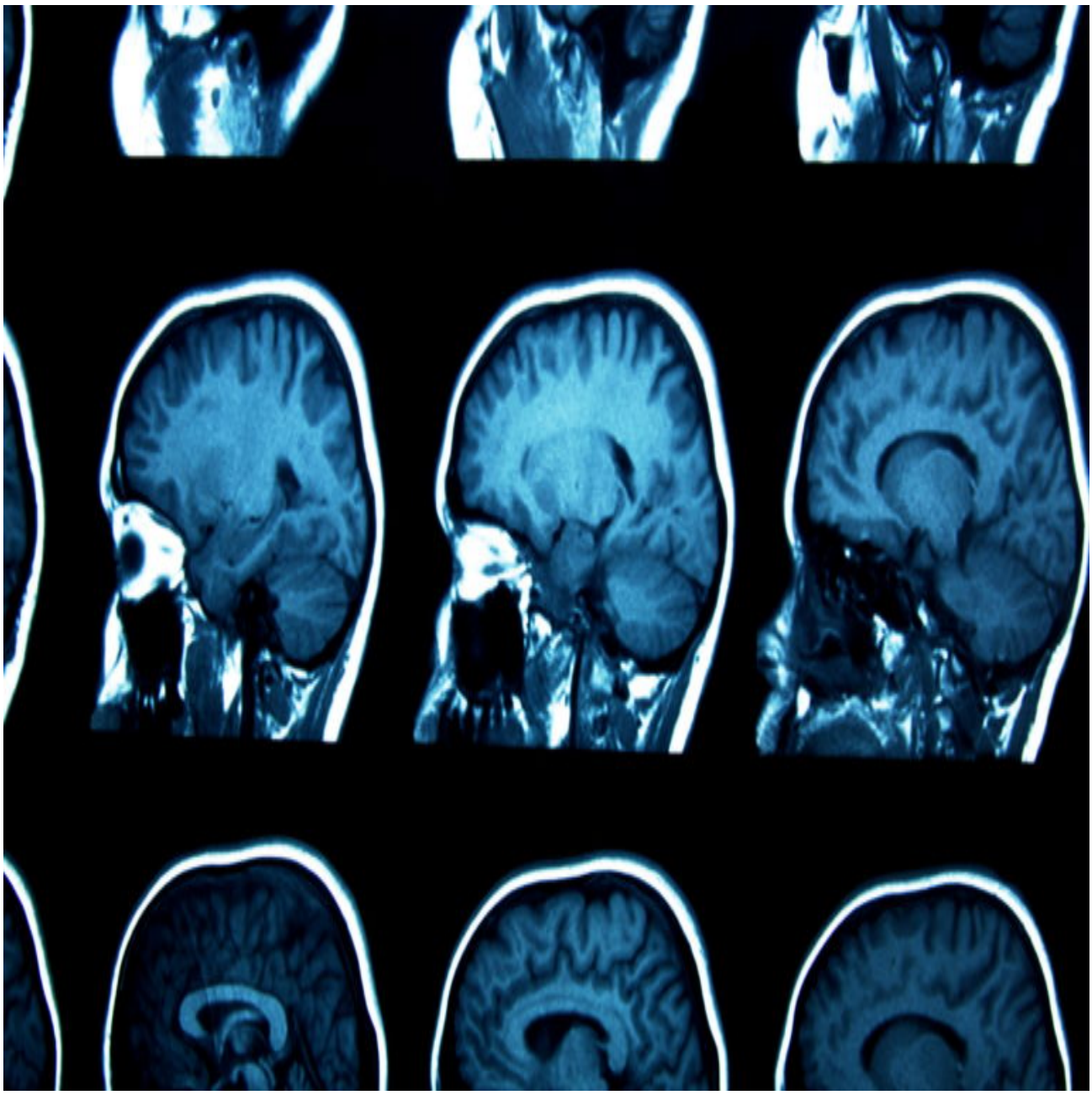
Death of patient in closely watched Alzheimer's trial raises concern about risk for some groups

By Jason Mast[2] [3]Oct. 28, 2022



APSTock

The experimental Alzheimer's drug lecanemab, hailed after it slowed patients' cognitive decline[5] in a clinical trial, may have contributed to the death in June of a patient in the study, STAT has learned.

One investigator on the study flagged the death, noting it came after the patient experienced bleeding in the brain, and concluded it was related to the drug, according to documents obtained by STAT. Eisai, the drugmaker behind lecanemab, disagreed, pointing to other possible factors, including

a series of setbacks in preceding months — multiple falls, a heart attack, a respiratory infection, and mini-stroke-like events.

Though still under investigation, the death suggests that new medicines to treat Alzheimer's, like medicines to treat anything else, will come with their own side effects and costs. It also raises the importance of waiting for the full lecanemab data before drawing conclusions based on the positive press release put out by Eisai and its partner Biogen last month.

In particular, the death underscores the risk of swelling and bleeding in the brain, particularly for patients on blood thinners. The patient who died took Eliquis, a common blood thinner, for atrial fibrillation, a heart condition that raises the risk of heart attack and stroke.

More than 8 million Americans take blood thinners for similar reasons. The potential use of drugs like lecanemab in these patients has been a longstanding concern.

"It is a tough issue, because so many older adults are on anticoagulants, and if that means they can't take these medications, that's going to be a big deal," said Joy Snider, a neurologist at Washington University in St. Louis and an investigator on the trial, adding that she didn't know much about this particular case and couldn't comment on it. "We don't know yet … [but] that's something we're going to need to think about."

A spokesperson for Eisai acknowledged the death, but said that "after looking at all the evidence … there's no reason to believe that lecanemab contributes to death overall in the study, or by any specific cause."

In suspect adverse events reports obtained by STAT, Eisai acknowledged there was "at least a reasonable possibility lecanemab may have contributed to the" hemorrhage. But the company also noted that the other factors made this case complex. The heart attack, in particular, required doctors to briefly give the patient another blood thinner, even after a bleed had already been discovered.

Accordingly, Eisai determined his death was unrelated. But it asked the data and safety monitoring board to look at data across the study and determine if patients on anticoagulants were at heightened risk.

In July, the board found an increased risk: 3.1% of all patients in the study on anticoagulants developed significant bleeds called macrohemorrhages, compared to 0.46% of patients not on anticoagulants, according to a suspect adverse event report (the figure includes those on placebo, as the original trial remains blinded). But the board said that was still a low risk and noted the "complexity of this individual case."

For fear of depriving patients access to a potentially important drug, the board didn't recommend excluding any patients from the study. But it asked Eisai to strengthen its consent forms to warn patients about the risk.

The concerns about bleeding involve a side effect relatively unique to drugs like lecanemab. Lecanemab consists of an antibody designed, like neuronal floss, to clear out amyloid, the hallmark protein that piles up into plaques in Alzheimer's patients' brains.

Since the first such antibodies were put into trials over a decade ago, neurologists reviewing brain scans found that a subset of patients developed mysterious lesions. The lesions appeared to be indicative of swelling but were generally small, transitory, and asymptomatic. They were also theorized to be a signal the drug was working, collateral damage from amyloid being dragged out of the brain.

Researchers gave the phenomenon the unusually elegant name ARIA, for amyloid-related imaging abnormalities, and developed procedures for monitoring patients in trials but largely kept dosing.

"It's important — we need to minimize it," said Reisa Sperling, a director of the Center for Alzheimer Research and Treatment at Brigham and Women's Hospital and one of the neurologists who first identified ARIA. "But I just think Alzheimer's disease is a very bad disease. And I think what we found is that we need drugs that are pretty biologically active and really move amyloid around. And when we move amyloid around, I think we're going to see some ARIA."

Not every case of ARIA is asymptomatic. The side effect is part of what doomed aducanumab, also known as Aduhelm, the amyloid-clearing drug approved last year by FDA but spurned by doctors[9] and payers[10]. Roughly 40% of patients who received the high dose of the drug developed ARIA in clinical trials and one death[11] was potentially linked to the drug after approval. (A Biogen spokesperson said in an email that they are still investigating the case.)

Around 2% to 3% of ARIA patients require serious medical attention, as swelling — or edema — progresses into bleeds. (Small bleeds can also happen without swelling. The swelling form is called ARIA-E; the bleeding form is called ARIA-H, for hemorrhage.)

"It's a continuum," said Sam Gandy, a neurologist at Mount Sinai School of Medicine. "It starts out as edema, and if there's enough inflammation and vessel walls are weakened, then there's a rupture."

With evidence for that drug's effectiveness murky at best, many physicians decided the risks outweighed the benefits.

The Mass General Brigham network decided against administering the drug in part because it didn't know[13] how those side effects would play out in patients on blood thinners. Biogen, aducanumab's developer, had excluded such patients from the trial.

Lecanemab is different for two reasons: Although researchers debate how meaningful the benefit is, the drug clearly slows patients' cognitive decline. And data show it's safer: Less than 10% of patients who received[14] the drug in early trials developed ARIA-E, possibly because it latches onto a different form of amyloid.

Because of that reduced risk, Eisai elected to allow patients on blood thinners into its Phase 3 study, said Michael Irizarry, Eisai's senior VP of clinical research. He estimated about 5% of Alzheimer's patients were on blood thinners.

"It's important to understand the safety in those populations," he said. "To be able to balance the benefit-risk, they would need that information."

The final data indeed showed an ARIA-E rate of only 12%, far below aducanumab's.

The patient who died developed the condition after the Phase 3 study, when, in January, he was enrolled in an open-label extension to all

participants. (It's unknown if he had previously been receiving drug or placebo.)

Suspected ARIA first appeared on an MRI taken on May 18 after the patient, who was in his late 80s, came in for a scheduled infusion and reported he had suffered a second fall in as many months, according to a suspect adverse event report STAT obtained. Treatment was paused and he was taken for scans. Central examiners ultimately determined the patient had ARIA-E and ARIA-H, with the bleed in the back left of the brain. They advised him to stop taking his blood thinner, Eliquis.

He died on June 12, after suffering both a heart attack that the investigator at the site determined was unrelated to lecanemab and four mini-stroke-like events the investigator determined were probably not related but could be. (Later in the reports, both Eisai and the investigator classify the mini-stroke-like events as related.) In classifying his death, the investigator said the patient's underlying cerebral amyloid angiopathy — a technical term for when amyloid builds in the blood vessels — his anticoagulants, and the study drug conspired to trigger the brain bleed, which contributed to his death.

Other researchers agreed a link was plausible.

"Similar patients were discussed with aducanumab and now there's one with lecanemab," said Gandy.

Keith Vossel, director of the Mary S. Easton Center for Alzheimer's Research and Care at UCLA, said the case raised a broader concern.

"I agree that it is a complicated situation," he said. "But there needs to be a better, more thorough investigation in terms of patients on blood thinners, especially older, older patients that are at risk for falling."

The reports note that an autopsy was to be conducted. An Eisai spokesperson declined to comment on its status, citing patient privacy.

What the death ultimately means for the drug and Alzheimer's patients more broadly will depend in large part on the complete data Eisai presents in a month at the Clinical Trials on Alzheimer's Disease Conference.

That presentation may offer the first broad look at the drug's effects on patients who take anticoagulants. It will also give a full account of the drug's efficacy, allowing researchers to better determine whether the cognitive benefit announced in September would actually be meaningful[16] for patients — and, in turn, in which patients the benefits outweigh the risks.

For many patients, even those on anticoagulants, it may still be worth it[17].

"I would count this as among these diseases that taking a risk to pursue a benefit is reasonable, akin to diseases like lung cancer, multiple sclerosis, etc.," said Jason Karlawish, an Alzheimer's physician and bioethicist at the University of Pennsylvania.

Clinical trials almost always underestimate the risks of drugs, Karlawish said, in part because patients tend to be healthier than average. But even so, there are ways to mitigate those risks.

Doctors, for example, could start patients on a smaller dose and slowly titrate up.

Brigham and Women's Sperling is using such measures in the AHEAD study, an academic trial testing whether lecanemab can delay the onset of Alzheimer's in high-risk but healthy patients. She and her fellow investigators too debated what to do after the patient's death this summer,

ultimately deciding that excluding patients on blood thinners would limit the generalizability of their results.

Sperling also pointed to data that suggests that patients who have vascular diseases and other risk factors for ARIA decline the fastest. Depriving them of lecanemab could mean depriving patients who stand to benefit the most.

"I don't think there's one right answer," she said.

Going forward, she added, researchers will have to do a better job of drilling down on which groups are most at risk. It will likely be the start of a broader conversation about benefit-risk that has taken place among stakeholders in most other diseases. Alzheimer's doctors and their patients have simply never had to grapple with effective drugs — or the toxicities they often bring.

"It's a cultural conversation," said Karlawish. "We'll work it out as a society."

About the Author

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