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ORIGINAL ARTICLE

No short-term mortality from benzodiazepine use post-acute ischemic stroke after accounting for bias

Lidia M.V.R. Moura[a,b,*], Zhiyu Yan[a], Maria A. Donahue[a], Louisa H. Smith[c], Lee H. Schwamm[a,b], John Hsu[d,e,f], Joseph P. Newhouse[d,g,h,i], Sebastien Haneuse[j], Deborah Blacker[c,k,l], Sonia Hernandez-Diaz[c]

[a]*Department of Neurology, Massachusetts General Hospital, Boston, MA, USA*
[b]*Department of Neurology, Harvard Medical School, Boston, MA, USA*
[c]*Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA*
[d]*Department of Health Care Policy, Harvard Medical School, Boston, MA, USA*
[e]*Mongan Institute, Massachusetts General Hospital, Boston, MA, USA*
[f]*Department of Medicine, Harvard Medical School, Boston, MA, USA*
[g]*National Bureau of Economic Research, Cambridge, MA, USA*
[h]*Department of Health Policy and Management, Harvard T.H. Chan School of Public Health, Boston, MA, USA*
[i]*Harvard Kennedy School, Cambridge, MA, USA*
[j]*Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA*
[k]*Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA*
[l]*Department of Psychiatry, Harvard Medical School, Boston, MA, USA*

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Abstract

Background and Objectives: Older adults receive benzodiazepines for agitation, anxiety, and insomnia after acute ischemic stroke (AIS). No trials have been conducted to determine if benzodiazepine use affects poststroke mortality in the elderly.

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* Corresponding Author: Massachusetts General Hospital, 55 Fruit Street, Boston, MA, 02114, USA. Tel.: +1 617 726 3311; fax: +1 617 726 9250.

E-mail address: lidia.moura@mgh.harvard.edu (L.M.V.R. Moura).

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Methods: We examined the association between initiating benzodiazepines within 1 week after AIS and 30-day mortality. We included patients ≥65 years, admitted for new nonsevere AIS (NIH-Stroke-Severity[NIHSS]≤ 20), 2014−2020, with no recorded benzodiazepine use in the previous 3 months and no contraindication for use. We linked a stroke registry to electronic health records, used inverse-probability weighting to address confounding, and estimated the risk difference (RD). A process of cloning, weighting, and censoring was used to avoid immortal time bias.

Results: Among 2,584 patients, 389 received benzodiazepines. The crude 30-day mortality risk from treatment initiation was 212/1,000 among patients who received benzodiazepines, while the 30-day mortality was 34/1,000 among those who did not. When follow-up was aligned on day of AIS admission and immortal time was assigned to the two groups, the estimated risks were 27/1,000 and 22/1,000, respectively. Upon further adjustment for confounders, the RD was 5 (−12 to 19) deaths/1,000 patients.

Conclusion: The observed higher 30-day mortality associated with benzodiazepine initiation within 7 days was largely due to bias.

Keywords: Neurology; Stroke; Mortality; Benzodiazepines; Acute ischemic stroke; Polytherapy

1. Introduction

Acute ischemic stroke (AIS) is a common cause of both short-term mortality and long-term disability in older adults [1]. For those ≥ 65 years, stroke is the second leading cause of hospitalization and carries a 10-fold higher mortality risk compared with younger patients [2]. Benzodiazepines are often indicated for complications and procedures related to stroke care. For instance, poststroke insomnia, periprocedural anxiety, and delirium may complicate stroke hospitalizations and are increasingly treated with benzodiazepines [3−6]. Medical organizations suggest avoiding benzodiazepines in those ≥ 65 years [3−8] because they may cause adverse effects including excessive somnolence and falls [9,10]. Older adults on polytherapy are more sensitive to drug toxicity, as are those with acute brain insults such as an AIS. Since older adults are typically excluded from randomized clinical trials [11,12], the effect of benzodiazepines remains unclear in this population [13,14].

We evaluated the association of benzodiazepine initiation during the acute phase of AIS recovery on 30-day mortality among patients ≥ 65 years. To reduce confounding by indication in the context of a nonrandomized study we restricted to patients with nonsevere AIS and adjusted for clinical and sociodemographic characteristics [15−19]. The study design aligned start of follow-up for treatment groups while accounting for the immortal time between AIS admission and benzodiazepine administration.

2. Methods

2.1. Study design

We used a target trial approach to emulate a hypothetical pragmatic randomized clinical trial [15,16,18,20−23]. Specifying the ideal trial that would answer the research question forces a rigorous conceptualization of the study design components, as well as the assumptions necessary to answer the question using observational data [18]. One potential target trial to answer the question of interest would randomly assign eligible patients at the time of AIS admission to one of two treatment strategies: (a) initiate benzodiazepines at the label-recommended dose regimen within 7 days of admission, or b) no benzodiazepines within the same 7-day post-AIS period. Next, we describe the observational study we conducted to emulate this target trial (Table 1).

2.2. Setting & data sources

We used electronic health records stored in the Mass General Brigham (MGB) system to identify the eligible sample: patients admitted to the Massachusetts General Hospital [24]. These records had data on inpatient diagnoses, procedures, outpatient, and inpatient drug administration. We linked these data to the American Heart Association's Get With The Guidelines (GWTG) Stroke Registry [25]. The GWTG collected patient sociodemographic, health history, and clinical data detailing the stroke admission including stroke severity assessment defined by the validated Stroke Severity scale, NIHSS [26,27]. Each patient discharged from MGB with a stroke diagnosis had their data checked for quality and submitted to the GWTG Registry [25].

2.3. Study population

From January 1, 2014 to December 31, 2020, we identified 3,343 patients ≥ 65 years who were admitted for AIS [25], and had no recorded diagnosis of prior AIS in the last 12 months. We excluded 44 patients without the minimum information in the electronic health records to determine eligibility (NIHSS recorded at admission). We also excluded patients with a diagnosis of myasthenia gravis, a contraindication to benzodiazepines, in the previous 12 months, or who received one or more recorded prescriptions of benzodiazepines in the 3 months before admission. The final eligible sample was 2,584 (Figure 1). Because those with a severe AIS would be most likely intubated and medicated with anesthetics, they would not be suitable

for examining the effect of benzodiazepines on mortality due to respiratory depression or falls. Also, the confounding by indications (for example, procedures, palliative care) would be largest in observational data. Therefore, we restricted the sample to those with an NIHSS $\leq$20, meaning mild, moderate, and moderate-to-severe AIS [24]. We estimated that our study would have a power greater than 80% for any sample size over 250 individuals for any risk difference greater than or equal to 10, given any pooled standard deviation smaller than or equal to 20 and minimum acceptable probability of preventing type I error of 95%.

2.4. Treatment strategies

We defined the following treatment strategies: a) initiate benzodiazepines within 7 days of admission, or b) do not treat with benzodiazepines during these 7 days. In the target trial emulation, we obtained information on benzodiazepine use from inpatient and outpatient pharmacy claims data. Unlike in a randomized trial, we could not know which treatment strategy the patient had been assigned to until the day of the prescription (for those exposed) or 7 days post-AIS (for those unexposed). Therefore, for patients who died within 7 days without initiation, we could not know if they would have received treatment had they not died. Thus, for the 7 days post-AIS, follow-up days until treatment initiation or death count toward both treatment strategies. To carry out such counting, we duplicated the dataset, creating ''clones'' of each patient so that each clone would contribute to both treatment strategies until their strategy is known. The follow-up of a clone is censored when its treatment strategy is violated, that is, clones assigned to no-initiation were censored if they initiated treatment within those 7 days, and clones assigned to initiation were censored if they did not initiate by day seven. At most, one clone remains in the dataset after the first 7 days of follow-up. Lastly, the generated pseudopopulation of clones for each treatment strategy is weighted by inverse probability weights to correct for the fact that the same patient does not adhere to both treatment strategies [28−32]. To mimic randomization, these weights also account for the nonrandom treatment initiation [18,33,34]. This ''cloning-censoring-weighting'' approach has been used in previous studies [28] and avoids a common methodological problem in observational data in the presence of staggered treatment initiation.

2.5. Emulated randomization & 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.

As our measure of stroke severity at baseline, we chose the NIHSS [26,27], a summary measure that has been strongly associated with benzodiazepine initiation and mortality. 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 prior to the AIS using data from 90 days before admission and obtained several sociodemographic measures from the MGB database such as age, sex, race, and ethnicity [35].

As time varying characteristics, during the 7-day window, we used a comprehensive list of clinical and healthcare utilization variables, including inpatient and outpatient visits and pertinent procedures related to AIS management and cumulative in-hospital prescription count (excluding benzodiazepines). Further, we used Comfort-Measures-Only (CMO) status to adjust for adverse outcomes and end-of-life decisions made during the hospitalization but prior to the administration of benzodiazepines that may have influenced the decision to prescribe them. The Supplementary Text and Table B.1 detail each measure of interest, including ICD codes used to identify delirium for the analysis.

2.6. Follow-up & outcome−30-day mortality

Patients were followed from AIS admission for 30 days or until death (Figure A.1). We examined a 30-day mortality because it has been previously endorsed by medical practice societies as a hospital performance measure and has been increasingly used in the context of value-based healthcare assessment and public reporting [36−38]. We extracted death date from the Electronic Health Records (EHR) Demographics data file (Death Master File). MGB updated death data monthly from the Social Security Administration. Deaths were captured even if the patient was transferred to a nursing home or another non-MGB facility (that is, no losses to follow-up).

2.7. Statistical analysis

We first described the characteristics of the eligible sample [39,40]. We obtained naïve crude 30-day mortality estimates for benzodiazepine initiators from treatment during the first-week post-AIS and for noninitiators from AIS admission [41,42].

To evaluate the effect of benzodiazepine 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. To do so, we first estimated inverse-probability weights by modeling treatment initiation in the original dataset, duplicated the dataset to create ''clones'', censored the clones as previously described, and assigned them appropriate weights to rebalance the two groups (cloning-censoring-weighting) [20]. The model for treatment initiation during the grace period was a pooled logistic

Table 1. Description of a randomized trial and the corresponding observational study

Randomized trial specification	Emulation (observational study)
Eligibility criteria	
Admission for cerebrovascular accident between 1/2014 and 12/2020 at Massachusetts General Hospital	Same
Age ≥65	Same
Confirmed acute ischemic stroke (AIS)	Same
Exclude those with severe AIS, as defined by an NIHSS above 20	Same, and exclude those without NIHSS recorded at hospital admission
No previous history of AIS	No recorded diagnosis of AIS in the last 12 months
No benzodiazepines in the last 3 months	No recorded prescription of benzodiazepines in the last 3 months
Treatment strategies	
Treatment arm: Initiate benzodiazepine within 7 days of admission. Control arm: Do not initiate benzodiazepine within 7 days of AIS admission.	Same
Treatment assignment	
Open label, randomized treatment assignment	Emulate randomization by balancing baseline confounders using IPTW for treatment initiation.
Outcomes	
Death during first 30 days	Same. Date of death in EHR (i.e., MGH system[a]) and/or GWTG (Registry data).
Follow-up	
Starts at randomization (at admission) and ends at date of death, or end of the study (that is, 30 days post-AIS admission), whichever occurs first.	Same
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 losses to follow up.	Same, additionally accounting for baseline confounding.[b]

Abbreviations: AIS, acute ischemic stroke; ICD, international classification of diseases; GWTG, get-with-the-guidelines stroke registry; IPTW, inverse probability of treatment weights; MGB, mass general brigham; IPCW, inverse probability of censoring weights.

[a] MGB reliably updates death information from national systems.

[b] Observational analog of intention-to-treat analysis may involve using pooled logistic regression with IPTW and IPCW.

regression over person-days and included age, race, and NIHSS, all measured at admission, and postadmission measures of daily prescription count and CMO status, as well as a time-varying intercept (see Table B.2 for model parameters for estimating benzodiazepine initiation weights). We provide model specifications and additional details on statistical analysis in the Supplementary Text.

In the weighted dataset, we fit a time-varying pooled logistic regression model for death as a function of treatment strategy (that is, an indicator of which strategy a given clone belonged to) and interaction terms between treatment strategy and time, measured in days from admission until the end of the follow-up to allow for time-varying effects. From this model, we predicted mortality probabilities for each day under each treatment strategy [43–45]. We estimated absolute differences in mean 30-day mortality. To illustrate the magnitude of confounding bias beyond the selection or immortal person-time biases avoided by the clone-censor-weight approach we repeated the analysis without confounders in the model for treatment initiation during the grace period (the model corrected only for the duplications in the pseudopopulation of clones).

We later examined the adequacy of this assumption using a visual inspection of the standardized mortality curves. We obtained 95% confidence intervals (CIs) for all measures using the bootstrap with 500 replications.

2.8. Missing data & preplanned stratified analysis

We examined patterns of missingness for all pertinent variables to confirm that the analysis had negligible information. Benzodiazepines may be more harmful to older patients, as well as for patients with moderate-to-severe stroke relative to less severe stroke, as both are more likely to suffer adverse events like falls or intubation after the sedating effects of benzodiazepines. Therefore, we repeated the above analyses stratified by categories of age and NIHSS.

3. Results

3.1. Characteristics of the study population

Among AIS patients ≥ 65 years, 2,584 were eligible for our emulated trial. Of those, 389 initiated a

benzodiazepine within 7 days poststroke. Table 2 describes patient characteristics among benzodiazepine initiators and vs. noninitiators (Table B.3 includes additional time-varying measures). Tables B.4−B.6 show the population characteristics stratified by age and NIHSS category. The most frequently prescribed benzodiazepine was lorazepam (89.16%; Table B.7). 14.81% of the benzodiazepine initiators received a second anticonvulsant on or after the day of benzodiazepine initiation (Table B.8.).

3.2. Outcome−mortality

Figure 2 provides crude and standardized curves for all 2,584 eligible patients, by benzodiazepine initiation strategy during the first 30 days poststroke admission. The crude 30-day mortality counted from treatment initiation was 212 deaths/1000 patients who initiated benzodiazepines within 7 days. The crude 30-day mortality counted from AIS admission was 34/1000 among non-initiators. When further correcting for confounding, standardized 30-day mortality was 27 (95% CI, 12-39) deaths/1000 patients who initiated benzodiazepines and 22 (95% CI, 11-33) per 1000 noninitiators, yielding a risk difference of 5 (95% CI, -12−19) deaths/1000 patients.

Inspection of the curves suggests greater mortality rates for the initiate-benzodiazepine strategy compared to no-initiation, especially early after the admission, although confidence intervals overlap.

Among AIS patients 65−74 years and ≥ 74 years, there were −4 (95% CI -31−11) and 13 (95% CI -23−77) excess deaths per 1,000 patients, respectively. Among patients with moderate-to-severe stroke (NIHSS 16−20), 30-day mortality was 115 (95% CI, 60−297) per 1,000 patients who initiated benzodiazepines and 135 (95% CI, 37−236) deaths per 1,000 patients in the no initiation of benzodiazepine strategy, a difference of −21 (95% CI, −122 to 200) deaths per 1,000. Figures B.2 and B.3 and Tables B.9 and B.10, present the additional standardized survival curves and results, stratified by age groups, and stroke severity, respectively. When CMO determination happened after admission, we accounted for CMO status as a time-varying characteristic. Table B.11 displays this study's compliance with reporting recommendations. The Supplementary Text provides the Statistical Code used to conduct the main analysis.

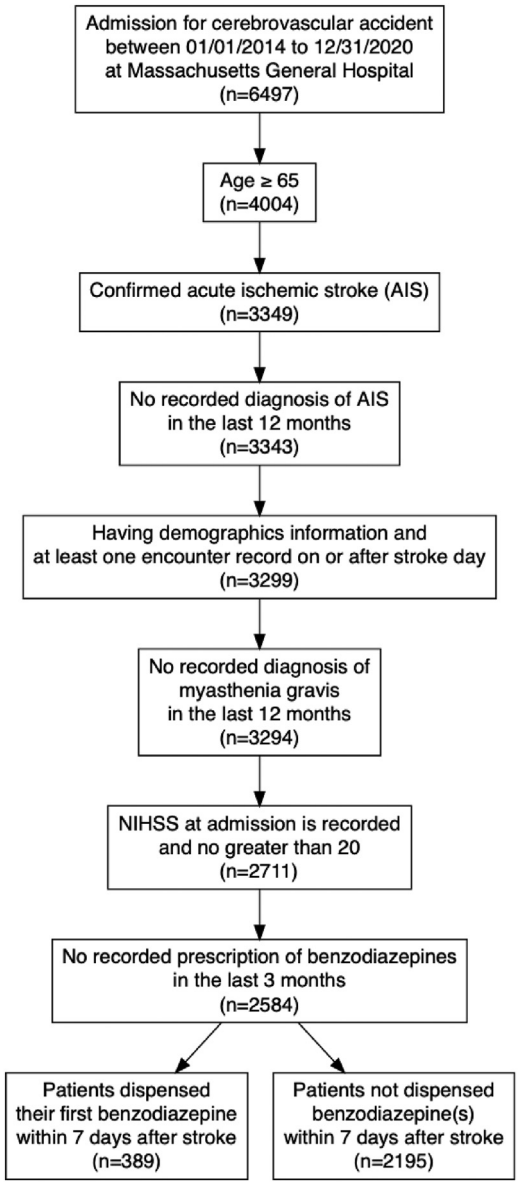

Fig. 1. Selection of eligible patients with new acute ischemic stroke (AIS) ≥ 65 years, 1/2014−12/2020.

Figure 1 describes the sampling process that resulted in a sample of 2,584 subjects, including patients ≥ 65 years, at the time of new acute ischemic stroke admission, patients with available data in the electronic health record system, and patients who had not received benzodiazepines in the months prior to admission.

4. Discussion

In this study, using the information on predictors of benzodiazepine use and mortality among AIS patients ≥ 65 years, the estimated difference in 30-day mortality was reduced from 178 excess cases per 1,000 initiators in the crude naïve analysis to 27 per 1,000 cases after avoiding selection and immortal time biases, to five per 1000 cases after additionally addressing bias from measured confounders.

Benzodiazepine use has been associated with an earlier need for intubation due to oversedation, consequently increasing the risk of hospital-acquired pneumonia and further increasing patient morbidity [46]. However, providers commonly treat anxiety, insomnia, and agitation with benzodiazepines, even among patients at advanced ages, despite growing concerns that these medications could precipitate death and should be avoided in this population [4,47]. Existing guidelines are unclear with respect to which type of patients would be harmed more by benzodiazepines and do not highlight which vulnerable subgroups merit

Table 2. Characteristics of patients, by benzodiazepine initiator vs. nonbenzodiazepine initiator (with start of follow-up aligned at admission)

Characteristics	Benzodiazepine initiator (*N* = 389)	Benzodiazepine noninitiator (*N* = 2,195)	SMD
Socio-Demographic Characteristics (recorded at admission)			
Age, mean (SD)	77.96 (8.32)	77.85 (8.42)	0.013
Female (%)	223 (57.3)	1,038 (47.3)	0.202
Non-White (%)	34 (9.1)	325 (15.7)	0.200
Ethnicity Hispanic or Latino (%)	2 (0.5)	33 (1.6)	0.103
Primary Insurance Medicare or other government (vs. private) (%)	314 (80.7)	1,783 (81.3)	0.015
Baseline Medication Use (recorded during the 90 days before admission)			
Prescription Count, Mean (SD)	7.86 (28.81)	4.45 (17.78)	0.143
Categories of Medication use (%)			0.179
No prescription recorded[a]	275 (70.7)	1,661 (75.7)	
1–4 drugs	38 (9.8)	247 (11.3)	
5–9 drugs	21 (5.4)	89 (4.1)	
>9 drugs	55 (14.1)	198 (9.0)	
Baseline Clinical Characteristics (recorded during 12 months before admission)			
Charlson Comorbidity Score, mean (SD)	1.18 (1.82)	1.09 (1.66)	0.053
Pertinent Comorbid Conditions (%)			
Sleep disturbance, insomnia	14 (3.6)	55 (2.5)	0.064
Anxiety, dissociative, somatoform disorders	24 (6.2)	101 (4.6)	0.070
Baseline Health-Resource Utilization (recorded during 12 months before admission), %			
Hospitalization	85 (21.9)	505 (23.0)	0.028
Emergency Department (ED)	44 (11.3)	227 (10.3)	0.031
Fall-Related Injury (FRI)	42 (10.8)	227 (10.3)	0.015
Seizure-Like Event (SLE)	17 (4.4)	133 (6.1)	0.076
EEG	5 (1.3)	22 (1.0)	0.027
EEG (Long-term)	1 (0.3)	4 (0.2)	0.016
Acute Ischemic Stroke Severity (recorded at admission), %			
NIHSS (mean (SD))	7.06 (6.56)	5.80 (5.66)	0.205
Minor (0–4)	188 (48.3)	1,223 (55.7)	
Moderate (5–15)	131 (33.7)	768 (35.0)	
Moderate-to-severe (16–20)	70 (18.0)	204 (9.3)	

Abbreviations: SD, standard deviation; SMD, standardized mean difference; EEG, electroencephalogram; ED, emergency department; FRI, fall-related injuries; SLE, seizure-like event; NIHSS, national institutes of health stroke severity.

This table describes patient characteristics among benzodiazepine initiators and vs. noninitiators, after standardization by age, race, NIHSS and prescription count on the day of admission.

Mild (0–4), Moderate (5–15), Moderate-Severe (16–20).

[a] No prescription recorded: the prescription information was a) missing from the MGB structured health system data warehouse, b) the patient was not taking any prescription drug, c) the patient was taking prescription drugs given elsewhere (for example, over the counter, prescribed and recorded in other healthcare systems), d) other unknown reason.

special attention [48,49]. Since a clinical trial is implausible, we used real-world evidence to emulate a hypothetical pragmatic trial. Quantifying the effect of benzodiazepines on mortality using observational data is not straightforward because of confounding by indication, as demonstrated by our results in which benzodiazepine initiators had a more severe stroke, were more often CMO, and had more comorbidities and concomitant medication [28].

Benzodiazepine use could affect mortality by affecting complications (increasing or preventing), but also affecting the length of hospitalization (increasing observation), or discharge destination (for example, more likely to a clinical facility). While there was no marginal 30-day mortality risk difference in this study, there could still be potential short-term effects caused by benzodiazepine initiation, such as increased delirium risk, aspiration pneumonia, and other complications. In resource-limited settings, patients may suffer from prescription discontinuation inertia, and medication management strategies could be directed toward those at righter risk for drug utilization. This manuscript describes the populations most at risk of adverse effects caused by benzodiazepine use and challenges further

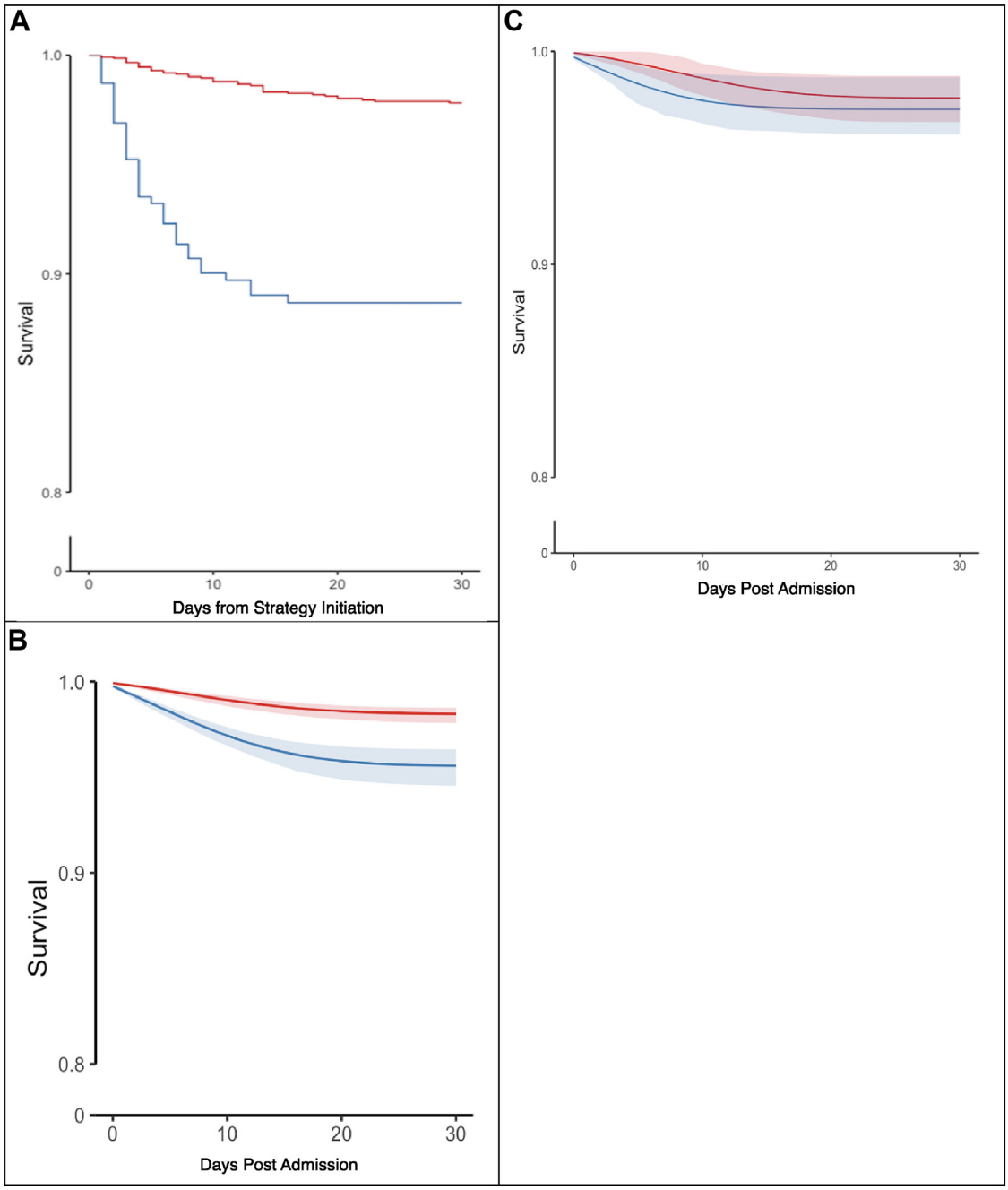

Fig. 2. Crude and standardized survival curves by benzodiazepine initiation strategy during the first 30 days poststroke admission. (A). Crude—naïve crude comparison of 30-day mortality with misaligned time zero [a]. [a] Red: No initiation of benzodiazepine within 7 days post-AIS admission. Blue: initiation of benzodiazepine within 7 days post-AIS admission. (B). Survival curve that fixed the immortal person-time without confounders' standardization [a, b]. [b] Shaded area: 95% confidence intervals constructed using bootstrap with 500 replications. (C). Survival curve fixed the immortal person-time with confounders' standardization [b, c]. [c] This survival curve includes weights for treatment initiation.

studies that could inform current guidelines to ultimately decrease benzodiazepine-related mortality.

4.1. Strengths

Our approach has several important strengths when compared to previous studies in the presence of staggered treatment initiation [29–32]. First, rather than using post-baseline information to define exposure strategies at AIS admission [19], allowed patients to contribute person-time to both treatment strategies during the grace period before they start benzodiazepines or die. [20] This avoids immortal time bias by not counting the time between the start of follow-up and benzodiazepine initiation only in

the exposed group. Second, rather than starting follow-up on day 7, it aligned the start of follow-up at admission for every patient in the study, thus avoiding a biased selection of survivors in the benzodiazepine group. Third, rather than moving the start of follow-up for the benzodiazepine group to the time of treatment initiation, it aligned time-zero for exposed and reference groups, thus comparing the same periods post-AIS, when there is substantially larger mortality in the first days.

To address confounding we linked multiple data sources, incorporating granular measurements of both baseline variables and time-dependent covariates up to treatment strategy assignment, and statistical methods of addressing time-dependent confounding [15]. Lastly, there were no losses to follow-up since we had information on mortality, even after the patient stopped using the healthcare system.

4.2. Limitations

4.2.1. Residual confounding

Our crude vs. standardized analysis on the additive scale showed substantial confounding raising concern about potential residual confounder. Intubation is an indication of benzodiazepines that can be associated with mortality because it is more commonly done for severe patients. We tried to account for severity by restricting to those less severe cases (for example, NIHSS$\leq$20) and by adjusting for stroke severity markers directly (for example, NIHSS, prescription counts, etc.). Specific measures of frailty (for example, unintentional weight loss, exhaustion, low energy expenditure, low grip strength, and/or slowed walking speed) would have been helpful to have for this population. However, variables regarding adverse outcomes or complications such as aspiration pneumonia, DVT, tracheostomy, or percutaneous endoscopic gastrostomy, would have provided additional confounding. The assumption is that after adjustment for several determinants of mortality the residual confounding by unrecorded measures would be minimal.

Among 389 benzodiazepine initiators, 15% received a nonbenzodiazepine anticonvulsant on or after the day of benzodiazepine initiation (Table B.8), consistent with the common indication of periprocedural anxiety or agitation, where use is frequently ‘‘as needed’’, where the medication may or may not be used and where the frequency of administration is more difficult to determine based on documentation in the EHR. Therefore, most measures associated with receipt of benzodiazepine and mortality were highly correlated with baseline stroke severity (for example, CMO), which suggests that adjustment for NIHSS scores is likely adjusting for other unmeasured confounders.

4.2.2. Generalizability

Our inclusion and exclusion criteria might have favored the selection of patients with greater previous use of the healthcare system. In the tradeoff between generalizability and internal validity, we favored the latter by obtaining rich baseline data from those using healthcare to control for confounding. We examined benzodiazepines not typically used for anesthesia (that is, we did not include midazolam infusions in this study); the most frequent benzodiazepines given in our study population was lorazepam (89%). Future studies could examine the mortality effect by drug type, dose, and duration of use in different care settings (inpatient vs. outpatient).

4.2.3. Power

Overall mortality risk was low in our sample, especially in the mild or moderate stroke severity stratum, which generated large confidence intervals. Our mortality results likely represent the lower bounds of benzodiazepine exposure risk in comparison to other settings because our study took place in a certified Advanced Stroke Center that can treat patients with AIS with high quality, despite receiving the most complex cases [3]. The stratified analyses for stroke severity and age subgroups were based on small numbers, and thus confidence intervals were wide. Further efforts are warranted to determine the benefit or harm to older patients from different treatment strategies during the acute and postacute stroke recovery periods.

5. Conclusions

Among patients $\geq$ 65 years, the higher 30-day mortality associated with initiating benzodiazepines within 7 days post-AIS compared to no benzodiazepines was largely due to bias. This study highlights the importance of appropriate methods to address selection and confounding biases.

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Transparency Statement: The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2022.12.013.

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