CORRESPONDENCE

# Multiple Cerebral Hemorrhages in a Patient Receiving Lecanemab and Treated with t-PA for Stroke

**TO THE EDITOR:** The results of the phase 3 trial of the anti–amyloid-$\beta$ drug lecanemab for the treatment of early Alzheimer's disease, reported in the *Journal* by van Dyck et al.,[1] have suggested a beneficial effect on cognition scores and daily activities over a period of 18 months. An extension phase of the trial is ongoing. We report a case of numerous acute intracerebral hemorrhages that developed after treatment with intravenous tissue plasminogen activator (t-PA) for acute ischemic stroke syndrome in a patient who received three doses of intravenous lecanemab.

A 65-year-old patient who was homozygous for the *APOE* $\varepsilon$4 allele and was in the early stages of cognitive decline presented to an emergency department 30 minutes after the acute onset of aphasia and left gaze preference due to an ischemic stroke. The patient had participated in the randomized phase of the trial of lecanemab, during which the treatment assignment is not known, followed by participation in the open-label phase, in which three intravenous lecanemab infusions were received (one infusion every 2 weeks), with the latest infusion administered 4 days before the stroke. Magnetic resonance imaging (MRI) of the head that had been performed 81 days before the stroke showed mild small-vessel disease, with no microhemorrhages, edema, or amyloid-related imaging abnormalities (Figs. S1 and S2 in the Supplementary Appendix, available with the full text of this letter at NEJM.org), and computed tomography (CT) performed just before t-PA administration showed hypodensities in the left temporal–parietal regions and a distal left middle cerebral artery branch occlusion but no hemorrhage. (Further clinical information is provided in the Supplementary Appendix.)

The patient had no contraindications to thrombolysis (blood pressure, 163/84 mm Hg; platelet count, $256\times10^3$ per microliter; international normalized ratio, 1.0; fibrinogen level, 304 milligrams per deciliter) and was within the conventional time window for thrombolysis. After intravenous administration of an 8-mg t-PA bolus and 50 minutes into the t-PA infusion (when 65.7 mg of the total dose of 76 mg had been administered), hypertension suddenly developed (blood pressure, 250/111 mm Hg) and the t-PA infusion was stopped. A CT scan showed extensive, multifocal intraparenchymal hemorrhages. There was no systemic bleeding. Cryoprecipitate and tranexamic acid were administered. The patient had global aphasia and severe agitation; frequent, nonconvulsive seizures seen on electroencephalography were treated successfully with multiple antiseizure medications. Three days after presentation for the stroke, the patient underwent endotracheal intubation. MRI of the head showed acute right thalamocapsular infarction and innumerable multifocal cortical and subcortical hemorrhages with surrounding edema (Fig. 1A and 1B). The patient was treated with comfort measures at the

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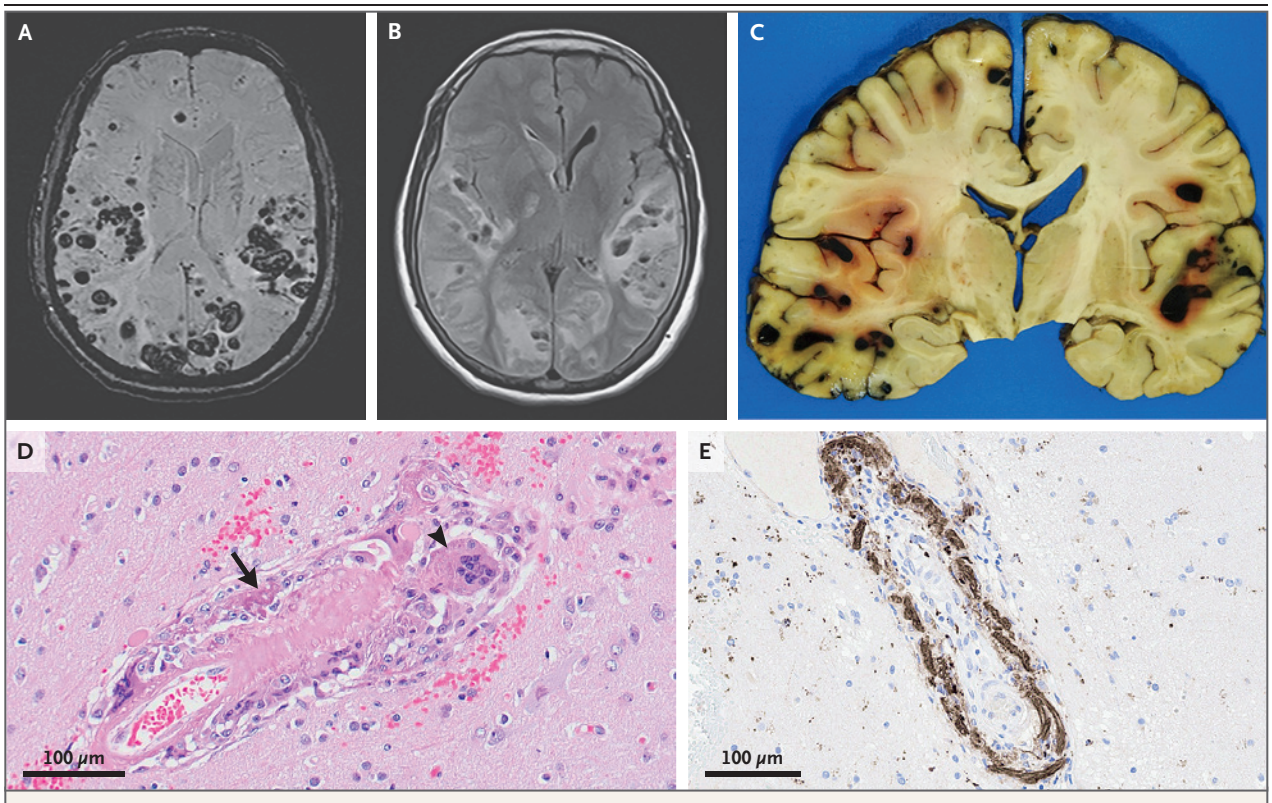


**Figure 1. MRI and Neuropathological Findings.**

Panel A shows a magnetic resonance imaging (MRI) susceptibility-weighted sequence in which extensive multifocal cortical intraparenchymal hemorrhages are visible. Panel B shows an MRI T2 fluid-attenuated inversion recovery (FLAIR) sequence in which extensive cerebral cortical and subcortical edema is seen in association with multifocal hemorrhages, as well as a right thalamocapsular acute ischemic infarct. Panel C shows a coronal section of the formalin-fixed cerebral hemispheres in which numerous cortical intracerebral hemorrhages are present. Panel D shows a representative hematoxylin and eosin–stained section of the left parietal cortex, in which a blood vessel with probable amyloid angiopathy and histiocytic infiltration of the blood-vessel wall is visible. Multinucleated histiocytes (arrowhead) and focal fibrinoid degeneration (arrow) are present. Panel E shows amyloid-$\beta$ immunohistochemical staining of a cortical blood vessel affected by cerebral amyloid angiopathy. The vascular amyloid is fragmented, and the blood-vessel wall shows infiltration by lymphocytes and histiocytes.

request of the family and subsequently died. The autopsy showed extensive multifocal intraparenchymal hemorrhages, cerebral amyloid angiopathy, "high" Alzheimer's disease neuropathologic changes,[2] and diffuse histiocytic vasculitis with necrotizing vasculopathy involving amyloid deposition within (but not outside) the blood-vessel walls (Fig. 1C, 1D, and 1E).

The extensive number and variation in sizes of the cerebral hemorrhages in this patient would be unusual as a complication of t-PA solely related to cerebrovascular amyloid. The findings raise the possibility of cerebral hemorrhages and necrotizing vasculopathy associated with t-PA infusion in a patient with cerebrovascular amyloid who had received lecanemab.

Nicholas J. Reish, M.D., Ph.D.
Pouya Jamshidi, M.D.
Brian Stamm, M.D.
Margaret E. Flanagan, M.D.
Elizabeth Sugg, M.D.
Mengxuan Tang, M.D.
Kelly L. Donohue, M.D.
Matthew McCord, M.D.
Chase Krumpelman, M.D., Ph.D.
Marek-Marsel Mesulam, M.D.
Rudolph Castellani, M.D.
Sherry H.-Y. Chou, M.D.

Northwestern University Feinberg School of Medicine
Chicago, IL
sherry.chou@nm.org

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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1. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. N Engl J Med 2023;388:9-21.
2. Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. Acta Neuropathol 2012;123:1-11.

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# Response to: Multiple Cerebral Hemorrhages in a Patient Receiving Lecanemab and Treated with t-PA for Stroke

**THE AUTHORS REPLY:** Reish and colleagues have brought forward a case of acute intracerebral hemorrhage that occurred after treatment with tissue plasminogen activator (t-PA) in a patient who had been participating in the open-label extension of the Clarity AD trial (Jan. 5 issue).[1] The case did not appear in the original report of the randomized trial of lecanemab because the open-label extension phase, including adverse events that occurred during that phase, was not the topic of the article.[2] These events had not been accumulated and fully adjudicated at the time of publication. A summary of adverse events up to April 2022 in the randomized and open-label extension phases, including the adverse event in this patient, is shown in Tables S1 and S2 in the Supplementary Appendix, available with the full text of this letter at NEJM.org.

We agree that this case raises important management issues for patients with Alzheimer's disease, particularly patients who are homozygous for the *APOE* ε4 allele. Stroke in association with acute antithrombotic therapy is a clinical situation that differs from that of long-term anticoagulation therapy. The patient received t-PA and had a cerebral hemorrhage, with the first symptom occurring 8 minutes after the t-PA infusion. A computed tomographic (CT) scan of the head was performed immediately and showed the presence of cerebral hemorrhages. Although it is not clear in the letter, magnetic resonance imaging was performed 3 days after the CT scan, and death occurred after the decision by the family to withdraw life support 4 days after the CT scan. Intervening events from the time of hemorrhage to the autopsy, including a period in which the systolic blood pressure was greater than 200 mm Hg, may have also affected the autopsy findings. There has been another case of cerebral hemorrhage in a patient who had received lecanemab in the extension phase and had been taking apixaban for atrial fibrillation. (Both cases have been adjudicated and are included in the last row of Table S2.)

Although t-PA appears to be the proximate cause of death, this was an unusual case, and we understand why the authors want to highlight a potential concern. This is the first fatal hemorrhagic event occurring after t-PA treatment that has been reported from the Clarity AD trial. However, there have been earlier reports of fatal large catastrophic intracerebral hemorrhages after t-PA treatment in persons with cerebral amyloid angiopathy (CAA) in the absence of any antiamyloid medications.[3] These reports are consistent with the known increased risk of intracerebral hemorrhage in persons with CAA. An analysis of 306 cases of autopsy-confirmed Alzheimer's disease showed increased severity of CAA in persons homozygous for *APOE* ε4; however, the variation in CAA severity within this cohort remained unexplained by *APOE* genotype alone.[4] In addition, the letter by Reish et al. mentions the finding of vasculitis. Vasculitis has not previously been reported in association with lecanemab. There have been more than 95 previous reports in the literature describing uncommon cases of vasculitis associated with CAA that were not associated with antiamyloid therapy.[5,6]

Marwan Sabbagh, M.D.
Barrow Neurological Institute
Phoenix, AZ

Christopher H. van Dyck, M.D.
Yale School of Medicine
New Haven, CT
christopher.vandyck@yale.edu

Since publication of their article, the authors report no further potential conflict of interest.

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1. Reish NJ, Castellani R, Chou SH-Y, et al. Multiple cerebral hemorrhages in a patient receiving lecanemab and treated with t-PA for stroke. N Engl J Med 2023;388:478-9.
2. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. N Engl J Med 2023;388:9-21.
3. Felling RJ, Faigle R, Ho C-Y, Llinas RH, Urrutia VC. Cerebral amyloid angiopathy: a hidden risk for IV thrombolysis? J Neurol