associated with a lower risk of Parkinson disease. They found no relationship between beta-carotene intake or nonenzymatic antioxidant capacity and Parkinson disease. Kawada notes that a previous study found beta-carotene and vitamin E intake was inversely associated with a risk of Parkinson disease, but there was no significant relationship between intake of vitamin C and nonenzymatic antioxidant capacity and Parkinson disease. They suggest that sex differences may be relevant to these findings. Hantikainen et al. acknowledge that there are discrepancies across studies, but they did not find any sex differences. Both authors agree more research is needed to evaluate the relationship between antioxidants and Parkinson disease and whether there are sex differences that might play a role.

Ariane Lewis, MD, and Steven Galetta, MD
Neurology® 2021;97:510. doi:10.1212/WNL.0000000000012531

Author disclosures are available upon request (journal@neurology.org).

Reader Response: Dietary Antioxidants and the Risk of Parkinson Disease: The Swedish National March Cohort

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Neurology® 2021;97:511. doi:10.1212/WNL.0000000000012532

Hantikainen et al. examined the associations of high baseline dietary antioxidants and total nonenzymatic antioxidant capacity (NEAC) with Parkinson disease. The adjusted hazard ratios (HRs)—95% confidence intervals (CIs)—of dietary vitamin E and vitamin C for Parkinson disease were 0.68 (0.52–0.90) and 0.68 (0.52–0.89), respectively.[1] By contrast, there was no significant association of estimated intake of dietary beta-carotene or NEAC with Parkinson disease.

However, according to a study by Yang et al.,[2] the associations of dietary antioxidant vitamins C, E, beta-carotene, and NEAC with Parkinson disease were examined. The adjusted HRs (95% CIs) of dietary intake of beta-carotene for Parkinson disease in women and men were 0.86 (0.78–0.95) and 0.91 (0.84–0.99), respectively.[2] In addition, the adjusted HRs (95% CIs) of dietary intake of vitamin E for Parkinson disease in women and men were 0.87 (0.79–0.96) and 0.93 (0.88–0.99), respectively.[2] By contrast, dietary intake of vitamin C and NEAC were not significantly associated with PD.

As such, discrepancy exists regarding the effect of vitamin C and beta-carotene on Parkinson disease in these studies.[1,2] As the risk reduction of dietary antioxidants for Parkinson disease was stronger in women, sex difference might be proposed with caution as a related factor. In any case, further prospective studies are needed to verify the association.

1. Hantikainen E, Trolle Lagerros Y, Ye W, et al. Dietary antioxidants and the risk of Parkinson disease: the Swedish National March Cohort. *Neurology.* 2021;96(6):e895-e903.
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Author Response: Dietary Antioxidants and the Risk of Parkinson Disease: The Swedish National March Cohort

Essi Hantikainen (Milan, Italy), Ylva Trolle Lagerros (Solna, Sweden), and Stephanie Bonn (Solna, Sweden)
Neurology® 2021;97:511–512. doi:10.1212/WNL.0000000000012533

We are grateful for Dr. Kawada's interest in our paper.[1] There are indeed discrepancies between findings on vitamin C, beta-carotene, and the risk of Parkinson disease, while the evidence for vitamin E is consistent when considering findings by Yang et al.[2] and those in our study.[1] Furthermore, 2 meta-analyses reported that a higher intake of vitamin E was found to protect against Parkinson disease,[3] whereas no such association was seen with vitamin C[3] or beta-carotene.[3,4] A recent publication from the Nurses' Health Study and the Health Professionals Follow-up Study reported an inverse association between dietary vitamin C and Parkinson disease, although the results were nonsignificant after excluding cases occurring during the first 4 years of follow-up. No association was seen between vitamin E and beta-carotene.[5]

Given the stronger effect of dietary antioxidants on Parkinson disease risk in women reported by Yang et al.,[2] possible sex differences might exist. We investigated potential effect modification by sex—however, we did not find any evidence for such an interaction. Nevertheless, more research is needed to confirm findings on different antioxidants and the risk of Parkinson disease and potential sex differences of such an effect.

Author disclosures are available upon request (journal@neurology.org).

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CORRECTIONS

Low-Dose vs Standard-Dose Alteplase in Acute Lacunar Ischemic Stroke

The ENCHANTED Trial

Neurology® 2021;97:512. doi:10.1212/WNL.0000000000012302

In the article "Low-Dose vs Standard-Dose Alteplase in Acute Lacunar Ischemic Stroke: The ENCHANTED Trial" by Zhou et al.,[1] the first sentence under Methods in the Abstract should read "In a cohort of 3,297 ENCHANTED participants, we identified those with lacunar or non-lacunar AIS with different levels of confidence (definite/probable/possible) according to prespecified definitions based on clinical and adjudicated imaging findings." The publisher regrets the error.

Reference

1. Zhou Z, Delcourt C, Xia C, et al. Low-dose vs standard-dose alteplase in acute lacunar ischemic stroke: the ENCHANTED trial. *Neurology*. 2021;96(11):e1512-e1526.

In Defense of the AAN Position on Lawful Physician-Hastened Death

Neurology® 2020;97:512. doi:10.1212/WNL.0000000000010536

In the special editorial "In Defense of the AAN Position on Lawful Physician-Hastened Death" by Vucic et al.,[1] the author contributions should read:

J.A.R. is the principal author of this editorial and of "Lawful physician-hastened death: AAN position statement."[2]

L.G.E., R.J.B., R.C., W.D.G., M.K., J.A.K., D.L., R.M.P., M.R., J.A.S., Z.S., L.T., and M.A.W., coauthors of "Lawful physician-hastened death: AAN position statement,"[2] reviewed relevant literature and were actively involved in editing multiple iterations of this editorial.

A.T., coauthor of "Lawful physician-hastened death: AAN position statement," elected not to contribute to this editorial.

The publisher regrets the error.

Reference

1. Russell JA, Epstein LG, Bonnie RJ, et al. In defense of the AAN position on lawful physician-hastened death. *Neurology*. 2020;94(15):641-643.

Author disclosures are available upon request (journal@neurology.org).