RESEARCH ARTICLE

Benzodiazepine Initiation and the Risk of Falls or Fall-Related Injuries in Older Adults Following Acute Ischemic Stroke

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Abstract

Background and Objectives

Benzodiazepine (BZD) use in older adults after acute ischemic stroke (AIS) is common. We aimed to assess the risk of falls or fall-related injuries (FRIs) in older adults after the use of BZDs during the acute poststroke recovery period.

Methods

We emulated a hypothetical randomized trial of BZD use during the acute poststroke recovery period using linked data from the Get With the Guidelines Stroke Registry and Mass General Brigham's electronic health records. Our cohort included patients aged 65 years and older with an AIS admission between 2014 and 2021, no documented previous stroke, and no BZD prescriptions in the 3 months before admission. The potential for immortal time and confounding bias was addressed separately using inverse probability weighting.

Results

We analyzed data from 495 patients who initiated inpatient BZDs within 3 days of admission and 2,564 who did not. After standardization, the estimate was 694 events per 1,000 (95% CI 676–709) for the BZD initiation strategy and 584 events per 1,000 (95% CI 575–595) for the noninitiation strategy. Subgroup analyses showed risk differences of 142 events per 1,000 (95% CI 111–165) and 85 events per 1,000 (95% CI 64–107) for patients aged 65–74 years and 75 years and older, respectively. Risk differences were 187 events per 1,000 (95% CI 159–206) for patients with minor (NIH Stroke Severity Scale score $\leq$ 4) AIS and 32 events per 1,000 (95% CI 10–58) for those with moderate-to-severe AIS.

Discussion

Initiating BZDs within 3 days of an AIS is associated with an elevated ten-day risk of falls or FRIs, particularly for patients aged 65–74 years and for those with mild stroke. This underscores the need for caution when initiating BZDs, especially among individuals likely to be ambulatory during the acute and subacute poststroke period.

MORE ONLINE

Supplementary Material

Introduction

In the United States, stroke is a leading cause of morbidity[1] and predominantly affects older adults (aged 65 years and older).[2] Stroke has an increasing prevalence (7.8%)[1] and can lead to poststroke seizures (with an incidence of 2%–23% and 3%–67% for early and late poststroke seizures, respectively)[3] and poststroke depression (with a cumulative incidence of 38% in the first year after stroke).[4] Other complications of stroke include swelling of the ischemic tissue

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causing mass effect (which can subsequently lead to sudden apnea from brainstem compression and cardiac arrhythmias) and insomnia.[5,6]

Benzodiazepines (BZDs) are often used to manage insomnia, depression, and anxiety.[7,8] However, guidelines warn against BZD use among older adults because these can interfere with poststroke recovery (i.e., may increase hemiparesis produced by small motor cortex lesions),[9,10] exacerbate adverse events (e.g., falls and FRIs),[11-13] and potentially reinduce neurologic deficits in patients who have experienced transient ischemic attacks.[14] This risk is amplified in older adults when polypharmacy, acute brain injury, gait disorders, or depression is present.[7,15] Among patients with acute ischemic stroke (AIS), falls and fall-related injuries (FRIs) have incidence rates of 0.88 per person-year and 2.8 per 100 person-years, respectively,[16] thus contributing significantly to medical emergencies and loss of independence.[17]

While falls, FRI risks, and impaired recovery are associated with BZD use,[8,11,18] guidelines must be strengthened with accurate, evidence-based data and the use and safety of short-term BZD in an acute clinical setting must be assessed.[9,10,13,14,17] We used a range of novel analytical methods[19,20] to evaluate fall and FRI risks after short-term inpatient use of BZDs in the immediate post-AIS recovery period among adults aged 65 years and older.

Methods

This study was approved by the Institutional Review Board (IRB) of Mass General Brigham (MGB), and informed consent was waived. The data supporting the findings of this study are available from the corresponding author on reasonable request and institutional approval. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[21]

Study Design and Treatment Strategies

To mitigate the influence of confounding and selection biases in the context of nonrandomized studies, we used a target trial methodology to emulate a pragmatic randomized clinical trial to assess the effect of short-term inpatient BZD use on both inpatient and outpatient falls or FRIs.[20,22,23]

The target trial involved random assignment of eligible patients on admission for AIS to one of 2 arms: (1) treatment with BZDs within the window extending from AIS admission to the third day after admission or discharge date (should discharge happen before the third day); (2) a control arm in which no BZDs were given within the defined window extending from AIS admission to either the third day after admission or discharge, whichever occurred first.

We assessed the primary outcome of a fall or FRI during a ten-day follow-up period starting from the day of hospital admission. Further details regarding the analysis proposed to emulate this target trial are presented in Table 1.

Data Sources

We leveraged the American Heart Association's Get With The Guidelines (GWTG) Stroke Registry to identify eligible patients.[24] The GWTG collects demographic, medical history, and clinical data, including stroke severity (as defined by the validated National Institute of Health Stroke Severity Scale [NIHSS]).[25-27] We identified eligible patients and then linked GWTG data to each patient's electronic health record (EHR) from the MGB health care system to obtain additional patient information, including health care utilization data (i.e., diagnoses, procedures, and outpatient and inpatient drug administration).[28] We completed data quality checks for each patient discharged with a stroke diagnosis.[24] We used the MGB Research Patient Data Repository (RPDR) to extract BZD descriptions.[29] RPDR is a clinical data registry within the MGB system, and it details inpatient drug administration and outpatient drug prescriptions recorded during a visit or listed in the medication record at the time of medication reconciliation.[28]

Study Population and Eligibility Criteria

We identified 3,532 patients aged 65 years and older admitted to Massachusetts General Hospital (MGH) for an AIS between January 1, 2014, and June 28, 2021, with no recorded diagnosis of AIS in the previous 12 months. We excluded 35 patients with no demographic information and 10 with missing encounter records. We excluded additional 269 patients with no recorded NIHSS score at admission. Patients with missing NIHSS scores at admission had been transferred to MGH from another hospital one or more days after the initial cerebrovascular event.[30] We also excluded patients with one or more recorded prescriptions of BZDs within 3 months before admission. The final eligible sample consisted of 3,059 patients (Figure 1). We list patient characteristics stratified by the BZD initiation strategy in Table 2.

BZD Exposure and Treatment Assignment Procedures

In the target trial emulation, we obtained information on BZD use from inpatient and outpatient pharmacy data. The BZD list can be found in eTable 1 in the Supplementary Materials.

Data analysis must account for the specified immortal time and confounding bias in the target trial.[31] Immortal time bias occurs if there is a time gap between AIS admission and the initiation of BZD treatment, during which the patient must survive to receive treatment. By contrast, confounding bias arises from the absence of randomized treatment assignment within the study sample, potentially distorting the observed treatment effects. We "cloned" patients to address these issues, duplicating each patient's data.[22,23,31] We assigned the treatment the original patient did not receive to the corresponding clone, thus creating a balanced comparison between the 2 treatment arms. This approach doubles the data

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

Target trial	Emulated trial (observational study)
Eligibility criteria	
Admission for cerebrovascular accident between 01/01/2014 and 06/28/2021 at MGH	Same
Age 65 and older	Same
Confirmed AIS	Same, and exclude those without NIHSS scores recorded at hospital admission
No history of AIS in the past 12 mo	No recorded diagnosis of AIS in the past 12 mo
No use of BZDs in the past 3 mo	No recorded prescription of BZDs in the past 3 mo
Treatment strategies	
Treatment arm: initiate BZD[a] within a defined window extending from AIS admission to either discharge or the third d after admission, whichever occurs first	
Control arm: refrain from giving BZDs within the defined window extending from AIS admission to either discharge or the third day after admission, whichever occurs first	Same
Assignment procedures	
Open-label, randomized treatment assignment	Emulated randomization[b]
Outcomes	
Time to fall or fall-related injury from the d of AIS admission	Same. Time to fall or fall-related injury as determined by NLP algorithms
Follow-up	
Starts at randomization (at admission)	Starts at admission
Ends at date of fall or fall-related injury, death, or end of study (i.e., 10 d after admission including the admission d), whichever occurs first	Ends at date of fall or fall-related injury, death (as recorded in the EHR and/or GWTG Stroke Registry), or end of study (i.e., 10 d after admission including the admission d), whichever occurs first
Causal contrast	
Intention-to-treat effect	Observational analog of intention-to-treat effect[c]
Statistical analysis	
Intention-to-treat effect analysis of time to fall or fall-related injury, accounting for censoring	Same, further accounting for baseline confounding

Abbreviations: AIS = acute ischemic stroke; BZD = benzodiazepine; EHR = electronic health record; GWTG = Get With The Guidelines; IPCW = inverse probability of censoring weighting; MGH = Massachusetts General Hospital; NIHSS = NIH Stroke Scale.
[a] Benzodiazepine: listed in eTable 1 of the Supplementary Materials.
[b] Emulated randomization by balancing confounders using IPCW for treatment selection. Additional statistical analysis details are given in Methods to address immortal time bias.
[c] Analysis can be consistent with "intention-to-treat" (concerning treatment assignment as a strategy [treat vs not]). However, the effect can also be analogous to the "per-protocol" (when treatment strategy is considered a "protocol" that must be followed over time [the grace period]).

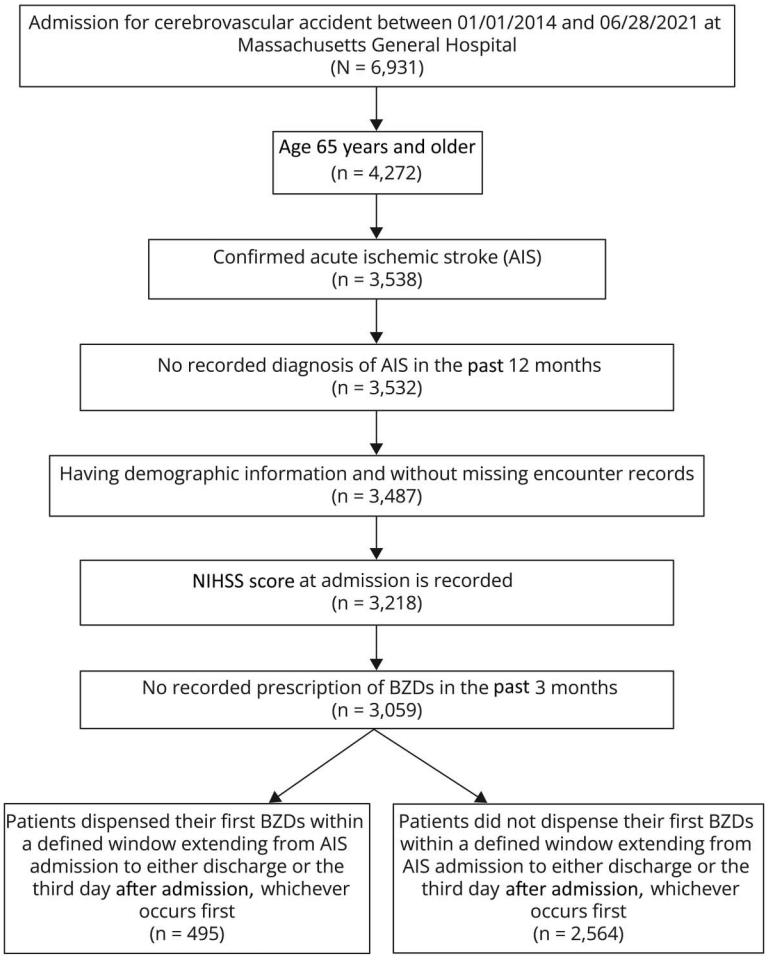
set size and ensures that baseline confounders are equally distributed across both arms. To account for this artificial duplication, person-time for each patient/clone is censored if the treatment deviates from the assigned treatment.

For example, if a patient received BZD during the exposure period, their clone would have been initially "assigned" to the control arm, with their person-time censored at the time BZD by the patient was initiated.[23,31,32] This approach ensures alignment of eligibility, start of follow-up, and assignment to a treatment strategy, and patients can be represented in both arms until treatment can be determined. As such, baseline confounding bias has been addressed. We provide details of the cloning method in eFigure 1 and eMethods 1 in the online Supplementary Materials.

Covariate Adjustment to Account for Artificial Censoring

Although the cloning method ensures that the baseline confounding factors are balanced, the artificial censoring itself may introduce time-dependent selection bias, which can be addressed with the inverse probability of censoring weighting (IPCW).[33,34] The variable selection in the IPCW model is guided by clinical relevance, a preliminary analysis assessing the balance between the BZD initiation group and

Figure 1 Selection of Eligible Patients With New Acute Ischemic Stroke (AIS) Aged 65 Years and Older, 2014–2021



The sampling process resulted in a sample of 3,059 patients, including patients aged 65 years and older at the time of new acute ischemic stroke admission, with available data in the electronic health record system, and who had not received benzodiazepine in the 3 months before admission. AIS = acute ischemic stroke; BZD = benzodiazepine.

noninitiation, and the model selection criteria using the Akaike Information Criterion (AIC). As a measure of stroke severity at baseline, we chose the NIHSS, a summary severity measure strongly associated with drug initiation.[26,27] It is important to note that the NIHSS score was reliably assessed, measured, and documented on hospital admission (study time zero), making it an ideal baseline for use in the weights. An NIHSS score ≤ 4 indicated mild stroke, and an NIHSS score > 4 indicated a moderate-to-severe stroke.[25-27] Note that data for individual items on the NIHSS, such as lower extremity strength, are not available in the data set used for this study. We also used age and time-varying characteristics, including time after AIS and daily neurophysiology monitoring with an EEG .[30]

Results from EEG can influence the decision to start medications, especially those with antiseizure activity. EEG monitoring also questionably improves the probability of survival by diagnosing subclinical seizures or status epilepticus. We have built baseline and time-varying variables for EEG performed, along with the duration of EEG monitoring (e.g., EEG routine vs prolonged 12–24 h monitoring).[30]

This data set contains daily EEG information, including EEG codes, types, and procedure names. We precisely obtained a baseline EEG measure with the count of EEGs obtained 6 months before the stroke admission date. We created a time-varying EEG variable for each day. If a patient had prolonged EEG monitoring (e.g., 24–48 hours), the measure would reflect the days of monitoring. If the patient had a routine EEG (e.g., <2 hours), we marked that day as 1 day of EEG surveillance and resumed the search for other codes on a subsequent day. Statistical analysis details in the Supplementary Materials provide the steps to perform the IPCW method (eMethods 1).

Follow-Up and Outcome Measures

Patients were followed from AIS admission to the earliest of the following events: the date of inpatient or outpatient fall or FRI, or right censoring, which includes death as recorded in the EHR and GWTG Stroke Registry or the end of study (i.e., 10 days after admission including the admission day).

To accurately detect inpatient and outpatient falls or FRIs from various unstructured clinical notes, we used a validated

Table 2 Characteristics of Patients Stratified by Benzodiazepine Initiation

	Benzodiazepine initiator (N = 495)	Noninitiators (N = 2,564)	SMD
Age, mean (SD)	78.03 (8.65)	78.10 (8.45)	0.009
Female (%)	283 (57.2)	1,265 (49.3)	0.158
Race (non-White) (%)	55 (11.6)	425 (17.3)	0.164
Ethnicity (Hispanic) (%)	7 (1.5)	35 (1.4)	0.004
Medicare (%)	395 (79.8)	2072 (80.9)	0.027
Prescription count, mean (SD)	6.75 (24.74)	5.09 (19.43)	0.075
Prescription count by amount[a] (%)			0.121
No prescription recorded	361 (72.9)	1913 (74.6)	
1–4 drugs	46 (9.3)	289 (11.3)	
5–9 drugs	23 (4.6)	113 (4.4)	
>9 drugs	65 (13.1)	249 (9.7)	
Baseline characteristics (%)			
Charlson Comorbity Score, mean (SD)	0.98 (1.65)	1.07 (1.67)	0.055
Dementia	17 (3.4)	86 (3.4)	0.004
Sleep disorder	15 (3.0)	60 (2.3)	0.043
Restlessness	2 (0.4)	8 (0.3)	0.015
Anxiety	34 (6.9)	105 (4.1)	0.122
Claustrophobia	0 (0.0)	1 (0.0)	0.028
Delirium	9 (1.8)	45 (1.8)	0.005
Hospitalization[b]	92 (18.6)	580 (22.6)	0.100
ED[b]	55 (11.1)	264 (10.3)	0.026
Fall or fall-related injury[c]	103 (20.8)	625 (24.4)	0.085
Seizure-like events	23 (4.6)	146 (5.7)	0.047
DVT	21 (4.2)	123 (4.8)	0.027
AP	19 (3.8)	122 (4.8)	0.045
EEG (routine)	6 (1.2)	19 (0.7)	0.048
EEG (long term)	3 (0.6)	12 (0.5)	0.019
NIHSS scores by categories[d] (%)			0.292
Minor (0–4)	213 (43.0)	1,287 (50.2)	
Moderate (5–15)	135 (27.3)	814 (31.7)	
Moderate to severe (16–20)	61 (12.3)	240 (9.4)	
Severe (>20)	86 (17.4)	223 (8.7)	
NIHSS score median (IQR)	6.0 (2.0–18.0)	4.0 (2.0–12.0)	0.262
NIHSS score mean (SD)	9.75 (9.18)	7.54 (7.65)	

Abbreviations: AIS = acute ischemic stroke; AP = aspiration pneumonia; DVT = deep vein thrombosis; ED = emergency department; IQR = interquartile range; NIHSS = NIH Stroke Scale; SMD = standardized mean difference.
Characteristics of patients stratified by benzodiazepine initiation within a defined window extending from AIS admission to discharge or the third day after admission vs nonbenzodiazepine initiation within a defined window extending from AIS admission to discharge or the third day after admission. We included the baseline Charlson Comorbidity Score and conditions.
[a] No benzodiazepines were included in any prescription count category. If a patient did not have any prescription recorded, the prescription information was either (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 (e.g., over-the-counter or prescribed and recorded in another health care system), or (4) other unknown reasons.
[b] ED visits and hospitalizations recorded for patients; these might not be directly related to falls, FRIs, or benzodiazepine prescriptions.
[c] Baseline fall-related injuries are measured using a validated NLP model.
[d] NIHSS scores recorded at admission to measure AIS severity.

natural language processing (NLP) model, RoBERTa.[19] Specifically, outpatient falls were identified from evaluation and management visits with selected professional service types, including surgery, office/home, preventive physical examinations, and urgent care visits. This model was applied daily to all notes for each patient in our study sample, determining whether the patient experienced a fall or FRI on that day. This process was repeated for each day of the observation period. Using a held-out benchmark evaluation data set, our NLP model has been validated explicitly for fall detection during acute hospitalizations within this population. The model demonstrated high accuracy, with a precision of 0.90 (95% CI 0.88–0.91), a recall of 0.91 (95% CI 0.90–0.93), and an F1 score of 0.90 (95% CI 0.89–0.92).[19] In addition, it showed excellent area under the receiver operating characteristic and area under the precision-recall curves, with scores of 0.96 (95% CI 0.95–0.97).[19] Additional details are available in the supplementary text (eMethods 1).

We extracted death dates from the EHR Demographics data file (Death Master File). Given that MGB updates the deaths of patients monthly with data from the Social Security Administration, deaths were captured even if the patient was transferred into a nursing home or another non-MGB facility.

Statistical Analysis

We emulated a hypothetical randomized trial and evaluated the effect of BZD initiation within the defined post-AIS exposure period on ten-day falls or FRIs. The general principle of trial emulation is using observational data to mimic a target trial to answer the causal effect of inpatient BZD initiation on the risk of falls or FRIs in older adults.[20,22] Steps to emulate a target trial include the following: (1) specify the protocol of the target trial as in Table 2; (2) expand the original data by creating clones and artificially censor the clones as previously described; (3) weigh the expanded data by stabilized IPCW to account for artificial censoring; (4) model the survival probability of a fall or FRI to estimate the causal contrast.

To estimate the stabilized IPCW in Step (3), we used pooled linear logistic regressions over person days, including age, NIHSS score, daily use of neurophysiologic monitoring (EEG), days after AIS admission, and potential interactions between them, separately for the 2 treatment strategies. To estimate the survival probability in Step (4), we used the expanded weighted data to fit a pooled logistic regression model for falls or FRIs as a function of the following covariates: treatment strategy, time (measured in days after AIS admission), a quadratic term of time, and an interaction term of treatment strategy and time to allow for time-varying effects. These variables were chosen based on their clinical relevance and the smallest AIC value. We obtained estimated survival probabilities for each day under each treatment strategy and estimated the ten-day fall or FRI risk difference. Specifically, *pooled logistic regression* pools observations over multiple time points into 1 sample, and logistic regression is used to relate the risk factors (i.e., covariates) to the occurrence of a fall or FRI. Previous literature has demonstrated that the pooled logistic regression is close to the time-dependent covariate Cox regression analysis.[35]

For comparison, we estimated the unadjusted Kaplan-Meier and cubic spline model–based survival probabilities of falls or FRIs in the 10 days using the cloned data set. Here, "unadjusted" implies using the expanded data without adjusting for variables except for time without weighting by stabilized IPCW. Consequently, the results are biased because of insufficient consideration for artificial censoring. eFigure 1 shows the cloning method. Additional analysis considering the potential different inpatient and outpatient risks of falls or FRIs is provided in eMethods 2 in the Supplementary Materials. Other technical details, including CI calculations, are provided in eMethods 1.

Missing Data and Preplanned Stratified Analysis

We examined missing data patterns for all relevant variables to confirm that the analysis had minimal missing information with less than 5% missingness on all variables.[29,30] The sedating effects of BZDs on ambulation might be more pronounced among AIS survivors who can walk during the early days of recovery (e.g., those with mild AIS) and are at risk of falls or FRIs. In addition, BZDs may be more detrimental to older patients. Therefore, we repeated the analyses given above, stratifying by NIHSS categories and age. We also conducted 2 secondary analyses related to the length of follow-up, specifically at 8 and 30 days after admission (eMethods 2).

Standard Protocol Approvals, Registrations, and Patient Consents

This study was conducted with the approval of our IRB under protocol number 2017P001146.

Data Availability

Requests for access to deidentified individual patient data may be submitted to the study investigators. All data access proposals must first receive approval from our institution and undergo evaluation by an independent review panel to ensure compliance with ethical and regulatory standards. On approval, a data sharing agreement could be established to govern the responsible use of the data.

Results

Study Population Characteristics

Among patients aged 65 years and older, 3,059 were eligible for the emulated target trial. Of those, 495 (16%) initiated a BZD within the third day after admission or discharge, whichever occurred first. Table 2 presents the demographic and clinical characteristics stratified by BZD initiation strategies. The most frequently prescribed BZD was lorazepam (86%, eTable 2). The mean length of stay was 6.6 days, with a median of 5 days (interquartile range [IQR]: 3–8).

Outcome: Falls or FRIs

We obtained standardized survival functions averaging over the distribution of covariates for the selected population after cloning by BZD initiation strategies for all 3,059 eligible patients during the first 10 days after AIS admission (Figure 2). After target trial emulation with cloning, the unadjusted Kaplan-Meier 10-day risk of falls or FRIs was 530 events per 1,000 patients among those under the BZD initiation strategy and 561 events per 1,000 patients under the noninitiation strategy. Among all patients, 276 deaths were captured. There was no loss to follow-up in this study. eFigure 2 displays the unadjusted Kaplan-Meier and cubic spline model–based survival probabilities of falls or FRIs in the 10 days using the cloned data set.

After target trial emulation with cloning and adjustment for artificial censoring, the standardized ten-day risk of falls and FRIs was 694 events per 1,000 (95% CI 676–709) for those under the BZD initiation strategy and 584 events per 1,000 (95% CI 575–595) for those under the noninitiation strategy, resulting in a risk difference of 110 events per 1,000 patients (95% CI 89–125).

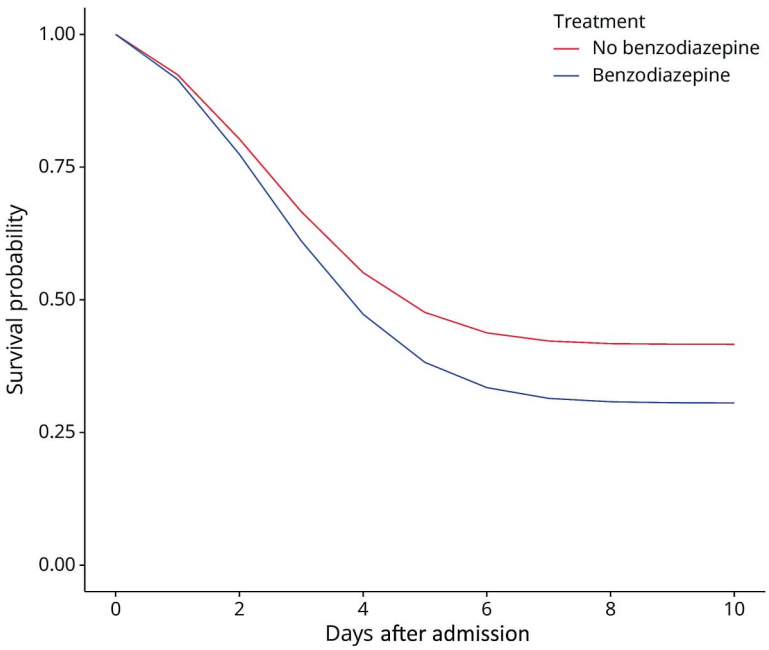
Among patients with AIS aged 65–74 years and those aged 75 years or older, the 10-day risk differences were 142 events per 1,000 patients (95% CI 111–165) and 85 events per 1,000 patients (95% CI 64–107), respectively (Figure 3). Among patients with AIS with minor AIS (NIHSS score $\leq$ 4) and moderate-to-severe AIS (NIHSS score $>$ 4), risk differences were 187 events per 1,000 patients (95% CI 159–206) and 32 events per 1,000 patients (95% CI 10–58), respectively (Figure 4). The standardized ten-day risks of falls or FRIs stratified by age and NIHSS scores are displayed in eTable 3 in the Supplementary Materials. The outcome model parameter estimates are summarized in eTable 4.

Repeating the analysis with eight-day and thirty-day follow-up windows yielded similar results, consistent with an excess of standardized risk of falls or FRIs associated with initiating BZDs. Considering that the inpatient and outpatient risk of falls or FRIs could differ, we repeated the analysis by adding a time-varying discharge indicator in the outcome model with a ten-day follow-up window. The results seemed to be consistent with the main result in the article, as described in eMethods 2 in the Supplementary Materials (which also includes eTables 5–8 and eFigures 3–11). eAppendix 1 provides the statistical code used for the primary analysis.

Discussion

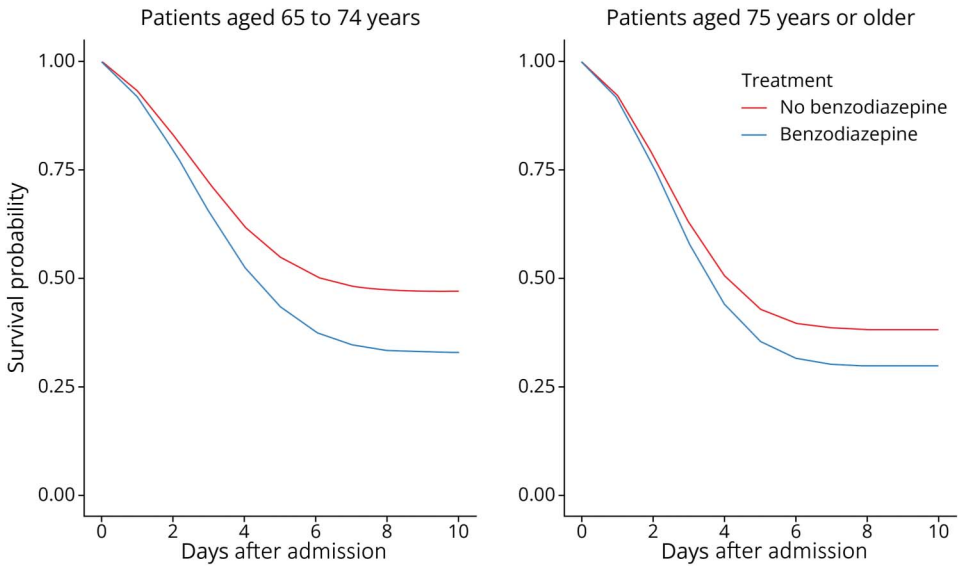
Assessing the safety of short-term BZD usage during the acute AIS recovery phase using a randomized trial (i.e., the target trial) is not feasible, ethical, or timely. Thus, we emulated the target trial, and the observational data yielded exact effect estimates as a target trial would have, except for random variability. To assess the incidence of falls or FRIs, our study emulated a hypothetical randomized trial of inpatient BZD use among older adults during the acute post-stroke recovery period. We estimated 110 more events per 1,000 patients in the BZD initiator strategy group. Our findings indicate a robust causal effect linking BZD use to falls and FRIs.[23]

Figure 2 Standardized Survival Curves by Benzodiazepine Initiation Strategy



Pooled logistic regression survival curves for all patients. Blue: strategy for benzodiazepine initiation within 3 days after AIS admission (or discharge). Red: strategy for no initiation of benzodiazepine within 3 days after AIS admission. Shaded areas: 95% CIs constructed using bootstrap with 500 replications.

Figure 3 Standardized Survival Curves by Benzodiazepine Initiation Strategy Across Categories of Age



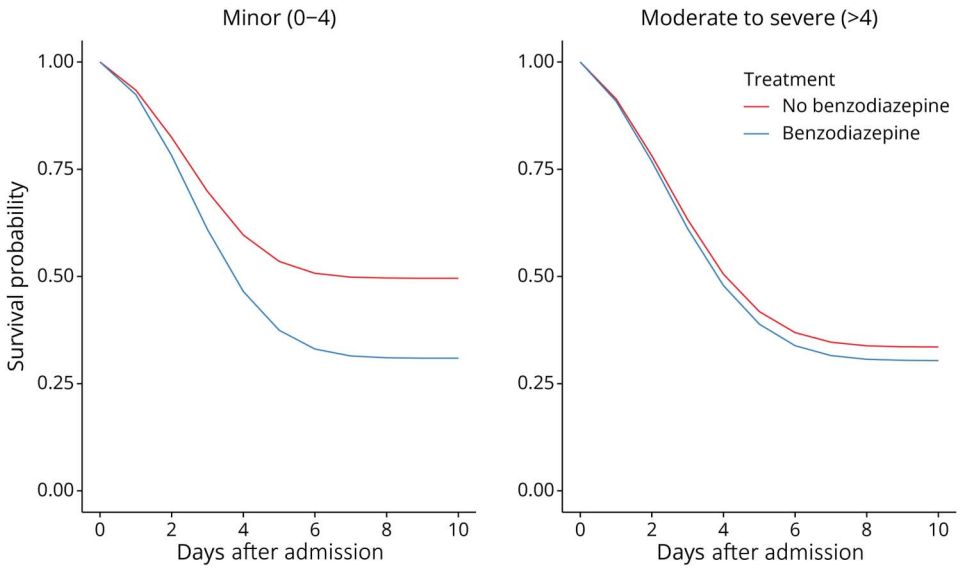
Blue: strategy for benzodiazepine initiation within 3 days after AIS admission (or discharge). Red: strategy for no initiation of benzodiazepine within 3 days after AIS admission. Shaded areas: 95% CIs constructed using bootstrap with 500 replications.

We observed higher fall or FRI risk estimates among patients aged 65–74 years, with an excess rate of 142 events per 1,000 patients. Higher fall/FRI risk was also observed among patients with mild stroke (i.e., NIHSS score ≤4), explained by differences in ambulatory status. The ability to walk inherently increases fall risk while being bed-bound reduces it. Older patients using BZDs with brain injuries and who can ambulate are at an increased fall risk because of reduced dexterity and mobility.[15]

This is particularly concerning because guidelines are ambiguous regarding BZD short-term use among older patients (e.g., for periprocedural sedation and severe generalized anxiety in inpatient care).[7,36] Although BZDs may have some protective effects in the poststroke acute phase (i.e., these reduce excitotoxicity),[37,38] their use in the subacute and chronic phases hinders motor recovery.[39] In addition, BZDs can be detrimental to the poststroke recovery period because these may reinduce neurologic deficits and enhance GABAergic inhibition in the brain, which can impede neuroplasticity and the brain's ability to reorganize and make new connections after a stroke.[9,10,14,38]

Given the risks of treatment with BZDs, alternative therapy should be considered for older adults. For example, cognitive

Figure 4 Predicted Pooled Logistic Regression Survival Curves Stratified by NIHSS Scores



Blue: strategy for benzodiazepine initiation within 3 days after AIS admission (or discharge). Red: strategy for no initiation of benzodiazepine within 3 days after AIS admission. Shaded areas: 95% CIs constructed using bootstrap with 500 replications. NIHSS = NIH Stroke Scale.

TAKE-HOME POINTS

- For patients aged 65 years and older, there is a greater likelihood of falls and fall-related injuries (FRIs) if inpatient benzodiazepines are initiated within 3 days of an AIS.
- Similar to what has been noted with chronic use, BZD-associated fall risk for older adults is also significant in the short term, including in the inpatient setting.
- Higher fall or FRI estimates were observed for patients aged 65–74 years, with mild AIS (NIHSS score ≤4), and ambulatory patients.

behavioral therapy and lifestyle changes can benefit patients with stroke struggling with anxiety, depression, and chronic insomnia. Alternative safe drug treatments for poststroke anxiety and depression include selective serotonin reuptake inhibitors, serotonin, and norepinephrine reuptake inhibitors.[39-41] As for insomnia, some sedatives could be considered or treatment with melatonin may provide a safer alternative, especially for patients with sleep-wake cycle disorders.[6]

We captured falls or FRIs from unstructured data rather than relying solely on the International Classification of Diseases (ICD) codes, which have historically underdocumented such events in structured data sets, limiting research validity.[42-45] We used a validated NLP model to identify falls or FRIs within unstructured clinical notes to address this.[19] Our patient selection criteria and comprehensive data registry ensured minimal to no missing data on relevant variables because of patient selection criteria and a detailed data registry.

Limitations

Residual Confounders

The unadjusted analysis yielded results that contrasted with those from the standardized analysis, indicating the presence of multiple confounding factors. For example, when BZDs are used for intubation, they prevent or reduce the risk of falls because sedated patients lack mobility. Using NIHSS admission scores, we assessed stroke severity and conducted stratified analyses to account for the overall clinical picture and its impact on mobility. Another scale used to measure stroke severity and the degree of disability or dependence in daily activities for stroke survivors is the modified Rankin Scale (mRS).[46] The mRS score in our data repository is recorded at discharge rather than admission, and we could not use it as a baseline variable. In addition, the baseline ambulatory data had significant missing data (>20%). Other relevant frailty markers, such as walking speed, gait metrics (e.g., time to stand), and overall strength and energy, would have offered further insights but were unavailable.

Factors associated with BZD use and falls were strongly correlated with baseline stroke severity and comorbidities. For instance, the mRS score and ambulatory status were highly correlated with the NIHSS score ($p < 0.001$), which emerged as the strongest confounder. We used NIHSS score for adjustment because of its reliability and widespread use as a baseline variable in the literature. Adjusting NIHSS scores and relevant comorbidities helps balance other unmeasured confounders. While including additional baseline variables, such as mRS score and ambulatory variables, could reduce variance and improve precision, it would not necessarily enhance the validity of the model because of their strong correlation with NIHSS score. After these adjustments, residual confounding from unmeasured factors is likely minimal.

Although refined, the output of the NLP-based strategy to measure the outcome of interest (falls or FRIs) included the date of documentation but not the specific dates of actual events. For instance, if a fall occurred 1 night, it could have been documented the following day or in the discharge notes. This may introduce misclassification bias concerning time to event, but it is expected to have occurred randomly (independent of treatment strategy). The documentation of remote events is still possible but less likely in this study because we selected a sample with an acute ischemic event and focused our analysis on the inpatient context, where the documentation of remote acute events is less likely to occur. An ideal outcome measure would have integrated the time of the events and when these were documented.

Our data were collected from a large academic institution with a predominantly White, non-Hispanic, and insured patient population, which yielded patients with more considerable recorded health care system utilization. This favored our internal validity and allowed for better confounder control at the expense of generalizability and representativeness. While the demographic characteristics reflect our institution's population, we recognize that outcomes may vary in health care settings or among diverse ethnic backgrounds. Future research should replicate our findings in broader and more diverse populations to enhance the applicability of our results. There is potential for incomplete inclusion, such as patients prescribed BZD outside the MGB system, for whom we lack data. This limitation may affect the generalizability of our findings.

In this study, 495 patients initiated inpatient BZDs within 3 days of admission and 2,564 did not. The imbalance in sample sizes between the 2 groups may reduce statistical power to detect significant differences between the 2 groups. In addition, the estimates from the smaller group (initiators) may have increased variability, which leads to broader CIs around the point estimates.

While the focus of this study is on stroke survivors, specifically after AIS, future studies examining patients admitted for

neurologic (e.g., insomnia, dementia, and anxiety disorders) and non-neurologic (e.g., muscle spasms and alcohol withdrawal) conditions in the acute setting would be impactful and could serve for risk comparison. Future research could examine dose-response effects by incorporating it in the trial emulation framework or analyzing multiple dosage levels. This would require a larger sample size containing clear initiation category definitions, dose switching, and treatment interruption.

This study examined the likelihood of ten-day fall or FRI risk associated with the initiation of inpatient BZD in patients aged 65 years and older within 3 days after an AIS. After standardization, we found a greater likelihood of a fall or FRI within 10 days of admission associated with inpatient BZD being initiated within 3 days of an AIS. This reflects that BZD-associated fall risks are also significant in the short term and highlights the need for new guidelines.

Author Contributions

S. Sun: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. V Lomachinsky: drafting/revision of the manuscript for content, including medical writing for content. L. H Smith: study concept or design. J.P. Newhouse: major role in the acquisition of data. M.B. Westover: study concept or design. D.L. Blacker: study concept or design. L.H. Schwamm: study concept or design. S. Haneuse: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. L.M.V.R. Moura: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design.

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