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RESEARCH ARTICLE

Choice of antiseizure medications and associated outcomes in Medicare beneficiaries after acute ischemic stroke

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Abstract

Objective: We examined choice of outpatient epilepsy-specific antiseizure medication (ESM) after a stroke discharge and outcomes in a sample of US older adults.

Methods: In this matched cohort study, we analyzed a 20% sample of US Medicare beneficiaries aged 65 years and older hospitalized for acute ischemic stroke (AIS) between 2009 and 2021 who were discharged home. Individuals met insurance coverage criteria and were not taking ESM before hospitalization. We matched individuals on days from discharge to ESM initiation. Individuals who initiated ESMs other than levetiracetam within 30 days of discharge ($n = 229$) were matched to levetiracetam initiators ($n = 687$). We did not include antiseizure medications used for treatment of pain or psychiatric disorders such as gabapentin and benzodiazepines. We investigated the time to seizurelike events, emergency department (ED) visits, and readmissions using a semicompeting risk framework.

Results: The matched cohort of 916 ESM initiators had a median age of 73 years (interquartile range = 69–81) and was 57% female and 71% non-Hispanic White. Using the semicompeting risk framework, those who received other ESM had a 37% lower hazard of seizurelike events compared to those receiving levetiracetam, given that death had not occurred (hazard ratio = .63, 95% confidence interval [CI] = .43–.91). Among other ESM initiators, the hazard of ED visits and hospital readmissions, given that death had not occurred, did not differ significantly from initiating levetiracetam (hazard ratios = 1.00 [95% CI = .80–1.25] and .98 [95% CI = .75–1.28], respectively).

Significance: In a sample of US Medicare beneficiaries hospitalized for AIS and discharged home, initiating levetiracetam in the outpatient setting was associated with a higher risk of seizurelike events compared to other ESMs. However, there remains a possibility of residual confounding by indication, as individuals with greater risk of seizures may have been started on levetiracetam. We did not

observe significant differences in the risk of ED visits or readmissions, suggesting comparable safety profiles in broader clinical outcomes.

KEYWORDS

acute ischemic stroke, antiseizure medication, epidemiology, epilepsy, Medicare, older adults, retrospective cohort, seizure

1 | INTRODUCTION

Stroke is the most common cause of seizures in older adults.[1] Epilepsy-specific antiseizure medications (ESMs) are used for poststroke seizure management.[2,3] Several ESM options are available, including levetiracetam (LEV), lamotrigine (LTG), valproate (VPA), lacosamide (LAC), and others. Studies indicate that second-generation ESMs, such as LEV and LTG, and third-generation options, including LAC, are better tolerated in adults aged 65 years and older compared to first-generation drugs like phenytoin and carbamazepine (CBZ).[4,5] These newer classes of ESMs are associated with fewer drug–drug interactions and adverse outcomes, making them more suitable for older populations.

However, despite these advancements, there remains a critical gap in understanding the effectiveness and safety of second- and third-generation ESMs in older adults recovering from stroke. Current evidence often focuses on younger populations, leaving older patients underrepresented.[3,6,7] This is especially concerning given the well-documented adverse effects of ESMs, including dizziness, fatigue, unsteadiness, and mood or behavioral changes.[7,8] For older stroke survivors, these side effects can exacerbate existing functional impairments and neuropsychiatric conditions. Bridging this evidence gap is vital to guide clinicians in selecting the most effective and safest ESMs following acute ischemic stroke (AIS) for this vulnerable population, optimizing recovery outcomes and quality of life.[9,10]

Among US Medicare beneficiary prescribed antiseizure medications, LEV is the most commonly initiated drug for new onset seizures and is often used as monotherapy.[11,12] Its popularity is largely attributed to its ease of administration (available in both intravenous and tablet forms, with no titration required) and minimal drug–drug interactions.[13,14] These characteristics are particularly important for elderly stroke survivors, who often have multiple comorbidities and are prescribed anticoagulants, antiarrhythmics, or antihypertensive medications that may interact with other ESMs.[15,16]

Although LEV's profile makes it a practical choice, known side effects such as drowsiness and impaired balance can lead to falls, a critical concern in this population.[2,17]

Key points

- There is a critical gap in the literature regarding the effectiveness and safety of ESM use in older adults recovering from stroke.
- Our study examined the relationship between ESM choice and outcomes in older adults in the United States, including >10 years of claims-based data.
- Levetiracetam is the most initiated ESM post-stroke. Our results show an increased risk of seizurelike events for levetiracetam compared with other ESMs.
- There was no difference in ED visits or hospitalizations between patients treated with levetiracetam compared to other ESMs.

Falls often result in emergency department (ED) visits, hospitalizations, and loss of independence, highlighting the heightened vulnerability of older ambulatory stroke survivors discharged home—a less supervised yet highly at-risk group.[18] Despite this, there is limited evidence examining the impact of ESM choice on adverse outcomes such as unsteadiness or seizurelike events in community-dwelling older stroke survivors. To address these gaps, we investigated the relationship between outpatient ESM choice within 30 days of stroke discharge and subsequent health care utilization and seizurelike events in AIS survivors aged 65 years and older discharged home.

2 | MATERIALS AND METHODS

This study was approved by the Mass General Brigham Institutional Review Board and followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines. The requirement for informed consent was waived in our study, as we performed a secondary analysis of data routinely collected for billing. The data supporting this study's findings were collected by the US Centers for Medicare & Medicaid Services (CMS) and were made available by CMS with

no direct identifiers.[19] All results were aggregated following CMS Cell Suppression Policies. Restrictions apply to the availability of these data, which were used under license for this study. Medicare data are available through CMS with their permission. We have included the code that produced the findings in the supplemental materials (Supplementary Materials—Analytical Code).

2.1 | Study design

We conducted a retrospective analysis of US administrative claims data using a matched cohort study design.[20] Our focus was on individuals >65 years old, because this population is more vulnerable to adverse outcomes due to frequency of multiple comorbidities.[21] We analyzed US Medicare beneficiaries aged 65 years and older discharged home after a hospitalization for AIS between January 1, 2009 and September 30, 2021. The dataset used for this analysis was created by the CMS Research Data Assistance Center and contains a 20% random sample of all individuals enrolled in Medicare, a health insurance program covering 96% of all US citizens aged 65 years and older and people with certain disabilities and end stage renal disease.[22] Hospitalizations were selected from the Medicare Provider Analysis and Review (MedPAR) database based on principal diagnosis codes for AIS. We selected International Classification of Diseases, 9th Revision (ICD-9) codes 433, 434, and 436 and ICD-10 code I63, a validated strategy to capture AIS in administrative databases.[23] We included individuals who were hospitalized for AIS because they are at risk for new prescriptions and poststroke sequelae.

We included Medicare beneficiaries who were enrolled in the traditional Medicare Part A (hospital insurance), Part B (medical insurance), and Part D (drug prescription coverage) continuously for 12 months before their admission for stroke to ensure we could capture baseline comorbidities and ESM prescription history. We included first stroke admission, looking back at least 1 year to identify prior stroke, because treatment plans and outcomes may vary for those with prior history of stroke.[24] We focused on outpatient medication initiation and outcomes in community-dwelling stroke survivors. We included individuals who were discharged home and did not include those who were discharged to a skilled nursing facility or other inpatient facility. Medicare Part D prescription data contain records of outpatient prescription claims and do not include inpatient prescriptions, which is why individuals in long-term inpatient settings were excluded from the study. Community-dwelling stroke survivors may be less supervised than those discharged to inpatient facilities and therefore are more susceptible to falls from medication side effects or seizurelike events and related ED visits.

We excluded Medicare beneficiaries with ESM prescriptions prior to stroke hospitalization, focusing on new ESM initiators to support decision-making for starting outpatient ESMs after stroke. Our sample selection minimizes bias by excluding those with prior treatment for seizures and epilepsy as evidenced by having a prescription claim for ESM within 120 days prior to hospitalization. Accordingly, we assumed individuals with ESM claims after stroke should be new users and seizure claims after stroke should capture time to first seizure. A 120-day lookback period accounts for patients with prescriptions of 90-day supplies, as well as a 30-day grace period to capture stockpiling of earlier medication refills. We focused on ESM monotherapy, so patients prescribed more than one ESM were excluded. Additional details on sample selection are included in Methods S1 and Table S1.

2.2 | Participant characteristics

We described the following demographic characteristics for the sample: age, sex, race, and ethnicity. Reported race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian, other) were categorized using the Research Triangle Institute race and ethnicity variable provided in the Master Beneficiary Summary File (MBSF).[25]

We identified baseline comorbid conditions using Medicare's Chronic Condition Warehouse (CCW).[26] We considered a patient to have a condition at baseline if they met the diagnosis definition prior to their stroke admission. In addition, we reported the presence of a claim with an ICD code for arrhythmia (ICD-9 code 427.x and ICD-10 codes I48.x and I49.x) within the 12 months prior to admission, as certain ESMs are less appropriate for individuals with specific types of arrhythmia (e.g., lacosamide and its dose-dependent association with atrioventricular block and PR interval prolongation).[27] We identified beneficiaries with baseline dementia using a validated definition of Alzheimer disease and related dementia (AD/ADRD), which had excellent accuracy as demonstrated by a cross-validated area under the curve (AUC) of .94.[28] The validated definition of dementia was developed using ICD-10 codes, so we used a previously published crosswalk of ICD-10 to ICD-9 codes to identify beneficiaries with dementia with ICD-9 claims (Table S1).[29]

Using claims data, we captured clinical factors that may influence ESM choice and are associated with seizure outcomes and health care utilization. Stroke severity is a well-established risk factor for late seizures[30] and correlates with higher modified Rankin Scale (mRS)

scores.[17] Additionally, individuals with higher mRS scores at discharge are more likely to have unfavorable outcomes, which may lead to ED visits and hospitalizations. The mRS has seven total categories ranging from no or low disability to death: 0 (no symptoms), 1 (no significant disability), 2 (slight disability), 3 (moderate disability), 4 (moderate to severe disability), 5 (severe disability), and 6 (death).[31,32] For this study, we used a validated claims-based algorithm to classify mRS as a binary outcome, grouping scores of 0–3 and 4–6. The algorithm was able to accurately identify disability status with an area under the receiver operating characteristic curve of .85.[33]

2.3 | Matching characteristics

Matching is a method used to help control for baseline confounding variables when estimating an effect of a binary exposure. The matched cohort design helps address confounding bias by imposing balance on the covariates included in the matching process. Matching is then coupled with analytic, regression-based adjustment for remaining (observed) confounding. In our setting, we have misaligned treatment starts, a common issue in real-world time-to-event analysis.[20] If we compare treated to control patients without aligning on treatment timing, we may include periods where treated individuals had to survive long enough to receive treatment, but control individuals were at risk of the event. This creates immortal time bias, leading to an overestimation of treatment benefit. In addition, time-related confounders can also introduce selection bias. We utilized a matched cohort design, matching on days to treatment initiation.[34] This approach can help mitigate the immortal time bias by aligning treated and control individuals on the time to treatment initiation, therefore ensuring a valid comparison between the two groups during a similar risk period.

The ESM initiators were defined as the beneficiaries with therapy initiation within 30 days of poststroke discharge, beginning at the index acute hospitalization discharge date. Prescription claims were identified in the Medicare Part D prescription data using the generic and commercial brand names listed in Table S3. We used an intention-to-treat strategy, so we categorized individuals based on whether they were prescribed a drug, indicated by a prescription claim for ESM.

We grouped ESM initiators into two groups for matching: LEV initiators and other ESM Initiators, which includes LTG, LAC, CBZ, VPA, and other ESMs. For each beneficiary in use of other ESM, we identified three matches undergoing treatment with LEV. We calculated the Mahalanobis distance from other ESM Initiators to LEV initiators based on days from discharge to medication initiation and selected matches based on the shortest distance.[35] In this matching process, patients on LEV were used as controls for each patient using another ESM (matching without replacement).

2.4 | Outcomes

The outcomes measured were the time to seizurelike events, time to hospital readmissions, and time to ED visits, with a follow-up period of 180 days after initiation. We treated mortality as a competing risk.

We measured the time to seizurelike events using claims with diagnosis codes for seizurelike events from the inpatient, outpatient, and carrier claims files. A list of seizure diagnosis codes was identified from the CCW definition of epilepsy and is included in Table S4. We considered individuals to meet the definition for a seizurelike event if they had one inpatient claim or two outpatient claims occurring >1 day apart. In the case the individual had two outpatient claims > 1 day apart, we considered the time to the first claim (Figure 1).

We identified hospital readmissions using acute hospitalization claims occurring after the index stroke hospitalization in the MedPAR file. ED visits were identified using outpatient and inpatient claims with revenue center code indicative of an ED visit (0450, 0451, 0452, 0456, 0459, 0981).[36] We identified ED visits for seizurelike events using the seizure diagnosis codes listed in Table S4 on any position on in the claim.

We used the beneficiaries' date of death [BENE_DEATH_DT] from the Medicare MBSF, which comes from several sources, including the Social Security Administration. Overall, 99% of the death information in the MBSF has been validated.[37]

Individuals were followed from the day of medication initiation to the first occurrence of the outcome, mortality, or a censoring event. Censoring events included the end of the study observation period (180 days after initiation). Using Medicare claims data, we were able to follow individuals to the end of the study period.

2.5 | Statistical analysis

Our matching method allows us to estimate the average treatment effect in the treated group, the Other ESM group. In other words, we estimated the effect of receiving treatment with other ESMs compared with those individuals receiving LEV.

We used a semicompeting risks framework to analyze time to seizurelike events, ED visits, and hospital

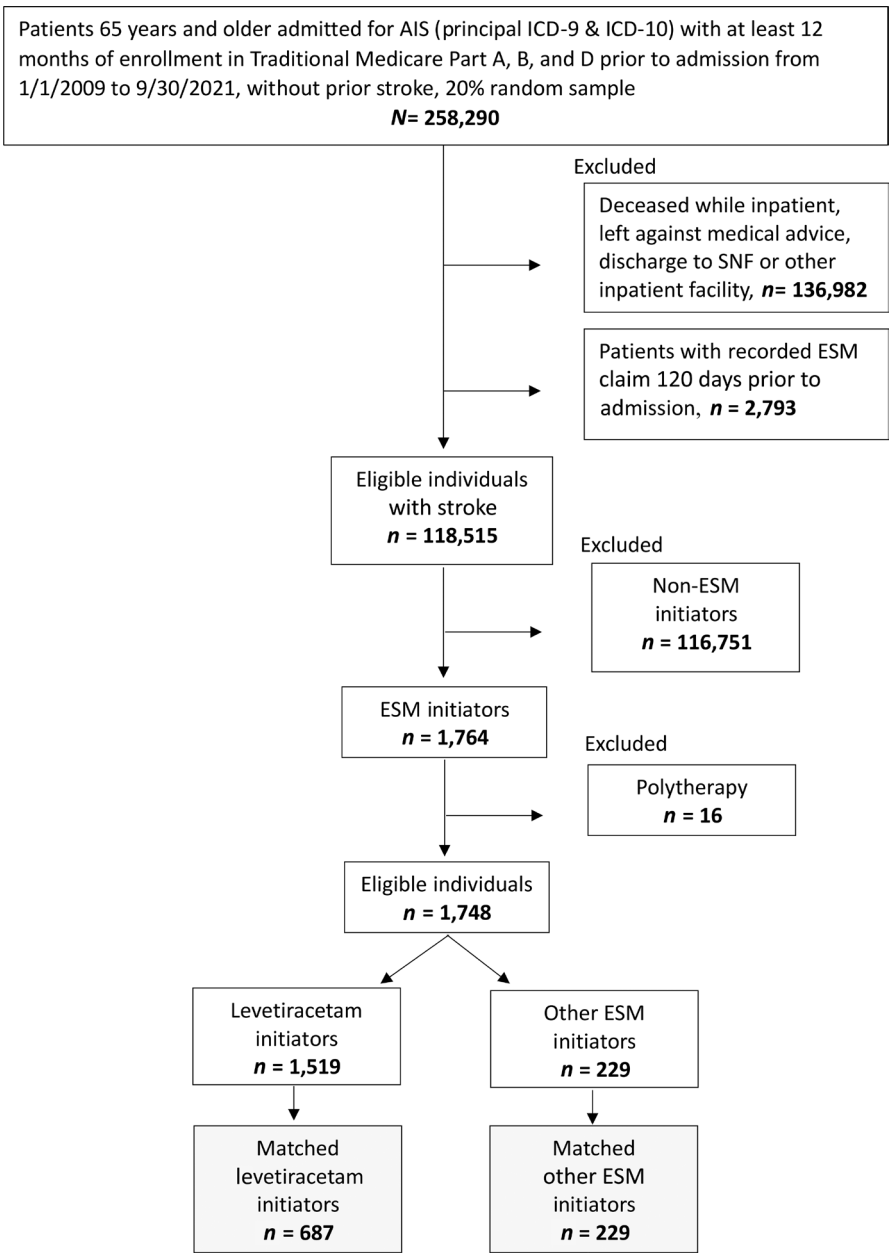

FIGURE 1 Sample inclusion criteria. AIS, acute ischemic stroke; ESM, epilepsy-specific antiseizure medication; ICD, International Classification of Diseases; SNF, skilled nursing facility.

readmission, with mortality as a competing risk. The semi-competing risks framework was described previously in Haneuse and Lee.[38] In brief, this framework allows us to consider the occurrence of a nonterminal event (seizurelike events, readmission, ED visit) that is subject to a terminal event (death). We used an illness–death model, which defines three hazard functions. The first hazard function is for seizurelike events, given that neither seizurelike events nor death has occurred. The second hazard function is for death, given that neither seizurelike events nor death has occurred. The third function is for time to death after a seizurelike event has occurred. Baseline hazard functions for all survival models were structured using B-splines. We present results for the illness–death model based on the semi-Markov specification. We used the SemiCompRisk and SemiCompRiskFreq packages for R.

Models were adjusted for days from discharge to initiation, age, mRS, and baseline depression. We did not have missing data for the covariates included in the model. A table with covariates incrementally added to the model specification can be found in Table S5. We adjusted for age and mRS, as these are related to the outcomes of interest but did not meet the definition of confounding, because they were not related to the exposure. We used a .2 threshold for defining a substantial difference based on standardized mean difference (SMD).

2.6 | Secondary preplanned analysis

We also repeated our analysis, stratifying by age of ≤75 and >75 years.

2.7 | Sensitivity analysis

A potential concern is the misclassification of seizurelike events when using claims data. To assess the extent to which our results might vary with different definitions of the same construct, we conducted sensitivity analyses using alternative methods to identify seizurelike events. First, we applied the standard CCW definition, which requires one inpatient claim, or two outpatient claims suggestive of epilepsy, occurring on different dates. Second, we employed a more sensitive approach that included any inpatient or outpatient claim for seizurelike events irrespective of date. Third, we tested the inclusion of additional ICD codes for seizurelike events, incorporating less specific codes for convulsions. These alternative definitions and their impact on the results are detailed in Tables S4 and S6.

In addition, we conducted sensitivity analysis using a longer follow-up period of 360 days for outcomes (Tables S7 and S8).

3 | RESULTS

Descriptive statistics for the sample are provided in Table 1 and our sampling strategy is shown in Figure 1. The 229 other ESM initiators were matched to 687 LEV initiators, for a total sample size of 916 individuals. We presented the counts of initiators in the matched sample by medication name in Table 2. The study sample was 57% female, had a median age of 73 years (interquartile range [IQR] = 69–81), and was 71% non-Hispanic White. Matched LEV initiators had a median age of 72 years (IQR = 68–79), and other initiators had a median age of 76 years (IQR = 71–82, SMD = .32). The percentage of individuals with AD/ADRD in the matched sample was 8% for other ESM and 4% for LEV initiators (SMD = .16). Depression was present at baseline in 60% of other ESM versus 36% of LEV initiators (SMD = .5). At discharge, 50% of other ESM and 41% of LEV initiators had an mRS indicative of moderate to severe disability (SMD = .18). In the 12 months prior to admission, 33% of LEV and 38% of other ESM initiators had a claim for arrhythmia (SMD = .11).

Using a .2 threshold for defining a substantial difference based on SMD, age and baseline depression were found to be significantly associated with drug choice.

3.1 | Association of ESM choice and outcomes

In the matched sample of 916 individuals, there were 298 seizurelike events, 465 ED visits, 155 ED visits for seizurelike event, 382 hospital readmissions, and 137 mortality events within a follow-up period of 180 days. The average follow-up time (to end of the follow-up window or death) was 163 days, and the total follow-up time was 410 person-years. Cumulative incidence curves for the outcomes are shown in Figures S1–S4. We report the results from the adjusted multivariable models investigating the association between ESM choice and outcomes in Tables 3–7. Survival curves for the outcomes are shown in Figures S5–S8. Among those who initiated ESMs other than LEV, the hazard of seizurelike events (given death has not occurred) was 37% lower than if they had initiated LEV (hazard ratio = .63, 95% CI = .43–.91; Table 3). The hazard of ED visits, given death had not occurred, was not different for the Other ESM group compared with those receiving LEV, with a hazard ratio of 1.00 (95% CI = .80–1.25) for ED visits (Table 4). The hazard of ED visits for seizurelike events was 27% lower for those who initiated other ESMs compared to if they had initiated LEV, but the result was not statistically significant, with a hazard ratio of .73 (95% CI = .46–1.14; Table 5). The hazard ratio was .98 (95% CI = .75–1.28) for hospital readmission (Table 6).

3.2 | Results of secondary preplanned analysis

In our analysis stratified by age, the hazard ratio for seizurelike events, given that death had not occurred, was .54 (95% CI = .28–1.04) for those ≤75 and .68 (95% CI = .45–1.01) for individuals >75 years old (Table 7). The results of the sensitivity analysis did not alter our conclusions (Tables S5–S7).

4 | DISCUSSION

In a sample of Medicare beneficiaries hospitalized for AIS, we compared outcomes for matched individuals initiated on different ESMs. We found greater risk of seizurelike events in those who initiated on LEV compared to those receiving other medications. In the context of insufficient guidance for seizure treatment in older patients, who are typically not included in randomized controlled trials, our study brings novel, real-world information on poststroke seizure control and ESM choice in this vulnerable population.

We identified several previous randomized controlled studies on ESM choice for treatment of poststroke seizures and epilepsy that are relevant to our study. Gilad et al. compared LTG (n = 32) with controlled-release CBZ (CR-CBZ; n = 32), and Consoli et al. compared LEV (n = 52) with CR-CBZ (n = 54).[39,40] A detailed review of these studies has been

TABLE 1 Sample characteristics.

Variable, *n* (%)		Overall, *n* = 916	Matched levetiracetam initiator, *n* = 687	Other ESM initiator, *n* = 229	SMD
Age, years	Median [IQR]	73 [69–81]	72 [68–79]	76 [71–82]	.32
	65–69	266 (29.0)	222 (32.3)	44 (19.2)	.37
	70–74	241 (26.3)	188 (27.4)	53 (23.1)	
	75–79	156 (17.0)	106 (15.4)	50 (21.8)	
	80–84	110 (12.0)	75 (10.9)	35 (15.3)	
	85+	143 (15.6)	96 (14.0)	47 (20.5)	
Sex	Male	391 (42.7)	304 (44.3)	87 (38.0)	.13
	Female	525 (57.3)	383 (55.7)	142 (62.0)	
Race	Non-Hispanic White	652 (71.2)	483 (70.3)	169 (73.8)	.17
	Black or African American	126 (13.8)	95 (13.8)	31 (13.5)	
	Hispanic	98 (10.7)	[a]	[a]	
	Other/unknown	40 (4.4)	[a]	[a]	
Length of hospital stay	1–5 days	710 (77.5)	538 (78.3)	172 (75.1)	.13
	6–10 days	139 (15.2)	105 (15.3)	34 (14.8)	
	10+ days	67 (7.3)	44 (6.4)	23 (10.0)	
Modified Rankin Scale	0 [no disability]	519 (56.7)	404 (58.9)	115 (50.2)	.18
	1 [disability]	396 (43.3)	282 (41.1)	114 (49.8)	
Dementia	Yes	49 (5.3)	30 (4.4)	19 (8.3)	.16
	No	867 (94.7)	657 (95.6)	210 (91.7)	
Arrhythmia	Yes	315 (34.4)	227 (33.0)	88 (38.4)	.11
	No	601 (65.6)	460 (67.0)	141 (61.6)	
Acute MI		83 (9.1)	67 (9.8)	16 (7.0)	.10
Atrial fibrillation		211 (23.0)	153 (22.3)	58 (25.3)	.07
Cataract		571 (62.3)	403 (58.7)	168 (73.4)	.31
Chronic kidney		415 (45.3)	302 (44.0)	113 (49.3)	.11
COPD		330 (36.0)	235 (34.2)	95 (41.5)	.15
CHF		355 (38.8)	246 (35.8)	109 (47.6)	.24
Diabetes		492 (53.7)	354 (51.5)	138 (60.3)	.18
Ischemic heart disease		597 (65.2)	433 (63.0)	164 (71.6)	.18
Depression		383 (41.8)	246 (35.8)	137 (59.8)	.50
Osteoporosis		176 (19.2)	123 (17.9)	53 (23.1)	.13
Rheumatoid arthritis/ osteoarthritis		536 (58.5)	383 (55.7)	153 (66.8)	.23
Asthma		169 (18.4)	121 (17.6)	48 (21.0)	.09
Hyperlipidemia		784 (85.6)	580 (84.4)	204 (89.1)	.14
Hypertension		842 (91.9)	623 (90.7)	219 (95.6)	.20
Hypothyroidism		266 (29.0)	184 (26.8)	82 (35.8)	.20

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ESM, epilepsy-specific antiseizure medication; IQR, interquartile range; MI, myocardial infarction; SMD, standardized mean difference.

[a]Small counts are censored in accordance with the US Centers for Medicare & Medicaid Services cell suppression policy.

previously published by Brigo et al.[4] In both previous studies of ESM choice, no difference was found in seizure freedom between groups, but both studies had a small number of patients included and thus may have been underpowered. In addition, randomized controlled trials are restrictive in their enrollment criteria and may have selection bias due to withdrawal from the trial. The average age of participants in Gilad et al. was 67.2 years (SD = 2.4) for LTG and 67.7 years

(SD = 2.6) for CR-CBZ, compared with our study population, which had a median age of 74 years (IQR = 69–81) and participants ranging from 65 to >85 years old. In Gilad et al., 3% of participants taking LTG and 31% of those taking CR-CBZ withdrew from the trial due to adverse effects. Our study showed lower hazard of seizurelike events for other ESM initiators compared to receiving LEV.

We identified a population-based registry study on ESM choice in poststroke epilepsy. Winter et al. followed 216 patients initiated on ESM monotherapy (LEV, LTG, LAC, VPA and eslicarbazepine [ESL]) for 12 months.[7] The study reported lower seizure frequency in ESMs with selectivity to the slow-inactivated state of sodium channels (LAC, ESL) compared with other mechanisms of action.

Monotherapy with LEV has been previously found to have an effectiveness of >80% in preventing seizures.[41] Unlike our study, other smaller studies did not find statistically significant differences in seizurelike events in poststroke patients treated with LEV compared with other ESMs.[40] These findings highlight the necessity of future guidelines for ESM therapy to distinguish older populations, considering the impact of increased seizure relapse in this group with an existing high risk of deficits and adverse outcomes.[42] Moreover, previous randomized controlled studies present comparisons of ESM versus placebo, which does not help in drug type choice and can result in seizure relapse outcomes, as presented in our results.[43–45]

Stroke patients have a high risk of hospital readmission.[46–48] A previous study found a total of >30% of stroke survivors being readmitted.[47] The presence of a seizure diagnosis in this population has been reported as a contributing factor to both new hospitalizations and mortality risk.[46,48] We did not identify any studies on ESM choice and differences in health care utilization (ED visits and readmission). In our cohort, there was no difference in ED visits and hospitalizations between patients treated with LEV compared to other ESM.

Our study used a nationally representative sample to examine the relationship between ESM choice and outcomes, including >10 years of claims-based data. Currently available clinical data for ESM treatment choice for poststroke epilepsy in the older population are not robust. Real-world evidence studies can help fill this knowledge gap and provide clinicians with more information on ESM treatment options. Our sample permitted well-measured outcomes for hospitalizations, ED visits, and seizure outcomes, providing valuable, real-world information on ESM choice and outcomes.

TABLE 2 Count of initiators by medication in the matched sample.

Medication	*n* (%)
Levetiracetam	687 (75)
Lamotrigine	56 (6.1)
Carbamazepine	46 (5.0)
Oxcarbazepine	33 (3.6)
Lacosamide	32 (3.5)
Phenytoin	29 (3.2)
Valproic Acid	14 (1.5)
Zonisamide	[a]
Phenobarbital	[a]
Brivaracetam	[a]

[a]Data censored in accordance with US Centers for Medicare & Medicaid Services cell suppression policy due to small counts.

5 | LIMITATIONS

The findings for our population sample might not be generalizable to groups not included in this study, such as Medicare beneficiaries enrolled in Part C (Medicare Advantage) or patients not enrolled in Medicare prescription drug plans (Part D). Furthermore, our sample of

TABLE 3 Hazard ratios for seizurelike events.

Variable	Seizurelike event	Death prior to seizurelike event	Death after seizurelike event
ESM treatment group [0 = LEV, 1 = other ESM]	.63 (.43–.91)	.64 (.37–1.11)	1.02 (.46–2.24)
Days to initiation	1.00 (.98–1.01)	1.00 (.98–1.03)	1.02 (.98–1.05)
Age [standardized at age 80 years, 10-year bins]	.88 (.72–1.08)	1.14 (.86–1.51)	1.19 (.81–1.77)
Modified Rankin Scale	1.38 (.95–1.99)	2.82 (1.68–4.73)	2.35 (1.19–4.64)
Baseline depression	1.26 (.94–1.69)	1.24 (.79–1.95)	1.12 (.58–2.15)

Note: Hazard ratios for seizurelike events with a follow-up period of 180 days after medication initiation with 95% confidence intervals. Hazard ratios were calculated using a semicompeting risk framework, with death as a competing risk. Hazard ratios were adjusted for age, modified Rankin Scale, baseline depression, and days from discharge to medication initiation.

Abbreviations: ESM, epilepsy-specific antiseizure medication; LEV, levetiracetam.

TABLE 4 Hazard ratios for ED visits.

Variable	ED visit	Death prior to ED visit	Death after ED visit
ESM treatment group [0 = LEV, 1 = other ESM]	1.00 (.80–1.25)	.83 (.44–1.55)	.74 (.43–1.27)
Days to initiation	1.00 (.99–1.01)	.98 (.95–1.01)	1.02 (1.00–1.04)
Age [standardized at age 80 years, 10-year bins]	1.02 (.90–1.17)	1.34 (.98–1.85)	1.04 (.79–1.38)
Modified Rankin Scale	1.47 (1.16–1.87)	2.77 (1.51–5.07)	1.80 (1.11–2.94)
Baseline depression	1.22 (.99–1.49)	1.20 (.70–2.06)	1.06 (.67–1.66)

Note: Hazard ratios for ED visits with a follow-up period of 180 days after medication initiation with 95% confidence intervals. Hazard ratios were calculated using a semicompeting risk framework, with death as a competing risk. Hazard ratios were adjusted for age, modified Rankin Scale, baseline depression, and days from discharge to medication initiation.

Abbreviations: ED, emergency department; ESM, epilepsy-specific antiseizure medication; LEV, levetiracetam.

TABLE 5 Hazard ratios for ED visits for seizurelike event.

Variable	ED visit for seizurelike event	Death prior to ED visit for seizurelike event	Death after ED visit for seizurelike event
ESM treatment group [0 = LEV, 1 = other ESM]	.73 (.46–1.14)	.70 (.42–1.17)	1.19 (.45–3.15)
Days to initiation	1.01 (.99–1.03)	1.00 (.98–1.03)	1.02 (.98–1.06)
Age (standardized at age 80 years, 10-year bins)	.97 (.76–1.24)	1.08 (.83–1.42)	1.49 (.94–2.37)
Modified Rankin Scale	1.79 (1.04–3.09)	2.95 (1.64–5.31)	1.86 (.78–4.46)
Baseline depression	1.29 (.89–1.87)	1.38 (.90–2.12)	.66 (.28–1.53)

Note: Hazard ratios for ED visits where there was a diagnosis code for seizure on the claim with a follow-up period of 180 days after medication initiation with 95% confidence intervals. Hazard ratios were calculated using a semicompeting risk framework, with death as a competing risk. Hazard ratios were adjusted for age, modified Rankin Scale, baseline depression, and days from discharge to medication initiation.

Abbreviations: ED, emergency department; ESM, epilepsy-specific antiseizure medication; LEV, levetiracetam.

TABLE 6 Hazard ratios for hospital readmissions.

Variable	Readmission	Death prior to readmission	Death after readmission
ESM treatment group [0 = LEV, 1 = other ESM]	.98 (.75–1.28)	.84 (.43–1.63)	.69 (.40–1.19)
Days to initiation	1.01 (.99–1.02)	.97 (.94–1.01)	1.02 (.99–1.04)
Age [standardized at age 80 years, 10-year bins]	.96 (.82–1.12)	1.42 (1.01–1.99)	1.04 (.79–1.37)
Modified Rankin Scale	1.64 (1.22–2.19)	3.98 (1.96–8.06)	1.48 (.91–2.40)
Baseline depression	1.12 (.89–1.40)	1.14 (.64–2.05)	1.14 (.73–1.78)

Note: Hazard ratios for hospital readmissions with a follow-up period of 180 days after medication initiation with 95% confidence intervals. Hazard ratios were calculated using a semicompeting risk framework, with death as a competing risk. Hazard ratios were adjusted for age, modified Rankin Scale, baseline depression, and days from discharge to medication initiation.

Abbreviations: ESM, epilepsy-specific antiseizure medication; LEV, levetiracetam.

TABLE 7 Hazard ratios for seizurelike events, ED visits, and readmission, stratified by age group.

Variable	Seizure	ED visit	ED visit for seizurelike event	Readmission
Age ≤ 75 years	.54 (.28–1.04)	.86 (.57–1.30)	.61 (.27–1.39)	1.05 (.70–1.58)
Age > 75 years	.68 (.45–1.01)	1.09 (.82–1.45)	.66 (.39–1.13)	.98 (.68–1.39)

Note: Hazard ratios for outcomes, given that death did not occur, with a follow-up period of 180 days after medication initiation with 95% confidence intervals. Hazard ratios were calculated using a semicompeting risk framework, with death as a competing risk. Models were adjusted for age, modified Rankin Scale, baseline depression, and days from discharge to medication initiation.

Abbreviation: ED, emergency department.

dementia patients initiated on other ESM was too small to complete stratification as initially planned.

This study excluded beneficiaries discharged to inpatient rehabilitation units or skilled nursing facilities. Patients who are discharged to inpatient facilities usually have more severe stroke and disabilities and would benefit from assessment in future studies.[49] We focused on subacute outcomes of ESM treatment in AIS patients. Later studies could explore chronic outcomes, especially when considering the different patterns of ESM use and adverse effects in this population.[9]

Due to existing limitations in the dataset, some residual confounding factors could not be controlled. We were not able to adjust for factors associated with stroke severity and seizure outcomes, such as stroke territory. We found that as covariates were added incrementally to the model specification, the differences between treatment groups became larger, as indicated by lower hazard ratios (Table S5). Additional variables could reduce variance and improve precision but would not necessarily enhance the validity of the model because of their strong correlation with variables already included in the model. After the adjustments made, residual confounding from unmeasured factors is likely minimal.

Although the use of claims-based data is reliable, it also has limitations such as missing data and a lack of granular seizure outcome data. Data are also absent on seizure frequency, seizure type, date of last seizure episode, or indication for ESM treatment. We tried to address this last point by selecting ESMs that are primarily indicated for treatment of seizures. There remains a possibility of residual confounding by medication indication, as those at greater risk of seizure may have been more likely to be started on LEV than other ESM. Medications in the Other ESM group may also be used for other indications, including mood disorders, bipolar disorder, headache, and central poststroke pain management. Lastly, certain ESM presented with groups of insufficient size, and so we were not able to conduct individual medication comparisons. Further studies are needed to confirm the findings of this study, controlling for medication indication. Further studies are needed to conduct individual ESM comparisons.

6 | CONCLUSIONS

Real-world evidence studies can provide information on which ESM treatment choice leads to better outcomes in stroke survivors older than 65 years. In our sample of Medicare beneficiaries hospitalized for AIS and discharged home, those who initiated LEV in the outpatient setting had higher risk of seizures compared to those who initiated other ESMs. However, there remains a possibility that individuals with greater risk of seizures may have been started on LEV; further studies will be needed to confirm this finding. There was no difference in ED visits or hospitalizations by ESM choice.

AUTHOR CONTRIBUTIONS

Julianne D. Brooks completed the data analysis and drafted and edited the manuscript for intellectual content. Rafaella Cazé de Medeiros drafted, edited, and revised the manuscript for intellectual content. Shuo Sun and Madhav Sankaranarayanan were involved with study design, statistical analysis, and revision for intellectual content. M. Brandon Westover and Lee H. Schwamm were involved in study conceptualization and revised the manuscript for intellectual content. Joseph P. Newhouse facilitated data access and revised the manuscript for intellectual content. Sebastien Haneuse was involved in study design, supervising study development, and revising the manuscript for intellectual content. Lidia M. V. R. Moura was involved in study design and conceptualization, obtaining data access, supervising study development, and revising the manuscript for intellectual content.

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CONFLICT OF INTEREST STATEMENT

M.B.W. is a cofounder of and scientific advisor and consultant to and has personal equity interest in Beacon Biosignals. L.M.V.R.M. receives research support from the Epilepsy Foundation of America, the National Institute of Neurological Disorders and Stroke, and the National Institute on Aging and reports no conflict of interest. None of the other authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the US Centers for Medicare & Medicaid Services. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from https://resdac.org/research-identifiable-files-rif-requests with the permission of the US Centers for Medicare & Medicaid Services.

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