Stroke

BRIEF REPORT

# Glucagon-Like Peptide-1 Receptor Agonists and Decreased Subarachnoid Hemorrhage Risk in Patients With Intracranial Aneurysm

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**BACKGROUND:** The potential protective effect of GLP-1RAs against nontraumatic subarachnoid hemorrhage (SAH) in individuals with intracranial aneurysms (IAs) remains unclear. Since GLP-1RAs (glucagon-like peptide-1 receptor agonists) have known anti-inflammatory and antihypertensive properties, we proposed to evaluate whether they reduce the risk of nontraumatic SAH in patients with IA with type 2 diabetes.

**METHODS:** We conducted a retrospective cohort study using the global TriNetX database, which spans over 90 health care organizations across North America, South America, Europe, and Asia, with the majority of data contributed by the United States. Analysis included data from January 2010 to January 2025. Patients with unruptured IAs and type 2 diabetes who received GLP-1RAs (n=2517) were compared with those who did not (n=23 431). Propensity score matching (1:1) was performed on 95 demographic and clinical variables, including smoking and hypertension. A subgroup and matched analysis excluded patients who had a history of IA treatment. The primary outcomes were nontraumatic SAH and all-cause mortality over a 5-year follow-up period. Hazard ratios (HRs) and 95% CIs were calculated, and a falsification analysis was performed to evaluate whether patients taking GLP-1RAs were receiving more medical care.

**RESULTS:** After matching, each cohort comprised 2275 patients. GLP-1RA use was associated with a significantly lower rate of nontraumatic SAH (HR, 0.66 [95% CI, 0.50–0.87]) and all-cause mortality (HR, 0.63 [95% CI, 0.52–0.76]). In the matched subgroup analysis of untreated patients, GLP-1RA use was similarly associated with reduced risk of nontraumatic SAH (HR, 0.68 [95% CI, 0.47–0.98]) and all-cause mortality (HR, 0.64 [95% CI, 0.53–0.77]). Falsification analysis confirmed the absence of confounding by indication and health care access bias.

**CONCLUSIONS:** GLP-1RAs have a potential role in mitigating nontraumatic SAH and improving survival among patients with IA with type 2 diabetes. Prospective trials are warranted to confirm these findings.

**GRAPHIC ABSTRACT:** A graphic abstract is available for this article.

**Key Words:** cerebral hemorrhage ■ glucose ■ ischemic stroke ■ neuroprotection ■ smoking





GLP-1RAs (glucagon-like peptide-1 receptor agonists) have emerged as effective glucose-lowering agents and powerful cardioprotective therapies in large, prospective trials of patients with type 2 diabetes (T2DM).[1,2] More recently, their utility has extended into cerebrovascular conditions including ischemic stroke and intracerebral hemorrhage. These effects are attributed in part to suppression of neuroinflammation and enhancement of endogenous antioxidant production.[3–5] A recent population-based analysis using the TriNetX database reported a significantly lower incidence of intracerebral hemorrhage and all-cause mortality among patients with

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This manuscript was sent to Marc Fisher, Senior Guest Editor, for review by expert referees, editorial decision, and final disposition.
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.125.053599.
For Sources of Funding and Disclosures, see page XXX.



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## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **GLP-1RA** | glucagon-like peptide-1 receptor agonists |
| **HR** | hazard ratio |
| **IA** | intracranial aneurysm |
| **SAH** | subarachnoid hemorrhage |
| **T2DM** | type 2 diabetes |

T2DM receiving GLP-1RA therapy compared with those on other oral hypoglycemics.[6]

Subarachnoid hemorrhage (SAH), most often the catastrophic result of intracranial aneurysm (IA) rupture, carries a high burden of morbidity and mortality.[7] Given the central role of inflammation in aneurysm formation, growth, and eventual rupture, the anti-inflammatory properties of GLP-1RAs may potentially mitigate nontraumatic SAH risk in the IA population.[8,9] Yet, studies examining the potential protective role of these medications in patients with unruptured IA are limited.

We conducted a retrospective cohort study to compare the incidence of nontraumatic SAH in patients with IA taking GLP-1RAs versus those managed with other hypoglycemic medications. We used the global TriNetX database, a federated real-world data network aggregating electronic health records from over 90 health care organizations across North America, South America, Europe, and Asia, covering around 130 million patients. Through this exploratory work, we aim to elucidate the potential role of GLP-1RAs in preventing nontraumatic SAH in patients with IA, which may inform future prospective clinical trials.

## METHODS

The TriNetX database is accessible to researchers under license from TriNetX, LLC. Data access requires a data-use agreement and may incur licensing fees. Because of third-party licensing restrictions, the underlying data cannot be made publicly available. This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[10] Because this analysis used deidentified data from the TriNetX Research Network, institutional review board approval and informed consent were waived in accordance with institutional policy. TriNetX is a curated clinical-research platform that aggregates real-time electronic medical data from a global network of health care organizations encompassing academic medical centers, community hospitals, and outpatient clinics. Most of the data is contributed by the United States, including all regions (Northeast, Midwest, South, West). The platform integrates demographics, diagnoses (*International Classification of Diseases, Tenth Revision, Clinical Modification* codes), and procedures (*International Classification of Diseases, Tenth Revision*, Procedure Coding System or Current Procedural Terminology codes) into a single longitudinal record derived from electronic health records. On November 9, 2025, we queried TriNetX to identify all adults (≥18 years) with a recorded diagnosis of T2DM and unruptured IA between January 1, 2010, and January 1, 2025. Cohorts were divided into those on GLP-1RA (with or without additional oral agents or insulin) versus those receiving other oral hypoglycemics (metformin, sulfonylureas, meglitinides, sodium-glucose cotransporter 2 inhibitors, dipeptidyl peptidase 4 inhibitors, thiazolidinediones, alpha-glucosidase inhibitors) or insulin analogues without GLP-1RAs. All *International Classification of Diseases* and Current Procedural Terminology codes used are listed in Table S1. Baseline patient characteristics were captured at any time before IA diagnosis. To reduce confounding, we performed 1:1 propensity score matching using the nearest-neighbor method on 95 baseline covariates, including age, sex, race, smoking, hypertension, history of IA treatment, and hemoglobin A1C values (Tables S2 and S3).

The primary outcomes were incidence of nontraumatic SAH and all-cause mortality occurring up to 5 years of follow-up. Five-year follow-up was selected since 96% of aneurysms that ruptured in the International Study of Unruptured Intracranial Aneurysms ruptured within 5 years of diagnosis.[11] In all analyses, follow-up started at IA diagnosis in both groups of patients with diabetes; for the GLP-1RA group, initiation of GLP-1RA therapy was allowed to occur anywhere between 5 years before up to the same day of IA diagnosis. This limited the effects of immortal-time bias. In a subgroup analysis of nontraumatic SAH and all-cause mortality, we excluded patients who had a history of IA repair and then matched the remaining patients on 70 covariates (excluding 25 treatment codes). To verify the absence of confounding by indication and health care access bias, we conducted a falsification analysis using 2 diagnoses unrelated to GLP-1RA use: prostate cancer and breast cancer.[6] A propensity-matched analysis of nontraumatic SAH was also performed in a broader population of patients with IA, comparing GLP-1RA users versus nonusers (not restricting to diabetics). We additionally evaluated propensity-matched 6-month outcomes after nontraumatic SAH in the GLP-1RA versus non-GLP-1RA groups of patients with IA while adjusting for T2DM. All statistical analyses, including cohort comparisons and outcome assessments, were performed within the TriNetX web platform. Baseline demographic and clinical variables were compared between the GLP-1RA and non-GLP-1RA groups using the Compare Cohorts tool before and after matching, and univariable Cox proportional hazards models were fitted using the matched cohort while including GLP-1RA use as an independent variable. Adjusted hazard ratios are reported with 95% CIs. The Kaplan-Meier cumulative incidence graphs were made using R Studio.

## RESULTS

A flowchart of final cohort selection can be found in Figure 1. We identified 2 cohorts of patients with T2DM and IA: those treated with GLP-1RAs (n=2517) and those receiving other hypoglycemic agents (n=23 431). After 1:1 propensity score matching to balance 95 baseline characteristics (Table S2), each cohort comprised 2275 patients (mean follow-up: 2.4±1.6 years for GLP-1RA group versus 2.6±1.8 years for non-GLP-1RA group). In the matched analysis (Table), GLP-1RA







*Stroke.* 2026;57:00–00. DOI: 10.1161/STROKEAHA.125.053599

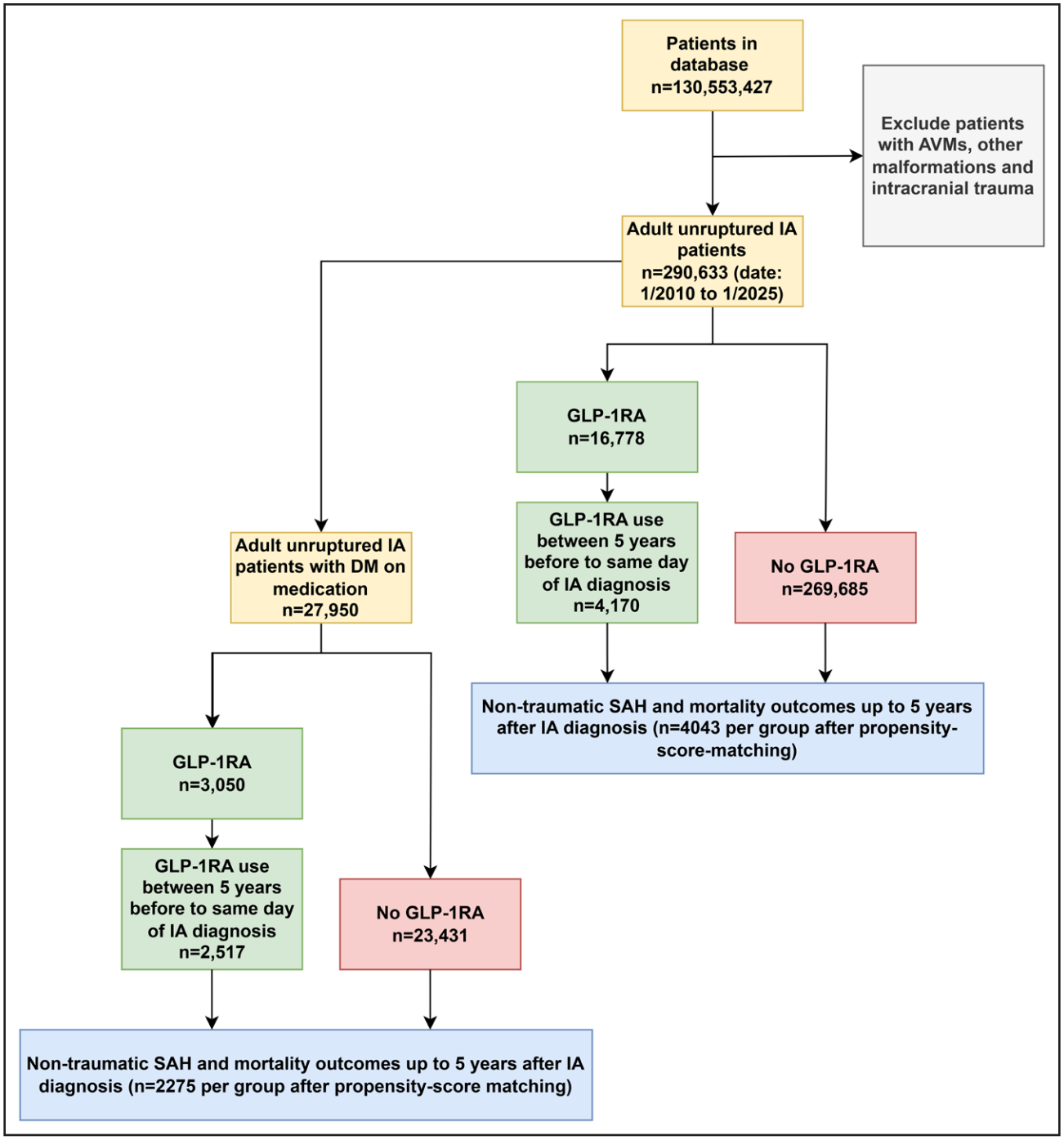


**Figure 1. Flowchart of patient selection.**
AVM indicates arteriovenous malformation; DM, diabetes; GLP-1RA, glucagon-like peptide-1 receptor agonist; IA, intracranial aneurysm; and SAH, subarachnoid hemorrhage.

use was associated with a significantly lower risk of nontraumatic SAH (hazard ratio [HR], 0.66 [95% CI, 0.50–0.87]; Figure 2) and all-cause mortality (HR, 0.63 [95% CI, 0.52–0.76]). Falsification analyses demonstrated no significant difference in the incidence of breast cancer (HR, 1.40 [95% CI, 0.72–2.74]). In the broader population of patients with IA (n=4043 patients per group, mean follow-up: 2.0±1.6 years for GLP-1RA group versus 2.6±2.0 years for non-GLP-1RA group), including diabetics and nondiabetics, while adjusting for T2DM, GLP-1RA use was significantly associated with lower incidence of nontraumatic SAH (HR, 0.62 [95% CI, 0.50–0.76]; Figure S1). Falsification analyses additionally showed no significant difference in prostate (HR, 0.88 [95% CI, 0.58–1.33]) or breast cancer (HR, 1.43 [95% CI, 0.83–2.50]).

**Table. Clinical Outcomes of the Matched Cohorts in All Analyses**

| Outcome | Patients on GLP1-RA<br>Event rate per 100 person-years | Patients not on GLP1-RA<br>Event rate per 100 person-years | HR (95% CI)* |
|---|---|---|---|
| Diabetic patients with treated and untreated intracranial aneurysms (n=2275 per group) | | | |
| Subarachnoid hemorrhage | 0.89 | 1.39 | 0.66 (0.50–0.87) |
| All-cause mortality | 2.73 | 4.41 | 0.63 (0.52–0.76) |
| Diabetic patients with untreated intracranial aneurysms (n=2147 per group) | | | |
| Subarachnoid hemorrhage | 0.60 | 0.82 | 0.68 (0.47–0.98) |
| All-cause mortality | 2.96 | 4.58 | 0.64 (0.53–0.77) |
| All patients with treated and untreated intracranial aneurysms (n=4043 per group) | | | |
| Subarachnoid hemorrhage | 1.88 | 3.01 | 0.62 (0.50–0.76) |
| All-cause mortality | 2.38 | 3.58 | 0.65 (0.55–0.77) |

GLP-1RA indicates glucagon-like peptide-1 receptor agonist; and HR, hazard ratio.
*HR were derived from univariable Cox proportional hazards models performed in the propensity-score–matched cohort, with GLP-1RA exposure as the predictor.

For a subgroup analysis, we excluded patients who had received IA-directed treatment and matched the new cohorts (Table S3) to get 2147 patients per group (mean follow-up: 2.4±1.6 years for GLP-1RA group versus 2.7±1.8 years for non-GLP-1RA group). Among these untreated patients, GLP-1RA therapy remained associated with reduced nontraumatic SAH risk (HR, 0.68 [95% CI, 0.47–0.98]; Figure S2). Falsification analyses demonstrated no significant associations with prostate cancer (HR, 1.2 [95% CI, 0.52–2.78]) or breast cancer (HR, 1.63 [95% CI, 0.81–3.29]).

In a propensity-matched analysis of patients with IA that developed nontraumatic SAH (n=765 patients per group), GLP-1RA use was significantly associated lower all-cause mortality (HR, 0.36 [95% CI, 0.26–0.51]), hydrocephalus incidence (HR, 0.49 [95% CI, 0.31–0.77]), and cognitive decline (HR, 0.74 [95% CI, 0.56–0.97]). There were no significant associations with shunt-dependency, caregiver dependency, or headache (Table S4; Figure S3).

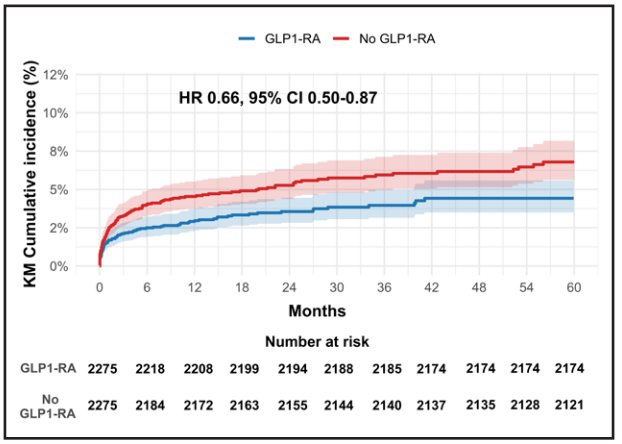


**Figure 2. Kaplan-Meier–based cumulative incidence curve for the end point of nontraumatic subarachnoid hemorrhage according to GLP-1RA (glucagon-like peptide-1 receptor agonist) use in patients with diabetes with treated and untreated intracranial aneurysms.**
HR indicates hazard ratio.

## DISCUSSION

In our study, GLP-1RA use in patients with IAs was associated with a reduced risk of nontraumatic SAH and all-cause mortality. GLP-1RAs have demonstrated both cardiovascular and neuroprotective effects. Studies of GLP-1RAs have focused primarily on cardiovascular disease and ischemic stroke,[1,12] with little attention to nontraumatic SAH, likely because of the low incidence of IAs in the general population. Nonetheless, encouraging data on GLP-1RA benefits in ischemic stroke, and more recently in intracerebral hemorrhage, motivated us to explore their impact on nontraumatic SAH in patients with IA.

Several studies have reported a paradoxical protective effect of DM on SAH.[13,14] By examining only patients with T2DM, we were able to isolate the influence of GLP-1RA therapy and found that these agents confer an additional protective benefit against SAH. This finding highlights the potential of GLP-1RAs to mitigate aneurysm rupture risk in patients with known IAs. In a case-control study utilizing an institutional cohort of patients presenting with an IA, Can et al[15] reported that antihyperglycemic agent use, rather than hyperglycemia, was associated with an unruptured presentation status. Main limitations included a case-control design that did not evaluate longitudinal incidence of aneurysm rupture, as well as the inability to perform a powered analysis of different antihyperglycemics (only 55 patients were taking newer-generation antihyperglycemics such as GLP-1RAs). Patients taking antihyperglycemic agents in the study may have benefited from greater access to health care, leading to earlier diagnosis of aneurysms while still unruptured. Our time-to-event analysis after diagnosis and falsification analyses mitigated

this bias; moreover, a larger sample size of patients on GLP-1RAs allowed us to demonstrate an incremental benefit in rupture prevention and mortality over other antihyperglycemics. One plausible mechanism for this protective effect is the anti-inflammatory action of newer-generation oral antihyperglycemics. Aneurysm rupture is driven by a combination of hemodynamic stress and chronic inflammation.[8,9] GLP-1RAs have been shown to reduce vascular inflammation, which may slow aneurysm progression or promote stabilization, thereby lowering the rupture likelihood. GLP1 receptors are highly expressed in neurons and glial cells of several regions in the brain.[16] GLP-1 receptor stimulation activates adenylate cyclase, increasing cAMP levels and triggering downstream cellular responses.[17] These include enhanced neuroprotection, memory consolidation, neuroplasticity, repair, growth, and regeneration, as well as increased neurotransmitter release and activation of voltage-gated calcium channels. In neurodegenerative diseases such as Parkinson's disease and multiple sclerosis, GLP-1 receptor activation has also been shown to reduce astrocytosis and microgliosis.[18]

GLP-1RAs have also been shown to improve blood pressure control, thereby reducing stress on the aneurysm wall and potentially protecting against rupture. A 2015 preclinical study demonstrated that GLP-1 receptor stimulation increased atrial natriuretic peptide production in atrial myocytes, leading to smooth muscle relaxation and natriuresis, which ultimately lowered blood pressure.[19] Furthermore, multiple clinical studies and a meta-analysis of 33 trials have all indicated that GLP-1RAs significantly reduce systolic blood pressure.[20,21]

We noted an early separation of the cumulative incidence curves for nontraumatic SAH and mortality over the first 3 to 6 months of follow-up. Acknowledging a degree of potential variability in duration of GLP-1RA therapy before start of follow-up, this mirrors the timeline for very early outcome separation (months) seen in the SELECT trial, whereby semaglutide significantly prevented death from cardiovascular causes, stroke, and myocardial infarction in obese patients, even before weight loss occurred.[22,23] Another plausible hypothesis for early separation of outcome would be that GLP-1RAs may be most effective for high-risk aneurysms that are near-rupture and in a highly proinflammatory state. Finally, confounding by indication cannot be fully excluded and can contribute to early separation of survival curves.

Our analysis of this large, real-world database has several limitations. First, because our cohort comprises patients engaged with health care systems, there is an inherent selection bias toward individuals who seek or receive care, with an added inability to control for insurance coverage status. Second, reliance on administrative codes introduces miscoding and misclassification, although *International Classification of Diseases* codes for SAH demonstrate high negative predictive (≥95%) and positive predictive (≥93%) values in some reports.[24] Third, TriNetX is not a closed system, and variability in data capture across participating institutions may affect data completeness and consistency. Fourth, outcome capture is limited to events documented within participating TriNetX health systems. SAH or death occurring at external hospitals are not systematically captured, and TriNetX does not link to the National Death Index. As a result, some events may be missed, and patients may be censored at their last recorded encounter. Fifth, rupture of cerebral aneurysms has been linked to family history, location, size, and shape of the aneurysm, which were not available. Sixth, TriNetX does not provide the means to account for within-pairs cluster effects. Finally, our findings are exploratory and pertain mostly to patients with both T2DM and IAs, and they should not be generalized to the broader population. Despite the limitations of utilizing TriNetX, it enabled the pooling of a large number of patients who both take GLP-1RAs and have the rare diagnosis of IA. This facilitated adequate covariate overlap for propensity matching methods, precision for subgroup/sensitivity analyses, and improved generalizability beyond a single center.

Our study suggests a potential neuroprotective effect of GLP-1RAs in reducing nontraumatic SAH risk among patients with T2DM with IAs. As the use of GLP-1RA becomes more prevalent, future analysis could validate these results. Prospective, controlled trials are needed to confirm these observations and to define the role of GLP-1RAs in SAH prevention within this high-risk population.





## ARTICLE INFORMATION

Received August 30, 2025; final revision received December 6, 2025; accepted December 10, 2025.

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### Sources of Funding

None.

### Disclosures

Dr Jackson is a consultant for Egret Therapeutics with equity interests in the company. He receives research support from Biohaven Pharmaceuticals Inc and Grifols Biologicals Inc. Dr Huang reports compensation from Longeviti Neuro Solutions LLC for other services; service as Director for the American Board of Neurological Surgery; and intellectual property for the textbook Fundamentals of Operative Neurosurgery. The other authors report no conflicts.

### Supplemental Material

Tables S1–S4
Figures S1–S3

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