October 6, 2023　14:30～14:45
Designated speech

Concerns about Lecanemab use in routine practice for MCI and early AD

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Scientists explore the world as it is, not as they would like it to be.

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Lecanemab in Early Alzheimer's Disease

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ABSTRACT

BACKGROUND

The accumulation of soluble and insoluble aggregated amyloid-beta (Aβ) may initiate or potentiate pathologic processes in Alzheimer's disease. Lecanemab, a humanized IgG1 monoclonal antibody that binds with high affinity to Aβ soluble protofibrils, is being tested in persons with early Alzheimer's disease.

METHODS

We conducted an 18-month, multicenter, double-blind, phase 3 trial involving persons 50 to 90 years of age with early Alzheimer's disease (mild cognitive impairment or mild dementia due to Alzheimer's disease) with evidence of amyloid on positron-emission tomography (PET) or by cerebrospinal fluid testing. Participants were randomly assigned in a 1:1 ratio to receive intravenous lecanemab (10 mg per kilogram of body weight every 2 weeks) or placebo. The primary end point was the change from baseline at 18 months in the score on the Clinical Dementia Rating–Sum of Boxes (CDR-SB; range, 0 to 18, with higher scores indicating greater impairment). Key secondary end points were the change in amyloid burden on PET, the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14; range, 0 to 90; higher scores indicate greater impairment), the Alzheimer's Disease Composite Score (ADCOMS; range, 0 to 1.97; higher scores indicate greater impairment), and the score on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL; range, 0 to 53; lower scores indicate greater impairment).

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. van Dyck can be contacted at christopher.vandyck@yale.edu or at the Alzheimer's Disease Research Unit, Division of Aging and Geriatric Psychiatry, Yale School of Medicine, 1 Church St., 8th Fl., New Haven, CT 06510.

RESULTS

A total of 1795 participants were enrolled, with 898 assigned to receive lecanemab and 897 to receive placebo. The mean CDR-SB score at baseline was approximately 3.2 in both groups. The adjusted least-squares mean change from baseline at 18 months was 1.21 with lecanemab and 1.66 with placebo (difference, −0.45; 95% confidence interval [CI], −0.67 to −0.23; P<0.001). In a substudy involving 698 participants, there were greater reductions in brain amyloid burden with lecanemab than with placebo (difference, −59.1 centiloids; 95% CI, −62.6 to −55.6). Other mean differences between the two groups in the change from baseline favoring lecanemab were as follows: for the ADAS-cog14 score, −1.44 (95% CI, −2.27 to −0.61; P<0.001); for the ADCOMS, −0.050 (95% CI, −0.074 to −0.027; P<0.001); and for the ADCS-MCI-ADL score, 2.0 (95% CI, 1.2 to 2.8; P<0.001). Lecanemab resulted in infusion-related reactions in 26.4% of the participants and amyloid-related imaging abnormalities with edema or effusions in 12.6%.

CONCLUSIONS

Lecanemab reduced markers of amyloid in early Alzheimer's disease and resulted in moderately less decline on measures of cognition and function than placebo at 18 months but was associated with adverse events. Longer trials are warranted to determine the efficacy and safety of lecanemab in early Alzheimer's disease. (Funded by Eisai and Biogen; Clarity AD ClinicalTrials.gov number, NCT03887455.)

https://www.nejm.org/doi/full/10.1056/NEJMoa2212948

The results obtained in clinical trials may not necessarily be replicable in real clinical practice as is.

In other word,

Statistical significance is not the same as clinical significance.
Nor does it imply patient benefit.

Table 3. Adverse Events.*

Event	Lecanemab (N=898)	Placebo (N=897)
Overall — no. (%)		
Any adverse event	798 (88.9)	735 (81.9)
Adverse event related to lecanemab or placebo†	401 (44.7)	197 (22.0)
Serious adverse event	126 (14.0)	101 (11.3)
Death	6 (0.7)	7 (0.8)
Adverse event leading to discontinuation of the trial agent	62 (6.9)	26 (2.9)
Adverse event that occurred in ≥5% of participants in either group		
Infusion-related reaction	237 (26.4)	66 (7.4)
ARIA with microhemorrhages or hemosiderin deposits	126 (14.0)	69 (7.7)
ARIA-E	113 (12.6)	15 (1.7)
Headache	100 (11.1)	73 (8.1)
Fall	93 (10.4)	86 (9.6)
Urinary tract infection	78 (8.7)	82 (9.1)
Covid-19	64 (7.1)	60 (6.7)
Back pain	60 (6.7)	52 (5.8)
Arthralgia	53 (5.9)	62 (6.9)
Superficial siderosis of central nervous system	50 (5.6)	22 (2.5)
Dizziness	49 (5.5)	46 (5.1)
Diarrhea	48 (5.3)	58 (6.5)
Anxiety	45 (5.0)	38 (4.2)
ARIA‡		
ARIA-E — no. (%)	113 (12.6)	15 (1.7)
Symptomatic ARIA-E — no. (%)§	25 (2.8)	0
ApoE ε4 noncarrier — no./total no. (%)	4/278 (1.4)	0/286
ApoE ε4 carrier — no./total no. (%)	21/620 (3.4)	0/611
ApoE ε4 heterozygote	8/479 (1.7)	0/478
ApoE ε4 homozygote	13/141 (9.2)	0/133
ARIA-E according to ApoE ε4 genotype — no./total no. (%)		
ApoE ε4 noncarrier	15/278 (5.4)	1/286 (0.3)
ApoE ε4 carrier	98/620 (15.8)	14/611 (2.3)
ApoE ε4 heterozygote	52/479 (10.9)	9/478 (1.9)
ApoE ε4 homozygote	46/141 (32.6)	5/133 (3.8)
ARIA-H — no. (%)	155 (17.3)	81 (9.0)
Microhemorrhage	126 (14.0)	68 (7.6)
Superficial siderosis	50 (5.6)	21 (2.3)
Macrohemorrhage	5 (0.6)	1 (0.1)
Symptomatic ARIA-H§	6 (0.7)	2 (0.2)
Isolated ARIA-H: no concurrent ARIA-E	80 (8.9)	70 (7.8)

Table 3. (Continued.)

Event	Lecanemab (N=898)	Placebo (N=897)
ARIA-H according to ApoE ε4 genotype — no./total no. (%)		
ApoE ε4 noncarrier	33/278 (11.9)	12/286 (4.2)
ApoE ε4 carrier	122/620 (19.7)	69/611 (11.3)
ApoE ε4 heterozygote	67/479 (14.0)	41/478 (8.6)
ApoE ε4 homozygote	55/141 (39.0)	28/133 (21.1)
ARIA-E or ARIA-H — no. (%)	193 (21.5)	85 (9.5)
Concurrent ARIA-E and ARIA-H — no. (%)	74 (8.2)	9 (1.0)

* ARIA denotes amyloid-related imaging abnormalities, ARIA-E ARIA with edema or effusions, ARIA-H ARIA with hemosiderin deposits, and Covid-19 coronavirus disease 2019.
† The relatedness of adverse events to lecanemab or placebo was determined by the investigators.
‡ ARIA events were based on central review of MRI studies and include events that occurred after the double-blind intervention period.
§ Symptomatic ARIA-H concurrent with ARIA-E were included under ARIA-E.

https://www.nejm.org/doi/full/10.1056/NEJMoa2212948

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LEQEMBI™ safely and effectively. See full prescribing information for LEQEMBI™.

LEQEMBI™ (lecanemab-irmb) injection, for intravenous use
Initial U.S. Approval: 2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269s000lbl.pdf

2.3 Monitoring and Dosing Interruption for Amyloid Related Imaging Abnormalities

LEQEMBI can cause amyloid related imaging abnormalities -edema (ARIA-E) and -hemosiderin deposition (ARIA-H) *[see Warnings and Precautions (5.1)]*.

Monitoring for ARIA

Obtain a recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment with LEQEMBI. Obtain an MRI prior to the 5th, 7th, and 14th infusions.

Recommendations for Dosing Interruptions in Patients with ARIA

ARIA-E
The recommendations for dosing interruptions for patients with ARIA-E are provided in Table 1.

ARIA-H
The recommendations for dosing interruptions for patients with ARIA-H are provided in Table 2.

---------- WARNINGS AND PRECAUTIONS ----------

- Amyloid Related Imaging Abnormalities (ARIA): Enhanced clinical vigilance for ARIA is recommended during the first 14 weeks of treatment with LEQEMBI. Risk of ARIA, including symptomatic ARIA, was increased in apolipoprotein E ε4 homozygotes compared to heterozygotes and noncarriers. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI scanning if indicated. (2.3, 5.1)
- Infusion-Related Reactions: The infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy administered as clinically indicated. Consider pre-medication at subsequent dosing with antihistamines, non-steroidal anti-inflammatory drugs, or corticosteroids. (5.2)

WARNINGS AND PRECAUTIONS
Incidence of ARIA: Summary

Monoclonal antibodies directed against aggregated forms of beta amyloid, including LEQEMBI, can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E), which can be observed on MRI as brain edema or sulcal effusions, and ARIA with hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis. ARIA-H can occur spontaneously in patients with Alzheimer's disease.

1.Symptomatic ARIA:
- Occurred in 3% (5/161) of patients treated with LEQEMBI in Study 1.
- Clinical symptoms associated with ARIA resolved in 80% of patients during the observation period.

2.Overall ARIA Incidence:
- ARIA, including asymptomatic radiographic events, was observed in 12% (20/161) of patients treated with LEQEMBI in Study 1.
- In comparison, ARIA occurred in 5% (13/245) of patients who received a placebo in Study 1.

3.ARIA Subtypes:
- ARIA-E (effusion) was observed in 10% (16/161) of patients treated with LEQEMBI in Study 1.
- In contrast, only 1% (2/245) of patients on placebo experienced ARIA-E.
- ARIA-H (hemorrhage) was observed in 6% (10/161) of patients treated with LEQEMBI.
- Among patients on placebo, 5% (12/245) experienced ARIA-H.
- There was no increase in isolated ARIA-H (i.e., ARIA-H in patients who did not also experience ARIA-E) for LEQEMBI compared to placebo.

4.Intracerebral Hemorrhage:
- Intracerebral hemorrhage greater than 1 cm in diameter was reported in one patient in Study 1 after treatment with LEQEMBI.
- None of the patients on placebo in Study 1 experienced this event.
- Events of intracerebral hemorrhage, including fatal events, have also been reported in patients taking LEQEMBI in other studies.

ApoE ε4 Carrier Status and Risk of ARIA: Summary

1.Study 1 Population Distribution in LEQEMBI Group:
- 6% (10/161) of patients were ApoE ε4 homozygotes.
- 24% (39/161) of patients were ApoE ε4 heterozygotes.
- 70% (112/161) of patients were ApoE ε4 noncarriers.

2.Incidence of ARIA in LEQEMBI Group:
- ApoE ε4 homozygotes had a higher incidence of ARIA compared to heterozygotes and noncarriers among patients treated with LEQEMBI.

3.Symptomatic ARIA in LEQEMBI Patients:
- Among the 5 patients treated with LEQEMBI who had symptomatic ARIA:
  - 4 were ApoE ε4 homozygotes
  - 2 of the ApoE ε4 homozygotes experienced severe symptoms.

4.Consistent Findings in Other Studies:
- Other studies have also reported an increased incidence of symptomatic and overall ARIA in ApoE ε4 homozygotes compared to heterozygotes and noncarriers in patients taking LEQEMBI.

5.Management Recommendations:
- Recommendations for managing ARIA do not differ between ApoE ε4 carriers and noncarriers, as indicated in the "Dosage and Administration (2.3)" section.
- Consider testing for ApoE ε4 status to inform the risk of developing ARIA when deciding to initiate treatment with LEQEMBI.

Concomitant Antithrombotic Medication and Other Risk Factors for Intracerebral Hemorrhage: Summary(1/2)

1.Study Exclusion Criteria:
Patients were excluded from enrollment in Study 1 if they were already using anticoagulant medications at baseline. However, antiplatelet medications like aspirin and clopidogrel were allowed.

2.Temporary Suspension of LEQEMBI:
If anticoagulant medication had to be used for intercurrent medical events lasting 4 weeks or less during the study, treatment with LEQEMBI was to be temporarily suspended.

3.Risk of ARIA-H:
Patients who received LEQEMBI and an antithrombotic medication (such as aspirin, other antiplatelets, or anticoagulants) did not have an increased risk of ARIA-H compared to patients who received placebo and an antithrombotic medication.

4.Predominance of Aspirin Use:
The majority of patients exposed to antithrombotic medications were using aspirin. Few patients were exposed to other antiplatelet drugs or anticoagulants, which limits drawing meaningful conclusions about the risk of ARIA or intracerebral hemorrhage with these medications.

5.Caution with Antithrombotics:
Given that intracerebral hemorrhages greater than 1 cm in diameter have been observed in patients taking LEQEMBI, additional caution should be exercised when considering the administration of antithrombotics or thrombolytic agents (e.g., tissue plasminogen activator) to a patient already being treated with LEQEMBI.

Concomitant Antithrombotic Medication and Other Risk Factors for Intracerebral Hemorrhage: Summary (2/2)

6. Additional Exclusion Criteria for Study 1:

Patients were also excluded from Study 1 if they had specific risk factors for intracerebral hemorrhage, which included:

- Prior cerebral hemorrhage greater than 1 cm in greatest diameter.
- More than 4 microhemorrhages.
- Superficial siderosis.
- Evidence of vasogenic edema.
- Evidence of cerebral contusion.
- Presence of aneurysm.
- Presence of vascular malformation.
- Presence of infective lesions.
- Multiple lacunar infarcts or stroke involving a major vascular territory.
- Severe small vessel or white matter disease.

Caution should be exercised when considering the use of LEQEMBI in patients who have these risk factors for intracerebral hemorrhage.

5.2 Infusion-Related Reactions

In Study 1, infusion-related reactions were observed in 20% (32/161) of patients treated with LEQEMBI compared to 3% (8/245) of patients on placebo; and the majority (88%, 28/32) occurred with the first infusion. Infusion-related reactions were mild (56%) or moderate (44%) in severity. Infusion-related reactions resulted in discontinuations in 2% (4/161) of patients treated with LEQEMBI. Symptoms of infusion-related reactions include fever and flu-like symptoms (chills, generalized aches, feeling shaky, and joint pain), nausea, vomiting, hypotension, hypertension, and oxygen desaturation.

In the event of an infusion-related reaction, the infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy initiated as clinically indicated. Prophylactic treatment with antihistamines, acetaminophen, nonsteroidal anti-inflammatory drugs, or corticosteroids prior to future infusions may be considered.

Concerns about Lecanemab use in clinical practice (1/2)

1. Aβ pathology ⋯AβPET
2. 1-hour IV infusion, once every 2 weeks
3. MRI prior to initiating treatment and prior to the 5th, 7th, and 14th infusions
4. Premedication
   Infusion-related reactions 20%
5. ARIA-E and H: 3-step evaluation and clinical decision on administration

Concerns about Lecanemab use in clinical practice (2/2)

6. Incidence of ARIA
    - Symptomatic ARIA →3 %
    - Asymptomatic ARIA →12 %
        - ARIA-E …10 %
        - ARIA-H …6 %
7. Risk determination based on ApoE ε4 status
8. Use of antiplatelet/anticoagulant medication may be troublesome
9. How long to continue treatment? Duration of effect? Unknown
10. Long-term efficacy and safety are unknown. Conversion rate of MCI to AD is unknown.

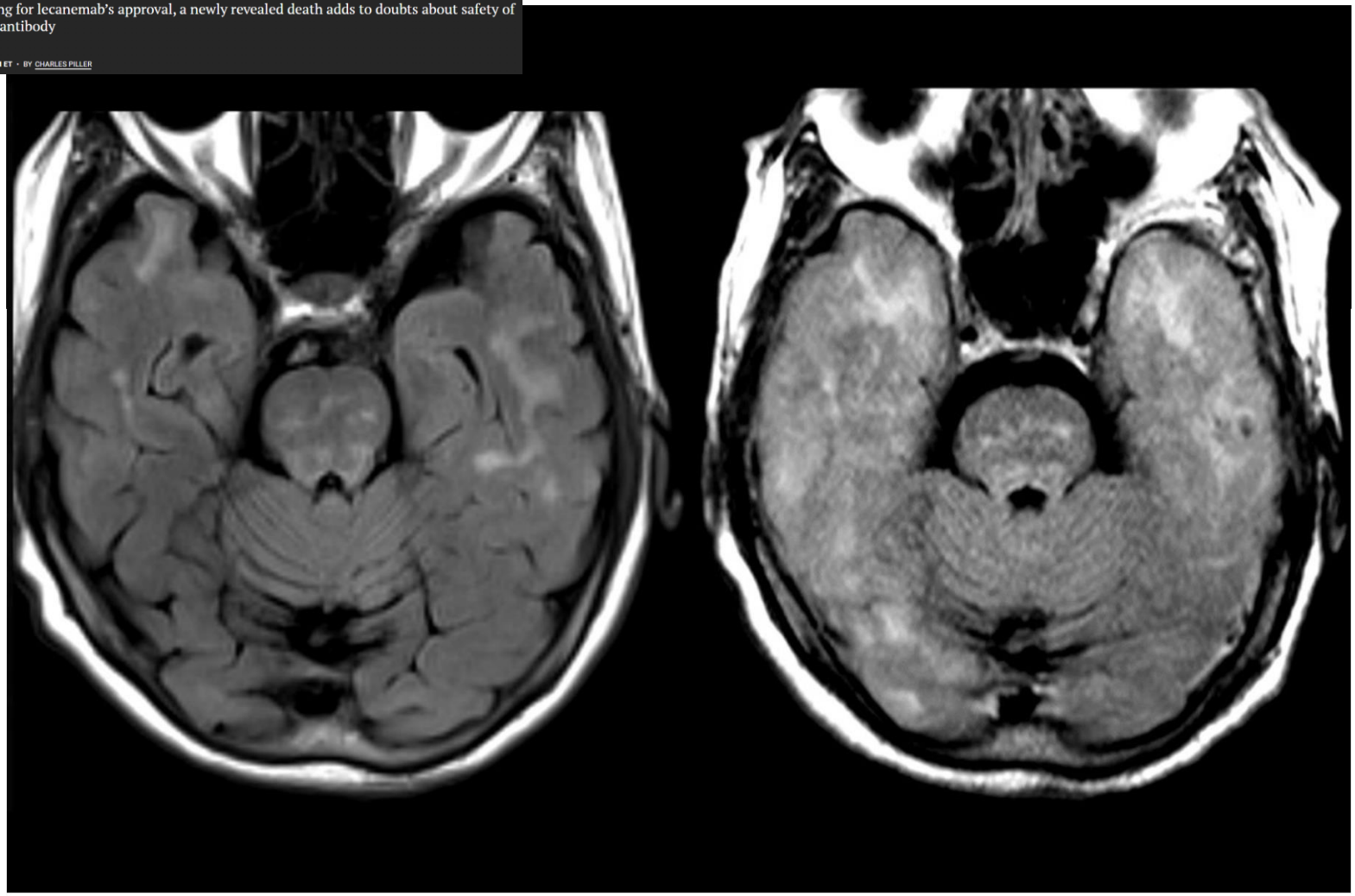
What is amyloid related imaging abnormality (ARIA) ?

SCIENCEINSIDER | HEALTH

Scientists tie third clinical trial death to experimental Alzheimer's drug

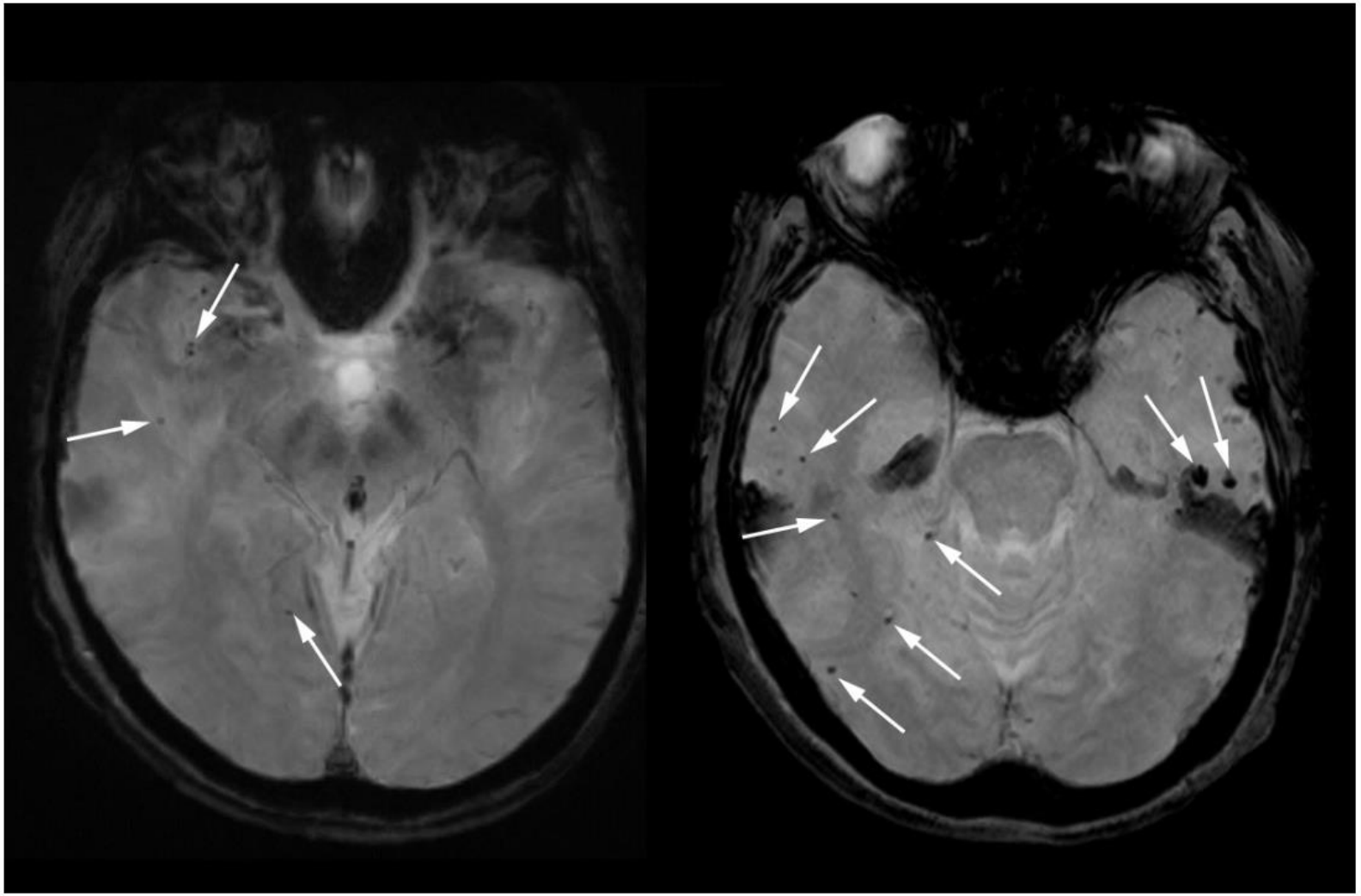
Amid lobbying for lecanemab's approval, a newly revealed death adds to doubts about safety of antiamyloid antibody

21 DEC 2022 • 5:40 PM ET • BY CHARLES PILLER



These MRI images show brain swelling in the cerebral cortex—the outer large section of the brain—of a Florida woman who died after receiving the experimental Alzheimer's drug lecanemab. Before treatment with the antibody, a scan of her cerebral cortex (left) reveals characteristic folds of the temporal lobes. Afterward (right), extreme swelling made those folds impossible to distinguish. PROVIDED ANONYMOUSLY TO *SCIENCE*

https://www.science.org/content/article/scientists-tie-third-clinical-trial-death-experimental-alzheimer-s-drug



Before a Florida woman received lecanemab in an extension phase of a clinical trial, an MRI scan of her brain (left) had a few microhemorrhages—tiny bleeds (dark spots, examples marked by arrows). Afterward (right), dozens of microhemorrhages were obvious (examples marked by arrows). PROVIDED ANONYMOUSLY TO *SCIENCE*

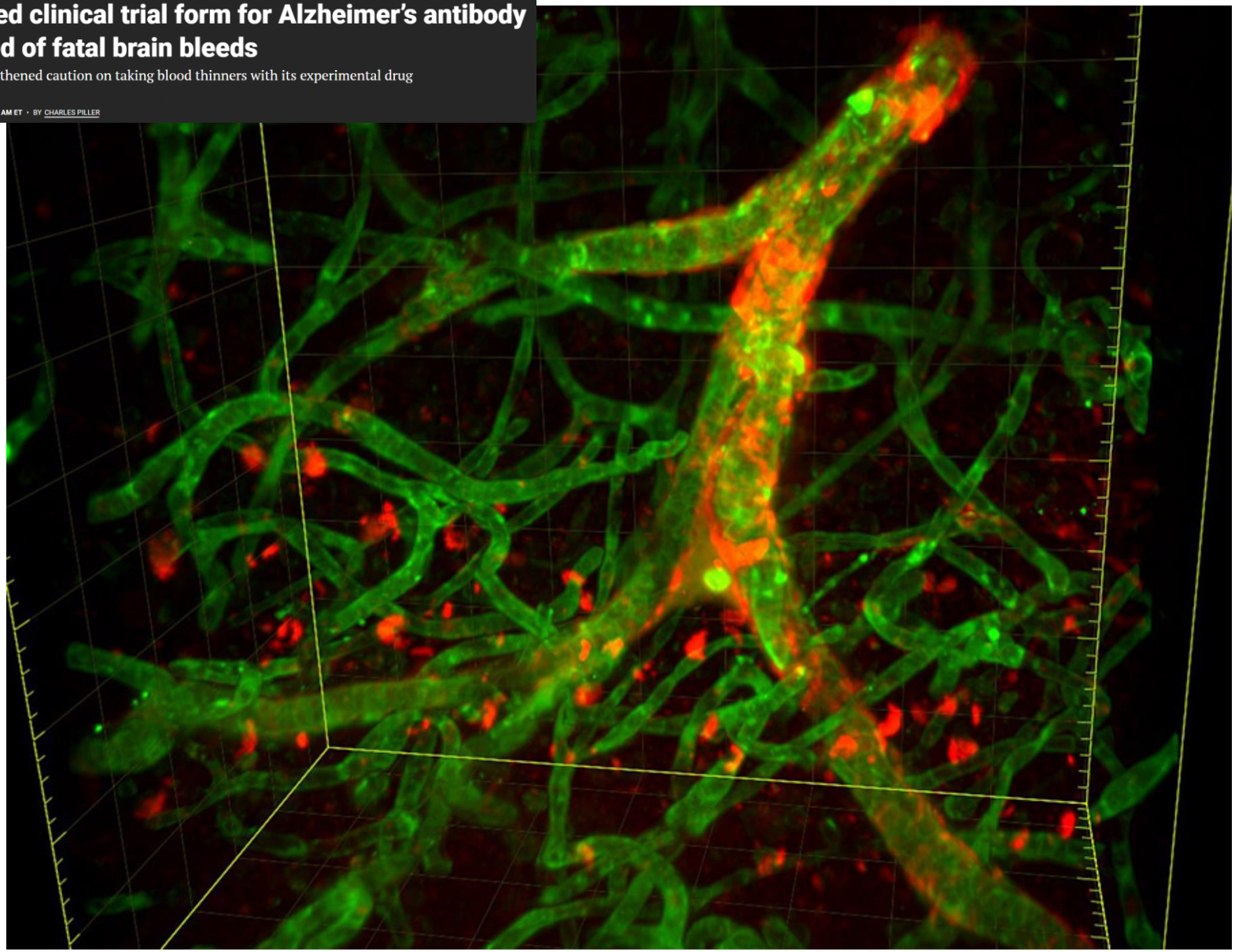
https://www.science.org/content/article/scientists-tie-third-clinical-trial-death-experimental-alzheimer-s-drug

SCIENCEINSIDER | HEALTH

Revised clinical trial form for Alzheimer's antibody warned of fatal brain bleeds

Eisai strengthened caution on taking blood thinners with its experimental drug

30 DEC 2022 • 11:30 AM ET • BY CHARLES PILLER



Alzheimer's patients with cerebral amyloid angiopathy—a condition in which beta amyloid deposits (red) replace the smooth muscle of blood vessels (green)—are particularly vulnerable to brain bleeds when taking lecanemab concurrently with blood thinners. LISSA VENTURA-ANTUNES

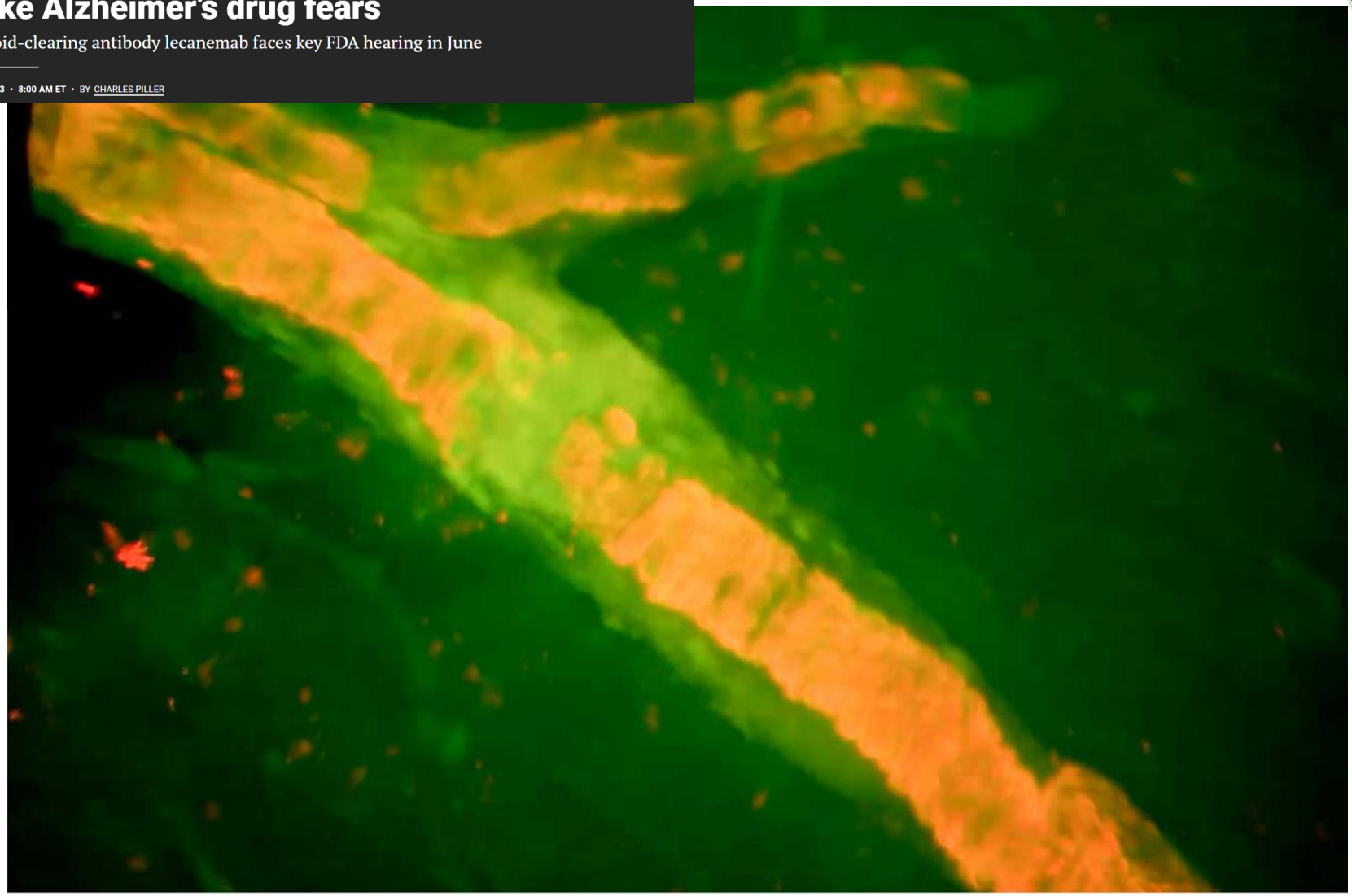
https://www.science.org/content/article/revised-clinical-trial-form-alzheimer-s-antibody-warned-fatal-brain-bleeds

SCIENCEINSIDER | BRAIN & BEHAVIOR

Clinical trial participant's autopsy and brain exam stoke Alzheimer's drug fears

Amyloid-clearing antibody lecanemab faces key FDA hearing in June

13 APR 2023 • 8:00 AM ET • BY CHARLES PILLER



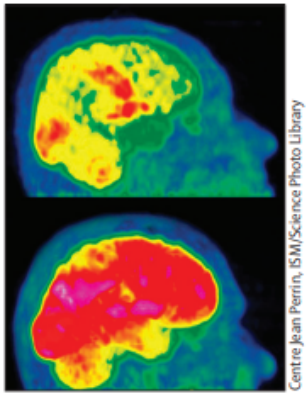
The brain of a woman who died after receiving a new Alzheimer's disease drug shows amyloid (orange) lining blood vessels and a site where a vessel ruptured and bled (yellow-green). LISSA VENTURA-ANTUNES

https://www.science.org/content/article/clinical-trial-participants-autopsy-brain-exam-stoke-alzheimers-drug-fears

Lecanemab for Alzheimer's disease: tempering hype and hope

The Alzheimer's disease community has become accustomed to false hope, disappointment, and controversy. With an estimated 55 million people worldwide affected by dementia, the need for an effective treatment is undeniable. But efforts to develop a drug that can modify the course of Alzheimer's disease, by using antibodies to clear amyloid-beta (Aβ) from the brain, have endured numerous setbacks over the past 20 years. Almost a decade ago, the first anti-Aβ antibodies tested in phase 3 trials, bapineuzumab and solanezumab, did not improve clinical outcomes in mild to moderate Alzheimer's disease. Hopes were dashed again in 2019 when two phase 3 trials of aducanumab—one of the next generation of anti-Aβ antibodies that specifically target Aβ aggregates—were halted early for futility. Aducanumab's resurrection and controversial approval in 2021 by the US Food and Drug Administration (FDA) under its accelerated approval programme, which allows lecanemab group; most cases were asymptomatic and detected incidentally. However, reports of a second death in the ongoing open-label extension phase of the study—possibly linked to co-administration of the thrombolytic drug alteplase—have heightened concerns about lecanemab's safety in patients taking blood-thinning drugs. An initial decision on the drug's approval by the FDA is expected by Jan 6, 2023, and from the European Medicines Agency later in 2023.

After such a long and fruitless wait for a successful therapy for Alzheimer's disease, a phase 3 trial showing efficacy on clinical outcomes is welcome news. However, a 0·45-point difference on the CDR-SB, an 18-point scale, might not be clinically meaningful. A 2019 study suggested that the minimal clinically important difference for the CDR-SB was 0·98 for people with mild cognitive impairment and presumed Alzheimer's aetiology, and 1·63 for those with mild Alzheimer's disease.



Centre Jean Perrin, ISM/Science Photo Library

DOI: https://doi.org/10.1016/S0140-6736(22)02480-1
https://www.thelancet.com/action/showPdf?pii=S0140-6736%2822%2902480-1

Drug Efficacy and Safety

*By **Shalini S. Lynch**, PharmD, University of California San Francisco School of Pharmacy*

Reviewed/Revised May 2022 | Modified Sep 2022

Efficacy and Effectiveness

- **Efficacy** is the capacity to produce an effect (eg, lower blood pressure).

Efficacy can be assessed accurately only in ideal conditions (ie, when patients are selected by proper criteria and strictly adhere to the dosing schedule). Thus, efficacy is measured under expert supervision in a group of patients most likely to have a response to a drug, such as in a controlled clinical trial.

- **Effectiveness** differs from efficacy in that it takes into account how well a drug works in real-world use

Often, a drug that is efficacious in clinical trials is not very effective in actual use. For example, a drug may have high efficacy in lowering blood pressure but may have low effectiveness because it causes so many adverse effects that patients stop taking it.

Patient-oriented outcomes, rather than surrogate or intermediate outcomes, should be used to judge efficacy and effectiveness.

MSD MANUAL
Professional Version

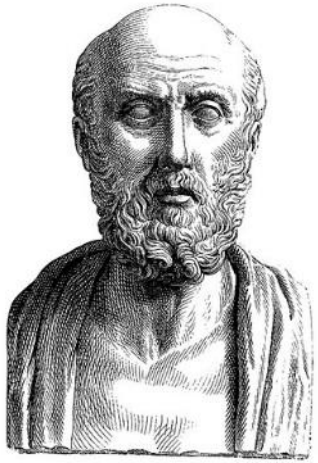
https://www.msdmanuals.com/en-jp/professional/clinical-pharmacology/concepts-in-pharmacotherapy/drug-efficacy-and-safety

Aphorism in Risk Management in Drug Therapy

1. Any drug is a foreign substance to the body
2. No drug is free of side effects
3. Risks must be weighed more heavily than benefits

Hippocratic Oath

I will use those dietary regimens which will benefit my patients according to my greatest ability and judgment, and I will do no harm or injustice to them. Neither will I administer a poison to anybody when asked to do so, nor will I suggest such a course.

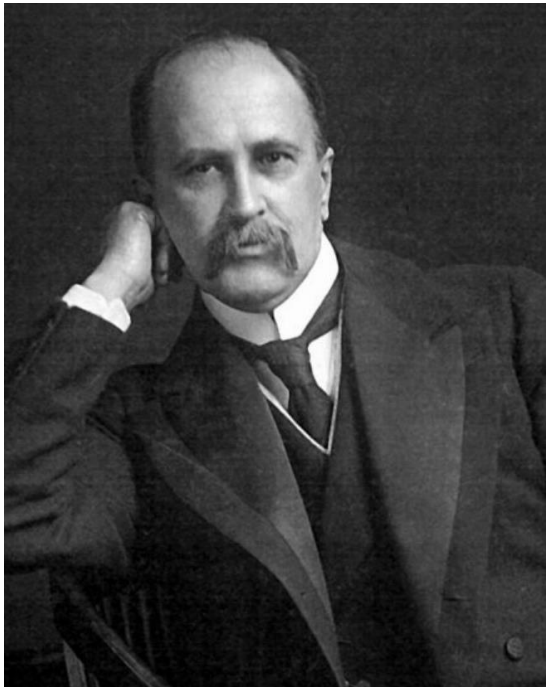


https://en.wikipedia.org/wiki/Hippocratic_Oath

病気を観ずして病人を診よ

高木兼寛男爵(1849～1920)
東京慈恵会医大創設

https://ja.wikipedia.org/wiki/%E9%AB%98%E6%9C%A8%E5%85%BC%E5%AF%9B



A Good doctor treats the disease, a great doctor treats the patient.

Sir William Osler(1849～1919)
近代医学教育の父
Johns Hopkins Univ.

https://www.americanosler.org/content/about/about-william-osler

Take home Message 1

Doctor should never disrupt (destroy) patients' daily life.

Take home Message 2

No more drug disaster !!

Those who cannot remember the past are condemned to repeat it.

George Santayana

Spanish-American philosopher, essayist, poet, and novelist
December 16, 1863 – September 26, 1952

Acknowledgements

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