Stroke

CLINICAL AND POPULATION SCIENCES

Comparative Effectiveness and Safety of Seizure Prophylaxis Among Adults After Acute Ischemic Stroke

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BACKGROUND: Older adults occasionally receive seizure prophylaxis in an acute ischemic stroke (AIS) setting, despite safety concerns. There are no trial data available about the net impact of early seizure prophylaxis on post-AIS survival.

METHODS: Using a stroke registry (American Heart Association's Get With The Guidelines) individually linked to electronic health records, we examined the effect of initiating seizure prophylaxis (ie, epilepsy-specific antiseizure drugs) within 7 days of an AIS admission versus not initiating in patients ≥65 years admitted for a new, nonsevere AIS (National Institutes of Health Stroke Severity score ≤20) between 2014 and 2021 with no recorded use of epilepsy-specific antiseizure drugs in the previous 3 months. We addressed confounding by using inverse-probability weights. We performed standardization accounting for pertinent clinical and health care factors (eg, National Institutes of Health Stroke Severity scale, prescription counts, seizure-like events).

RESULTS: The study sample included 151 patients who received antiseizure drugs and 3020 who did not. The crude 30-day mortality risks were 219 deaths per 1000 patients among epilepsy-specific antiseizure drugs initiators and 120 deaths per 1000 among noninitiators. After standardization, the estimated mortality was 251 (95% CI, 190–307) deaths per 1000 among initiators and 120 (95% CI, 86–144) deaths per 1000 among noninitiators, corresponding to a risk difference of 131 (95% CI, 65–200) excess deaths per 1000 patients. In the prespecified subgroup analyses, the risk difference was 52 (95% CI, 11–72) among patients with minor AIS and 138 (95% CI, 52–222) among moderate-to-severe AIS patients. Similarly, the risk differences were 86 (95% CI, 18–118) and 157 (95% CI, 57–219) among patients aged 65 to 74 years and ≥75 years, respectively.

CONCLUSIONS: There was a higher risk of 30-day mortality associated with initiating versus not initiating seizure prophylaxis within 7 days post-AIS. This study does not support the role of seizure prophylaxis in reducing 30-day poststroke mortality.

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

Key Words: anticonvulsants ■ ischemic stroke ■ neurology ■ seizures

Acute ischemic stroke (AIS) is a common cause of older adults' short-term mortality and long-term disability.[1,2] For those ≥65 years, stroke is the second leading cause of hospitalization and carries a poststroke 30-day mortality risk of 9% to 24%.[3] Seizures are common and challenging-to-predict stroke complications. Incidence of poststroke seizure risk varies widely and often measures different outcomes, for example, from a 1-year incidence of 5% to 7% in community-based studies to a 1-week incidence of 10% to 50% in patients with continuous electroencephalography.[4]

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Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
ASD	antiseizure drug
NIHSS	National Institutes of Health Stroke Scale

Over recent decades, continuous electroencephalography utilization has doubled.[5] Continuous electroencephalography shows epileptic abnormalities resembling seizures in 46% to 60% of patients in the acute symptomatic phase.[6] Because those patterns are associated with greater poststroke seizure risk, health care providers debate whether these epileptic abnormalities should be treated,[7] as observational studies suggest that antiseizure drug (ASD) treatment may cause net harm.[8] Others indicate that the inability to demonstrate benefit is due to confounding by indication (eg, failing to adequately adjust for traits that impact the probability of clinically significant seizures, treatment initiation, and death), since those at higher risk are more likely to receive seizure prophylaxis.[9] Nonetheless, continuous electroencephalography utilization has increased prophylaxis with levetiracetam and other ASDs.[4,10]

Despite the increasing concerns of the prevalence of use, there remains limited real-world information about the effectiveness and safety of seizure prophylaxis among older adults in the United States.[11–13] ASDs may lead to life-threatening adverse effects (eg, falls, infections, and somnolence).[14,15] Older adults on polytherapy are more sensitive to drug toxicity,[16,17] as are those with acute brain insults such as AIS. Since older adults are typically excluded from phase III and IV clinical trials,[18] the effect of seizure prophylaxis remains underexplored in this population.[16,17]

We used observational data to evaluate the effect of seizure prophylaxis initiation within 7 days post-AIS on 30-day mortality among patients ≥65 years.

METHODS

Study Design

We used a target trial approach to emulate a hypothetical pragmatic randomized clinical trial.[19,20] Specifying the ideal study to answer the research question forces a rigorous conceptualization of the study design components and the assumptions necessary to answer the question using observational data.[19] The target trial to answer the question of interest would randomly assign eligible patients at the time of AIS admission to one of the 2 treatment strategies: (1) initiate seizure prophylaxis (ASD hereafter refers to epilepsy-specific antiseizure drugs) within 7 days post-AIS; or (2) do not initiate within the same 7-day period. The outcome is mortality, evaluated in a follow-up period of 30 days following treatment initiation. The following sections describe the observational study to emulate this target trial (Table 1).

Setting and Data Sources

We used a comprehensive registry, the American Heart Association's Get With The Guidelines-Stroke Registry (Supplemental Material), to identify eligible patients.[21] We then linked the data to patients' electronic health records from the Mass General Brigham Healthcare System to obtain demographic, clinical, and health care utilization data (eg, inpatient diagnoses, procedures, outpatient and inpatient drug administration).[22]

This study was approved by the institutional review board of Massachusetts General Hospital, and informed consent was waived. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

From January 1, 2014 through June 28, 2021, we identified 3538 patients ≥65 years who had specifically AIS,[21,23] and had no recorded diagnosis of prior AIS in the last 12 months. We excluded 45 patients without the minimum information in the electronic health records to determine eligibility, for example, National Institutes of Health Stroke Scale (NIHSS) not recorded at admission. This enhanced the selection of AIS patients admitted at MGH on the day of the AIS because those with missing NIHSS values were typically transferred from another hospital one or more days after the AIS. We also excluded patients with severe NIHSS admitted for new nonsevere AIS (NIHSS score of ≤20), and patients with one or more recorded prescriptions of ASDs within the 3-month period before admission. The final eligible sample was 3171 (Figure 1).

Treatment Strategies

We obtained information on ASD use from inpatient and outpatient pharmacy data. We classified ASDs as those prescribed for seizure prophylaxis (ie, not used for other indications like pain management or anxiety; Table S1). We defined the following treatment strategies: (1) initiate seizure prophylaxis within 7 days of admission; or (2) no seizure prophylaxis during these 7 days.

Emulated Randomization and Covariates

In the target trial, balanced baseline characteristics would be attained through randomization. In the emulation, we ascertained information on clinical and sociodemographic characteristics, assessed differences in their distribution between treated and nontreated groups, and standardized for relevant confounders in the analysis.

We examined a comprehensive list of clinical (eg, stroke severity, seizures, and seizure-like events, comorbidities, code status) and health care utilization variables (inpatient visits, outpatient visits, procedures [electroencephalogram and brain imaging]). The Supplemental Material details the operational definition of each measure of interest.

As our measure of stroke severity at baseline, we chose the NIHSS,[24,25] a summary measure that has been strongly associated with seizure risk, seizure prophylaxis, and mortality.

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Table 1. Description of a Target Trial and the Corresponding Observational Study

Target trial specification	Emulation (observational study)
Eligibility criteria	
Admission for cerebrovascular accident between 1/2014 and 6/2021 at Massachusetts General Hospital	Same
Age≥65 y	Same
Confirmed AIS	Same
No previous history of AIS in the last 12 mo	No recorded diagnosis of AIS in the last 12 mo.
No use of ASD* in the last 3 mo	No recorded prescription of ASD in the last 3 mo.
Treatment strategies	
Treatment arm: Initiate seizure prophylaxis (ASD) within 7 d of AIS admission. Control arm: Do not initiate seizure prophylaxis (ASD) within 7 d of AIS admission.	Same
Treatment assignment	
Open label, randomized treatment assignment	Emulated randomization by balancing confounders using IPTW for treatment selection.
Outcomes	
Time to death from the day of AIS admission	Same. Time to death (as recorded in EHR or GWTG registry) from the day of AIS admission.
Follow-up	
Starts at randomization (at admission) and ends at death, or end of the 30-d observation period in the study, whichever occurs first.	Starts at AIS admission and ends at death, or 30 d of follow-up, whichever occurs first.
Causal contrast	
Intention-to-treat effect.	Observational analog of intention-to-treat effect.
Statistical analysis	
Intention-to-treat effect analysis of time to death, accounting for censoring.	Same, additionally accounting for baseline confounding.

AIS indicates acute ischemic stroke; ASD, antiseizure drugs; EHR, electronic health record; GWTG, Get With The Guidelines-Stroke Registry; and IPTW, inverse probability of treatment weights.

*ASDs: Acetazolamide, Acetazolamide XR, Brivaracetam, Cannabidiol, Eslicarbazepine, Ethosuximide, Felbamate, Lacosamide, Lamotrigine, Lamotrigine ER, Levetiracetam, Levetiracetam ER, Methsuximide, Perampanel, Phenobarbital, Phenytoin, Retigabine, Ezogabine, Rufinamide, Tiagabine, Vigabatrin.

NIHSS was reliably assessed, measured, and documented upon hospital admission (study time zero), making it an ideal baseline measure for use in the weights for treatment initiation. We also considered baseline comorbidities and prescription drug utilization before the AIS using data from 90 days before admission. We obtained several sociodemographic measures from the Mass General Brigham database (ie, age, sex, race, and ethnicity).[26]

As time-varying characteristics, during the 7-day window, we used a comprehensive list of clinical and health care utilization variables, including inpatient and outpatient visits and procedures related to AIS management and cumulative in-hospital prescription count, which we divided into 4 categories: no prescription recorded, 1 to 4 drugs, 5 to 9 drugs, and >9 drugs (excluding ASDs).[19,27–30]

Follow-Up and Outcome: 30-Day Mortality

Patients were followed from AIS admission for 30 days or until death (Figure S1). We extracted the death date from the electronic health record demographics data file (Death Master File). Mass General Brigham updates death data monthly from the Social Security Administration. Thus, deaths were captured even if the patient was transferred into a nursing home or another non-Mass General Brigham facility (ie, no losses to follow-up).

Statistical Analysis

We first described the characteristics of the eligible sample.[31] We obtained a naïve crude 30-day mortality estimate for ASD initiators from treatment during the first-week post-AIS and noninitiators from AIS admission.[32,33]

To evaluate the effect of ASD initiation in the first 7 days post-AIS on 30-day mortality, we estimated mortality probabilities using model-based predictions of the conditional survival for each day under each treatment strategy.[34,35] We provide details of the statistical approach, missing data, and preplanned stratified analysis in the Supplemental Material and we separately created inverse probability of treatment weights with some variables collected at baseline (ie, NIHSS, prescription count at baseline, and seizure-like events at baseline) to show the balance (ie, all standardized mean differences <0.2 after applying inverse probability of treatment weights; Table S2).

RESULTS

Study Population Characteristics

Among AIS patients ≥65 years, 3171 were eligible for our emulated trial. Of those, 151 received seizure prophylaxis within 7 days post-AIS, and 3020 did not. Table 2 describes patient characteristics among initiators

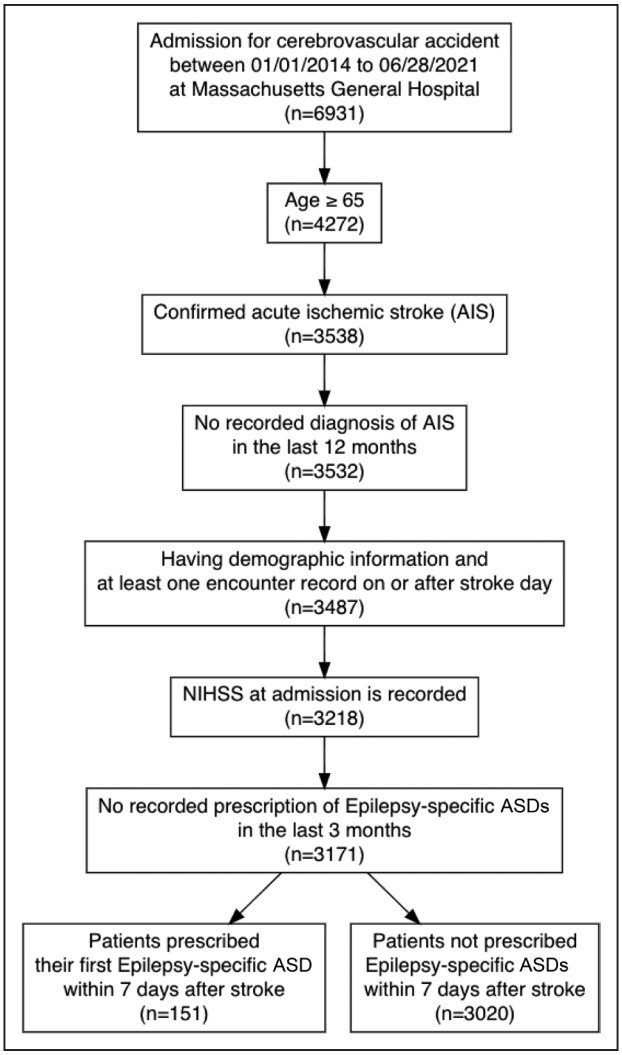

Figure 1. Selection of eligible patients with new acute ischemic stroke (AIS) ≥65 y, 2014–2021.
Describes the sampling process that resulted in a sample of 3171 subjects, including patients ≥65 y at the time of new AIS admission, with available data in the electronic health record (EHR) system and who had not received antiseizure drugs (ASDs) in the 3 mo before admission.

versus noninitiators. The most frequently administered ASD was levetiracetam at 84%, followed by phenytoin at 6% (Table S3). Additionally, in Figure S2 we provide a breakdown of when the medications of interest were started by post-AIS days within the 7 days exposure window (from day 0 through day 6). In the observational data, 64 patients (42%) received one of the ASDs of interest within the first 24 hours post-AIS admission. Cumulatively, 133 patients (88%) received one of the ASDs of interest within the first 72 hours post-AIS admission. In Figure S3, we demonstrate the counts of deaths over the same period to illustrate the issue of immortal time bias, which we have addressed using the proposed methods. Further, in Figure S3, we show that prophylaxis has been the primary use within the study cohort. Sixty-seven percent of the patients initiated on ASDs were discontinued within 24 hours; 85% of the patients continued within the first 7 days post-AIS but >90% were discontinued within 30 days.

Outcome: Mortality

Figure 2 provides the crude Kaplan-Meier and standardized survival curves for all 3171 eligible patients. The crude 30-day mortality risks were 219 deaths per 1000 patients among ASD initiators within 7 days (Figure 2A, Table S4) and 120 deaths per 1000 among noninitiators. Since we had no missing data with respect to death, we provided crude curves with 90 days in the *x* axis. The apparent difference in crude excess mortality in patients with seizure prophylaxis was predominantly seen during the first 30 days (Figure 2A). The standardized differences could increase beyond 30 days (Figures 2B and 3), but with a decreasing degree of certainty over time (ie, larger CI) because a model was run each day with fewer subjects and covariates in the data. We showed the most conservative analysis and produce standardized curves setting the follow-up to 30 days post-AIS.

The standardized 30-day mortality was 230 (95% CI, 210–254) deaths/1000 patients who initiated ASDs and 121 (95% CI, 116–127) per 1000 noninitiators, yielding a risk difference of 109 (95% CI, 91–132) deaths/1000 patients. When further corrected for confounding (Figure 2B, Table S4), standardized 30-day mortality was 251 (95% CI, 190–307) deaths/1000 patients who initiated ASDs and 120 (95% CI, 86–145) per 1000 noninitiators, yielding a risk difference of 131 (95% CI, 65–200) deaths/1000 patients. Inspection of the curves suggests greater mortality rates for the initiate-seizure prophylaxis strategy than no-initiation, especially later after admission.

Among AIS patients 65 to 74 years and ≥74 years, the risk differences were 86 (95% CI, 18–118) and 157 (95% CI, 57–219)/1000 patients, respectively (Figure 3A and 3B). Among patients with mild and moderate-to-severe AIS, the 30-day mortality risk difference was 52 (95% CI, 11–72) deaths/1000 and 138 (95% CI, 52–222), respectively (Figure 3C and 3D). Tables S5 and S6 present the main standardized estimates stratified by age group and AIS severity. Table S7 presents model parameters for estimating epilepsy-specific ASD initiation weights.

Table S8 displays this study's compliance with reporting recommendations. The Supplemental Material provides the Statistical Code used to conduct the analysis.

DISCUSSION

In this study, using rich information on predictors of seizure prophylaxis and mortality among AIS patients ≥65 years, we observed a crude higher risk of 30-day mortality associated with initiating seizure prophylaxis

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Table 2. Characteristics of Patients by ASD Exposure

	ASD initiator (N=151)	ASD noninitiator (N=3020)	SMD
Sociodemographic characteristics (recorded at admission)			
Age, mean (SD)	77.30 (8.49)	78.05 (8.43)	0.089
Female, %	71 (47.0)	1540 (51.0)	0.080
Non-White	22 (15.4)	472 (16.3)	0.026
Hispanic, %	1 (0.7)	42 (1.5)	0.073
Primary insurance Medicare or other government (vs private), %	120 (79.5)	2441 (80.9)	0.035
Baseline medication use (recorded during the 90 d before admission)			
Prescription count, mean (SD)	19.86 (37.09)	7.90 (30.49)	0.352
Categories of medication use, %			
No prescription recorded*	55 (36.4)	2161 (71.6)	
1–4 drugs	18 (11.9)	333 (11.0)	
5–9 drugs	13 (8.6)	141 (4.7)	
>9 drugs	65 (43.0)	385 (12.7)	
Baseline clinical characteristics (recorded during 12 mo before admission)			
Charlson comorbidity score, mean (SD)	2.27 (1.97)	1.15 (1.75)	0.604
Alzheimer disease and related dementias	10 (6.6)	104 (3.4)	0.146
Baseline health-resource utilization (recorded during 12 mo before admission), %			
Fall-related injury	22 (14.6)	325 (10.8)	0.115
Seizure-like events	51 (33.8)	160 (5.3)	0.770
EEG	13 (8.6)	23 (0.8)	0.378
Acute Ischemic Stroke Severity (recorded at admission), %			
NIHSS, mean (SD)	11.95 (8.91)	7.59 (7.80)	0.521
Mild (0–4)	39 (25.8)	1536 (50.9)	
Moderate (5–15)	54 (35.8)	920 (30.5)	
Moderate to severe (16–20)	23 (15.2)	287 (9.5)	
Severe (>20)	35 (23.2)	277 (9.2)	
In-hospital measures of stroke severity and complications (recorded during first day of admission),† %			
Observed large vessel occlusion	34 (39.5)	594 (34.4)	0.107
In-hospital prescription count	15.22 (12.84)	9.53 (11.83)	0.461
IV injection of tPA	8 (5.3)	220 (7.3)	0.082
EVT	2 (1.3)	67 (2.2)	0.068
CT/CAT scan	82 (54.3)	1854 (61.4)	0.144
MRI of the brain	42 (27.8)	1502 (49.7)	0.462
Comfort measures only, %			0.367
Day 0 or 1	8 (5.3)	134 (4.4)	
Day 2 or after	34 (22.5)	289 (9.6)	
Not on CMO	109 (72.2)	2597 (86.0)	

ASD indicates antiseizure drugs; CMO, comfort measures only; CT/CAT, computed tomography; EEG, electroencephalogram; EVT, endovascular thrombectomy; MGB, Mass General Brigham; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; SMD, standardized mean difference; and tPA, tissue-type plasminogen activator.

*No prescription recorded: the prescription information was as follows: (1) missing from the MGB structured health system data warehouse; (2) the patient was not taking any prescription drug; (3) the patient was taking prescription drugs given elsewhere (eg, over the counter, prescribed and recorded in another healthcare system); and (4) other unknown reason.

†For simplicity, we present just the values obtained during the first day of admission, but we include time-varying values of those measures in the model for treatment initiation (updated daily).

within 7 days post-AIS compared with not initiating. Although residual confounding by indication remains a concern, our findings suggest that any net-benefit is likely small (as illustrated in the standardized survival curves). Stated differently, this article does not support a role for short-term seizure prophylaxis in reducing poststroke mortality.

ASDs are occasionally used for primary seizure prophylaxis, even though the American Geriatrics Society's Beers Criteria explicitly states that ASDs

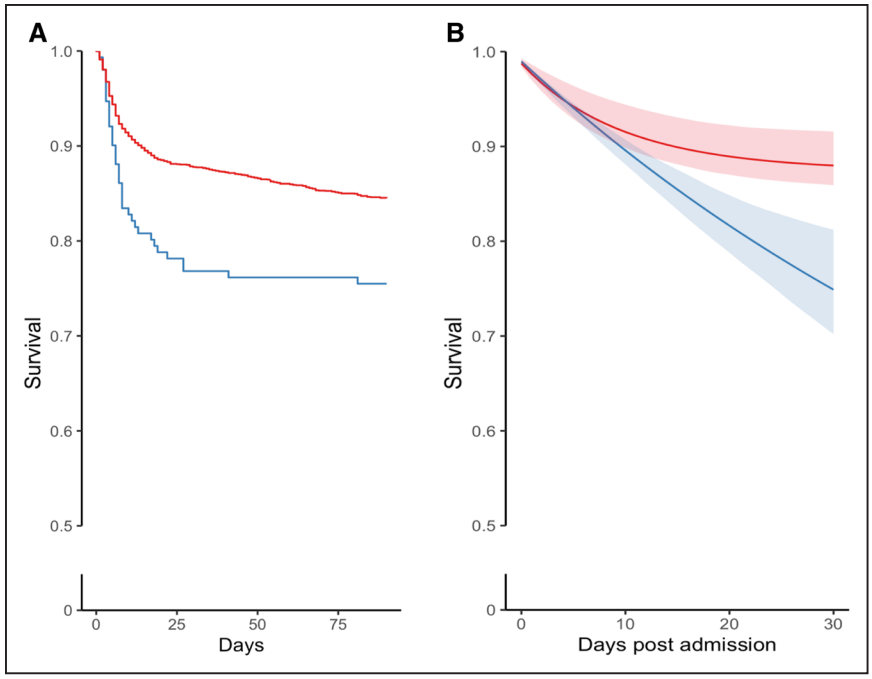

Figure 2. Crude and standardized survival curves by seizure prophylaxis initiation strategy during the first 30 d poststroke admission. **A**, Blue: antiseizure drugs (ASD) initiated within 7 d post-acute ischemic stroke (AIS) admission; and Red: ASD not initiated within 7 d post-AIS. **B**, Blue: Strategy for ASD initiation within 7 d post-AIS admission; and Red: Strategy for no initiation of ASD within 7 d post-AIS admission. Shaded areas: 95% CIs constructed using bootstrap with 500 replications.

should be "avoid[ed] unless safer alternatives are not available; avoid antiepileptics except for seizure and mood disorders."[36] However, there have been no well-designed randomized clinical trials with sufficient sample size to address the safety and effectiveness of ASDs during the acute stage of AIS among older adults.[37–41] Specifically, there is some understanding of seizure prophylaxis after specific stroke types: spontaneous intracerebral hemorrhage,[37,42] intracerebral hemorrhage,[43] subarachnoid hemorrhage,[44] cryptogenic stroke,[45] and least assessed, ischemic stroke.[40]

This study was motivated by the limitations of existing guidelines regarding which type of patients could benefit from seizure prophylaxis within the early symptomatic stroke recovery period and which type of patients could experience adverse effects from this treatment.[14,46] Seizures and seizure-like events are considered AIS symptoms (ie, symptomatic seizures), and prophylaxis may be unnecessary unless they recur after the acute AIS recovery period is over (ie, post-AIS epilepsy, by definition).[11,47,48]

The most examined ASDs have been levetiracetam,[37,39,40] valproic acid,[38] and sodium valproate,[41] with an urgent need to evaluate the safety and effectiveness of newer drugs such as lacosamide, carbamate, brivaracetam, vigabatrin, and eslicarbazepine.[49] Evidence shows the side effects of levetiracetam are as follows: behavioral disturbances (eg, anxiety, anger, and depression), nausea/vomiting, infections, somnolence, and fatigue that may precipitate fall-related injuries.[50] Additionally, documented phenytoin side effects include ataxia, incoordination, arrhythmia, cognitive impairment, and acute skin allergic reactions.[51] While ASDs might cause adverse reactions with potential long-term effects, their benefit may be limited, especially when used in the very short term (eg, 85% of the patients who were started on ASDs had stopped it in the first 7 days in this study).

Strengths

Our approach has several important strengths when compared to previous studies in the presence of staggered treatment initiation.[52–55] For instance, rather than moving the start of follow-up for the ASD group to the time of treatment initiation, we aligned time-zero for exposed and reference groups, thus comparing the same periods post-AIS, which is critical because there is substantially more significant mortality in the first day.

To address confounding and improve precision, we linked multiple data sources over numerous years, incorporating granular measurements of baseline variables and time-dependent covariates up to treatment strategy assignment and statistical methods of addressing time-dependent confounding.[20] Lastly, there were no losses to follow-up since we had information on mortality, even when the patient stopped using the health care system.

Limitations

Residual Confounding

Our crude versus standardized analysis showed that confounding was present in this setting. Residual confounding by unmeasured factors associated with prescribing ASDs could still explain some of the observed associations.

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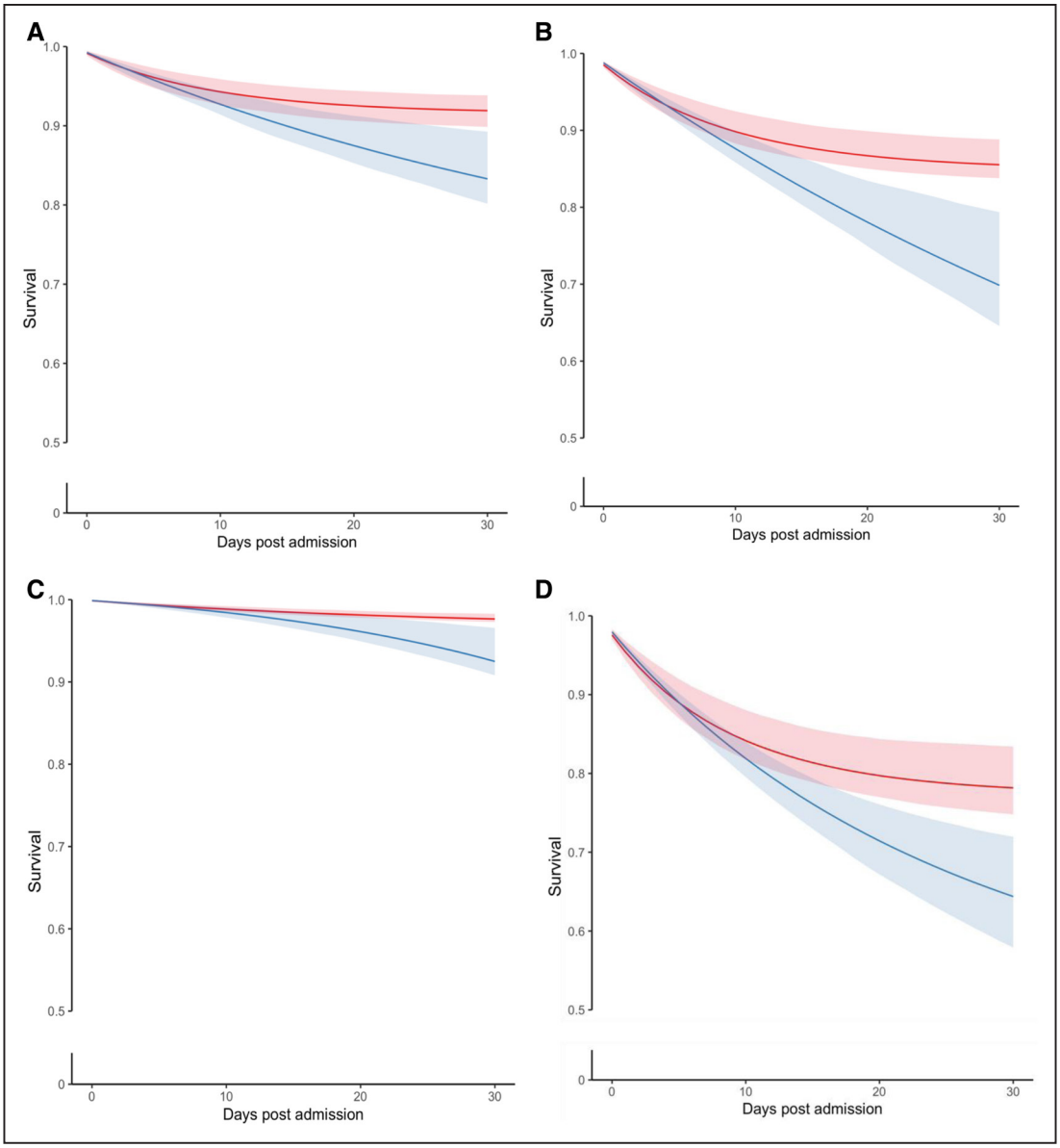

Figure 3. Standardized survival curves by antiseizure drugs (ASD) initiation strategy across categories of age and stroke severity. Blue: Strategy for ASD initiation within 7 d post-acute ischemic stroke (AIS) admission. Red: Strategy for no initiation of ASD within 7 d post-AIS admission. Shaded areas: 95% CIs constructed using bootstrap with 500 replications.

Generalizability

Our single-center study based on a large academic institution in a region with a predominantly white, non-Hispanic, and insured population might have favored the selection of those patients with greater previous use of the health care system. We favored the latter in the tradeoff between generalizability and internal validity by obtaining rich baseline data from those using health care to control for confounding. From our results, we observed that the primary use of antiseizure medication in this study cohort was seizure prophylaxis. Determining the duration and dosage of ASD prophylaxis is not part of the scope of this study, as our data was sparse and limited the type of analysis we could perform. We will apply this methodology in a larger, linked dataset to perform sensitivity analysis and increase the study's external validity by increasing its generalizability and representativeness.

Power

Our sample's overall mortality risk was low, especially in the mild stroke severity subset. Our mortality results represent the lower bounds of exposure patterns and outcome effects than other practice patterns.[56] This is partly because this study took place in a certified Advanced Comprehensive Stroke Center that aims to treat patients with AIS with the highest quality of care. Lastly, even though we were able to obtain accurate death dates, examining the cause of death for each patient was out of scope for this study. The cause of death is worth investigating further in future studies.

Conclusions

This study examined the 30-day mortality risk associated with the initiation of seizure prophylaxis within 7 days after an AIS in patients ≥65 years. Our findings suggest that any net-benefit is likely small and insufficient to support a role for short-term seizure prophylaxis in reducing poststroke mortality.

ARTICLE INFORMATION

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Supplemental Material

Supplemental Text
Figures S1–S3
Tables S1–S8
Statistical Code
References 6,19–21,23–25,27–30,47,48,52–55,57–70

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